Plague dynamics are driven by climate variation


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The bacterium *Yersinia pestis* causes bubonic plague. In Central Asia, where human plague is still reported regularly, the bacterium is common in natural populations of great gerbils. By using field data from 1949–1995 and previously undescribed statistical techniques, we show that *Y. pestis* prevalence in gerbils increases with warmer springs and wetter summers: A 1°C increase in spring is predicted to lead to a >50% increase in prevalence. Climatic conditions favoring plague apparently existed in this region at the onset of the Black Death as well as when the most recent plague pandemic arose in the same region, and they are expected to continue or become more favorable as a result of climate change. Threats of outbreaks may thus be increasing where humans live in close contact with rodents and fleas (or other wildlife) harboring endemic plague.

Generalized Threshold Mixed Model | historic and recent climatic conditions | time-series data | *Yersinia pestis*

Plague (*Yersinia pestis* infection) has in the past had devastating effects on human populations and has become an epithet for outbreaks of infectious disease (1, 2). It remains endemic in natural populations of rodents and a medical threat with numerous human cases per year throughout Asia, parts of Africa, the United States, and South America (3–5). There have previously been some suggestions of a link between plague and climate (6, 7).

The desert regions of Central Asia are known to contain natural foci of plague where the great gerbil (*Rhombomys opimus*) is the primary host (8–11). Plague spread requires both a high abundance of hosts and a sufficient number of active fleas as vectors transmitting plague bacteria between hosts. The biannual data used in our analysis derive from four sampling units [referred to as “large squares” (LSQs); see Methods] in one such focus in Kazakhstan, southeast of Lake Balkhash (Fig. 1), and consist of estimates of great gerbil abundance and bacteriological test data.

Davis *et al.* (12) documented the presence of an abundance threshold of hosts in this system, below which plague is unable to either invade or persist. Here we are able to go beyond this finding by using previously undescribed statistical methodology (see also ref. 13) to examine not simply presence but also prevalence of plague above the threshold, demonstrating that there is a clear effect of climate. We include seasonality and environmental covariates, by means of a previously undescribed piecewise linear model (14), namely, the Generalized Threshold Mixed Model (GTMM). Our analysis is done by pooling information across the four LSQs (Fig. 1). In the GTMM approach, the prevalence of plague is always zero if the (lagged) abundance of great gerbils is below the critical threshold. Estimation of the threshold, as in the study by Davis *et al.* (12), relies only on the abundance of great gerbils. Above the threshold, however, plague prevalence is evaluated as a function of the environmental conditions, gerbil abundance, and latent variables that account for some missing covariates (e.g., the local presence/absence and the virulence of the bacteria) (see Supporting Text and Table 2, which are published as supporting information on the PNAS web site).

Results and Discussion

Table 1 summarizes the maximum likelihood estimates of the Generalized Threshold Mixed Model defined by Eq. 1 in Methods. The fixed effect of a covariate refers to its common effect over the four LSQs, whereas the corresponding random effect in Table 1 refers to the between-square standard deviation (SD) of the covariate effect. Only the spring intercept, spring temperature, spring rainfall, and fall intercept are found to have substantial variation over the four LSQs; hence, these parameters are modeled with a random-effect component.

Diagnostics of the model fit, summarized in Supporting Text and Figs. 3–8, which are published as supporting information on the PNAS web site, show that the model given by Eq. 1, together with the parameter estimates summarized in Table 1, provides a good fit to the data. Although some of the epizootics (Fig. 1) appear to follow the expected pattern of a rapid rise in prevalence followed by a fade-out, there is no further serial correlation in the time series beyond that induced by the covariates, because the fitted model has no residual serial correlation. Note that the spring and fall delay parameters are estimated as 1.5 and 2 years, respectively; that is, the prevalence in the spring and fall are both predicted best by the same great gerbil fall population size, respectively, 1.5 and 2 years earlier. This result is consistent with the delay reported by Davis *et al.* (12) but extends their analysis by pinpointing fall abundance as critical. This finding is noteworthy because fall abundance is the annual peak abundance with less measurement error and hence is more informative; if the fall density estimate is not higher than the threshold, it is unlikely that the threshold was exceeded, whereas even if the spring density estimate were below the threshold, the threshold may still have been exceeded for extended periods.

From Table 1, it is apparent that, other things being equal, and when gerbil abundance at the appropriate time lag is above the threshold, increasing spring temperature (see Methods) will lead to an increased prevalence in the spring (Fig. 2a). In addition, increased summer precipitation will increase the fall prevalence (see Fig. 2b). Other data in the plague-data archive support the hypothesis that this climatic forcing effect on prevalence is mediated through fleas. Flea burden is found to correlate with climatic variables identified by the fitted model: Spring flea

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Abbreviation: LSQ, large square.

