

Classic flea-borne transmission does not drive plague epizootics in prairie dogs

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We lack a clear understanding of the enzootic maintenance of the bacterium (*Yersinia pestis*) that causes plague and the sporadic epizootics that occur in its natural rodent hosts. A key to elucidating these epidemiological dynamics is determining the dominant transmission routes of plague. Plague can be acquired from the bites of infectious fleas (which is generally considered to occur via a blocked flea vector), inhalation of infectious respiratory droplets, or contact with a short-term infectious reservoir. We present results from a plague modeling approach that includes transmission from all three sources of infection simultaneously and uses sensitivity analysis to determine their relative importance. Our model is completely parameterized by using data from the literature and our own field studies of plague in the black-tailed prairie dog (*Cynomys ludovicianus*). Results of the model are qualitatively and quantitatively consistent with independent data from our field sites. Although infectious fleas might be an important source of infection and transmission via blocked fleas is a dominant paradigm in the literature, our model clearly predicts that this form of transmission cannot drive epizootics in prairie dogs. Rather, a short-term reservoir is required for epizootic dynamics. Several short-term reservoirs have the potential to affect the prairie dog system. Our model predictions of the residence time of the short-term reservoir suggest that other small mammals, infectious prairie dog carcasses, fleas that transmit plague without blockage of the digestive tract, or some combination of these three are the most likely of the candidate infectious reservoirs.

disease modeling | disease reservoir | *Yersinia pestis* | *Cynomys ludovicianus*

The maintenance and epidemiological dynamics of plague, caused by the bacterium *Yersinia pestis*, are of critical interest because of the disease's high human mortality rate, widespread distribution, potential for rapid spread, and possible use in bioterrorism. Despite a large number of human deaths from plague, plague is mainly a disease of wild rodents and their associated fleas. Although questioned by some, it is commonly proposed that plague in North America is maintained at low levels in enzootic cycles between partially resistant rodent host species and their associated fleas (1, 2). Epizootics sporadically occur when the disease spills over into susceptible amplifying rodent hosts, with high mortality and rapid die-offs. Under this scenario, it is typically believed that the only important mode of transmission of *Y. pestis* to rodents is the bites of fleas that have become infectious as a result of occlusion or blockage in their proventriculus that leads to regurgitation of infectious bacteria as the flea feeds (3, 4). This blockage is composed of a mass of *Y. pestis* bacteria enmeshed in a biofilm (2, 5, 6). Ultimately, determining which routes of transmission dominate during enzootic persistence and epizootic outbreaks will reveal whether the same transmission pathways are responsible for both enzootic and epizootic dynamics and how transmission changes during different parts of the cycle. As a first step, in this paper we investigate transmission during epizootics.

Other modes of plague transmission have been proposed but are typically thought to be less important than transmission by

blocked fleas. These modes include the bites of infected, partially blocked fleas (7), mechanical transmission from flea mouthparts (8–10), direct contact with respiratory droplets from infected animals (e.g., ref. 11), and direct contact with sources of infection such as the tissues of infected animals or perhaps contaminated soils (12–19). We hypothesize that during epizootics, these alternative, often short-term, modes of transmission may play an important role in transmission that sustains outbreaks once they begin.

The dominant paradigm for plague transmission (3, 4) is based on the classic case of vector-mediated transmission by the Oriental rat flea (*Xenopsylla cheopis*), which transmits *Y. pestis* among commensal rats (*Rattus* sp.) and often to humans. Generally, efficient transmission of *Y. pestis* is thought to occur only through the bites of “blocked” fleas whose midguts become obstructed several days after feeding on an infected host by replicating *Y. pestis* enmeshed in a biofilm (2, 3, 5). This blockage results in starvation and aggressive feeding behavior by fleas that repeatedly attempt to clear their blockage by regurgitation, resulting in thousands of plague bacteria being flushed into the feeding site and the host becoming infected. The efficiency of *X. cheopis* as a vector for the disease is well cited because it usually has the highest blocking rate among studied fleas (20).

