Transmission of Flea-Borne Zoonotic Agents*

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Abstract

Flea-borne zoonoses such as plague (*Yersinia pestis*) and murine typhus (*Rickettsia typhi*) caused significant numbers of human cases in the past and remain a public health concern. Other flea-borne human pathogens have emerged recently (e.g., *Bartonella henselae*, *Rickettsia felis*), and their mechanisms of transmission and impact on human health are not fully understood. Our review focuses on the ecology and epidemiology of the flea-borne bacterial zoonoses mentioned above with an emphasis on recent advancements in our understanding of how these organisms are transmitted by fleas, maintained in zoonotic cycles, and transmitted to humans. Emphasis is given to plague because of the considerable number of studies generated during the first decade of the twenty-first century that arose, in part, because of renewed interest in potential agents of bioterrorism, including *Y. pestis*.

INTRODUCTION

Throughout the world, vector-borne diseases cause significant morbidity and mortality. The majority of recent research and reviews of vector-borne zoonoses focuses on tick- and mosquito-borne illnesses, such as Lyme disease and West Nile virus disease (15, 60, 98, 104). By contrast, relatively little attention has been paid to flea-borne zoonoses such as plague (*Yersinia pestis*) and murine typhus (*Rickettsia typhi*), which historically have caused significant numbers of human cases. Although the incidence of plague has declined considerably, it still causes regional outbreaks with many fatalities. Murine typhus also remains common in many areas, and neither disease has been eliminated or greatly reduced in its range. Other flea-borne human pathogens also have emerged recently (e.g., *Bartonella henselae*, *Rickettsia felis*), suggesting that much remains to be learned about the potential role of fleas as disease vectors. Our review focuses on the ecology and epidemiology of the flea-borne bacterial zoonoses mentioned above with an emphasis on recent advancements in our understanding of how these organisms are transmitted by fleas, maintained in zoonotic cycles, and transmitted to humans. Emphasis is given to plague because of the considerable number of studies generated during the first decade of the twenty-first century that arose, in part, because of renewed interest in potential agents of bioterrorism, including *Y. pestis*. The role of fleas in the transmission of myxoma virus, a disease of rabbits, and as intermediate hosts for tapeworms is beyond the scope of this review.

PLAGUE (*YERSINIA PESTIS*)

Overview of Plague Epidemiology

Plague, caused by the gram-negative bacterium *Y. pestis*, is a severe, primarily flea-borne, rodent-associated zoonosis characterized by natural cycles with quiescent periods that are punctuated by rapidly spreading epizootics (10). The majority of human infections are believed to occur during epizootic periods when susceptible rodent hosts perish in large numbers, thus increasing the likelihood of human encounters with infectious animals, animal carcasses, or fleas that abandon their dead or dying *Y. pestis*–infected hosts (56).

In humans, plague most commonly presents in the bubonic form of the disease, which is often associated with the bite of an infectious flea or direct contact between infectious host body fluids and open skin lesions or abrasions on human skin. Bubonic plague is characterized by sudden onset of fever, chills, headache, malaise, and regional lymphadenopathy (30). Primary septicemic plague, which is often attributed to cutaneous exposure to *Y. pestis*, is less common and is characterized by fever and sepsis without regional lymphadenopathy (30). Septicemic plague also can occur secondarily to bubonic plague. Finally, among the three most common plague presentations, the primary pneumonic form of the disease, which is acquired through inhalation of plague bacteria contained in respiratory droplets or other materials, is the least common, but the most severe and rapidly progressing, form. Pneumonic plague also can occur through hematogenous spread of *Y. pestis* to the lungs (30). Although human plague cases are rare in modern times, fatality rates range from 50% to 60% for the bubonic form of the disease to nearly 100% for pneumonic infections (80, 99). However, outcome of infection is substantially improved by early diagnosis followed by appropriate antimicrobial therapy (25). The low fatality rates reported frequently from some countries probably represent considerable levels of misdiagnosis (100).

Historically, *Y. pestis* has caused at least three pandemics. The first pandemic, known as Justinian's plague, occurred in the sixth century. It is believed to have begun in Central Asia, then it dispersed and caused epidemics that infected nearly 100,000,000 persons in Asia, Africa, and

Europe (114). The second pandemic, now referred to as the "Black Death," occurred in the fourteenth century and caused approximately 50,000,000 fatalities worldwide, with half the victims in Asia and Africa and the other half in Europe. That pandemic is notable for killing nearly one-quarter of Europe's population. The third pandemic, known as the "Modern Pandemic," originated in China's Yunnan Province in the 1850s and rapidly spread along the tin and opium routes to port cities in southeast China. Although India was the country most severely affected by this pandemic and most regions experienced case loads numbering only in the hundreds to thousands, the pandemic left a long-standing mark on other regions of the world, as ships carrying plague-infected rats and their fleas introduced *Y. pestis* into port cities around the world and established new plague foci in North America, parts of Africa, Madagascar, and southern Asia (31, 36, 56, 63, 81, 100). With improvements in sanitation, vector control, and availability of effective antibiotics, there has been a sharp decline in epidemicity of plague throughout the world (114). For example, from 1954 to 1997, the World Health Organization was notified of 80,613 human plague cases from 38 countries. During this 44-year period, the largest proportion of cases (58.4%) were reported from Asia (114). By contrast, in recent decades, most human plague cases have been reported from eastern Africa and Madagascar (91, 114, 126).

Overview of Plague Ecology

The distribution of *Y. pestis* is heterogeneous at global, regional, and local spatial scales. Despite global introductions of the pathogen, *Y. pestis* has become established only in localities with landscapes and climatic conditions that are suitable for maintaining rodent and flea populations at sufficiently high levels to support enzootic or epizootic transmission. For example, in the early 1900s, *Y. pestis* was introduced via rat-infested ships into the ports of New Orleans, Louisiana, and Galveston, Texas. Despite brief commensal rat-associated epidemics in both of these cities, the disease was eliminated through improvements in sanitation, such as reduction of food or harborage for rats, and through the improved wharf systems that included inspection and quarantine of ships (82). In contrast, following its introduction into the Port of San Francisco, California, *Y. pestis* spread from urban rats to sylvatic rodent hosts. Although improved sanitation reduced the number of human plague cases, *Y. pestis* became established in California and spread east until reaching its current extent, approximately along the 100th meridian, in the 1940s (3, 50, 82, 89). Within the western states where plague is established in enzootic cycles, its distribution is heterogeneous.

Recent studies have sought to identify landscape, vegetation, and meteorological variables that define the ecological niche of plague and identify areas of elevated risk for human exposure to plague bacteria within plague-endemic regions (24, 28, 41, 43, 44, 90, 93, 130). The majority of these studies have focused on Africa and North America. For example, at a continental scale, African plague foci were defined by positive associations with elevation, potential evapotranspiration, mean diurnal temperature range, annual rainfall, and December-normalized difference vegetation index; on the basis of these variables, much of sub-Saharan Africa was considered suitable for *Y. pestis* transmission (93). Studies that focused on more-local spatial scales determined that elevation and vegetation were key predictors of risk in Uganda and Tanzania. Specifically, in eastern Tanzania, plague was focused at higher elevations (1,200–2,000 m) and in areas with seasonal vegetation changes, suggesting that risk was lower in forested areas relative to surrounding areas (92). Similarly, in northwestern Uganda, plague risk was more elevated in sites situated above 1,300 m than in those below as well as in areas that were wetter with less vegetative growth and had more bare soil during the dry season when agricultural plots were typically fallow. These variables are suggestive of a positive association between elevated plague risk and cultivation of annual agricultural crops (44, 130). Indeed, a subsequent study that evaluated residential risk

ADVANCES IN SPATIAL RISK MODELING

Recent advances in the integration of geographic information systems and statistical analyses have allowed researchers to identify environmental risk factors for many vector-borne diseases. The resulting statistical models can be displayed in map format allowing for the visualization of disease risk probabilities across areas where surveillance may not have been performed. The use of such models and their integration into decision support systems for the prediction, prevention, and control of vector-borne diseases was reviewed recently (37).

factors for plague showed that homesteads situated in areas classified as elevated risk for plague on the basis of these remotely sensed variables were more likely to grow or dry corn within 30 m of the residence when compared with areas classified as low risk (84) (see sidebar, Advances in Spatial Risk Modeling).

Within the epidemiological focus in the southwestern United States, human risk of exposure to plague bacteria was determined to be highest around 2,300 m, in vegetation types defined as piñon-juniper or Ponderosa pine and in wetter areas (41, 43, 46). In California, the distribution of plague-infected California ground-squirrel populations was characterized on the basis of precipitation in the wettest quarter of the year and the warmest temperature in the warmest month of the year (65).

Spatial and temporal distributions of plague are often associated with temperature and rainfall patterns. Worldwide, more than 95% of plague cases are reported from areas with average temperatures that exceed 13°C, with most outbreaks occurring in regions where these temperatures vary from 24°C to 27°C; epidemic activity typically subsides when temperatures exceed 27°C (18, 19, 26). Within plague foci, epizootics occur sporadically. Although the drivers of plague epizootics are not well defined, their timing is often associated with temperature and rainfall patterns (42, 55, 56). Several quantitative models have revealed that, within the relatively arid plague-enzootic regions such as those in the western United States and Kazakhstan, increased moisture levels prior to a transmission season are typically favorable for epizootic activity, whereas elevated temperatures during the transmission season are often unfavorable (11, 16, 23, 49, 95, 109, 110, 112). Based on these observations, a trophic cascade hypothesis was proposed in which elevated precipitation is presumed to increase primary vegetative production, which enhances the supply of potential food sources and harborage for small mammals (49, 95). As small-mammal populations increase, flea-infestation rates may also increase. In addition, the added soil moisture may increase daily survival rates of fleas, which increases the probability that the contact rates between infectious fleas and susceptible hosts will increase, thus increasing the probability of an epizootic (38, 83).

