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 ac-

count 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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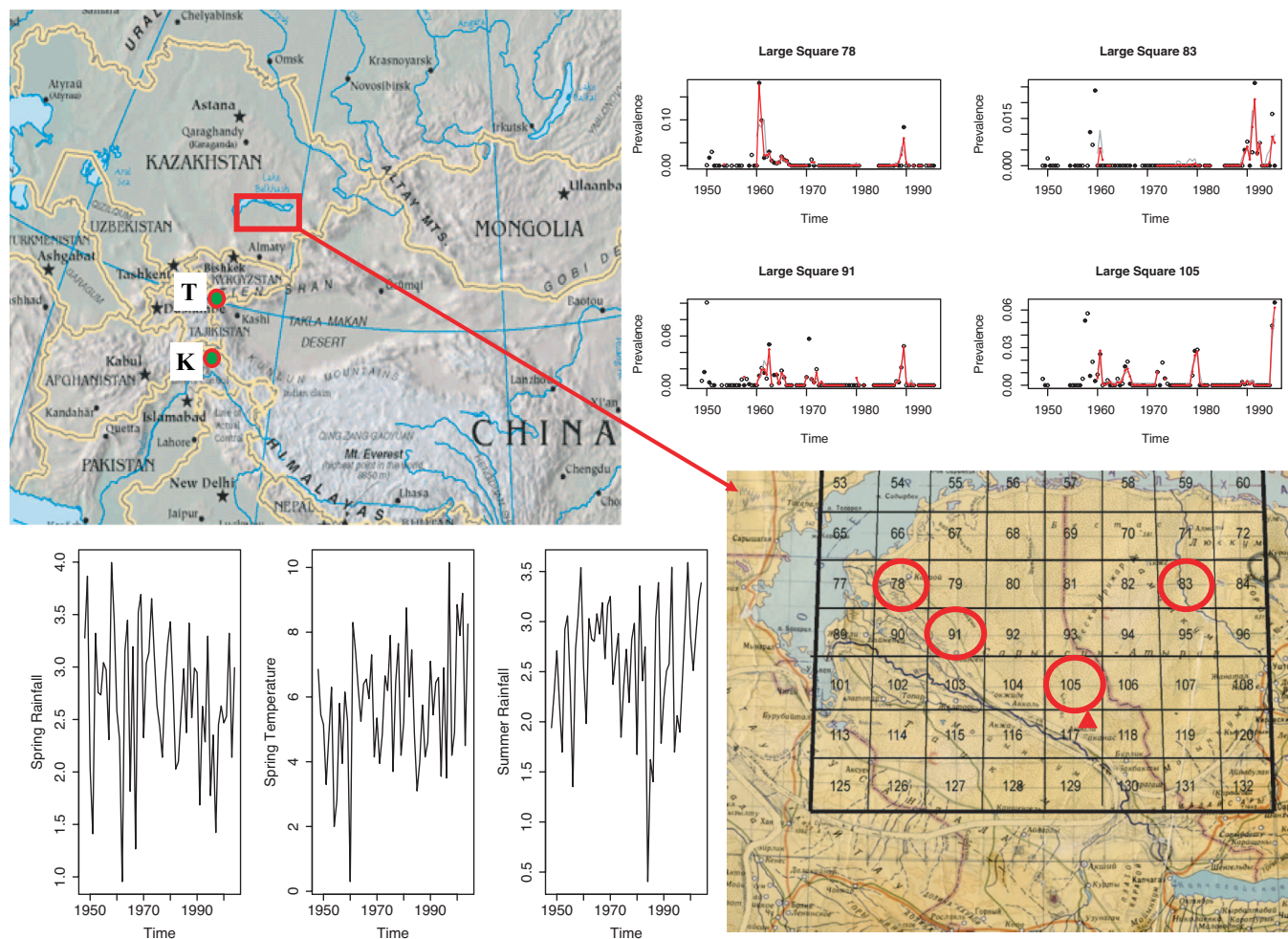
Fig. 1. The field data used in this study were collected in a natural plague focus in Kazakhstan. The data are plague prevalence in great gerbils, counts of fleas collected from trapped gerbils, and meteorological observations. (*Left Upper*) Kazakhstan on a map of Central Asia with the PreBalkhash focus (between 74 and 78°E and 44 and 47°N) marked as a square. The historic climate (tree-ring) measurement sites are circles marked K (Karakorum) and T (Tien Shan). These sites are located ≈1,000 and 600 km from the research area, respectively. (*Right Lower*) The LSQ in the PreBalkhash focus from which we have prevalence. The four LSQs (40 × 40 km) circled in red, namely LSQs 78, 83, 91, and 105, represent key sites where collection of samples for testing the presence of plague was more regular and continuous. The Bakanas meteorological station is located in LSQ 117, marked by a red triangle. (*Right Upper*) The time-series plots of the observed prevalence per LSQ. Open and filled circles denote the observed prevalence during the spring and fall, respectively. The time series of the prevalence fitted by using the model defined by Eq. **1** is shown in red. Using the same model but without any climatic covariates gives the time series shown in gray. Note that owing to the presence of missing values in some covariates (occupancy) and prevalence data, the curves of the fitted values are discontinuous. The fitted values from the model provide a closer fit and reproduce the peaks in prevalence far better than the model without the climatic variables. (*Left Lower*) Time-series plots of the climate variables, spring rainfall, spring temperature, and summer rainfall (from left to right) in the model defined by Eq. **1**.