We focus our research on one of the most dramatically susceptible wild rodent hosts in North America, the black-tailed prairie dog (*Cynomys ludovicianus*), which exhibits almost 100% mortality when infected with plague (21–23). The prairie dog flea (*Oropsylla hirsuta*) is abundant on black-tailed prairie dogs and is likely the main vector of plague in this system. *O. hirsuta* seldom develops complete blockage of the proventriculus (24). The high susceptibility of prairie dogs to plague and incomplete blockage in *O. hirsuta* combine to make this system significantly different from the classic rat system. Prairie dogs are a particularly appropriate focal species for investigating the epizootic spread of plague because *Y. pestis* might be transmitted through multiple routes in this system, and each of these routes might exert different influences on the course of epizootics.

We investigate the relative importance of different modes of transmission for epizootic plague spread within prairie dog towns by using a novel modeling approach. In this approach, we simultaneously include the three main routes of transmission within the same model: classic vector transmission by blocked fleas (2), airborne transmission from inhalation of bacteria from an infected individual (e.g., ref. 11), and transmission resulting from direct contact with other infected sources that serve as a relatively short-term reservoir. We then use sensitivity analysis of the model

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Abbreviation: PNG, Pawnee National Grasslands.

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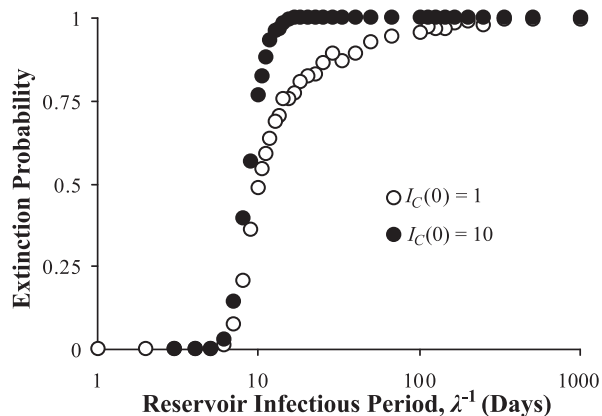


Fig. 3. The extinction probability exhibits a threshold behavior with respect to the reservoir infectious period. Open circles indicate extinction probabilities from the introduction of one host infected via a contact route (airborne or reservoir). Filled circles indicate extinction probabilities from the introduction of 10 contact-infected hosts.

near deterministic extinction (Fig. 3). The extinction time is also relatively sensitive to parameters associated with transmission from the short-term reservoir: reservoir transmission rate ($\Sigma_{\beta_r} = 0.27$), number of burrows that prairie dogs enter ($\Sigma_B = 0.25$), and the reservoir decay rate ($\Sigma_\lambda = 0.10$). The extinction probability is very insensitive ($\Sigma < 0.04$) to all of the parameters associated with blocked vector and airborne transmission. Extinction time is also very insensitive to the parameters associated with blocked vector and airborne transmission with the single exception of the contact mortality rate ($\Sigma_{\alpha_c} = 0.12$), which affects both the airborne and reservoir routes.

Alternative formulations of the model were developed where transmission from the short-term reservoir is frequency-dependent, where fleas from dead animals can quest for new hosts, and with two different flea growth functions. In each case, model dynamics are qualitatively similar, and changes in parameters result in similar patterns of sensitivity. Overall, the qualitative validation of the model and our results regarding dominant transmission routes in the system are robust to reasonable changes in parameter values and model structure. However, some such changes quantitatively affect both the extinction probability and extinction time, with the extinction time being most sensitive.