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burden is negatively correlated with the number of days with frost on the soil in spring ($r = -0.54, P = 0.015$) and positively correlated with spring temperature ($r = 0.38, P = 0.093$). Fall flea burden is correlated positively with summer relative humidity ($r = 0.49, P = 0.028$). When flea burden is included in the model given by Eq. 1 (which halves the above-threshold sample size due to many missing values), the climate variables become insignificant, whereas the spring flea burden is positive and significant, and the fall flea burden is positive and marginally significant (see Methods). Late winter/spring frost has been suggested as a factor determining plague dynamics (15–18) because it is thought to greatly reduce the activity and survival of fleas. Spring temperature is relevant because fleas are only active when the air temperature is above $\approx 10^\circ \text{C}$ (19). Increased host attack rate, migration to burrow entrances, egg maturation, and (in adults) egg production, etc., can thus start earlier and may last longer when spring warmth comes early. Turning to the summer, dry (and hot) conditions are known to have a harmful effect on the survival of both adult fleas and developing preadults (19, 20). Hence, under such conditions, flea abundance will be relatively low, and summer-generations are less likely to overlap. With more humid conditions (more summer precipitation), there are more fleas, and their generations overlap, favoring the transmission of plague. Based on data from 1948–2004, summer temperature is furthermore found to correlate negatively with summer precipitation ($r = -0.29, P = 0.027$) and relative humidity ($r = -0.37, P = 0.0056$). Hence, cooler summers also tend to be wetter, jointly amplifying these climatic effects on plague prevalence. [Whereas this negative correlation is apparent on the interannual scale (Fig. 1), temperature and precipitation are found to be positively correlated over longer time windows; see Methods.]

The fitted model predicts that, above the threshold, an increase in spring temperature of $1^\circ \text{C}$ will increase the average spring prevalence from 0.0077 to 0.0122, corresponding to a 59% jump in prevalence, across all LSQs and all years of the study.
Similarly, were summer rainfall to increase by 10% over the study period, fall prevalence would increase only marginally from an average of 0.0110 to 0.0118, a 7% jump. Notice that these prevalence figures refer to "instantaneous" bacteriological tests, and seroprevalence levels (hosts that have ever had plague) are typically at least twice as high as this amount (Kazakh Scientific Centre for Quarantine and Zoonotic Diseases, unpublished data). In public health terms, a single (bacteriologically) positive sample close to human habitation is deemed sufficient to warrant control intervention: if, during monitoring, plague is discovered, then control actions are started (Kazakh Scientific Centre for Quarantine and Zoonotic Diseases, unpublished data). Plague is a serious concern at the 0.8% average level and will certainly be even more so at a 1.2% level.

Clearly, changes in spring temperature are the most important environmental factor determining the prevalence level, and the following scenario emerges: Warmer spring conditions lead to an elevated vector–host ratio, which leads to a higher prevalence level in the gerbil host population. Moreover, these climatic conditions that favor increased prevalence among gerbils given unchanged gerbil abundance also favor increased gerbil abundance (K.L.K., H.V., V.M.D., J.E., and N.C.S., unpublished data), which means that the threshold density condition for plague will be reached more often, thus increasing the frequency with which plague can occur (see also Supporting Text). Altogether, therefore, the model here suggests that warmer springs (and wetter summers) can trigger a cascading effect on the occurrence and level of plague prevalence, in years with above-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter</th>
<th>Estimated value</th>
<th>Asymptotic standard error</th>
<th>Asymptotic, 95% CI</th>
<th>Bootstrap, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spring intercept</td>
<td>$\beta_0$</td>
<td>-9.51</td>
<td>1.0</td>
<td>(-11.5, -7.53)</td>
<td>(-12.1, -5.35)</td>
</tr>
<tr>
<td>Spring temperature</td>
<td>$\beta_1$</td>
<td>0.539</td>
<td>0.17</td>
<td>(0.199, 0.879)</td>
<td>(0.117, 0.979)</td>
</tr>
<tr>
<td>Fall intercept</td>
<td>$\beta_2$</td>
<td>-10.8</td>
<td>1.0</td>
<td>(-12.8, -8.86)</td>
<td>(-13.0, -5.56)</td>
</tr>
<tr>
<td>Summer rainfall</td>
<td>$\beta_3$</td>
<td>0.775</td>
<td>0.24</td>
<td>(0.301, 1.25)</td>
<td>(-0.182, 1.55)</td>
</tr>
<tr>
<td>Lag 1/2 occupancy in fall logistic model</td>
<td>$\beta_4$</td>
<td>6.15</td>
<td>0.88</td>
<td>(4.41, 7.89)</td>
<td>(2.54, 8.68)</td>
</tr>
</tbody>
</table>

Table 1. Maximum-likelihood estimates of the plague model parameters

Fig. 2. The effect of changes in the environmental conditions on prevalence. (a) The effect of spring temperature on prevalence in the spring. (b) The effect of summer precipitation on prevalence in the fall. Note that the curves in a and b illustrate the mean effect of spring temperature and (log) summer rainfall, respectively, with other covariates and random effects set at their mean values. The unit of temperature is °C, and rainfall is on the log-mm scale (i.e., the untransformed rainfall data are in millimeters). Open circles are the partial residuals for spring temperature and summer precipitation, respectively. The partial residuals are defined as the mean effect of spring temperature (summer precipitation) plus Pearson residuals (i.e., raw residuals rescaled so that they have constant variance, and the constant variance equals the mean-squared deviations of the raw residuals about their mean). Another approach to assess the climate effects is to calculate the induced average changes in the prevalence, with the other covariates unchanged (and held at their historical values and the random effects equal to their estimates). Results of the latter approach, which are reported in the text, are broadly similar but nonidentical to those shown in this figure.
threshold great gerbil abundance during the fall two calendar years earlier and in a region that is itself dry and continental [hot summers, cold winters (see, e.g., ref. 21)]. Analyses favor, moreover, the suggestion that enhanced flea survival and reproduction are critical in this effect, but given the multiple routes of plague transmission (flea-borne, direct via several pathways, transfer from other reservoirs), climatic influences on other epidemiological processes cannot be precluded. More generally, it is widely accepted that the distribution and dynamics of vector-borne infections are particularly sensitive to climatic conditions, by virtue of the sensitivity of the (arthropod) vectors themselves to variations in temperature, humidity, and often quantities of standing water used as breeding sites. This work has been dominated by mosquito-borne infections such as malaria and dengue and by tick-borne infections such as Lyme disease and tick-borne encephalitis (22–25). Much less attention has been focused on flea-borne infections or on direct effects on the (vertebrate) wildlife reservoirs.