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 ≈10°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 pre-adults (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°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

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

Variable	Parameter	Estimated value	Asymptotic standard error	Asymptotic, 95% CI	Bootstrap, 95% CI
Spring intercept	β_0^s	−9.51	1.0	(−11.5, −7.53)	(−12.1, −5.35)
Spring temperature	β_1^s	0.539	0.17	(0.199, 0.879)	(0.117, 0.979)
Fall intercept	β_0^f	−10.8	1.0	(−12.8, −8.86)	(−13.0, −5.56)
Summer rainfall	β_1^f	0.775	0.24	(0.301, 1.25)	(−0.182, 1.55)
Lag 1/2 occupancy in fall logistic model	β_2^f	6.15	0.88	(4.41, 7.89)	(2.54, 8.68)
Random effects					
Spring intercept	σ_1	1.34		(0.252, 7.10)	(0.00571, 3.22)
Spring temperature	σ_2	0.300		(0.109, 0.825)	(0.000870, 0.539)
Spring rainfall	σ_3	0.559		(0.240, 1.30)	(0.00307, 1.35)
Fall intercept	σ_4	0.500		(0.118, 2.13)	(0.00427, 1.02)
Contemporaneous within LSQ	ξ	1.82		(1.43, 2.31)	(2.20 × 10^{-19}, 2.30)
Spring and fall thresholds					
LSQ 78	r_{78}^s, r_{78}^f	0.380			(0.330, 0.38]
LSQ 83	r_{83}^s, r_{83}^f	0.644			(0.622, 0.644]
LSQ 91	r_{91}^s, r_{91}^f	0.463			(0.360, 0.463]
LSQ 105	r_{105}^s, r_{105}^f	0.380			(0.377, 0.380]