Discussion

Our model has a good qualitative and quantitative fit to data from our study sites on the Pawnee National Grasslands (PNG) in northern Colorado. First, the model dynamics exhibit a short-lived peak of infectious hosts. In fact, this peak is so short-lived that we would not expect to observe seropositive hosts in the field without intensive sampling efforts because most animals probably die before becoming seropositive. This prediction is consistent with our field observation that prairie dogs captured on a town with a confirmed plague outbreak all tested negative for plague antibodies during serological testing in the field (38 individuals, plague confirmation from carcass testing). Similar field observations have been reported by Hoogland *et al.* (29). The 98% extinction probability predicted by the stochastic model with default parameters is quantitatively consistent with our observations of epizootics. In the eight confirmed plague epizootics on the PNG during 2003–2005, prairie dog populations declined to extremely low (e.g., 6 individuals) or undetectable levels (ref. 21; M.F.A. and D. Tripp, personal observation). In the field, die-offs occurred rapidly within ≈ 6 –8 weeks after plague was first detected on the towns. Our stochastic model suggests an average extinction time of 7.4 weeks (95% confi-

dence interval: 5–10 weeks) for the default parameters, in close agreement with these field data.

Sensitivity analysis reveals that the extinction probability and extinction time are influenced most strongly by transmission from a short-term reservoir and that the model is insensitive to transmission via the blocked vector or airborne routes. This analysis is consistent with the finding that extinctions occur only if rates of blocked vector and airborne transmission are increased several orders of magnitude above values reported in the literature. Taken together, these results strongly suggest that transmission by blocked fleas cannot drive epizootics within prairie dog towns but that transmission from a short-term infectious reservoir can.

A number of other published observations are consistent with the idea that blocked flea transmission does not drive epizootics. Most notably, recent work on vector competence suggests that the plague bacterium is extremely poor at infecting even the most proficient flea vector for plague (*X. cheopis*) and that subsequent transmission efficiency by the vector is also very low (20, 30). Models of blocked vector transmission developed by Lorange *et al.* (20) suggest that very high flea loads are needed to drive plague epizootics by this mechanism in our system. When we reparameterized their model by using our default values for *O. hirsuta* instead of *X. cheopis*, the predicted flea loads are 500 times higher than those observed in the field, also suggesting that blocked vector transmission cannot drive the epizootics we observe.

Airborne contact also is unlikely to drive epizootics, because of the high virulence of plague (22). Plague's high virulence, with rapid death of infected individuals, means that the pool of individuals that become infected through the airborne route is never very large at any point in time. This small pool results in a force of infection from airborne transmission that is much smaller than the force of infection from the short-term reservoir. Despite the apparently similar transmission and mortality rates by the airborne pathway and from the short-term reservoir, the short-term reservoir creates a larger infectious pool because it persists longer than infected hosts.

Overall, the high virulence of plague results in a weak force of infection in our model from both the blocked vector and airborne transmission routes simply because vectors and hosts do not live very long. These results suggest that epizootics in other susceptible rodent species that die quickly from plague would not result from either blocked vector or airborne transmission. In North America, highly susceptible hosts include all other prairie dog species and several other sciurid species (2). In Asia, where plague is thought to have originated, we are struck by the remarkable similarity of plague dynamics in little souslik (*Spermophilus pygmaeus*; ref. 2 and references therein) and in black-tailed prairie dogs. However, for the more well known great gerbil (*Rhombomys opimus*) (31), we think blocked vector transmission may be a possibility. The vectors in this system are typically various *Xenopsylla* species, some of which are likely to block at high rates and have relatively short intervals between taking an infectious blood meal and becoming blocked (20, 24, 32). In any of these systems, the ability of our model to correctly predict outbreaks will be determined by tradeoffs between rates of transmission and the lifespans of infected fleas and rodent hosts.

Although transmission via blocked fleas does not appear to be sufficient to maintain the epizootic spread of plague in prairie dog populations, there is little doubt that fleas are important vectors of plague. Plague transmission rates in the world's plague foci typically peak during seasons of the year when flea densities are highest and on host species known to support heavy populations of fleas. Several studies have shown that insecticidal dusting can interrupt the spread of human bubonic plague epidemics (33), and recent studies of prairie dogs also show that applying insecticides during the early stages of epizootics can stop the spread of plague (29, 34). These results suggest that fleas

are directly involved in the short-term reservoir component of our model, perhaps transmitting plague through mechanical means or without the need for complete blockage (8). However, additional studies that applied insecticide during later stages of epizootics failed to stop them (34, 35). These results suggest the additional possibility that fleas are important in the initial introduction and establishment of plague in prairie dog towns, but that transmission from a different short-term reservoir drives the epizootic dynamics.

