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Ecological characteristics of flea species relate to their suitability as plague vectors

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Abstract The ability of vector-borne diseases to persist and spread is closely linked to the ecological characteristics of the vector species they use. Yet there have been no investigations of how species used as vectors by pathogens such as the plague bacterium differ from closely related species that are not used as vectors. The plague bacterium uses mammals as reservoir hosts and fleas as vectors. The ability of different fleas to serve as vectors is assumed to depend on how likely they are to experience gut blockage following bacterial multiplication; the blockage causes fleas to regurgitate blood into a wound and thus inject bacteria into new hosts. Beyond these physiological differences, it is unclear whether there exist fundamental ecological differences between fleas that are effective vectors and those that are not. Here, using a comparative analysis, we identify clear associations between the ability of flea species to transmit plague and their ecological characteristics. First, there is a positive relationship between the abundance of flea species on their hosts and their potential as vectors. Second, although the number of host species exploited by a flea is not associated with its potential as a vector, there is a negative relationship between the ability of fleas to transmit plague and the taxonomic diversity of their host spectrum. This suggests a correlation between some ecological characteristics of fleas and their ability to develop the plague blockage. The plague pathogen thus uses mainly abundant fleas specialized on a narrow taxonomic range of mammals, features that should maximize the persistence of the disease in the face of high flea mortality, and its transmission to suitable hosts only. This previously unrecognized pattern of vector use is of importance for the persistence and transmission of the disease.

Keywords Abundance · Fleas · Host specificity · Plague transmission · *Yersinia pestis*

Introduction

The evolution of vector-borne diseases involves numerous adaptations of a pathogen to its vector(s) and host(s). In particular, the evolutionary significance

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of vector selection by a pathogen should be a guarantee that the disease will be spread among susceptible hosts. In this respect, the ecological characteristics of vectors will have major repercussions on disease dynamics (Gillespie et al. 2004; Randolph 2004). One would expect that over evolutionary time, pathogens would adopt vector species that provide them with the ability to persist and frequent opportunities to spread.

Plague is one of the most notorious and legendary diseases having caused severe epidemics and pandemics during recent human history. For example, the Black Death was the most devastating epidemic that struck Europe in the mid fourteenth century, killing about a third of Europe's population (Kozlov 1979; Gage and Kosoy 2005). Plague is not an extinct medieval monster, and epidemics still happen frequently. About 38,000 (2,845 of them lethal) human plague cases were recorded in 25 countries during 1983–2003 (Anonymous 2004). Therefore, the importance of plague studies cannot be questioned, as they may provide vital information for the development of effective plague control.

A variety of mammals, mainly rodents and lagomorphs, serve as the main natural reservoirs of the plague pathogen, *Yersinia pestis*, whereas fleas, a highly specialized order of haematophagous insect parasites, are specific vectors of plague (Pollitzer and Meyer 1961). Although various modes of plague transmission are possible (pneumonic, septicemic, exposure to plagued carcasses), the flea-borne mode of transmission is commonly accepted as the main route of plague circulation (Suleimenov 2004; Gage and Kosoy 2005). Therefore, both links of the chain—vector and reservoir—are necessary for the plague pathogen to persist. Within the mammalian host, the pathogen must successfully survive, multiply and spread from the site of initial infection to other locations in the host's body, causing a high bacteremia that is a source of infection for fleas (Burroughs 1947; Anisimov 2002). More than 200 rodent and lagomorph species and about 250 flea species are naturally infected by plague (Pollitzer 1960; Serzhan and Ageyev 2000). However, not all rodents and lagomorphs are equally suitable reservoirs for plague bacteria and not all flea species can effectively transmit plague between hosts. The ability of a host species to serve as a suitable reservoir depends on various parameters such as its susceptibility, resistance, abundance, distribution, and behaviour (Rall 1965). In particular, a potential reservoir should not only become infected with the plague pathogen but also circulate sufficient numbers of bacteria in its blood to serve as a reliable source of infection for fleas (Pollitzer and Meyer 1961; Engelthaler et al. 2000). This may be related to some physiological and/or biochemical characteristics of a host species. In addition, a suitable reservoir should support large populations of flea vectors (Pavlovsky 1966). Large populations of fleas are usually characteristic of those host species that possess deep and/or complicated burrows or nests (Kucheruk 1983).