Several studies from North America and Central Asia lend credence to the trophic cascade hypothesis. For example, in the western United States, interannual variation in reported human plague cases was positively associated with the Pacific Decadal Oscillation value for March and a negative association with the mean number of days above 37°C. In this region, a positive Pacific Decadal Oscillation value is typically associated with milder and wetter conditions, which may be conducive for local transmission of *Y. pestis*: Fewer hot days and increased moisture may have relatively low impact on flea mortality, and vegetative cover would be expected to increase under these conditions (11). Within epidemiological foci in the southwestern United States, human and pet cases of plague occurred more frequently following periods with above-average precipitation (16, 49, 95), and case counts were negatively affected by elevated temperatures during the observation year (16, 49). Similarly, plague epizootics in prairie dog colonies in Montana were positively associated with time-lagged precipitation and number of warm days, but they were negatively

associated with the number of hot days (23). Likewise, in north-central Colorado, plague-related die-offs of prairie dogs frequently followed El Niño events (110). In Central Asia, continued persistence and spread of plague in great gerbils (*Rhombomys opimus*) in Kazakhstan is dependent on threshold population sizes of this important host species (27, 29). Furthermore, plague among great gerbils is positively correlated with wetter summers and warmer springs (112).

Pathogen Development within the Vertebrate Host

Owing to the small amount of blood that a flea consumes per blood meal (0.1–0.3 μl) (61, 94), for transmission from vertebrate host to vector to occur reliably, bacteremia must be at least 10^6 cfu ml^{-1} of blood (48, 83). In laboratory animals, bacterial concentrations usually reach 10^8 to 10^9 cfu ml^{-1} of blood (17, 32, 106). Achieving such high bacterial concentrations virtually guarantees that hosts will die of sequelae associated with late-stage *Y. pestis* infections. However, this apparent cost to *Y. pestis* of killing its host appears to be balanced by the benefit of increased probabilities that at least some fleas will complete feeding prior to the host's death and, thus, acquire sufficient numbers of bacteria to become infectious to other animals during subsequent blood feedings (56). In addition, plague-induced host mortality increases the likelihood of transmission to another host of the same or different species either through transmission by direct contact with the infectious carcass or by forcing newly infected fleas to seek alternative hosts (42, 61).

Y. pestis has adapted several strategies for attaining such high bacterial concentrations in its host. After plague bacteria are introduced into a susceptible vertebrate host through the bite of an infectious flea, several bacterial genes are upregulated that allow the bacteria to evade the immune system and disseminate to the lymphatic system. Although recent work has cast doubt on its role (59, 122), Pla, a surface protease encoded on the pPla plasmid, is typically believed to be required for dissemination from the intradermal bite site (78). Shortly after infection, *Y. pestis* infects macrophages that serve as transport for the bacteria to regional lymph nodes. Within the lymph nodes, they multiply, express F1 antigen (caf1) and pH6 antigen, and ultimately give rise to the characteristic buboes (highly swollen lymph nodes that are heavily infected with *Y. pestis)* that are associated with bubonic plague (115). Upon leaving the macrophage, *Y. pestis* bears F1 capsular antigen and expresses pH6 antigen (PsaA), both of these aid in resistance to further phagocytosis (34), thus enabling the bacteria to circulate freely in the bloodstream and multiply rapidly to reach quickly densities ($>10^6$ bacteria/ml blood) that are sufficient to infect feeding fleas (48, 106).

Mechanisms of Flea-Borne Transmission

Since it was first described by Bacot & Martin in 1914, the blocked flea model has endured as the dominant mechanism of flea-borne transmission of *Y. pestis*. Under this paradigm, fleas become infected with plague bacteria by consuming blood harboring high concentrations of *Y. pestis* (typically $\geq 10^6$ cfu ml^{-1}) (48, 83). Initially, bacteria colonize and multiply within the midgut and proventriculus, which is a globular structure situated between the esophagus and midgut and which is lined interiorly with a series of spines that prevent ingested blood from back-flowing to the mouthparts. Over a period of 2 to 3 weeks postinfection (p.i.), but as early as 5 days p.i., multiplication of bacteria within the proventriculus can cause an occlusion or blockage that prevents newly ingested blood from reaching the midgut. Recent studies have demonstrated that a group of chromosomal genes called the hemin storage locus is required for colonization of the proventriculus and production of the biofilm that is responsible for blockage formation (62). The blockage serves two functions that are likely to increase the probability of transmission. First, it prevents newly ingested blood from reaching the midgut, which causes the flea to starve. As a

result, the infected flea increases the number of blood meals it consumes per day, which is likely to result in higher vectorial capacity (47, 83). In addition, the increased feeding causes vigorous movements of blood in the foregut, which may cause cleavage of the *Y. pestis*–rich blockage that can be regurgitated during current or subsequent blood meals. Second, the blockage disrupts the normal function of the proventriculus and allows infected blood to reflux from the midgut to the mouthparts.

Vectorial capacity: a measure of the average number of infectious bites by all vectors feeding on a host in a single day

Extrinsic incubation period: the time elapsed from when a vector becomes infected until it is able to transmit the acquired pathogen

Early-phase transmission: a mechanism of *Y. pestis* transmission by unblocked fleas occurring prior to when a blockage would be expected to develop

Although Bacot & Martin noted that partially blocked fleas may be more efficient vectors than fully blocked fleas (9), the classical blocked flea paradigm that is based on the fully blocked flea model dominated the plague literature for nearly a century and presented this model as the primary and only significant mode of flea-borne transmission. Indeed, vector efficiency has often been equated with a flea's ability to form a proventricular blockage (50, 61, 63, 77, 79, 83, 100). However, most infected fleas do not form blockages, and among those that do, the time elapsed from becoming infected to forming the blockage is ordinarily at least 2 to 3 weeks (**Table 1**). Among *Xenopsylla cheopis* that form a blockage, laboratory-based studies have consistently demonstrated that vectorial capacity is quite low (**Table 1**). Given the absence of blockages in many flea species that are presumed to be important vectors (17, 40, 42, 50, 56) as well as the long extrinsic incubation period and low transmission efficiency associated with blocked flea transmission, recent studies have questioned whether this transmission mechanism is sufficient to explain the rapid rates of spread within susceptible host populations that typify plague epizootics (38, 120).

Alternative sources of infection that do not involve fleas (e.g., direct contact with infected hosts or carcasses and persistence of *Y. pestis* in soil) have been proposed as drivers of plague epizootics (33, 42, 120). However, empirical evidence demonstrates that ridding hosts of their fleas effectively halts pathogen transmission, thus the role of fleas in epizootic transmission cannot be eliminated (39, 58, 66, 100, 108). Although the blocked flea paradigm has been acknowledged as important during interepizootic transmission, some have suggested that mechanical transmission by unblocked fleas is significant during epizootics (17, 72, 73, 102). True mechanical transmission, which would occur as a result of contamination of the flea's mouthparts by viable *Y. pestis*, would render fleas infectious immediately after exposure to plague bacteria and would explain the observed rapid rates of transmission. However, this mechanism has been discounted by some because of their belief that plague bacteria survive on the mouth parts for fewer than 3 h (12).

Recently, an alternative flea-borne mode of transmission, termed early-phase transmission, was described (38). The early-phase model refers to transmission by unblocked fleas during the time period prior to the earliest time point during which a complete blockage is able to form. This mode of transmission is characterized by a short extrinsic incubation period (e.g., as early as 3 h p.i.) (38) and, in some cases, transmission efficiencies that rival those observed for blocked *X. cheopis* (38, 47, 127, 128). To date, early-phase vector efficiency has been tested for six North American flea species (38, 39, 45, 47, 127, 128); although each species was capable of early-phase transmission, efficiency was highly variable. These results were consistent with earlier studies that reported transmission by unblocked fleas 1 to 4 days p.i. (9, 17, 48, 64, 86, 100, 117, 125). In these instances, the results were often viewed as anomalous or attributed to occurring by mass action (i.e., unnaturally high flea loads) and were largely ignored. However, these findings suggest that numerous flea species are capable of early-phase transmission.

The biological mechanism of early-phase transmission has not been elucidated, but in contrast to the blocked flea model of transmission, biofilm is not required for early-phase transmission (118). Regardless of the biological mechanism of early-phase transmission, which may involve a combination of mechanical transmission and regurgitation of midgut or esophageal contents containing *Y. pestis*, several studies have demonstrated the significance of this mode of transmission at the population level. For example, simple vectorial capacity modeling concludes that, on the

Table 1 Experimentally confirmed flea vectors of *Yersinia pestis* in North America[a]