These results beg the question: what is the short-term reservoir? There are three reservoirs consistent with the model prediction that the short-term reservoir persists for at least 2 to 3 weeks. First, resistant rodent species, potentially important as enzootic reservoirs, also may serve as a short-term reservoir during epizootics. In data from our field sites in 2004, $\approx 8\%$ of *Onychomys leucogaster* (Northern grasshopper mouse) on towns with confirmed plague exhibited antibodies to plague in serological testing (50 individuals tested; P. Stapp, personal communication). Grasshopper mice trapped outside of prairie dog towns (217 observations; P. Stapp, personal communication) and other small mammal species on towns with plague (84 observations; P. Stapp, personal communication) did not exhibit antibodies. We speculate that resistant grasshopper mice (16) could serve directly as a reservoir or play an indirect role by providing maintenance feedings for infected vectors in the absence of prairie dogs. Second, live *Y. pestis* has been found in infected carcasses, tissues, and soil for up to 7 months (12), and transmission back to prairie dogs can occur when individuals cannibalize dead animals (15–17) or when they excavate collapsed burrows (13). Cannibalization of victims of infanticide is quite common (25, 36), and cannibalization of dead older animals also has been observed (25). Third, several species of fleas are known to transmit plague when unblocked (e.g., refs. 8, 18, and 19), and unblocked fleas that continue to feed can easily live the requisite 2 to 3 weeks, and probably much longer (8, 37). *O. hirsuta* commonly fails to develop a complete blockage (8). These three potential reservoirs may work in concert, and determining their relative importance should be the subject of future experimental, field, and modeling studies. Prairie dog predators also have been proposed as a potential reservoir (14), but a predator reservoir would act in a frequency-dependent manner, so our model does not directly address this hypothesis. Additionally, if predators were an important reservoir, we would expect to see outbreaks on a much larger spatial scale than we observe (21).

A final possibility is that fleas may transmit plague mechanically by carrying bacteria on their mouthparts (8–10). It seems somewhat unlikely that mechanical transmission is an important force of infection in epizootics because there is comparatively little opportunity for this type of transmission to occur. Infected prairie dogs are bacteremic for only 2 days before dying (38), reducing the opportunity for fleas to acquire bacteria on their mouthparts, and the bacteria may be short-lived in this environment (39). By making the exposed period of the vector extremely short (τ^{-1}), we reparameterized the blocked vector transmission route in our model to represent mechanical transmission but could not drive an epizootic.

The consistency of our model results with data from the literature and our field observations strongly suggests that transmission resulting from contact with a short-term reservoir is the driving mechanism in plague epizootics in prairie dogs and that transmission by blocked fleas or airborne transmission simply does not create a strong enough force of infection to drive epizootic outbreaks. To fully understand the maintenance of plague, the next step is to investigate transmission dynamics during enzootic cycles.

Methods

Deterministic Model. Field data from our study sites on the PNG suggest that prairie dog towns rapidly die off once infected with

plague, leading us to develop a continuous time, deterministic model to explore patterns of plague transmission within towns. The model is an ODE model, consisting of two susceptible–exposed–infected (SEI) submodels. One submodel describes disease dynamics within the prairie dog host (Eqs. 1–6), and the other describes disease dynamics within the flea vector (Eqs. 7–12). The SEI model includes an exposed class because transmission from infected prairie dogs and their fleas is delayed for several days. A recovered class is not included because recovery of infected hosts and vectors is very low (1).