Our insights also may shed light on the emergence of the Black Death and plague’s Third Pandemic, thought (26) to have spread from an outbreak-core region in Central Asia. Analyses of tree-ring proxy climate data (see Methods) show that conditions during the period of the Black Death (1280–1350) were both warmer and increasingly wet. The same was true during the origin of the Third Pandemic (1855–1870) when the climate was wetter and underwent an increasingly warm trend. Our analyses are in agreement with the hypothesis that the Medieval Black Death and the mid-19th-century plague pandemic might have been triggered by favorable climatic conditions in Central Asia.

Such climatic conditions have recently become more common (27), and whereas regional scenarios suggest a decrease in annual precipitation but with increasing variance, mean spring temperatures are predicted to continue increasing (21, 28). Indeed, during the period from the 1940s, plague prevalence has been high in its host-reservoir in Kazakhstan (29). Effective surveillance and control during the Soviet period resulted in few human cases (29). But recent changes in the public health systems, linked to a period of political transition in Central Asia, combined with increased plague prevalence in its natural reservoir in the region, forewarn a future of increased risk of human infections.

Methods

Data. Gerbil abundance. Each spring and autumn between 1949 and 1995, the proportion of burrows inhabited and site-count observations were done at different locations within the PreBalkhash area (see Fig. 1). At a given site, the great gerbil population densities were estimated at least twice per year. On ~85% of these occasions, there are independent data on plague prevalence where up to 8,576 gerbils (median = 640) were trapped per LSO and season and tested for Y. pestis infection. Here we use the proportion of burrows inhabited (referred to as occupancy) as a proxy for density to avoid the uncertainties connected to the site-count–based density estimates (see refs. 12 and 30). The LSOs chosen had the longest regular and continuous time series of data required by our analysis.

For a fixed delay \(d\), the spring (fall) threshold can be estimated by first sorting the spring (fall) occupancy in ascending order, and then the estimator equals the smallest such sorted occupancy for which the corresponding plague prevalence \(d\) time unit later is positive (see Supporting Text).

Bacteriological test. The prevalence data were mainly collected in May and June and in September and October. The trapped great gerbils were tested for plague by plating rodent samples (blood, liver, and spleen) on Hottinger’s agar containing 1% hemolyzed sheep erythrocytes. Note that a positive bacteriological test is usually only obtained from rodents with acute plague, which may considerably underestimate the number of rodents that carry the infection (31).

Flea burden. The flea burden was computed as the ratio of the number of rodent fleas divided by the number of rodents examined in each season. These ratios are available from 1975 when the numbers of fleas taken from rodents were recorded separately from the numbers of fleas taken from the burrow systems. Before 1975, only the total numbers of fleas were recorded. We computed the correlation of spring and fall flea burden in LSO 105 with, respectively, the total number of days with frost on the soil in March and April and spring temperature (spring burden) and summer relative humidity (fall burden).

Because the flea data have many missing values, including spring and fall, flea burden in the model reduces the above-threshold sample size from 120 to 54. Exploratory data analysis suggests that the coefficients of the spring and fall flea burden do not vary over the four LSOs and hence can be modeled as fixed-effect parameters. Overfitting the final model by including spring flea burden in the spring submodel and fall flea burden in the fall submodel, both as fixed effects, results in Akaike information criterion (AIC) = 281.2 and Bayesian information criterion (BIC) = 307.0. In contrast, the same model but with the climate covariates suppressed results in AIC = 276.3 and BIC = 294.2, confirming that, with flea burden in the model, climate no longer correlates with plague prevalence (see Table 3, which is published as supporting information on the PNAS web site). This finding is consistent with the hypothesis that the climate forcing on plague prevalence we have found is mediated through flea activity. Excluding climatic effects from the model, the coefficient of spring flea burden is estimated to be 0.0994, with the 95% confidence interval being (0.0256, 0.173), whereas that of fall flea burden is 0.0372, and the 95% confidence interval being (0.0256, 0.146). Thus, the spring flea effect is positive and significant. Although the coefficient estimate of fall flea burden is also positive, it is significant only at the \(\approx 15\%\) level. This result highlights the relative importance of spring flea activity in its impacts on plague prevalence.