Flea species	Natural hosts in North America	Pathogen-acquisition efficiency	Vector efficiency (number of fleas used)	Mean number of days for EIP (range)	Likelihood of infected fleas blocking (mean days to block)	Reference
Aetheca wagneri	Various mice	≥30% 79%	6% (18) 1% (185)	49 (49) 3 (3)	5% (ND) 0% (ND)	71 45
Ctenocephalides felis	Domestic cats	≥85% 93%	0% (14)[b] 0.6% (174)	ND 2 (2)	ND 0% (ND)	125 39
Echidnophaga gallinaceus	Poultry	80%	23% (48)[c]	ND	23% ND	17
Epitedia wenmanni	Deer mice	≥36%	12% (48)	30 (15–61)	18% (ND)	71
Eumolpianus eumolpi	Chipmunks	26%	6% (31)	78 (78)	ND	50
Hoplopsyllus anomalus	Ground squirrels	23%	20% (5)	35 (35)	ND	50
Hystrichopsylla linsdalei	Voles, mice	≥57%	4% (84)	ND	20% (ND)	72
Malaraeus telchinum	Mice, jumping mice, voles	≥17%	4% (115)[c]	23 (4–38)	0% (ND)	17
Megabothris abantis	Mice, jumping mice, voles	≥40% ≥75%	3% (75) 12% (8)	24 (22–26) 28 (9–47)	12% (17)[c] 37% (ND)	17 71
Nosopsyllus fasciatus	Domestic mice and rats	≥42% 26%	13% (47)[c] 20% (51)	20 (11–29) 41 (41)	23% (16)[c] ND	17 50
Opisodasys nesiotis	Deer mice	≥54%	4% (46)[c]	14 (5–19)	22% (8)[c]	17
Orchopeas sexdentatus	Wood rats	≥70% 28%	9% (53)[c] 6% (81)	11 (6–15) 38 (38)	28% (7)[c] ND	17 50
Oropsylla bruneri	Ground squirrels	61%	50% (8)	30 (21–34)	ND	101
Oropsylla hirsuta	Prairie dogs	28% 100%	4% (70) 5.2% (~270)	102 (102) 1 (1)	ND 0% (ND)	50 127
Oropsylla idahoensis	Various rodents	≥7%	0% (61)[b]	ND	0% (ND)	17
Oropsylla labis	Ground squirrels, prairie dogs	24% 24%	8% (178) 10% (~60)	35(35) ND	ND ND	50 69
Oropsylla montana	Ground squirrels	≥25% ≥73% ≥35% 84% 20% ≥51% 85% 20% 96% 100% 100% 100%	1.5% (66)[c] 2% (446)[c] 4% (65) 48% (67) 11% (19) 2% (196)[c] 52% (41) 11% (~20) ND >10% (317) >11% (48) 10% (69)	4 (4) ND ND 10 (3–27) 53 (53) 23 (4–37) ND ND 10 (4–20) <1 (<1) 1 (1) 1 (1)	3% (8)[c] ND 13% ND ND ND ND ND ND ND 0% (ND) 0% (ND) 0% (ND)	17 64 71 125 50 48 123 69 32 38 39 45
Oropsylla rupestris	Ground squirrels	42%	67% (3)	28 (28)	ND	50
Oropsylla tuberculata	Ground squirrels, prairie dogs	33%	10% (10)	32 (32)	ND	50
Oropsylla tuberculata cynomuris	Ground squirrels, prairie dogs	>88%	17% (~256)	1 (1)	0% (ND)	128

(*Continued*)

Table 1 (*Continued*)

Flea species	Natural hosts in North America	Pathogen-acquisition efficiency	Vector efficiency (number of fleas used)	Mean number of days for EIP (range)	Likelihood of infected fleas blocking (mean days to block)	Reference
Pleochaetis exilis	Grasshopper mice	≥42%	25% (8)	12.5 (12–13)	25% (ND)	71
Polygenis gwyni	Cotton rats	≥83%	27% (88)[c]	ND (2–23)	67% (ND)	64
Pulex irritans	Various mammals	≥31%	0% (57)[b,c]	ND	2% (11)[c]	17
Thrassis acamantis	Marmots	29%	13% (8)	7 (7)	ND	50
Thrassis arizonensis	Ground squirrels	44%	5% (58)	41 (41)	ND	50
Thrassis bacchi	Ground squirrels	≥53% 24%	33% (18) 40% (10)	25 (8–46) 28 (23–32)	33% (ND) ND	71 101
Thrassis fotus	Ground squirrels	≥47%	20% (10)	22 (15–28)	30% (ND)	71
Thrassis francisi	Ground squirrels	14%	19% (21)	27 (27)	ND	50
Thrassis pandorae	Ground squirrels	18% 18%	10% (58) 10% (~20)	45 (45) ND	ND ND	50 69
Xenopsylla cheopis	Domestic rats	72% >70% 100% 38% 54% 97% 96% 77% 96% ~75% 63% 96% 98%	38% (53) 13% (95) 6.4% (103) 20% (140) 33% (27) 72% (29) 30% (47) 48% (79) 69% (29) 45% (31) 38% (34) ND 29% (49)	12 (5–18) 16 (6–32) 1 (1) 21 (21) 21 (21) ND 16 (6–33) 22 (11–49) ND 14 (7–28) <14 16 (6–34) ND	58% (12) 2% (19) 0% (ND) ND 60% (10–40) 77% (ND) ND 70% (ND) 79% (5–30) 38% (14) ND ND ND	17 48 47 50 72 73 125 71 74 83 64 32 123

[a]Including data on pathogen-acquisition efficiency (percentage of fleas infected after feeding on an infected host), vector efficiency (percentage of infected fleas that transmit *Y. pestis*), time elapsed between *Y. pestis* acquisition and transmission [i.e., extrinsic incubation period (EIP)], and likelihood and timing of infected fleas becoming blocked. Previously published in the *Journal of Medical Entomology* (40).

[b]Transmission demonstrated only in mass-feeding experiments.

[c]Assuming that all fleas were infected.

ND, not determined.

basis of flea-infestation rates observed in the field, this mode of transmission could be sufficient to explain epizootic transmission for some flea species (38, 47, 127, 128).

Summary of Key Vertebrate Species Involved in Transmission Cycles

Although plague is primarily a disease of rodents, nearly all mammals can become infected with *Y. pestis*, but the response to infection differs between species or within populations of the same species (10, 56). As reviewed recently (42, 56), there are several theories to explain how *Y. pestis* is maintained during epizootic and interepizootic periods. Some have proposed that plague bacteria

are maintained in enzootic cycles by host species that display a heterogeneous response to infection. Within a population of "maintenance" or enzootic hosts, some individuals are highly susceptible to infection and harbor the very high concentrations of bacteria required for flea-borne transmission prior to perishing from the infection. As a result, fleas infesting these hosts acquire infection, and host death forces them to seek new hosts, thus perpetuating the transmission cycle. Other individuals in the same population may be capable of mounting a sufficient immune response to survive the infection. These immune hosts serve to slow the rate of transmission within the host population. Epizootics, or periods of rapid spread, are believed to occur when infectious fleas spill over from enzootic cycles into populations of highly susceptible epizootic or "amplifying" host populations. In contrast, others have proposed that plague could be maintained within epizootic host populations (not requiring multiple-species involvement) if the spatial structure of populations is sufficient. For example, a metapopulation structure that consists of several local populations connected via host or flea movement may allow for long-term persistence of plague bacteria through a series of local extinctions followed by recolonization. Across plague foci, host-flea complexes involved in *Y. pestis* transmission vary. A summary of such complexes was presented by Gratz (58) and is summarized in **Table 2**.

Summary of Key Flea Species Involved in Pathogen Transmission

Naturally acquired *Y. pestis* infections have been reported from approximately 250 flea species (40, 100, 111). However, only a small fraction of these are considered to be efficient vectors—that is, they (*a*) become infected after feeding on a bacteremic host, (*b*) live long enough for the bacteria to multiply to sufficient numbers to ensure transmission, and (*c*) are able to transfer *Y. pestis* to a susceptible host at concentrations adequate to cause infection (40, 58). In addition to possessing the ability to acquire, maintain, and transmit plague bacteria, the probability of a flea playing a key role in maintaining enzootic transmission cycles or serving as a bridging vector either between rodent species or from zoonotic hosts to humans is dependent on (*a*) how efficiently the infected flea is able to transfer bacteria to the host, (*b*) host preferences, (*c*) infestation rates, (*d*) the length of the extrinsic incubation period (i.e., the time period from when a flea becomes infected to when it is able to transmit), (*e*) the length of time an infected flea remains infectious in the presence or absence of subsequent blood meals, and (*f*) the flea's daily biting rate (40). For example, *X. cheopis* is considered a highly efficient vector, as it is capable of transmission by early-phase and classical mechanisms (17, 32, 47, 48, 50, 64, 71–74, 83, 123, 125). Thus, fairly low numbers of these rat fleas per host are required to maintain transmission cycles. Although they feed primarily on commensal rats, they also infest sylvatic rodents; thus, this flea has been implicated in enzootic transmission and as a bridging vector between rodent host species. In addition, the flea is common in human dwellings, readily bites humans, and has been implicated as a bridging vector to humans from zoonotic cycles (4, 50, 58, 63, 100). By contrast, cat fleas (*Ctenocephalides felis*) are commonly encountered in human dwellings within some plague foci, but they are inefficient vectors of *Y. pestis* and are rarely collected from commensal or sylvatic rodent hosts. Thus, they are unlikely to serve as bridging vectors or play a major role in plague epidemics or epizootics (4, 58)

A recent review of vector competency and efficiency studies for North American fleas revealed that among the approximately 230 species described in the western United States, only approximately 28 have been laboratory-confirmed vectors of *Y. pestis* (40) (for a summary of those studies, see **Table 2**). Most of these studies focused on flea species that were abundant on hosts affected by plague as the pathogen spread eastward in the United States during the first half of the twentieth century. It is quite likely that many more species are capable of serving as vectors of *Y. pestis*, but their competency to do so has not been evaluated in the laboratory. Furthermore, among the

Table 2 Primary rodent hosts and flea vectors of *Yersinia pestis* within established plague foci[a]