Host submodel.

$$\frac{dS}{dt} = rS(1 - N/K) - \frac{\beta_C S(I_C + I_F)}{N} - \beta_F F_{IQ} S(1 - e^{-aN/B}) - \beta_R S \frac{M}{B} - \mu S, \quad [1]$$

$$\frac{dE_F}{dt} = \beta_F F_{IQ} S(1 - e^{-aN/B}) - E_F(\sigma + \mu), \quad [2]$$

$$\frac{dE_C}{dt} = \beta_R S \frac{M}{B} + \frac{\beta_C S(I_C + I_F)}{N} - E_C(\sigma + \mu), \quad [3]$$

$$\frac{dI_F}{dt} = \sigma E_F - I_F \alpha_F, \quad [4]$$

$$\frac{dI_C}{dt} = \sigma E_C - I_C \alpha_C, \quad \text{and} \quad [5]$$

$$\frac{dM}{dt} = \alpha_C I_C + \alpha_F I_F - \lambda M. \quad [6]$$

Vector submodel.

$$\frac{dF_{SQ}}{dt} = \delta F_{SH} + r_F F_O \left(\frac{N}{1 + N + F_O} \right) - F_{SQ}[\mu_F + (1 - e^{-aN/B})], \quad [7]$$

$$\frac{dF_{SH}}{dt} = F_{SQ}(1 - e^{-aN/B}) - F_{SH} \left[\mu_F + \delta + \gamma \left(\frac{I_C + I_F}{N} \right) \right], \quad [8]$$

$$\frac{dF_{EQ}}{dt} = \delta F_{EH} - F_{EQ}[(1 - e^{-aN/B}) + \tau + \mu_F], \quad [9]$$

$$\frac{dF_{EH}}{dt} = F_{SH} \gamma \left(\frac{I_C + I_F}{N} \right) + F_{EQ}(1 - e^{-aN/B}) - F_{EH}(\tau + \mu_F + \delta), \quad [10]$$

$$\frac{dF_{IQ}}{dt} = \delta F_{IH} + \tau F_{EQ} - F_{IQ}[s + \mu_F + (1 - e^{-aN/B})], \quad \text{and} \quad [11]$$

$$\frac{dF_{IH}}{dt} = F_{IQ}(1 - e^{-aN/B}) + \tau F_{EH} - F_{IH}(s + \mu_F + \delta). \quad [12]$$

The host submodel contains six classes: susceptibles, S , those exposed, E_F , and infectious, I_F , by way of the blocked vector route, and those exposed, E_C , and infectious, I_C , through direct contact routes including airborne contact or contact with the short-term infectious reservoir, M . The total number of prairie dogs is $n = S + E_F + I_F + E_C + I_C$. The vector submodel contains

six classes, including fleas on hosts and fleas questing for hosts. On-host and questing vectors are modeled explicitly to accurately capture the biology of flea reproduction and flea questing. The six classes of vectors are: susceptible and questing, F_{SO} , susceptible and on the host, F_{SH} , exposed and questing, F_{EO} , exposed and on the host, F_{EH} , infectious and questing, F_{IO} , and infectious and on the host, F_{IH} . The total number of fleas that can reproduce is $F_O = F_{SH} + F_{EH}$.

Disease transmission is modeled as a mix of frequency- and density-dependent contacts, depending on the route of transmission (see Eq. 1). Within towns, close contact within maternally dominated family groups called coteries potentially affects disease spread. Contact among individuals is assumed to be well mixed within coteries with occasional contact between individuals of neighboring coteries. When the population structure created by coteries ultimately influences transmission dynamics, we use a constant contact rate modeled as frequency-dependent transmission. Population structure will affect the host-to-host contacts in airborne transmission, as well as vector-to-host contacts in blocked vector transmission, so the contact structure for these types of transmission is modeled as frequency-dependent in the second and third terms respectively of Eq. 1 (40). We additionally include a correction for low flea numbers to incorporate the reduced contact rate between vectors and hosts at very low host density (*sensu* refs. 27 and 41). The contact structure for blocked vector transmission is derived by including both the number of questing fleas and the proportion of those fleas that are infectious, leading to cancellation of the number of questing fleas. Therefore, although we model blocked vector transmission as frequency-dependent, the term describing it does not literally contain frequencies (Eqs. 1 and 2).