Recent climatic conditions. Climatic data were obtained from the Bakanas meteorological station (see Fig. 1). Spring climatic variables are the average monthly temperature during the spring (i.e., March and April) and the log average of the spring rainfall. The fall climatic variable used is the log average of summer (i.e., June, July, and August) temperature at Fergana. The Tien Shan ring-width data were detrended to remove tree-age–related biases and to emphasize high- to low-frequency climatic signals over the past millennium (32). Data were regressed against observational temperature measurements recorded at the Fergana meteorological station in eastern Uzbekistan (\(r = 0.46\)). The temperature signal is weighted toward the June–July–August–September season, but also indicates some response to March conditions. Temperature at Fergana was found to correlate positively with that of Bakanas in spring (\(r = 0.45, P = 0.0036\)) and summer (\(r = 0.60, P = 0.00011\)). Because the reconstructed temperature data are annually resolved, it seems relevant that these cor-
relations are 0.15 ($P = 0.33$) and 0.42 ($P = 0.0059$), when computed for annual mean temperature at Fergana and spring and summer temperatures in BAKANAS, respectively. The KARAKORUM oxygen isotope data were regressed against a regional average integrating five normalized precipitation records ($r = 0.58$). Monthly correlation analyses indicated that the signal is weighted toward late winter and spring (33). Annual precipitation at KARAKORUM correlated positively with relative humidity at BAKANAS in spring ($r = 0.31$, $P = 0.030$) and summer ($r = 0.46$, $P = 0.0011$). Consequently, the reconstructed historic climate variables are indicative of the climate conditions in BAKANAS for the past millennium.

Analyses of tree-ring proxy data showed that, during the Black Death (years 1280–1350), it was, on average, somewhat warmer (mean $= -0.0582$, $\pm 0.23$ SDs above the overall mean $= -0.152$ based on data from year 1000 to 1995) but also drier (mean $= -0.404$, $\pm 0.28$ SDs below the overall mean $= -0.279$ over the period from year 1000 to 1998). However, at the time of the emergence of the Black Death, there was a clear trend of increasing precipitation (see Fig. 9, which is published as supporting information on the PNAS website). Similarly, just at the time the latest (Third) plague pandemic started (year 1855–1870), the climate was warmer (mean $= -0.125$, $0.29$ SDs above the overall mean) but also slightly cooler (mean $= -0.213$, $0.15$ SDs below the overall mean). However, again the period of the Third Pandemic experienced a trend of increasingly warmer and wetter conditions. Indeed, precipitation is positively correlated with temperature over the past millennium ($r = 0.16$, $P = 0.0002$), suggesting that warmer springs and wetter summers tended to occur together.

Model. Let $N_t$ be the number of great gerbils examined at time $t$ in LSQ $l$. The number of great gerbils testing positive under a bacteriological test is assumed to be binomially distributed with parameters $(N_t, P_t)$, where if $t$ is a spring the true prevalence rate $P_{t,s}$ is zero when the lag-$d^2$ occupancy, namely, $X_{t-d;2}$, is below the spring threshold $r_1$ (the superscript $s$ signifies spring) but otherwise follows a logistic regression model (see below). A specific similarity holds for fall data.

Potential covariates related to the fixed and random effects include a large set of climate variables, current occupancy as well as lag-1/2 and lag-1 year occupancies. The parameters including the threshold parameters were estimated by a likelihood-based method (see ref. 13 and Supporting Text). Based on the model diagnostics and the significance of each covariate effect (whether it is fixed or random), we obtain the following final fitted trustworthy model:

$$
P_{t,s} = \begin{cases} 
0, & \text{if } X_{t-d^2} < r_1 \text{ and } t \text{ is a spring} \\
\log^{-1} \left\{ \left( b_0 + b_1 X_{t-2} \right) + \left( b_1^* + b_2^* T_{s,sp} + b_3^* R_{sp} + e_{1,t} \right) \right\}, & \text{if } X_{t-d^2} \geq r_1 \text{ and } t \text{ is a spring}; \\
0, & \text{if } X_{t-d^1} < r_1 \text{ and } t \text{ is a fall} \\
\log^{-1} \left\{ \left( b_0 + b_3 \right) + \left( b_4^{*} T_{sp} + b_4^{*} R_{sp} + e_{1,t} \right) \right\}, & \text{if } X_{t-d^1} \geq r_1 \text{ and } t \text{ is a fall};
\end{cases}
$$

where the superscript $s$ signifies fall, $X$ denotes the great gerbil occupancy, $T_{sp}$ is the spring temperature, $R_{sp}$ is the log spring rainfall, and $R_{sp}$ is the log summer rainfall. The parameters $\beta$ are the average covariate effects, known as fixed effects. The random effects $b_t = (b_{t,1}^*, b_{t,2}^*, b_{t,3}^*, b_{t,4}^*)$ represent the square-specific deviations of the covariate effects from the fixed effects and are normally distributed with mean 0 and a diagonal covariance matrix consisting of the variances $\sigma_i^2$, $i = 1, 2, 3, 4$. Only the spring intercept, spring temperature, spring rainfall, and fall intercept are found to admit random effects. The independent normally distributed latent processes $\epsilon_t$ of zero mean and SD $\xi$, account for possible overdispersion and missing covariates such as the virulence of bacteria (inf ectivity variable).

We thank the many hundreds of Kazakh plague zoologists who collected so many data over all these years. We also thank D. Ehrich for helpful discussions throughout the project leading to this work, including her translation between Russian and English; three anonymous reviewers for comments on an earlier version of the paper that helped us to sharpen the text; and Dr. M. Pletschette for his stimulating encouragement since the initial stages. This work was supported by European Union Projects ISTC K-159 and STEFICA (INCO-COPERNICUS, ICA 2CT2000-10046), the Norwegian Research Council, and Wellcome Trust Grant 063576/Z/01/Z, as well as by the authors’ respective institutions. K.-S.C. and N.I.S. were supported in part by National Science Foundation Grant DMS-0408267.

