Plague dynamics are driven by climate variation

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Edited by James H. Brown, University of New Mexico, Albuquerque, NM, and approved June 28, 2006 (received for review March 26, 2006)

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

Conflict of interest statement: No conflicts declared.

This paper was submitted directly (Track II) to the PNAS office.

Abbreviation: LSQ, large square.

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Table 1. Maximum-likelihood estimates of the plaque 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 $\times 10^{-19}$, 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.

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:

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

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.

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 STEPICA (INCO-COPENICUS, ICA 2-CT2000-10046), 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-0405267.

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