The suitability of a flea species to act as a plague vector is determined by a peculiarity of the mechanism of plague transmission described as early as 1914 (Bacot and Martin 1914). After arriving in a flea during a blood meal, the bacteria multiply rapidly in the flea's gut and clog the proventriculus, blocking the passage of blood from the foregut to the midgut (Bacot and Martin 1914; Pollitzer and Meyer 1961; Bibikova and Klassovsky 1974; Darby et al. 2005; Gage and Kosoy 2005). Blocked and starving fleas repeatedly attempt to feed but host blood cannot pass the proventricular block. Eventually the flea regurgitates blood (now with bacteria) into the open wound, thereby infecting a new host. However, complete blockage of the proventriculus is not crucial for transmission. Partial blockage can also result in efficient transmission (Bacot 1915; Lorange et al. 2005). Although some fleas that are blocked by the plague bacteria appear unable to transmit the disease, whereas others transmit plague without being blocked, the transmission by blocked vectors, at least in enzootic cycles (when little obvious host mortality occurs and the plague is transmitted between partially resistant animals), is thought to be the most important route of plague circulation (Burroughs 1947; Kartman et al. 1958; Bibikova and Klassovsky 1974; Hinnebusch et al. 1998; Darby et al. 2005; Gage and Kosoy 2005; Lorange et al. 2005). Consequently, the blocking rate by the plague pathogen under experimental conditions has been used as an indicator of a flea's transmission ability and, thus, as a measure of the suitability of a flea species to serve as a plague vector (Bibikova and Klassovsky 1974). However, earlier authors have dismissed the possibility that ecological differences among flea species can also influence whether or not they play roles as vectors (Bibikova and Klassovsky 1974). Recently, the suggestion has been made, but not tested, that ecology may determine to some extent whether a flea is a suitable vector (Gage and Kosoy 2005).

Here, we tested the hypothesis that ecological characteristics of fleas are correlated with their suitability as vectors of plague. Although gut blockage is not strictly synonymous with plague transmission, the blockage rate represents the best quantitative measure of the ability of fleas to act as plague vectors. This is because the actual rates of infection in natural flea populations are unavailable for the vast majority of flea species. We considered the blocking rate in experimental situations as an indicator of a flea's ability to transmit plague and compared this parameter among flea species that are characterized by different abundance and host specificity. As the plague block, in general, drastically shortens flea longevity (Vatschenok 1988) and as fleas demonstrate, in general, relatively low vector competency (Lorange et al. 2005), we predicted that suitable flea vectors should be characterized by relatively high abundance: (1) to guarantee the broad spread of the disease, (2) to compensate for losses of fleas during plague transmission, and (3) to compensate for the relatively low vector competency. We hypothesized that the suitability of a flea species as a vector will also be correlated with the size and taxonomic composition of its host spectrum. We predicted that highly host opportunistic fleas that exploit hosts belonging to distantly related taxa would not be suitable plague vectors because they might transmit the infection to host species that are unsuitable reservoirs. Consequently, besides taking the number of host species used by a flea as a measure of host specificity, we also applied a measure of host specificity that takes into account the taxonomic affinities of the host species (Poulin and Mouillot 2003). This measure places the emphasis on the taxonomic distance between host species used by a flea rather than on their number, providing a different perspective on flea specialization.

Materials and methods

Data on the blocking rate by *Y. pestis*, and data on host specificity and mean abundance in the enzootic for plague regions were obtained for 40 flea species for which quantitative data on both experimental blocking rate and natural abundance and host specificity (including sampling effort) were available (see Electronic Supplementary Material, Table S1).

Blocking rate is defined here as the percentage of fleas from one species that had their proventriculus blocked by plague infection in an experimental situation. Data on the blocking rate for the same flea species often varied among and within experiments depending on ambient temperature (Cavanaugh 1971), strain of the plague pathogen (Bibikova and Klassovsky 1974; Anisimov 2002), or host species (Bibikova and Klassovsky 1974; Vatschenok 1988). From the available data for each flea species, we selected the value of blocking rate obtained: (1) when a flea was fed on a rodent species that was either its natural host or was closest taxonomically to the natural host, and (2) for the ambient temperature closest to the range of favorable temperatures for the plague blocking rate reported for that particular flea species (Bibikova and Klassovsky 1974). In a few cases, when the reasons for variation in the blocking rate were unknown, the median value of the observed blocking rates was used.