Supporting Text

Bacteriological Test

The more *Y. pestis* there are in the sample, the more likely there will be a positive test result. However, samples taken from infected individuals may not include live bacteria, because the likelihood for bacteria to be included in the sample depends on the level of bacteremia (the amount and virulence of bacteria), the resistance to plague, and the phase of the infectious process in the great gerbil caught. Hence, only a proportion of the infected gerbils will give rise to a positive bacteriological test result. Additionally, it is possible that sick animals (due to reduced above-ground activity) are more difficult to trap than the more resistant individuals. Hence, the probability that a caught great gerbil is bacteriologically infected with plague is approximately equal to the probability that a random great gerbil is bacteriologically infected with plague up to a multiplicative factor that is between 0 and 1; the multiplicative factor quantifies the sensitivity of the bacteriological test (as well as the reduction in the trapping probability because of the likely lower mobility of an infected great gerbil). The multiplicative factor is assumed to be constant or seasonal. Consequently, the fraction of bacteriologically positive caught great gerbils is a biased estimator of the prevalence rate, with a downward bias. Fortunately, the (unknown) multiplicative factor can be absorbed by the intercept terms in the model (S. Park, K.-S.C., H.J., L. Nekrassova, B. Suleimenov, V.S.A., N.L.K., S.B.P., and N.C.S., unpublished data), and thus it does not affect the analysis of the covariate effects on plague prevalence.
Model Formulation

To assess the effect of rodent abundance and environmental conditions (such as climate) on the prevalence of plague among the great gerbils in Kazakhstan, we used a generalized threshold mixed model (GTMM) (see ref. 1). Our analysis is done by pooling information across different large squares (LSQs). A critical threshold abundance of great gerbils must be exceeded for infection to invade a susceptible population (2). In the GTMM approach, we assume that the prevalence of plague is identically equal to zero if the abundance of great gerbils is below this critical threshold. Moreover, it is assumed that a plague outbreak occurs only if the abundance is above the threshold but that the probability of an outbreak is influenced by environmental conditions.

Let $N_{t,l}$ be the number of great gerbils examined at time $t$ in LSQ $l$. The number of great gerbils testing positive under a bacteriological test is assumed to be binomially distributed with parameters $(N_{t,l}, P_{t,l})$ where the true prevalence rate $P_{t,l} = 0$ below the threshold (the threshold variable is the occupancy of the great gerbils, denoted by $X$), but otherwise follows a logistic regression model

$$P_{t,l} = \begin{cases} 0, & \text{if } X_{t-d^s,l} < r_l^s \text{ and } t \text{ is a spring} \\ \logit^{-1}(\beta^s Y_{t,l}^s + b^s_l Z_{t,l} + \epsilon_{t,l}), & \text{if } X_{t-d^s,l} \geq r_l^s \text{ and } t \text{ is a spring}; \\ 0, & \text{if } X_{t-d^f,l} < r_l^f \text{ and } t \text{ is a fall} \\ \logit^{-1}(\beta^f Y_{t,l}^f + b^f_l Z_{t,l} + \epsilon_{t,l}), & \text{if } X_{t-d^f,l} \geq r_l^f \text{ and } t \text{ is a fall}. \end{cases} \quad (A1)$$

The superscripts $s$ and $f$ in Eq. A1 refer to the spring and fall seasons, respectively; the prime superscript signifies the transpose of the given vector. The threshold delay, the threshold, and the covariates in the upper regime are assumed to be season-specific. The seasonal threshold delay is assumed to be the same across all LSQs; however, the model allows for the seasonal threshold to vary across LSQs. The delays are modeled as
unknown, fixed half-integers. Owing to possible overdispersion and missing covariates such as the virulence of bacteria (infectivity variable), a latent process $\varepsilon_{t,l}$, generally being independent normally distributed of zero mean and identical standard deviation $\xi$, is included in the model. $Y_{t,l}$ denotes the vector of spring covariates and $Z_{t,l}$ a subvector of $Y_{t,l}$ each variable of which has random effects; similarly defined are $Y_{t,l}$ and $Z_{t,l}$ for the fall seasons. The coefficients of the fixed effects $\beta^s$ and $\beta^f$ quantify the average effect of the corresponding covariate on the prevalence across all LSQs. The between-LSQ variation is modeled by incorporating the vector of random effects for LSQ $l$ during the spring (fall) season, denoted by $b^s_l$ ($b^f_l$). The standard deviations of these random effects provide estimates of the between-LSQ variability.

Potential covariates related to the fixed and random effects include several climate variables (relative humidity, number of days with frost, number of days with relative humidity <30%, precipitation, and temperature, for both the spring and fall seasons), current occupancy as well as lag-$\frac{1}{2}$ and lag-1 year occupancies (being proxies for and preferable to the great gerbil densities, because they have less measurement error and fewer missing values). The parameters including the threshold parameters were estimated by a likelihood-based method (see below and ref. 1). Based on the model diagnostics and the significance of each covariate effect (whether it is fixed or random), we obtain the following final fitted trustworthy model:

\[
P_{t,l} = \begin{cases} 
0, & \text{if } X_{t-d^s,l} < r^s_l \text{ and } t \text{ is a spring} \\
\logit^{-1}\{(\beta_0^s + b^s_{0,l}) + (\beta_1^s + b^s_{1,l}) T_{sp,l} + b^s_{2,l} R_{sp,l} + \varepsilon_{t,l}\}, & \text{if } X_{t-d^s,l} \geq r^s_l \text{ and } t \text{ is a spring}; \\
0, & \text{if } X_{t-d^f,l} < r^f_l \text{ and } t \text{ is a fall} \\
\logit^{-1}\{(\beta_0^f + b^f_{0,l}) + \beta_1^f R_{m,l} + \beta_2^f X_{t-1/2,l} + \varepsilon_{t,l}\}, & \text{if } X_{t-d^f,l} \geq r^f_l \text{ and } t \text{ is a fall.}
\end{cases}
\]