Plague focus (countries)	Rodent hosts	Flea vectors
Southern Africa (South Africa, Lesotho, Namibia, Zimbabwe)	*Tatera afra* *Tatera brantsi* *Tatera leucogaster* *Otomys irroratus* *Mastomys coucha* *Mastomys natalensis* *Rattus rattus* *Rhabdomys pumilio*	*Dinopsyllus ellobius* *Xenopsylla brasiliensis* *Xenopsylla cheopis* *Xenopsylla philoxera*
East Africa (Kenya, Tanzania, Uganda, Mozambique, Madagascar)	*Arvicanthis abyssinicus* *Arvicanthis niloticus* *Cricetomys gambianus* *Grammomys dloichurus* *Lemniscomys striatus* *Lophuromys flavopunctatus* *Lophuromys sikapusi* *Mastomys natalensis* *Otomys angoniensis* *Otomys denti* *Pelomys fallax* *Petrodromus tetradactylus* *Rattus rattus* *Rhabdomys pumilio* *Tatera robusta*	*Ctenophthalmus bacopus* *Ctenophthalmus cabirus* *Dinopsyllus lypusus* *Pulex irritans* *Xenopsylla brasiliensis* *Xenopsylla cheopis*
Central Africa (Democratic Republic of Congo)	*Arvicanthis abyssinicus* *Lemniscomys striatus* *Mastomys natalensis* *Rattus rattus*	*Ctenophthalmus cabirus* *Ctenophthalmus phyris* *Dinopsyllus lypusus* *Xenopsylla brasiliensis*
Northwest Africa (Mauritania)	*Gerbillus gerbillus* *Gerbillus nanus* *Jaculus jaculus* *Psammomys obesus*	*Synosternus cleopatrae* *Xenopsylla cheopis* *Xenopsylla ramesis* *Xenopsylla nubica*
North Africa (Libya)	*Gerbillus gerbillus* *Meriones shawi*	*Nosopsylla henleyi* *Xenopsylla cheopis* *Xenopsylla ramesis* *Xenopsylla taractes*
Arabian Peninsula (Yemen)	*Meriones rex* *Rattus rattus*	–
Southwestern Asia (Iran)	*Meriones tristrami* *Meriones vinogradovi* *Tatera indica*	*Stenoponia tripectinata* *Xenopsylla buxtoni*
Russian Federation and former Soviet Republics (northwest Caspian focus, focus between the Volga River and the Ural Mountains, focus on the left bank of the Ural River, focus in the Transcaucasia, central Asian desert focus, Tian-Shan focus, Pamir-Alai focus, Transbaikalian focus, High Altai and Tuva Autonomous Region focus)	*Citellus dauricus* *Citellus pygmaeus* *Citellus undulatus* *Marmota babacina* *Marmota caudata* *Marmota sibirica* *Meriones libycus erythrourus* *Meriones meridianus*	*Ceratophyllus caspius* *Ceratophyllus laeviceps* *Ceratophyllus lebedwi* *Ceratophyllus tesquorum* *Ctenophthalmus teres* *Ctenophthalmus wladimiri* *Frontopsylla luculenta* *Neopsylla setosa*

(*Continued*)

Table 2 (*Continued*)

Plague focus (countries)	Rodent hosts	Flea vectors
	Meriones tamariscinus *Microtus arvalis* *Putorius eversmanni* *Rhombomys opimus*	*Oropsylla silantiewi* *Rhadinopsylla cedestis* *Rhadinopsylla ventricosa* *Xenopsylla conformis* *Xenopsylla gerbilli* *Xenopsylla hirtipes* *Xenopsylla nuttalli* *Xenopsylla skrjabini*
Southeast Asia and the Western Pacific (India, Nepal, Myanmar, Indonesia, Vietnam, China)	*Apodemus chevrieri* *Apodemus speciosus* *Bandicota bengalensis* *Eothenomys miletus* *Marmota bobac* *Marmota baibacina* *Marmota caudata* *Marmota himalayana* *Meriones unguiculatus* *Microtus brandti* *Rattus exulans* *Rattus flavipectus* *Rattus nitidus* *Rattus norvegicus* *Rattus rattus* *Spermophilus alaschanicus* *Spermophilus dauricus* *Spermophilus undulatus* *Suncus murinus* *Tatera indica*	*Amphipsylla primaries* *Callopsylla dolabris* *Citellophilus tesquorum* *Citellophilus sungaris* *Ctenophthalmus quadrates* *Frontopsylla luculenta* *Neopsylla pleskei* *Neopsylla specialis* *Nosopsyllus fasciatus* *Nosopsyllus laeviceps* *Oropsylla silantiewi* *Rhadinopsylla li* *Pulex irritans* *Xenopsylla astia* *Xenopsylla brasiliensis* *Xenopsylla cheopis* *Xenopsylla conformis*
North America (United States)	*Cynomys gunnisoni* *Cynomys ludovicianus* *Cynomys leucurus* *Cynomys parvidens* *Eutamias* spp. *Neotoma* spp. *Spermophilus beecheyi* *Spermophilus variegatus*	*Hoplopsyllus anomalous* *Orchopeas sexdentatus* *Oropsylla montana* *Oropsylla hirsuta* *Oropsylla tuberculata*
South America (Bolivia, Brazil, Ecuador, Peru)	*Akodon mollis* *Galea musteloides* *Graomys griseoflavus* *Oryzomys andinus* *Oryzomys xanthaeolus* *Rattus rattus* *Sciurus stramineus* *Zygodontomys lasiurus pixuna*	*Polygenis litargus* *Xenopsylla cheopis*

[a]Data were tabulated using primary references cited in Reference 58.

species that have been examined, many of these studies focused on transmission via the classical blockage mechanism, and early-phase time points were often not evaluated. In short, it is quite likely that the list of plague vectors is considerably longer than what has been described to date, and when early-phase time points are considered, transmission efficiency for some flea species may be higher than initially realized.

MURINE TYPHUS (*RICKETTSIA TYPHI*)

Overview of Murine Typhus Epidemiology and Ecology

Murine typhus, also called flea-borne or endemic typhus, is a rickettsial illness caused by infection with the typhus group rickettsia, *Rickettsia typhi* (formerly *Rickettsia mooseri*) (5). The disease is widespread and occurs in many, if not most, areas where commensal rats (*Rattus rattus* and closely allied species as well as *Rattus norvegicus*) and the Oriental rat flea (*X. cheopis*) are found. In the past, thousands of cases occurred in the warmer southern regions of the United States, but this number has decreased to only a few hundred in recent decades, most of which occur in Texas, California, and Hawaii (2, 22, 85). Similar reductions in the incidence of this disease appear to have occurred in other developed countries in temperate zones. Although associated primarily with commensal rats and rat fleas (5, 116), *R. typhi* also is reported to occur in extramurine maintenance cycles involving such hosts and vectors as opossums (*Didelphis virginiana*) and cat fleas (*Ctenocephalides felis*), respectively (129). Murine typhus in humans is often relatively mild compared with louse-borne typhus, a disease caused by another related rickettsiae (*Rickettsia prowazekii*) (35). Typically, cases can be treated successfully with antibiotics, although fatalities occasionally occur, most often among elderly patients (5). Common signs and symptoms include a characteristic rickettsial rash (macular in appearance), fever, headache, chills, achiness, and prostration. Respiratory and gastrointestinal symptoms are not uncommon and multiorgan involvement is often indicated by abnormal laboratory findings in hematologic, respiratory, hepatic, and renal system tests. In addition to flea-bite exposures, humans reportedly have become infected through airborne exposures, presumably as a result of inhaling infectious flea fecal material in dust (116).

Pathogen Development within the Vertebrate Host

Upon invading the vertebrate host, *R. typhi* invades the endothelial cells lining the blood vessels of its host (119). Once inside these host cells, murine typhus rickettsia, which are obligate intracellular bacteria, multiply until they cause their host cells to burst, releasing large numbers of rickettsiae into the bloodstream where they can infect other endothelial cells or be picked up by a feeding flea vector. As more endothelial cells within capillary vessels are destroyed, blood cells leak from the vessels, resulting in the typical macular rash of murine typhus and causing pathological complications including detectable hemorrhaging, hypotension, and renal dysfunction in severe cases.

Mechanisms of Flea-Borne Transmission

Unlike many vector-borne disease agents, *R. typhi* can gain entry to its vertebrate hosts through contamination with infectious flea feces at the location of flea feeding, a process that can be aided by host rubbing or scratching of the bite site or transferring infectious rickettsia on contaminated fingers or other objects to mucus membranes or conjunctiva (5). Some have reported that infection also can occur directly from flea bites, although the importance of this route remains uncertain (8, 51). When a competent reservoir host becomes infected, the rickettsiae multiply in the endothelial

cells of the host's vasculature, resulting in the eventual destruction of infected cells and the release of large numbers of *R. typhi* into the host's bloodstream. Upon ingestion by a blood-feeding flea, the rickettsiae pass to the flea's midgut where they invade and multiply within epithelial cells. As occurs in the vertebrate host endothelial cells, proliferation of *R. typhi* in midgut epithelium cells eventually results in the destruction of these cells and release of hundreds of rickettsiae into the midgut lumen for each cell destroyed. Midgut infections typically begin at a particular focal point, and they eventually spread until most midgut epithelial cells are infected. Despite the large proportion of midgut epithelial cells infected, *R. typhi* seems to cause little damage to its flea vector, as indicated by the fact that fleas become infected for life and yet do not appear to suffer significant decreases in longevity or reproductive output (5). Presumably this is in part due to the fact that the epithelial layer in the flea's midgut is replaced at a sufficiently rapid rate to overcome any pathogenic effects of *R. typhi* infection. Once *R. typhi* burst from infected epithelial cells into the lumen of the midgut, a process that usually takes 3 to 4 days to become detectable, they can be incorporated into and shed with the flea's feces, which are infectious for mammalian hosts and the source of infection for most cases of murine typhus. Typically, fleas can become infectious approximately 10 days after acquiring infection and can remain infectious throughout the remainder of their adult lives. Although maintenance of *R. typhi* is thought to occur primarily through flea to vertebrate host to flea transmission, this rickettsia has been reported to invade the ovary tissues of female fleas, reportedly resulting in transovarial transmission (52).