In contrast to these first two routes, transmission from many types of short-term reservoirs can be modeled as a density-dependent process as in the fourth term of Eq. 1. As animals die and social structure breaks down, we assume that individuals expand their movements, leading to a contact rate that is proportional to the density of both susceptible hosts and the short-term reservoir. Thus, contact with environmental reservoirs, such as infected carcasses, is density-dependent. Similarly, as social structure breaks down, the likelihood of contact with unblocked fleas that are potentially infectious and questing for hosts in burrows where hosts have died is also density-dependent. Small mammals that live on prairie dog towns are not subject to prairie dog social structure, suggesting that contact between prairie dogs and the reservoir is again a function of density.

Our model structure aims to reflect the transitions that are important to plague dynamics. In the host submodel, susceptibles reproduce in a density-dependent manner and suffer natural mortality at rate μ (Eq. 1). Transmission of plague to susceptibles occurs from blocked vectors, the airborne route, or from the short-term reservoir at rates β_F , β_C , and β_R , respectively. In transmission from the short-term reservoir, the number of burrows that a prairie dog enters, B , is a surrogate for area (40). The exposed period for the host (σ^{-1}) reflects the time necessary for bacteria to reproduce within the host and cause bacteremic infection (42, 43) and, ultimately, clinical signs of disease (22). Once exposed, hosts die through natural mortality at rate μ or become infectious at rate σ (Eqs. 2 and 3). The disease-induced mortality rate for infectious individuals is α_F for the blocked vector route and α_C for the direct contact routes (airborne or from the reservoir) (Eqs. 4 and 5). Natural mortality is ignored in the infectious classes because the infectious period for plague is on the order of 2 days (22). The infectious reservoir increases proportionally to disease-induced mortality in both infectious classes and decays at rate λ (Eq. 6).

Within the vector submodel, all questing classes of fleas (Eqs. 7, 9, and 11) increase as on-host fleas leave prairie dog hosts at rate δ and decrease as fleas quest for new hosts at rate $1 - e^{-aN/B}$. The inverse is true for on-host classes (Eqs. 8, 10, and 12). The flea questing rate is a function of the number of prairie dogs within a fixed area (i.e., density as a function of the number of burrows in that area, N/B), and the searching efficiency of the flea given that density of hosts, a . Individuals in all classes of fleas suffer natural mortality at rate μ_F . We assume that reproduction is restricted to the on-host susceptible and exposed classes, F_O , because of the short duration of the infectious period and the necessity of obtaining a blood meal before reproduction can occur. Reproduction is based on a saturating functional response (Eq. 7) where the maximum number of blood meals is constrained by the handling time on the host (44). The conversion efficiency, r_F , is defined as the number of new fleas produced per blood meal. Eggs and larvae are assumed to fall off the hosts and hatch, increasing the susceptible, questing class. Transmission from host to flea at rate, γ , occurs as a function of a constant contact rate between susceptible fleas on infectious hosts, thus host-to-flea transmission is a frequency-dependent process (Eq. 8). The exposed period for the flea vector, τ^{-1} , reflects the time needed for blockage of the proventriculus to develop (Eqs. 9 and 10) (24). Infectious fleas suffer additional, disease-induced mortality at rate s (Eqs. 11 and 12) as a result of starvation due to blockage (24).

Stochastic Model. We also developed a stochastic realization of the model in JAVA (source code available upon request). This stochastic model allowed exploration of details associated with extinction events, specifically the extinction probability and the extinction time (the amount of time it takes for extinction to occur). By assuming that all events in the model occur only one at a time, that all events occur independently, and that the probability of an event occurring is constant per unit time, we could describe the original model as a Poisson process, where transition rates between classes in the model were distributed exponentially based on the rates in the ODE model (45, 46). This stochastic model occurs in continuous time and has an expected behavior described by the deterministic model with two minor differences. In the stochastic version of the model, individuals are discrete, in contrast to the continuous classes in the ODE model. The rate of airborne exposure to plague (including both transmission and contact rates; Eqs. 1 and 3), and the rate of exposure of susceptible vectors to plague (Eqs. 8 and 10) also differ slightly in that they are set to zero when the number of prairie dogs, N , is zero.