(A2)

The random effects vector $b_l = (b^s_{0,l}, b^s_{1,l}, b^s_{2,l}, b^f_{0,l})'$ has a multivariate normal distribution with mean 0 and a diagonal covariance matrix consisting of the variances $\sigma_i^2$, $i = 1, 2, 3, 4$. 
Occupancy of the great gerbils is the $X$-variable. Because of the seasonal nature of the data, we used lag-$\frac{1}{2}$ occupancy. Spring climate covariates are the average monthly temperature during the spring, denoted by $T_{sp,t}$ and the (log) average of spring rainfall denoted by $R_{sp,t}$. Fall climate covariate is the (log) average summer rainfall, namely $R_{su,t}$. Except for the seasonal intercept and the coefficients of average spring temperature and average spring rainfall, all other coefficients are fixed but unknown across LSQs. The latent processes $\varepsilon_{t,l}$ are modeled as identical within year but independent across years and LSQs.

The seasonal delay parameters $d^s$ and $d^f$ are found to be 1.5 for the spring and 2 for the fall, respectively. The spring delay estimate, 1.5 years, is the first best choice for all LSQs except for LSQ 83, for which it is the second best choice. The fall delay estimate, 2 years, is the first best choice for all LSQs except for LSQ 105, for which it is the third best choice. Although the model allows the threshold parameters $r^s_l$ and $r^f_l$ to vary seasonally and across LSQs, their estimates turn out to vary between LSQs, but not between seasons, because the estimates of $d^s$ and $d^f$ point back to the same fall season (see Table 1).

With much finer data than we have, a random-delay approach may be used as warranted by the underlying process that likely takes a variable length of time (e.g., time for infection to “take off”) centring around the fixed delays in the GTMM defined by Eq. A2.

In Table 1, we report the maximum-likelihood estimate (together with their asymptotic standard errors and asymptotic 95% confidence intervals) of each of the parameters in the model defined by Eq. A2. Because the number of data points in the upper regime is small per LSQ, we calibrate the uncertainty of the parameter estimates by using the parametric bootstrap with bootstrap size 1,000 and with the covariates fixed at the observed values and the seasonal delays fixed at $d^s = 1.5$ and $d^f = 2$ (see Table 1).

In Table 1, the fixed effect of a covariate refers to its common effect over the four LSQs. If a particular covariate affects each LSQ somewhat differently, then the specific
covariate effect for each LSQ can be decomposed into the sum of the fixed and the random effects, the latter of which is assumed to be uncorrelated across LSQs and normally distributed about 0 and of a finite variance. The standard-deviation estimates are labeled as the random effects in Table 1. Note that only the spring intercept, spring temperature, spring rainfall, and fall intercept are found to have substantial variation over the four LSQs; hence, they are modeled with a random-effect component. On the other hand, spring rainfall is found to have a zero common effect over the four LSQs, which suggests that the specific spring rainfall effects for the four LSQs are not of the same sign.

**Model Estimation**

Let $B_{t,l}$ be the observed prevalence rate (i.e., the fraction of positive bacteriological tests among the great gerbils examined at time $t$ and in LSQ $l$). For each LSQ and assuming a fixed spring delay $d$, the spring square-specific threshold $\hat{r}(d)$ is estimated as follows. Sort the $X_{t-d,l}$ in ascending order, where $t$ is a spring. The spring square-specific threshold $\hat{r}(d)$ is the smallest $X_{t-d,l}$ for which the corresponding $B_{t,l}$ is positive. The spring delay $d$ is estimated to be $\tilde{d}$, the smallest integer $d$ between 0 and $D$ where $\hat{r}(d)$ is largest, $D$ being some known upper bound of the delay, namely 3 in our case. Then the spring square-specific threshold is defined as $\hat{r} = \hat{r}(\tilde{d})$. The fall square-specific threshold can be similarly estimated. The regression parameters are estimated by using the glmmPQL function with the data in the upper regime of the spring season (i.e., whose $X_{t-d,l} \geq \hat{r}$) as well as those of the fall season. The glmmPQL function implements approximate maximum-likelihood estimation for the associated mixed-effect logistic regression model (3, 4). The large-sample properties of the estimation scheme are obtained by Samia et al. (1): Under suitable conditions, the estimators are consistent and $\hat{r}$ is “superconsistent” (i.e., the magnitude of the estimation error is of the order $1/T$ where $T$ is the sample size; the “superconsistency” property is reflected by the rather narrow confidence intervals of the thresholds in Table 1). Consequently, the large-sample distribution of the regression parameters is approximately the same as that of the associated generalized linear mixed-effect models with data defined by the known threshold and delay.
The large-sample inference is augmented by an analysis based on the parametric bootstrap, which may provide more reliable inference with small samples. The bootstrap 95% confidence intervals for the seasonal square-specific threshold parameters are found by using the method discussed in ref. 1. The bootstrap 95% confidence intervals for the remaining parameters in the upper regime are obtained by the percentile method with the 2.5 and 97.5 percentiles of the bootstrap estimates being the end points of these 95% confidence intervals (see chap. 13 of ref. 5). Interestingly, Table 1 shows that whereas the bootstrap intervals for the fixed-effect parameters tend to be wider than their theoretical counterparts, the bootstrap confidence intervals of the random-effect parameters tend to be narrower than their theoretical counterparts. Overall, the inference based on the large-sample theory is consistent with that based on bootstrap.