Summary of Key Vertebrate Species Involved in Transmission Cycles

In most instances, commensal rats are the primary vertebrate species involved in local transmission cycles of *R. typhi*. These rats serve not only as blood meal sources for fleas, but also as amplifying hosts for infecting fleas with *R. typhi*. Although evidence of *R. typhi* infection in nonmurine vertebrate hosts has been reported, the importance of extramurine cycles of *R. typhi* remains unclear (5, 116). Infection of opossums (*Didelphis virginiana*) has been reported in the United States, and these animals appear to be epidemiologically important in Texas and California and serve as primary vertebrate hosts for extramurine transmission cycles in these areas. In California, cats frequently have been found to have *R. typhi* antibodies and may be important hosts in this state as well as other areas (22). Elsewhere in the world, murine rodents other than *Rattus* spp., including the African giant pouched rat (*Cricetomys gambiae*), have been suggested to play roles in local *R. typhi* cycles (5, 7, 116).

Summary of Key Flea Species Involved in Pathogen Transmission

X. cheopis is the primary vector of *R. typhi* in most locations around the world. Other flea species, however, have been demonstrated to transmit *R. typhi* under experimental conditions or have been found infected under natural conditions (5, 116) and may be locally important vectors. Among the ten flea species identified by Azad (5) as potential vectors, eight frequently occur on rats. In addition to *X. cheopis*, two other *Xenopsylla* species (*X. astia* and *X. brasiliensis*) appear to be effective vectors. The northern rat flea (*Nosopsyllus fasciatus*), which is common on commensal rats in temperate latitudes, becomes infected with *R. typhi* and could transmit this rickettsia among rats, but most epidemiological evidence suggest this flea plays little role in the transmission of murine typhus to humans. The widespread flea *Leptopsylla segnis*, which occurs on house mice and rats, has been found infected with *R. typhi* and can support multiplication of this rickettsia in its midgut. Another flea species, *Pulex irritans*, which is often called the human flea, is rarely found on rats and occurs most commonly on larger animals, such as carnivores, pigs and certain other

ungulates, as well as opossums. This species is an efficient vector for *R. typhi* under laboratory conditions, but its lack of association with rats under natural conditions makes it unlikely to be an important vector in most locations. It should be noted, however, that *P. irritans* is found fairly often on opossums, and as previously stated, these animals have been implicated as natural hosts in Texas and California. Probably the best evidence that a nonmurine-infesting flea can serve as a significant vector of *R. typhi* is provided by studies done in Texas and California on extramurine cycles involving opossums and cat fleas (*Ctenocephalides felis*) (6, 22). In addition to being found frequently infected with *R. typhi* in nature, this flea is also a competent vector of *R. typhi* under laboratory conditions (52).

RICKETTSIA FELIS

R. felis is a relatively recently identified rickettsial species that was initially referred to as the ELB agent (so termed for the EL Laboratory in Soquel, California) following its identification in a cat flea colony (1). First believed to be a typhus or spotted fever group rickettsia, more recent phylogenetic analyses have placed *R. felis* in a genetically distinct "transitional group" of rickettsiae (57). Further studies have found this rickettsial species to be nearly worldwide in its distribution, an observation attributed by some to its association with the similarly cosmopolitan cat flea (103). Although genetically distinct from *R. typhi*, *R. felis* has been identified in patients suffering murine typhus-like illnesses, frequently accompanied by an eruption or eschar (96, 97, 105), suggesting that the pathology of *R. felis* infections may be similar to that of other rickettsial infections and primarily related to the destruction of endothelial cells lining the host's blood vessels. A serosurvey of humans in Spain indicated that 7.1% of humans tested in the study area were seropositive for *R. felis* antibodies, suggesting human infection with this rickettsia is common but under-recognized (103).

At present, relatively little is known about the ecology and epidemiology of *R. felis* and *R. felis*–related illness. Presumably, humans acquire infection following exposure to infectious cat fleas or perhaps other infected flea species, including *Ctenocephalides canis*, that at least occasionally feed on humans. Despite its widespread association with cat fleas, *R. felis* has been identified in a variety of other flea species, including those that normally feed on domestic animals, rodents, insectivores and marsupials (97, 103). These other fleas include widespread species with low host specificity such as *C. canis*, *P. irritans*, *Echidnophaga gallinacea*, and *Tunga penetrans*, as well as rat fleas (*X. cheopis* and *X. brasiliensis*) and other fleas of rodents or insectivores (*Archaeopsylla erinacei*, *Anomiopsyllus nudata*, *Polygenis atopus*, *Ctenophthalmus* sp., and other unidentified rodent fleas). Although the distribution of *R. felis* is commonly assumed to coincide closely with that of the cat flea, other flea species have been found infected in sites that have few, if any, cat fleas (113), suggesting that *R. felis* is either more widespread than currently believed or perhaps consists of multiple genotypes, including some that are not closely associated with cat fleas. Ticks also have been reported to be naturally infected, but the significance of these reports remains to be demonstrated (103). Although laboratory transmission by cat fleas or other potential vectors through exposure of vertebrate hosts to infectious flea bites or flea feces, and subsequent recovery of viable *R. felis* from these hosts, has yet to be demonstrated, it is inferred on the basis of the identification of wild-caught mammals that are seropositive for *R. felis* antibodies and experiments demonstrating the appearance of *R. felis* antibodies and polymerase chain reaction (PCR)-positive blood samples from cats that had been fed upon by *R. felis*–infected cat fleas (103). Among the mammalian species found to be seropositive or PCR positive in nature are the Virginia opossum, cats, and dogs (103). Other mammalian species harboring *R. felis*–infested fleas also may become infected, but this has yet to be demonstrated. In addition to any flea to mammal to flea transmission that may occur, *R. felis*

also can be transmitted transovarially for at least 12 generations without feeding on infectious, rickettsemic hosts, suggesting such transmission is important for the maintenance of this rickettsia in nature (121). No evidence for sexual transmission between male and female fleas was observed in these studies. Experiments to test whether *R. felis* could be transmitted from flea to flea through feeding of flea larvae on infectious flea feces also failed to yield positive results (103). Within the flea, *R. felis* has been identified in cells of the midgut epithelium, muscles, fat bodies, ovaries, tracheal matrix, epithelial sheath of the testes, and salivary glands (103). Identification of *R. felis* in salivary gland tissue suggests that secretion of infectious saliva during feeding is a possible mode of transmission to mammalian hosts, but this awaits confirmation. Another potential mode of horizontal transmission may be infectious cofeeding involving infected and uninfected fleas feeding in close proximity to each other, a process that has been reported for tick-borne viruses and *Borrelia burgdorferi* (103).

BARTONELLOSIS

Bartonella is a gram-negative bacteria that infects primarily red blood cells but can also be found associated with host endothelial, dendritic, and CD34+ cells, which include lymphopoietic stem and progenitor cells, small-vessel endothelial cells, and embryonic fibroblasts (13). Of the more than 20 species described, more than half infect either healthy or immune-compromised humans (88). Among the most important of these are the causative agents of three well-characterized illnesses: Oroya fever (*Bartonella bacilliformis*), trench fever (*Bartonella quintana*) and cat scratch disease (*B. henselae*). Among these three diseases, only the last is believed to be transmitted by fleas, although *B. henselae* can also be spread by the bites or scratches of infected cats (87). Typical symptoms of cat scratch infection include an erythema or pustule at the site of inoculation, fever, mild headache, and regional lymphadenopathy that can persist for several months. Occasionally (5–15% of cases), cases experience more severe complications, including encephalitis, retinitis, and endocarditis (87). Other *Bartonella* species, including those associated with rodents, rabbits, and dogs or cats also have been implicated as likely sources of human illness owing to their association with cases of endocarditis, retinitis, septicemia, myocarditis, and illnesses that appear very similar to cat scratch disease (13, 88). In addition, newly recognized species continue to be implicated as human pathogens, as demonstrated by the recent isolation and characterization of *Bartonella tamiae* from human patients in Thailand (76).

An even greater array of new genospecies continues to be described from a wide variety of mammal species, including various rodents, bats, insectivores, wild and domestic ungulates, and carnivores (13, 20, 75). Even nonmammalian species, such as loggerhead sea turtles, reportedly are infected with species of *Bartonella* (13), suggesting that these microbes are among the most widely distributed blood-associated bacteria in the world. What is less certain, however, is the medical and ecological significance of this wide diversity of species. Although some are pathogenic, others are collected from apparently healthy hosts who appear to be suffering few, if any, ill effects as a result of their infections. As noted for *R. felis*, much remains to be learned about how these bacteria are transmitted and maintained in nature. Although arthropod vectors have been implicated as sources of transmission for a few species, this is not true for most. The relative importance of vector-borne and other modes of transmission, such as scratching or biting by the host, also has yet to be determined for many species, including *B. henselae*, which apparently can spread through flea bites, cat bites, and cat scratches.

The list of flea species found naturally infected with various species of *Bartonella* continues to grow, but as noted by Billeter et al. (13), who reviewed this evidence, it is difficult to evaluate the significance of many of these reports because blood-feeding arthropods, including fleas, would be

expected to ingest large numbers of *Bartonella* as a result of this bacteria's utilization of erythrocytes as their primary host cells. Nevertheless, there is an emerging body of experimental evidence indicating that fleas are vectors of some species of *Bartonella* (13). *Bartonella* sp. also appear to be important members of the microbial communities naturally found infecting fleas (70), although their effects on these fleas remain unknown. When cat fleas collected from bacteremic, commercially reared cats were placed on kittens demonstrated to be free of detectable *B. henselae* infections, the kittens became bacteremic (21). Unfortunately, a similar group of control kittens were not maintained in the absence of fleas to ensure that they were free of *B. henselae* infection prior to the experiment. Despite this problem, it seems likely that *C. felis* did transmit *B. henselae* to the susceptible kittens. In another experiment, *B. henselae* was transmitted to cats through inoculation of infectious fleas feces, suggesting this species can be transmitted in a manner similar to that observed for the murine typhus rickettsia (54). These results also suggest that humans could become infected with *B. henselae* as a result of being scratched by a cat that had claws contaminated by *B. henselae*–containing flea feces (53). In another study, wild-caught rodent fleas (*Ctenophthalmus nobilis nobilis*) removed from wild bank voles were later able to transmit both *Bartonella grahamii* and *Bartonella taylorii* to laboratory-reared bank voles over a period of four weeks, as indicated by the fact that 21 of 28 voles developed PCR-detectable *Bartonella* bacteremias involving one or both of these bacteria (14).