Data on host specificity and abundance of fleas were extracted from 21 published surveys (see Electronic Supplementary Material, Table S1) that reported flea distribution and abundance on small mammals in regions where the natural foci of plague occur (Caucasus, central Asia and North America). For each species of flea, one measure of abundance (mean number of fleas per individual host) and two measures of host specificity (the number of mammalian species on which the flea species was found and the specificity index (S_{TD}) (Poulin and Mouillot 2003) were used. Mean number of fleas per host individual was calculated for each of a flea's host species. To ensure that variation in among-host sampling effort and body size (hosts of different sizes presumably support different numbers of fleas) did not bias estimates of flea abundance, we regressed log-transformed estimates of flea abundance per host against the log-transformed number of hosts examined and the log-transformed body surface area of hosts across all flea species, all host species and in all regions. Body surface area of a host species was estimated from host body mass (Walsberg and Wolf 1995). Estimates of flea abundance per host were significantly affected by sampling effort (r^2=0.15, $F_{1,513}$=90.8, P<0.01) but not affected by host body size (r^2=0.007, $F_{1,513}$=0.03, P>0.85). Therefore, we substituted the original values of flea abundance by residuals of the regression of log-transformed flea abundance against the log-transformed number of hosts examined. Data on abundance for each flea species were averaged across host species and across regions.

The index S_{TD} measures the average taxonomic distinctness of all host species used by a parasite species. When these host species are placed within a taxonomic hierarchy, the average taxonomic distinctness is simply the mean number of steps up the hierarchy that must be taken to reach a taxon common to two host species, computed across all possible pairs of host species (Poulin and Mouillot 2003). The greater the taxonomic distinctness between host species, the higher the number of steps needed, and the higher the value of the index S_{TD}. The details of calculation of S_{TD} for fleas can be found elsewhere (Krasnov et al. 2004). Some flea species occurred in more than one region; measurements of host specificity for these species were averaged across regions. The number of mammalian species on which the flea species was found was correlated with sampling effort (after log-transformation, r^2=0.25, $F_{1,38}$=12.8, P<0.005). The number of host species exploited by a flea species correlated positively with S_{TD} (after log-transformation, r^2=0.52, $F_{1,38}$=42.48, P< 0.001), indicating that this measure was influenced by the number of species in a flea's host spectrum. We corrected the measures of host specificity for sampling effort or number of host species by substitution of the original values by their residual deviations of the regressions on sampling effort (for number of host species) or number of host species (for S_{TD}) after log-transformation.

To test for the correlation between the blocking rate and measures of flea abundance and host specificity, we applied both separate and multiple stepwise (forward procedure) regressions for the arcsine-transformed values of blocking rate (dependent variable) against mean abundance, number of host species exploited and their taxonomic distinctness (S_{TD}) (independent variables). We also controlled for the effects of flea phylogeny, using the method of independent contrasts (Felsenstein 1985). To compute independent contrasts, we used the PDAP:PDTREE program (Midford et al. 2005) implemented in Mesquite Modular System for Evolutionary Analysis (Maddison and Maddison 2005). The phylogenetic trees for fleas were based on morphological taxonomy (see Krasnov et al. 2004 for details). We standardized each contrast as suggested by Garland et al. (1992). No significant linear or non-linear trend was found in the plots of the absolute values of standardized contrasts against their SDs, suggesting that the contrasts were adequately standardized. We regressed standardized contrasts of the dependent variable against standardized contrasts of the independent variables using both separate and multiple regressions forced through the origin (see Garland et al. 1992 for details).

In addition, we tested for the relationship between the proportion of suitable plague reservoirs in the flea's host spectrum and the fleas' blocking rate using both conventional regression and the method of independent contrasts. Categorization of a host species as either a suitable or unsuitable plague reservoir followed Rall (1965) and Kozlov (1979).

Results

The percentage of flea individuals blocked by plague bacteria in experiments was positively correlated with the mean abundance of fleas in nature (r^2=0.45, $F_{1,38}$=30.7, P<0.001; Fig. 1a). The same results were obtained using the method of independent contrasts (r=0.33, P<0.03, Fig. 1b).

Whether controlling for phylogenetic influences or not, the percentage of flea individuals blocked by the plague bacteria was not correlated with the number of host species exploited in nature (r^2=0.01, $F_{1,38}$=0.4 for conventional statistics and r=−0.18 for independent contrasts; P>0.2 for both). In contrast, the blockage rate correlated negatively with S_{TD} (r^2=0.15, $F_{1,38}$=6.9, P<0.02, Fig. 2a). After removal of the confounding effect of phylogeny, the taxonomic distinctness of the host spectrum remained significantly negatively correlated with vector efficiency of fleas (r=−0.34, P<0.02, Fig. 2b).