period. 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-
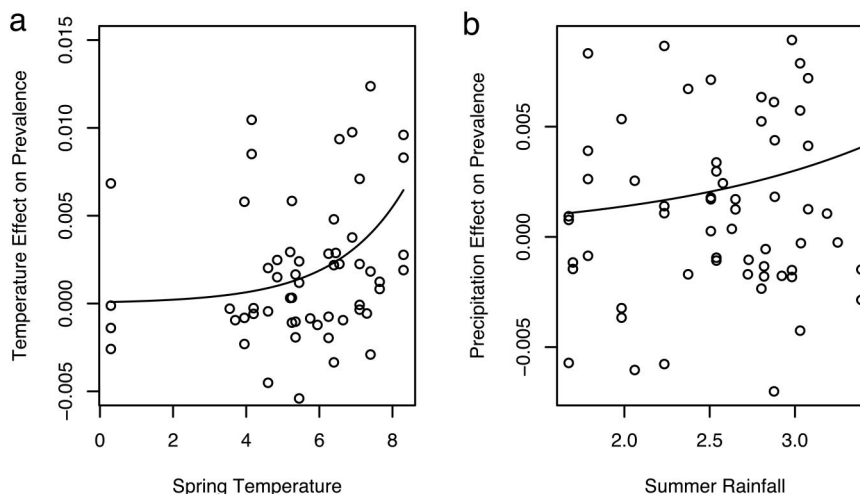
Fig. 2. The effect of changes in the environmental conditions on prevalence. (*a*) The effect of spring temperature on prevalence in the spring. (*b*) The effect of summer precipitation on prevalence in the fall. Note that the curves in *a* and *b* illustrate the mean effect of spring temperature and (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 most twice per year. On ≈85% of these occasions, there are independent data on plague prevalence where up to 8,576 gerbils (median = 604) were trapped per LSQ 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 LSQs 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 LSQ 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 LSQs 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 (−0.0721, 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 the ≈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 rainfall over June, July, and August. Incorporating the climatic effects in the model resulted in fitted values that track the peak occurrences in prevalence (Fig. 1) more closely than the model without the climatic variables.

Historic climatic conditions and their implications for historic levels of plague prevalence. Climate variability over the past millennium was estimated by using a large data set of 203 *Juniperus turkestanica* tree-ring width series to reconstruct temperature variations in the Tien Shan Mountains (Kirghizia) (32), and a total of 40 stable oxygen isotope ($\delta^{18}O$) series to reconstruct precipitation variations in the Karakorum Mountains (Pakistan) (33). Climatic variations at these sites are found to be correlated with those in the study area (see ref. 34 and below).

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 data are indicative of the climate condition 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 $= -0.0582$, ≈ 0.23 SDs above the overall mean -0.152 based on data from year 1000 to 1995) but also drier (mean $= -0.404$, ≈ 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 web site). Similarly, just at the time the latest (Third) plague pandemic started (year 1855–1870), the climate was wetter (mean $= -0.123$, 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 $N_{t,l}$ 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 if t is a spring the true prevalence rate $P_{t,l} = 0$ when the lag-d^s occupancy, namely, $X_{t-d^s,l}$, is below the spring threshold r_l^s (the superscript s signifies spring) but otherwise follows a logistic regression model (see below). A similar specification 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:

$$
P_{t,l}
$$

$$
= \begin{cases} \begin{cases} 0, & \text{if } X_{t-d^s,l} < r_l^s \text{ and } t \text{ is a spring} \\ \text{logit}^{-1}\{(\beta_0^s + b_{0,l}^s) + (\beta_1^s + b_{1,l}^s)T_{sp,t} + b_{2,l}^s R_{sp,t} + \varepsilon_{t,l}\}, \\ \qquad \text{if } X_{t-d^s,l} \geq r_l^s \text{ and } t \text{ is a spring}; \end{cases} \\ \begin{cases} 0, & \text{if } X_{t-d^f,l} < r_l^f \text{ and } t \text{ is a fall} \\ \text{logit}^{-1}\{(\beta_0^f + b_{0,l}^f) + \beta_1^f R_{su,t} + \beta_2^f X_{t-1/2,l} + \varepsilon_{t,l}\}, \\ \qquad \text{if } X_{t-d^f,l} \geq r_l^f \text{ and } t \text{ is a fall}; \end{cases} \end{cases}
$$

$$[1]$$

where the superscript f signifies fall, X denotes the great gerbil occupancy, $T_{sp,t}$ is the spring temperature, $R_{sp,t}$ is the log spring rainfall, and $R_{su,t}$ is the log summer rainfall. The parameters β are the average covariate effects, known as fixed effects. The random effects $b_l = (b_{0,l}^s, b_{1,l}^s, b_{2,l}^s, b_{0,l}^f)'$ 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 σ_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 $\varepsilon_{t,l}$, of zero mean and SD ξ, account for possible overdispersion and missing covariates such as the virulence of bacteria (infectivity variable). They are specified as identical within year but independent across years and LSQs.

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