TULAREMIA (*FRANCISELLA TULARENSIS*)

Tularemia is a bacterial zoonosis of rodents and lagomorphs caused by infection with *Francisella tularensis*. Cases in humans can be serious, although fatality rates are typically less than 5%. Common symptoms include fever, swollen and painful lymph glands, and skin ulcers that are often located at the site of an arthropod bite. The disease can be transmitted not only through arthropod bites, but also by direct contact with body fluids of infected animals, ingestion of contaminated food or water, or, rarely, by inhalation of infectious materials. The most important vectors are ticks and deer flies. Fleas appear to play little role in transmitting tularemia under natural conditions. However, fleas have been reported to be capable of transmitting *F. tularensis* infrequently under some circumstances (67), presumably through mechanical transmission, as demonstrated by one study that reported positive results in only 6 of 116 experiments performed with fleas and another study where transmission occurred only within the first five days after fleas had taken an infectious blood meal (68).

SUMMARY POINTS

1. In the past decade, associations between plague risk and environmental variables have been quantified within a statistical framework and used to generate predictive risk models.
2. For nearly a century, the dominant theory in the medical entomology literature for transmission of *Y. pestis* was based on the blocked flea model. Recently, studies have demonstrated that blockage is not required for efficient transmission and that the extrinsic incubation period is shorter than previously assumed. This mode of transmission, termed early-phase transmission, provides an explanation for how plague spreads so rapidly during epizootic periods. The exact mechanism by which early-phase transmission occurs has not yet been defined.

3. *R. felis* is a recently identified rickettsial species that has a worldwide distribution. Serosurveys suggest that human infections with this agent are common but under-recognized. Laboratory-based transmission studies have not yet conclusively demonstrated vector competence of cat fleas or other vector species. Furthermore, it is largely unknown how *R. felis* is maintained in enzootic cycles.
4. Among the numerous *Bartonella* species described to date, only a few have been implicated as disease agents in humans, and only one of these, *B. henselae*, is believed to be flea borne. *Bartonella* species may be the most widely distributed blood-associated bacteria in the world, but their medical and ecological significance is uncertain.

DISCLOSURE STATEMENT

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LITERATURE CITED

1. Adams JR, Schmidtmann ET, Azad AF. 1990. Infection of colonized cat fleas, *Ctenocephalides felis* (Bouche), with a rickettsia-like microorganism. *Am. J. Trop. Med. Hyg.* 43:400–9
2. Adjemian J, Parks S, McElroy K, Campbell J, Eremeeva ME, et al. 2010. Murine Typhus in Austin, Texas, USA, 2008. *Emerg. Infect. Dis.* 16:412–17
3. Adjemian JZ, Foley P, Gage KL, Foley JE. 2007. Initiation and spread of traveling waves of plague, *Yersinia pestis*, in the western United States. *Am. J. Trop. Med. Hyg.* 76:365–75
4. Amatre G, Babi N, Enscore RE, Ogen-Odoi A, Atiku LA, et al. 2009. Flea diversity and infestation prevalence on rodents in a plague-endemic region of Uganda. *Am. J. Trop. Med. Hyg.* 81:718–24
5. Azad AF. 1990. Epidemiology of murine typhus. *Annu. Rev. Entomol.* 35:553–69
6. Azad AF, Beard CB. 1998. Rickettsial pathogens and their arthropod vectors. *Emerg. Infect. Dis.* 4:179–86
7. **Azad AF, Radulovic S, Higgins JA, Noden BH, Troyer JM. 1997. Flea-borne rickettsioses: ecologic considerations. *Emerg. Infect. Dis.* 3:319–27**
8. Azad AF, Traub R. 1989. Experimental transmission of murine typhus by *Xenopsylla cheopis* flea bites. *Med. Vet. Entomol.* 3:429–33
9. Bacot AW, Martin CJ. 1914. Observations on the mechanism of the transmission of plague by fleas. *J. Hyg.* 13(Plague Suppl. III):423–39
10. Barnes AM. 1982. Surveillance and control of bubonic plague in the United States. *Symp. Zool. Soc. Lond.* 50:237–70
11. Ben Ari T, Gershunov A, Gage KL, Snall T, Ettestad P, et al. 2008. Human plague in the USA: the importance of regional and local climate. *Biol. Lett.* 4:737–40
12. Bibikova VA. 1977. Contemporary views on the interrelationships between fleas and the pathogens of human and animal diseases. *Annu. Rev. Entomol.* 22:23–32
13. **Billeter SA, Levy MG, Chomel BB, Breitschwerdt EB. 2008. Vector transmission of *Bartonella* species with emphasis on the potential for tick transmission. *Med. Vet. Entomol.* 22:1–15**
14. Bown KJ, Bennett M, Begon M. 2004. Flea-borne *Bartonella grahamii* and *Bartonella taylorii* in bank voles. *Emerg. Infect. Dis.* 10:684–87
15. Brault AC. 2009. Changing patterns of West Nile virus transmission: altered vector competence and host susceptibility. *Vet. Res.* 40:43
16. Brown HE, Ettestad P, Reynolds PJ, Brown TL, Hatton ES, et al. 2010. Climatic predictors of the intra- and inter-annual distributions of plague cases in New Mexico based on 29 years of animal-based surveillance data. *Am. J. Trop. Med. Hyg.* 82:95–102

7. Reviews the ecology and transmission of *R. typhi* and provides early observations on *R. felis* and its ecology and potential role in human disease.

13. Summarizes the limited amount of information known about the transmission of *Bartonella* by fleas and other arthropods.

17. Burroughs AL. 1947. Sylvatic plague studies: the vector efficiency of nine species of fleas compared with *Xenopsylla cheopis*. *J. Hyg.* 43:371–96
18. Cavanaugh DC, Marshall JD. 1972. The influence of climate on the seasonal prevalence of plague in the Republic of Vietnam. *J. Wildl. Dis.* 8:85–93
19. Cavanaugh DC, Williams JE. 1980. Plague: some ecological interrelationships. In *Fleas*, ed. R Traub, H Starcke, pp. 245–56. Rotterdam: AA Balkema
20. Chomel BB, Kasten RW. 2010. Bartonellosis, an increasingly recognized zoonosis. *J. Appl. Microbiol.* 109:743–50
21. Chomel BB, Kasten RW, Floyd-Hawkins K, Chi B, Yamamoto K, et al. 1996. Experimental transmission of *Bartonella henselae* by the cat flea. *J. Clin. Microbiol.* 34:1952–56
22. Civen R, Ngo V. 2008. Murine typhus: an unrecognized suburban vectorborne disease. *Clin. Infect. Dis.* 46:913–18
23. Collinge SK, Johnson WC, Ray C, Matchett R, Grensten J, et al. 2005. Testing the generality of the trophic-cascade model for plague. *Ecohealth* 2:102–12
24. Collinge SK, Johnson WC, Ray C, Matchett R, Grensten J, et al. 2005. Landscape structure and plague occurrence in black-tailed prairie dogs on grasslands of the western USA. *Landsc. Ecol.* 20:941–55
25. Crook LD, Tempest B. 1992. Plague. A clinical review of 27 cases. *Arch. Intern. Med.* 152:1253–56
26. Davis DHS. 1953. Plague in Africa from 1935 to 1949: a survey of wild rodents in African territories. *Bull. WHO* 9:655–700
27. Davis S, Begon M, De Bruyn L, Ageyev VS, Klassovskiy NL, et al. 2004. Predictive thresholds for plague in Kazakhstan. *Science* 304:736–38
28. Davis S, Klassovskiy N, Ageyev V, Suleimenov B, Atshabar B, et al. 2007. Plague metapopulation dynamics in a natural reservoir: the burrow system as the unit of study. *Epidemiol. Infect.* 135:740–48
29. Davis S, Trapman P, Leirs H, Begon M, Heesterbeek JA. 2008. The abundance threshold for plague as a critical percolation phenomenon. *Nature* 454:634–37
30. Dennis DT, Gage KL. 2003. Plague. In *Infectious Diseases*, ed. J Cohen, WG Powderly, pp. 1641–48. London: Mosby
31. Dennis DT, Mead PS. 2010. *Yersinia* species, including plague. In *Mandell: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 17th edition*, ed. GL Mandell, JE Bennett, R Dolin, pp. 2943–49. Philadelphia: Elsevier
32. Douglas JR, Wheeler CM. 1943. Sylvatic plague studies. II. The fate of *Pasteurella pestis* in the flea. *J. Infect. Dis.* 72:18–30
33. Drancourt M, Houhamdi L, Raoult D. 2006. *Yersinia pestis* as a telluric, human ectoparasite-borne organism. *Lancet Infect. Dis.* 6:234–41
34. Du Y, Rosqvist R, Forsberg A. 2002. Role of fraction 1 antigen of *Yersinia pestis* in inhibition of phagocytosis. *Infect. Immun.* 70:1453–60
35. Dumler JS, Taylor JP, Walker DH. 1991. Clinical and laboratory features of murine typhus in south Texas, 1980 through 1987. *JAMA* 266:1365–70
36. Echenberg MJ. 2007. *Plague Ports: The Global Human Impact of Bubonic Plague 1894–1901*. New York: N.Y. Univ. Press
37. Eisen L, Eisen RJ. 2011. Using geographic information systems and decision support systems for the prediction, prevention, and control of vector-borne diseases. *Annu. Rev. Entomol.* 56:41–61
38. Eisen RJ, Bearden SW, Wilder AP, Montenieri JA, Antolin MF, Gage KL. 2006. Early-phase transmission of *Yersinia pestis* by unblocked fleas as a mechanism explaining rapidly spreading plague epizootics. *Proc. Natl. Acad. Sci. USA* 103:15380–85
39. Eisen RJ, Borchert JN, Holmes JL, Amatre G, Van Wyk K, et al. 2008. Early-phase transmission of *Yersinia pestis* by cat fleas (*Ctenocephalides felis*) and their potential roles as vectors in a plague endemic region of Uganda. *Am. J. Trop. Med. Hyg.* 78:949–56
40. Eisen RJ, Eisen L, Gage KL. 2009. Studies of vector competency and efficiency of North American fleas for *Yersinia pestis*: state of the field and future research needs. *J. Med. Entomol.* 46:737–44
41. Eisen RJ, Enscore RE, Biggerstaff BJ, Reynolds PJ, Ettestad P, et al. 2007. Human plague in the southwestern United States, 1957–2004: spatial models of elevated risk of human exposure to *Yersinia pestis*. *J. Med. Entomol.* 44:530–37