Parameter Values and Sensitivity Analysis. To develop a parameter set that reflects the biology of plague in black-tailed prairie dogs on the PNG, where our validation data were collected, we used parameter values both from the literature and our own field studies. The default parameter set is in Table 1. Table 2, which is published as supporting information on the PNAS web site, describes the region of parameter space around the default parameter set that we explored. When possible, we used published data for the black-tailed prairie dog and *O. hirsuta*, or the most closely related species for which data were available. Prairie dog carrying capacity, mortality, and population growth rates are from a life table analysis of a black-tailed prairie dog population in South Dakota (25). Parameters associated with blocked vector transmission are from laboratory transmission experiments with guinea pigs (*Cavia porcellus*) to determine the efficiency of *O. hirsuta* as a vector for plague (24). Because few data exist on pneumonic plague in wild rodents, we use data from humans for parameters associated with airborne transmission (11). Transmission from the short-term reservoir is assumed to occur through direct contact. Thus, in the absence of published data,

the default airborne transmission rate is also used for the transmission rate from the reservoir. The length of the latent period and the time to death for blocked vector infection in black-tailed prairie dogs (*C. ludovicianus*) is taken from data on experimental infections by s.c. injection of *Y. pestis* for a related species, *Cynomys leucurus* (ref. 22 and references therein). We use data from the California vole (*Microtus californicus*) and the ground squirrel flea (*Malariaeus telchinum*) for the rate at which fleas jump on and off hosts (26). The questing rate, or the searching ability of fleas, is taken from a model study of plague in fleas, rats, and humans (27, 41).

Using our field data, we estimated the number of burrows visited by prairie dogs, B , conversion efficiency of fleas, r_F , and the infectious period of the short-term reservoir, λ . The number of burrows an individual prairie dog visits, B , was estimated from Geographic Information System maps of burrow distribution by using a technique called edge thinning (*sensu* refs. 47 and 48). We assumed that the burrows of a coterie are clustered in space and determined clusters by using a threshold distance that reflects the potential movement of individuals. Using this relationship for one of our study sites, we estimated that individuals regularly use 20 burrows, which is in close agreement with estimates based on direct observation at another site ($B = 19$; ref. 25). Conversion efficiency of fleas, r_F (the number of new fleas produced per blood meal), was estimated by fitting the flea load on prairie dogs in the absence of plague in our ODE model (4 fleas per prairie dog) to the median flea load on prairie dogs in the field (median = 5 fleas per prairie dog in uninfected towns; D. Tripp and M.F.A., unpublished data).

We also estimated the reservoir infectious period, λ^{-1} . Analysis of long-term data for our study sites suggests that plague die-offs in black-tailed prairie dog towns result in local extinc-

tions and that these towns are eventually recolonized (21). To make our estimate of λ^{-1} , we assumed that prairie dogs attempt to recolonize extinct towns each year and that residual infectious material prevents recolonization. We then fit the average time in our stochastic model from when prairie dogs went extinct to when the infectious reservoir had completely decayed (2.73 ± 0.73 years) to the average length of time between extinction and recolonization observed in the PNG (2.59 ± 1.59 years, based on 24 extinction-recolonization events since 1981).

The average sensitivity of the model over 1,000 simulation runs was evaluated for the extinction probability and the extinction time. Here we define sensitivity, Σ , conventionally, as the proportional change in the output variable, V (e.g., extinction probability), for a given change in the value of a parameter, P (see equation 2.13 in ref. 27).

$$\Sigma \approx \frac{\ln(V(P)) - \ln(V(P_0))}{\ln(P) - \ln(P_0)} \quad [13]$$

This calculation is based on a pair of parameter values, the default value, P_0 , and a second arbitrary value, P . Sensitivity is a measure of the relative importance of the input parameter with respect to the output variable. Sensitivities of the extinction probability and the extinction time indicate which parameters and their associated transmission routes drive plague epizootics in our model.

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