Multiple regression analyses provided the same results. The percentage of experimentally blocked fleas (BR) correlated positively with the mean flea abundance (AB), negatively with S_{TD} and was not correlated with the number of exploited host species as $\mathrm{BR}=0.16+0.27\mathrm{AB}-0.47\times S_{\mathrm{TD}}$ (r^2=0.57, $F_{1,36}$=23.6, P<0.001). The same relationships remained after the original values were substituted with independent contrasts. Contrasts in the blocking rate (BR_c) were positively correlated with contrasts in mean abundance (AB_c) and negatively correlated with contrasts in S_{TD} (S_{TDc}) as $\mathrm{BR}_c=0.12\mathrm{AB}_c-0.56\times S_{\mathrm{TDc}}$ (r=0.55, P<0.01).

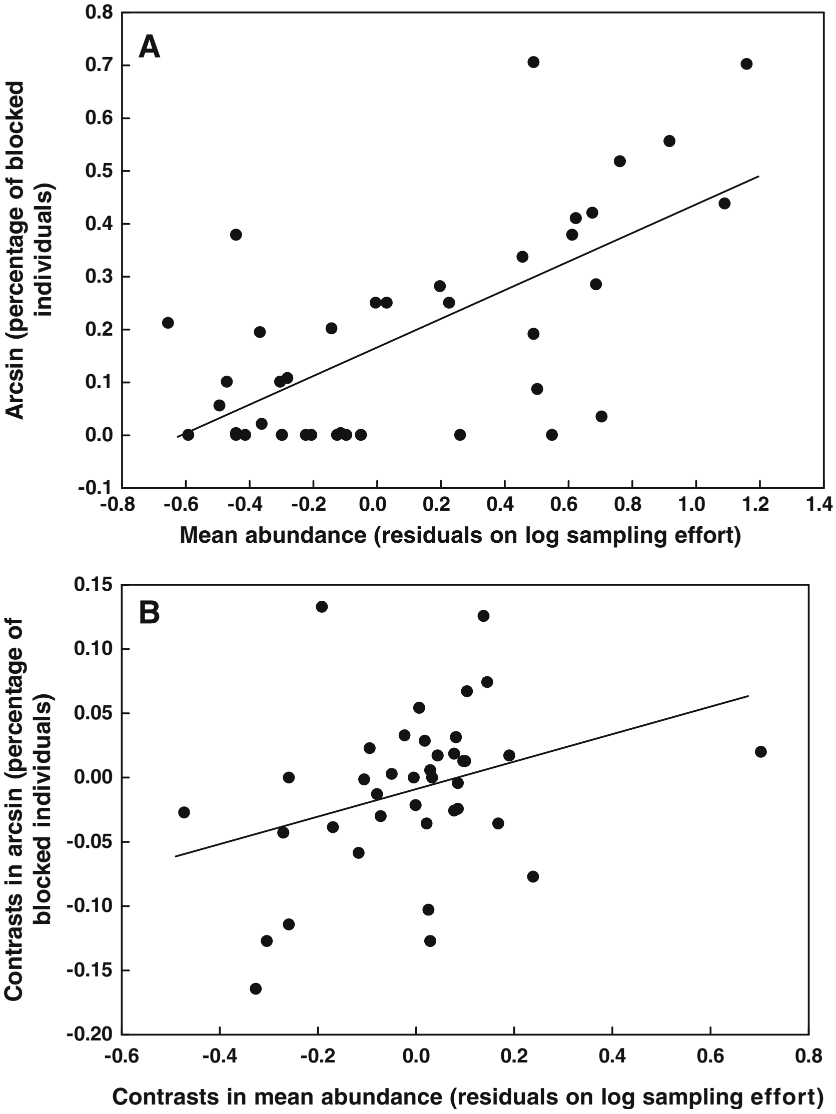
The distribution of data points in Fig. 2a is clearly triangular suggesting that flea species exploiting closely related host species may or may not be efficient plague vectors, whereas a high blocking rate never occurs in flea species exploiting distantly related hosts.

However, no relation was found between the proportion of suitable plague reservoirs in the flea's host spectrum and the fleas' blocking rate (r^2=0.01, $F_{1,38}$=0.5 for conventional regression and r=−0.1, $F_{1,37}$=0.5 for the method of independent contrasts; P>0.4 for both).