38. First to describe early-phase transmission of *Y. pestis* by unblocked fleas, noting its importance in explaining the rapid rate of spread observed during plague epizootics.

42. Eisen RJ, Gage KL. 2009. Adaptive strategies of *Yersinia pestis* to persist during inter-epizootic and epizootic periods. *Vet. Res.* 40:1

43. Eisen RJ, Glass GE, Eisen L, Cheek J, Enscore RE, et al. 2007. A spatial model of shared risk for plague and hantavirus pulmonary syndrome in the southwestern United States. *Am. J. Trop. Med. Hyg.* 77:999–1004
44. Eisen RJ, Griffith KS, Borchert JN, MacMillan K, Apangu T, et al. 2010. Assessing human risk of exposure to plague bacteria in northwestern Uganda based on remotely sensed predictors. *Am. J. Trop. Med. Hyg.* 82:904–11
45. Eisen RJ, Holmes JL, Schotthoefer AM, Vetter SM, Montenieri JA, Gage KL. 2008. Demonstration of early-phase transmission of *Yersinia pestis* by the mouse flea, *Aetheca wagneri*, and implications for the role of deer mice as enzootic reservoirs. *J. Med. Entomol.* 45:1160–64
46. Eisen RJ, Reynolds PJ, Ettestad P, Brown T, Enscore RE, et al. 2007. Residence-linked human plague in New Mexico: a habitat-suitability model. *Am. J. Trop. Med. Hyg.* 77:121–25
47. Eisen RJ, Wilder AP, Bearden SW, Montenieri JA, Gage KL. 2007. Early-phase transmission of *Yersinia pestis* by unblocked *Xenopsylla cheopis* (Siphonaptera: Pulicidae) is as efficient as transmission by blocked fleas. *J. Med. Entomol.* 44:678–82
48. Engelthaler DM, Hinnebusch BJ, Rittner CM, Gage KL. 2000. Quantitative competitive PCR as a technique for exploring flea-*Yersinia pestis* dynamics. *Am. J. Trop. Med. Hyg.* 62:552–60
49. Enscore RE, Biggerstaff BJ, Brown TL, Fulgham RE, Reynolds PJ, et al. 2002. Modeling relationships between climate and the frequency of human plague cases in the southwestern United States, 1960–1997. *Am. J. Trop. Med. Hyg.* 66:186–96
50. Eskey CR, Haas VH. 1940. Plague in the western part of the United States. *Public Health Bull.* 254:1–83
51. Fahrang-Azad A, Traub R. 1985. Transmission of murine typhus rickettsiae by *Xenopsylla cheopis*, with notes on experimental infection and effects of temperature. *Am. J. Trop. Med. Hyg.* 34:555–63
52. Fahrang-Azad A, Traub R, Baqar S. 1985. Transovarial transmission of murine typhus rickettsiae in *Xenopsylla cheopis* fleas. *Science* 227(4686):543–45
53. Finkelstein JL, Brown TP, O'Reilly KL, Wedincamp J Jr, Foil LD. 2002. Studies on the growth of *Bartonella henselae* in the cat flea (Siphonaptera: Pulicidae). *J. Med. Entomol.* 39:915–19
54. Foil L, Andress E, Freeland RL, Roy AF, Rutledge R, et al. 1998. Experimental infection of domestic cats with *Bartonella henselae* by inoculation of *Ctenocephalides felis* (Siphonaptera: Pulicidae) feces. *J. Med. Entomol.* 35:625–28
55. Gage KL, Burkot TR, Eisen RJ, Hayes EB. 2008. Climate and vectorborne diseases. *Am. J. Prev. Med.* 35:436–50
56. Gage KL, Kosoy MY. 2005. Natural history of plague: perspectives from more than a century of research. *Annu. Rev. Entomol.* 50:505–28
57. Gillespie JJ, Williams K, Shukla M, Snyder EE, Nordberg EK, et al. 2008. Rickettsia phylogenomics: unwinding the intricacies of obligate intracellular life. *PLoS One* 3:e2018
58. Gratz N. 1999. Rodent reservoirs and flea vectors of natural foci of plague. In *Plague Manual: Epidemiology, Distribution, Surveillance and Control*, pp. 63–96. Geneva: World Health Org.
59. Guinet F, Ave P, Jones L, Huerre M, Carniel E. 2008. Defective innate cell response and lymph node infiltration specify *Yersinia pestis* infection. *PLoS One* 3:e1688
60. Hayes EB, Piesman J. 2003. How can we prevent Lyme disease? *N. Engl. J. Med.* 348:2424–30
61. Hinnebusch BJ. 2005. The evolution of flea-borne transmission in *Yersinia pestis*. *Curr. Issues Mol. Biol.* 7:197–212
62. Hinnebusch BJ, Perry RD, Schwan TG. 1996. Role of the *Yersinia pestis* hemin storage (hms) locus in the transmission of plague by fleas. *Science* 273:367–70
63. Hirst LF. 1953. *The Conquest of Plague*. Oxford: Clarendon. 478 pp.
64. Holdenried R. 1952. Sylvatic plague studies: VII. Plague transmission potentials for the fleas *Diamanus montanus* and *Polygnis gwyni* compared with *Xenopsylla cheopis*. *J. Infect. Dis.* 90:131–40
65. Holt AC, Salkeld DJ, Fritz CL, Tucker JR, Gong P. 2009. Spatial analysis of plague in California: niche modeling predictions of the current distribution and potential response to climate change. *Int. J. Health Geogr.* 8:38

42. Compares competing hypotheses of how *Y. pestis* is maintained during interepizootic periods and transmitted during epizootic periods.

50. Compilation of initial studies conducted during the early twentieth century while *Y. pestis* spread across the western United States.