**Square-Specific Effects**

Table 2 provides the estimated deviation from the overall mean of each covariate for each LSQ, which is basically the estimate of the random effect of the corresponding covariate in each LSQ. Table 2 also provides the estimate of the square-specific mean of each covariate effect used in the fitted model, which is the sum of the estimates of the fixed (i.e., overall mean) and random effects of the corresponding covariate in each LSQ. The square-specific mean of the spring intercept is estimated to be negative for all LSQs. The square-specific mean of the slope of the average spring temperature is estimated to be positive for all LSQs. The square-specific mean of the slope of the (log) spring rainfall is estimated to be positive for LSQs 91 and 105 and negative for LSQs 78 and 83. The square-specific mean of the fall intercept is estimated to be negative for all LSQs.

All other covariates being fixed, the average spring temperature is positively correlated with the prevalence of plague during the spring season. In other words, a warm spring increases the chance of a plague outbreak during the spring season. On the other hand, the average spring rainfall is positively correlated with the prevalence of plague during the spring season in LSQs 91 and 105, but negatively correlated in LSQs 78 and 83. This
variation in the behavior of the average spring rainfall among LSQs might be due to the location of the meteorological station and the spatial variation in spring rainfall among the studied LSQs (see Fig. 1). Average summer rainfall is positively correlated with the prevalence of plague during the fall season. Thus, a dry summer decreases the chance of a plague outbreak during the fall. The occupancy of last spring is positively correlated with the prevalence of plague during the fall season.

**Model Diagnostics**

We have checked the adequacy of the fitted model by assessing the validity of the model assumptions. The plot of the standardized residuals vs. the fitted values (on the logistic scale) in Fig. 3 shows that the residuals are symmetrically distributed around zero, with approximately constant variance. The normal probability plot of the estimated large-square random effects is shown in Fig. 4. Because there are only four random effects per covariate at the large-square level, it is difficult to identify any patterns in Fig. 4. The normal probability plot of the estimated contemporaneous random effects within each LSQ in Fig. 5 does not indicate any departures from normality. Sample autocorrelations (Fig. 6) show that the estimated contemporaneous random effects are uncorrelated over time. Fig. 7 displays the sample autocorrelations of the standardized residuals for each LSQ. Of the 57 sample autocorrelations examined, only two of them are marginally significant and negative. Because we expect ≈2.8 false positives out of 57 tests, the plots suggest that the standardized residuals are essentially uncorrelated over time. Furthermore, the standardized residuals for each of the four LSQs are deemed independent over time, based on the nonparametric method of runs test, with the $P$ values all $>0.35$. Moreover, the good agreement between the observed values and the fitted values (on the original scale) in Fig. 8 attests the adequacy of the fitted model. Therefore, we conclude that the model is adequate.

To ensure that the fitted model has not omitted any important variables, we overfitted the model by including other potentially useful covariates. Table 3 provides the AIC, BIC, and log likelihood of different seasonal models that overfitted the model defined by Eq.
A2. We note that for the fitted model defined by Eq. A2, the AIC, BIC, and log
likelihood are found to be 556.88, 587.54, and -267.44, respectively. Therefore, it has
smaller AIC and BIC and higher log likelihood than the models considered in Table 3,
except for the AIC and log likelihood of the model that we overfitted by adding the fixed
effect of spring rainfall (0.316, with asymptotic standard error 0.305) in the submodel for
the spring season. However, to assess the significance of terms in the fixed effects, it is
preferable to use the t test, which indeed shows that the additional fixed effect of spring
rainfall is not statistically significant at the 5% level of significance (see ref. 6, pp. 90–
91). Consequently, we conclude that the fitted model has included all important available
covariates. (Finally, we note that the AIC and BIC values in Table 3 are not comparable
with those of the models including flea burden as reported in the main text, because of
difference in sample size.)

Including Flea Burden in the Model

To obtain some further insight into the mechanism underlying the climate forcing, we
have overfitted the final model by including spring flea burden in spring and fall flea
burden in fall, both as fixed effects:

\[
P_{ij} = \begin{cases} 
0, & \text{if } X_{i-t-d'}, d < r_i^s \text{ and } t \text{ is a spring} \\
\logit^{-1}\{(\beta_0^s + b_{0,j}) + (\beta_1^s + b_{1,j}) T_{sp,d} + b_{2,j} R_{sp,d} + \beta_3^s F_{sp,d} + \epsilon_{i,j}\}, & \text{if } X_{i-t-d'}, d \geq r_i^s \text{ and } t \text{ is a spring}; \\
0, & \text{if } X_{i-t-d'}, d < r_i^f \text{ and } t \text{ is a fall} \\
\logit^{-1}\{(\beta_0^f + b_{0,j}) + \beta_1^f R_{wp,d} + \beta_2^f X_{i-t-1/2,d} + \beta_3^f F_{f,d} + \epsilon_{i,j}\}, & \text{if } X_{i-t-d'}, d \geq r_i^f \text{ and } t \text{ is a fall}; 
\end{cases}
\]