Discussion

Our results demonstrate clear ecological differences between fleas that experience frequent blockage by the plague pathogen in experiments (and thus likely serve as plague vectors) and those that demonstrate low rates of blockage (and probably do not play an important role in plague circulation). First, fleas that appear highly effective as plague vectors are, in general, more abundant (in terms of their number per host individual) than inefficient vectors. This can be viewed as a kind of compensation for the high mortality of infected fleas. Many fleas die quickly after becoming blocked by plague bacteria, although some blocked fleas can survive for long periods at low ambient temperatures (Burroughs 1947; Bibikova and Klassovsky 1974). In addition, highly abundant vectors can guarantee the

Fig. 1 Relationships between the percentage of flea individuals blocked by plague bacteria in experiments and mean abundance of the flea species in nature **a** across 40 flea species, and **b** using the method of independent contrasts



broader dispersal of bacteria among host individuals. Highly abundant fleas can also inhibit the host's immune response (Schmid-Hempel and Ebert 2003; Khokhlova et al. 2004), thus enhancing host susceptibility and increasing the probability of high bacteremia, which, in turn, increases the probability of transmission to new hosts. Finally, despite fleas being specific vectors of the plague, their transmission efficiency (at least, for some studied species, e.g., *Xenopsylla cheopis*) appears to be relatively low (Lorange et al. 2005). Consequently, high flea abundance might be an important means of compensating for this low vector competency. All these explanations are not mutually exclusive.

Second, host specificity, in terms of the taxonomic diversity of a flea's host spectrum, is an important character explaining, at least partly, why some flea species, but not others, serve as vectors for the plague pathogen. All fleas that use hosts from distantly related taxa are characterized by a relatively low blocking rate in experimental situations and, thus, their role as plague vectors is expected to be limited. It should be noted, however, that some flea species in which *Y. pestis* does not form a blockage, can, nevertheless, transmit the disease, although the transmission of plague by these species is more likely mechanical (Bibikova and Klassovsky 1974). In contrast, all fleas that demonstrate a relatively high blocking rate exploit mainly closely related hosts. The reason for this can be that phylogenetically close host species are likely more similar in their ecological, physiological and/or immunological characters (including those related to their suitability as reservoir for the plague bacteria) than phylogenetically more distant host species (Harvey and Pagel 1991). On the other hand, fleas with a taxonomically diverse host spectrum may exploit both suitable and