where \(F_{sp,t}\) is the spring flea burden and \(F_{f,t}\) is the fall flea burden, and \(\beta_2^s\) and \(\beta_3^f\) are their
corresponding coefficients. Note that the flea effects are assumed to be identical across
the LSQs. Because the flea data have many missing values, including spring and fall flea
burden in the model reduces the above-threshold sample size from 120 to 54. The fitted
model results in AIC = 281.2 and BIC = 307.0. In contrast, fitting to the reduced set of
data the same model but without climate effects, i.e.,
results in AIC = 276.3 and BIC = 294.2, confirming that, with flea burden in the model, climate no longer correlates with plague prevalence. This finding is consistent with the hypothesis that the found climate forcing on plague prevalence is mediated through flea activity. The coefficient of spring flea burden in Eq. A4 is estimated to be 0.0994 with the 95% confidence interval being (0.0256, 0.173), whereas that of fall flea burden is 0.0372, and the 95% confidence interval equals (-0.0721, 0.146). Thus, the spring flea effect is positive and significant. Although the coefficient estimate of fall flea burden is also positive, it is significant only at \( \approx 15\% \) level. This highlights the relative importance of spring flea activity in its impacts on plague prevalence.

Assessing the Cascading Effects of Great Gerbil Abundance on Plague Prevalence

Owing to the logistic link function, the model specifies that the mean prevalence rate is a nonlinear function of the covariates, resulting in interactive effects between the covariates. Specifically, we show below that the climatic effects on the fall plague prevalence are amplified approximately linearly with great gerbil abundance, which is also positively affected by the same climate factors (K.L.K., H.V., A. Frigessi, V.M.D., J.E., and N.C.S., unpublished data).

The instantaneous rate of change in the prevalence per unit change in a particular covariate is measured by the partial derivative of the prevalence with respect to the covariate and is equal to \( p(1 – p)\beta \), where \( p \) is the prevalence and \( \beta \) is the coefficient of the covariate. The product \( p(1 – p) \) is an increasing function of the prevalence, for \( 0 \leq p \leq 0.5 \), never being exceeded over the study period. Because the spring abundance of the
great gerbils affects the fall prevalence positively, above the threshold, there is an exponential-like increase with abundance of the gerbils; hence, this nonlinear effect will have some cascading effect on the prevalence: with more gerbils, the effect of changing climate will be increased even further.

The summer rainfall effect, as quantified by the partial derivative \( \frac{\partial p}{\partial R_{su}} = p(1 - p)\beta_R \), with \( \beta_R \) being the coefficient of summer rainfall \( R_{su} \), is a function of all covariates in the model for fall prevalence. The average of the partial derivative \( \frac{\partial p}{\partial R_{su}} \) equals 0.00815, as computed over all data in the upper regime with the covariates fixed at their observed values and the random effects fixed at their estimated values. All other things being equal, the fitted model predicts that above the threshold, if the log-average summer rainfall increases additively by \( \delta \), then the prevalence during the fall will, on average, increase additively by \( 0.00815 \times \delta \) across all LSQs and all years of the study period. That is, were summer rainfall higher by 10% over the study period [i.e., \( \delta = \log(1.1) = 0.0953 \)], it would lead to an additional increase of 0.000777 in the fall prevalence.

The interactive effect between climate and great gerbil abundance may be assessed by considering the second partial derivative \( \frac{\partial^2 p}{\partial X \partial R_{su}} = (1 - 2p)pq\beta_R\beta_X \), where \( \beta_X \) is the coefficient of the lag-\( \frac{1}{2} \) occupancy \( X \). For the plague data, the observed prevalence rate is notably small, leading to the following approximation: \( \frac{\partial^2 p}{\partial X \partial R_{su}} \approx pq\beta_R\beta_X = \beta_X \frac{\partial p}{\partial R_{su}} \). In other words, the climatic effects due to the same degree of shift in the climatic conditions will be approximately amplified by \( \beta_X \delta X \times 100\% \), were the great gerbil occupancy increased by \( \delta \) times the mean occupancy \( X \), all other things being equal. Specifically, the instantaneous climatic effects on the fall plague prevalence are amplified approximately linearly with great gerbil abundance. For example, repeating the above calculation by increasing both rainfall and the lag-\( \frac{1}{2} \) occupancy by 10% over the study period, the fitted model predicts that, above the threshold, \( \frac{\partial p}{\partial R_{su}} = 0.0111 \) on the average when the lag-\( \frac{1}{2} \) occupancy values are 10% higher than their historical values, and other covariates (random effects) are fixed at their historical (estimated) values. Consequently, the observed prevalence in the fall would have approximately increased
additively by $0.0111 \times \log(1.1) = 0.00106$, on average, as compared with 0.000777 were rainfall increased by 10% but lag-$\frac{1}{2}$ occupancy unchanged. Note that $\beta_X = 6.15$, $\delta = 0.1$, and $\bar{X} = 0.435$ for above-threshold falls, and 0.0111 is approximately equal to $(1 + \beta_X \delta \bar{X}) \times (\partial p / \partial R_{su}) = (1 + 6.15 \times 0.1 \times 0.435) \times 0.00815 \approx 0.0103$, confirming the above approximation scheme for $(\partial^2 p / \partial X \partial R_{su})$.

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**Figure a:** Precipitation (z-score) over time.

**Figure b:** Temperature variation over time.