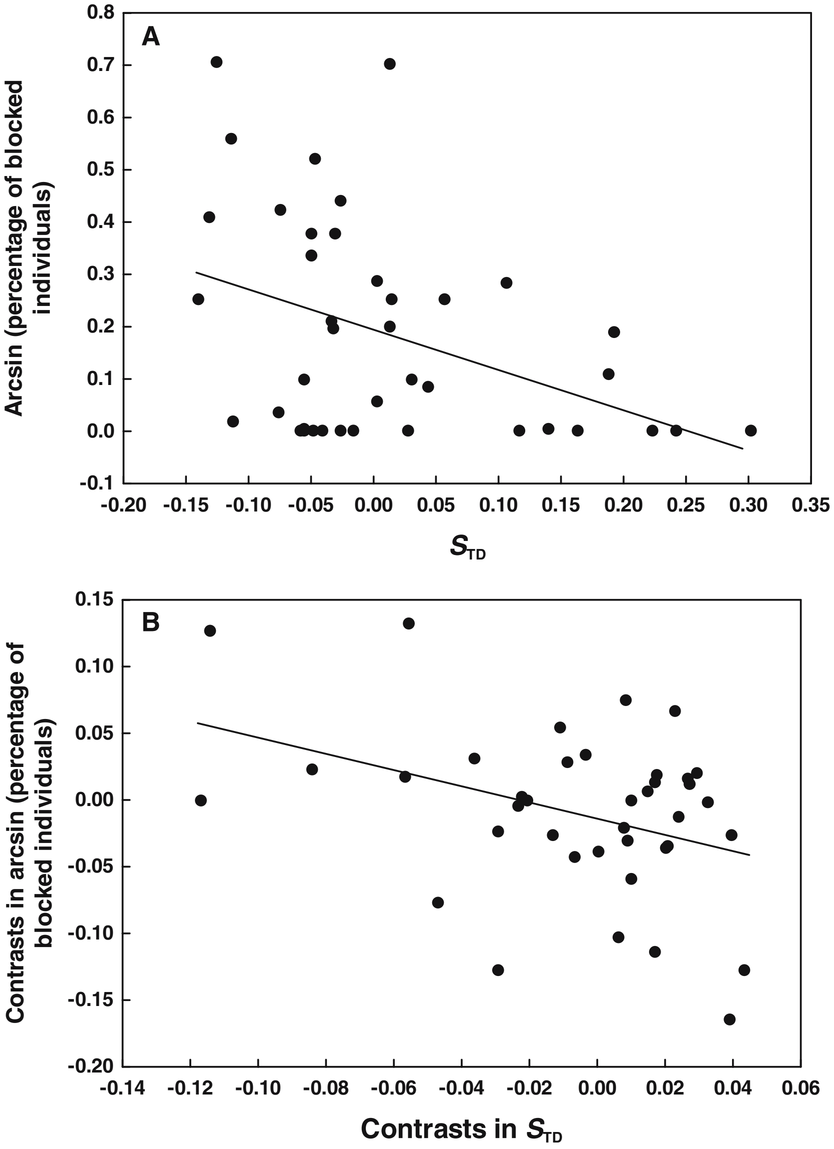


Fig. 2 Relationships between the percentage of flea individuals blocked by plague bacteria in experiments and the index of taxonomic distinctness (S_{TD}), of a flea's host spectrum in nature **a** across 40 flea species, and **b** using the method of independent contrasts

unsuitable (for the plague) host species. Consequently, the probability of the plague pathogen landing in an unsuitable reservoir, when using a flea with highly taxonomically diverse hosts, must be high. The taxonomic diversity of hosts appears to be a more important feature of plague vectors than merely the number of host species exploited. Nevertheless, the number of hosts used can play a certain role in the ability of a flea species to maintain and/or amplify plague circulation (Gage et al. 1995; Gage and Kosoy 2005). For example, extremely host-specific fleas (e.g., those that use a single host species) might transmit plague within a particular host species but are probably unable to spread the infection to other species (Gage and Kosoy 2005). Such vectors can ensure long-term persistence of the plague bacteria in enzootic cycles (Gage et al. 1995), but are unlikely to support the dispersal of the disease in epizootic cycles (i.e., transmission of the pathogen from maintenance to amplifying hosts, rapid spreading and die-offs). Alternatively, during enzootic cycles, the plague pathogen might rely on host-opportunistic fleas with low blocking rate so that fleas would live longer and spread the disease further. However, it is still unclear whether plague jumps between host and flea species to ensure its long-term persistence or circulates at low rates in particular host–flea associations between epizootics.

The negative but triangular distribution of points in the relationship between the taxonomic diversity of hosts and the blocking rate of fleas (Fig. 2a) implies that fleas with taxonomically narrow host spectra include both suitable and unsuitable plague vectors, whereas fleas with taxonomically broad host spectra are unsuitable vectors. We suggest that this pattern arises because the taxonomic diversity of the host spectrum is a necessary but insufficient prerequisite for a flea species to be adopted as a vector by the plague bacterium. The fleas themselves must provide a suitable environment for the bacteria. This suitability differs among flea species depending on the morphology of the proventriculus (Eskey and Haas 1940; Bibikova and Klassovsky 1974), the frequency of bloodmeals (Vatschenok 1988) and other still unknown flea-related factors, all else (e.g., strain of *Y. pestis* and ambient temperature) being equal.

The presence of a suitable reservoir host in a flea's host spectrum is, evidently, another necessary prerequisite for a flea species to be a suitable plague vector. To become a plague vector, a flea must exploit at least one susceptible host species that exhibits heterogeneous responses to infection (Rall 1965; Gage et al. 1995). However, we found no relation between the proportion of suitable plague reservoirs in the flea's host spectrum and the fleas' blocking rate. One possible reason for this result is that there has been no study of the blocking rate in fleas that only exploit plague-unrelated hosts.

The use of flea species as vectors by the plague pathogen is not merely a consequence of their physiological attributes: contrary to conventional wisdom, their ecological traits matter as well. The evolution of plague, besides all other factors, was thus linked with the ecological affinities of its vector organisms. This strategic use of the vector species with features that facilitate disease spread highlights the rapid evolutionary fine-tuning of the plague's transmission cycle. Indeed, recent findings (Achtman et al. 1999, 2004) based on the molecular analyses of a variety of plague strains suggest the unexpected evolutionary youth of the plague pathogen, dating back to only 1500–20,000 years. We would expect similar non-random use of vector species to exist in other vector-borne transmission, a phenomenon that needs to be taken into account for their epidemiology and control (Randolph et al. 2002; Gillespie et al. 2004).

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