56. Summarizes plague ecology and evolution, *Y. pestis* transmission dynamics, and molecular biology.

61. Summarizes flea anatomy and physiology and key *Y. pestis* genes that are important for flea-borne transmission.

66. Hoogland JL, Davis S, Benson-Amram S, Labruna D, Goossens B, Hoogland MA. 2004. Pyraperm kills fleas and halts plague among Utah prairie dogs. *Southwest. Nat.* 49:376–83
67. Hopla CE. 1974. The ecology of tularemia. *Adv. Vet. Sci. Comp. Med.* 18:25–53
68. Hopla CE. 1977. *Fleas as vectors of tularemia in Alaska*. Presented at Fleas Proc. Int. Conf. Fleas, Ashton Wold, Peterborough, UK
69. Hubbard CA. 1947. *Fleas of Western North America: Their Relation to Public Health*. Ames: Iowa State Coll. Press. 533 pp.
70. Jones RT, McCormick KF, Martin AP. 2008. Bacterial communities of *Bartonella*-positive fleas: diversity and community assembly patterns. *Appl. Environ. Microbiol.* 74:1667–70
71. Kartman L, Prince FM. 1956. Studies on *Pasteurella pestis* in fleas. V. The experimental plague-vector efficiency of wild rodent fleas compared with *Xenopsylla cheopis*, together with observations on the influence of temperature. *Am. J. Trop. Med. Hyg.* 5:1058–70
72. Kartman L, Prince FM, Quan SF. 1958. Studies on *Pasteurella pestis* in fleas. VII. The plague-vector efficiency of Hystrichopsylla linsdalei compared with *Xenopsylla cheopis* under experimental conditions. *Am. J. Trop. Med. Hyg.* 7:317–22
73. Kartman L, Prince FM, Quan SF, Stark HE. 1958. New knowledge on the ecology of sylvatic plague. *Ann. N.Y. Acad. Sci.* 70:668–711
74. Kartman L, Quan SF, McManus AG. 1956. Studies on *Pasteurella pestis* in Fleas. IV. Experimental blocking of *Xenopsylla vexabilis hawaiiensis* and *Xenopsylla cheopis* with an avirulent strain. *Exp. Parasitol.* 5:435–40
75. Kosoy M, Bai Y, Lynch T, Kuzmin IV, Niezgoda M, et al. 2010. *Bartonella* spp. in bats, Kenya. *Emerg. Infect. Dis.* 16:1875–81
76. Kosoy M, Morway C, Sheff KW, Bai Y, Colborn J, et al. 2008. *Bartonella tamiae* sp. nov., a newly recognized pathogen isolated from three human patients from Thailand. *J. Clin. Microbiol.* 46:772–75
77. Krasnov BR, Shenbrot GI, Mouillot D, Khokhlova IS, Poulin R. 2006. Ecological characteristics of flea species relate to their suitability as plague vectors. *Oecologia* 149:474–81
78. Lahteenmaki K, Kukkonen M, Jaatinen S, Suomalainen M, Soranummi H, et al. 2003. *Yersinia pestis* Pla has multiple virulence-associated functions. *Adv. Exp. Med. Biol.* 529:141–45
79. Laudisoit A, Leirs H, Makundi RH, Van Dongen S, Davis S, et al. 2007. Plague and the human flea, Tanzania. *Emerg. Infect. Dis.* 13:687–93
80. Levy CE, Gage KL. 1999. Plague in the United States, 1995–1997. *Infect. Med.* 16:54–64
81. Lien-Teh W. 1926. *A Treatise on Pneumonic Plague*. Geneva: Leag. Nations
82. Link VB. 1955. A history of plague in the United States. *Public Health Monogr. 26*, Dep. Health Educ. Welf., Washington, DC
83. Lorange EA, Race BL, Sebbane F, Hinnebusch BJ. 2005. Poor vector competence of fleas and the evolution of hypervirulence in *Yersinia pestis*. *J. Infect. Dis.* 191:1907–12
84. MacMillan K, Enscore RE, Ogen-Odoi A, Borchert JN, Babi N, et al. 2011. Landscape and residential variables associated with plague-endemic villages in the West Nile region of Uganda. *Am. J. Trop. Med. Hyg.* 84:435–42
85. Manea SJ, Sasaki DM, Ikeda JK, Bruno PP. 2001. Clinical and epidemiological observations regarding the 1998 Kauai murine typhus outbreak. *Hawaii Med. J.* 60:7–11
86. McCoy GW. 1910. A note on squirrel fleas as plague carriers. *Publ. Health. Rep.* 25:465
87. McElroy KM, Blagburn BL, Breitschwerdt EB, Mead PS, McQuiston JH. 2010. Flea-associated zoonotic diseases of cats in the USA: bartonellosis, flea-borne rickettsioses, and plague. *Trends Parasitol.* 26:197–204
88. Mogollon-Pasapera E, Otvos L Jr, Giordano A, Cassone M. 2009. *Bartonella*: emerging pathogen or emerging awareness? *Int. J. Infect. Dis.* 13:3–8
89. Morelli G, Song YJ, Mazzoni CJ, Eppinger M, Roumagnac P, et al. 2010. *Yersinia pestis* genome sequencing identifies patterns of global phylogenetic diversity. *Nat. Genet.* 42:1140–51
90. Nakazawa Y, Williams R, Peterson AT, Mead P, Staples E, Gage KL. 2007. Climate change effects on plague and tularemia in the United States. *Vector-Borne Zoonotic Dis.* 7:529–40
91. Neerinckx S, Bertherat E, Leirs H. 2009. Human plague occurrences in Africa: an overview from 1877 to 2008. *Trans. R. Soc. Trop. Med. Hyg.* 104:97–103

92. Neerinckx S, Peterson AT, Gulinck H, Deckers J, Kimaro D, Leirs H. 2010. Predicting potential risk areas of human plague for the Western Usambara Mountains, Lushoto District, Tanzania. *Am. J. Trop. Med. Hyg.* 82:492–500
93. Neerinckx SB, Peterson AT, Gulinck H, Deckers J, Leirs H. 2008. Geographic distribution and ecological niche of plague in sub-Saharan Africa. *Int. J. Health Geogr.* 7:54
94. Oyston PC, Isherwood KE. 2005. The many and varied niches occupied by *Yersinia pestis* as an arthropod-vectored zoonotic pathogen. *Antonie Van Leeuwenhoek* 87:171–77
95. Parmenter RR, Yadav EP, Parmenter CA, Ettestad P, Gage KL. 1999. Incidence of plague associated with increased winter-spring precipitation in New Mexico. *Am. J. Trop. Med. Hyg.* 61:814–21
96. Parola P, Raoult D. 2006. Tropical rickettsioses. *Clin. Dermatol.* 24:191–200
97. Perez-Osorio CE, Zavala-Velazquez JE, Arias Leon JJ, Zavala-Castro JE. 2008. *Rickettsia felis* as emergent global threat for humans. *Emerg. Infect. Dis.* 14:1019–23
98. Piesman J, Eisen L. 2008. Prevention of tick-borne diseases. *Annu. Rev. Entomol.* 53:323–43
99. Poland JD, Barnes AM. 1979. Plague. In *CRC Handbook Series in Zoonoses. Section A: Bacterial, Rickettsial and Mycotic Diseases*, ed. JH Steele, 1:515–59. Boca Raton, FL: CRC Press
100. Pollitzer R. 1954. Plague. *WHO Monogr. Ser. 22*, World Health Org., Geneva, Switz. 698 pp.
101. Prince FM. 1943. Report on the fleas *Opisocrostis bruneri* (Baker) and *Thrassis bacchi* (Roths.) as vectors of plague. *Public Health Rep.* 58:1013–16
102. Quan SF, Burroughs AL, Holdenried R, Meyer KF. 1953. Studies on the prevention of experimental plague epizootics instituted among mice by infected fleas. *Estratto VI Congr. Int. Microbiol.* 5:1–4
103. Reif KE, Macaluso KR. 2009. Ecology of *Rickettsia felis*: a review. *J. Med. Entomol.* 46:723–36
104. Reisen WK. 2010. Landscape epidemiology of vector-borne diseases. *Annu. Rev. Entomol.* 55:461–83
105. Schriefer ME, Sacci JB Jr, Dumler JS, Bullen MG, Azad AF. 1994. Identification of a novel rickettsial infection in a patient diagnosed with murine typhus. *J. Clin. Microbiol.* 32:949–54
106. Sebbane F, Gardner D, Long D, Gowen BB, Hinnebusch BJ. 2005. Kinetics of disease progression and host response in a rat model of bubonic plague. *Am. J. Pathol.* 166:1427–39
107. Deleted in proof
108. Seery DB, Biggins DE, Montenieri JA, Enscore RE, Tanda DT, Gage KL. 2003. Treatment of black-tailed prairie dog burrows with deltamethrin to control fleas (Insecta: Siphonaptera) and plague. *J. Med. Entomol.* 40:718–22
109. Snall T, O'Hara RB, Ray C, Collinge SK. 2008. Climate-driven spatial dynamics of plague among prairie dog colonies. *Am. Nat.* 171:238–48
110. Stapp P, Antolin MF, Ball M. 2004. Patterns of extinction in prairie dog metapopulations: Plague outbreaks follow El Niño events. *Front. Ecol. Environ.* 2:235–40
111. Stark H, Hudson BW, Pittman MS. 1966. Plague epidemiology. Atlanta, GA: US Dep. Health Educ. Welf. 117 pp.
112. Stenseth NC, Samia NI, Viljugrein H, Kausrud KL, Begon M, et al. 2006. Plague dynamics are driven by climate variation. *Proc. Natl. Acad. Sci. USA* 103:13110–15
113. Stevenson HL, Bai Y, Kosoy MY, Montenieri JA, Lowell JL, et al. 2003. Detection of novel *Bartonella* strains and *Yersinia pestis* in prairie dogs and their fleas (Siphonaptera: Ceratophyllidae and Pulicidae) using multiplex polymerase chain reaction. *J. Med. Entomol.* 40:329–37
114. Tikhomirov E. 1999. Epidemiology and distribution of plague. In *Plague Manual: Epidemiology, Distribution, Surveillance and Control*, ed. DT Dennis, KL Gage, N Gratz, JD Poland, E Tikhomirov, pp. 11–37. Geneva: World Health Org.
115. Titball RW, Hill J, Lawton DG, Brown KA. 2003. *Yersinia pestis* and plague. *Biochem. Soc. Trans.* 31:104–7
116. Traub R, Wisseman CL. 1978. The ecology of murine typhus—a critical review. *Trop. Dis. Bull.* 75:237–317
117. Verjbitski DT. 1908. The part played by insects in the epidemiology of plague. *J. Hyg.* 8:162–208
118. Vetter SM, Eisen RJ, Schotthoefer AM, Montenieri JA, Holmes JL, et al. 2010. Biofilm formation is not required for early-phase transmission of *Yersinia pestis*. *Microbiology* 156:2216–25
119. Walker DH, Ismail N. 2008. Emerging and re-emerging rickettsioses: endothelial cell infection and early disease events. *Nat. Rev. Microbiol.* 6:375–86

103. Reviews the ecology of *R. felis*; its potential modes of transmission, development, and distribution within fleas; and its geographic distribution and possible medical significance.

120. Webb CT, Brooks CP, Gage KL, Antolin MF. 2006. Classic flea-borne transmission does not drive plague epizootics in prairie dogs. *Proc. Natl. Acad. Sci. USA* 103:6236–41
121. Wedincamp J Jr, Foil LD. 2002. Vertical transmission of *Rickettsia felis* in the cat flea (*Ctenocephalides felis* Bouché). *J. Vector Ecol.* 27:96–101
122. Welkos SL, Friedlander AM, Davis KJ. 1997. Studies on the role of plasminogen activator in systemic infection by virulent *Yersinia pestis* strain C092. *Microb. Pathog.* 23:211–23
123. Wheeler CM, Douglas JR. 1941. Transmission studies of sylvatic plague. *Proc. Soc. Exp. Biol. Med.* 47:65–66
124. Deleted in proof
125. Wheeler CM, Douglas JR. 1945. Sylvatic plague studies. V. The determination of vector efficiency. *J. Infect. Dis.* 77:1–12
126. World Health Org. 2003. Human plague in 2000 and 2001. *Wkly. Epidemiol. Rec.* 16:130–35
127. Wilder AP, Eisen RJ, Bearden SW, Montenieri JA, Gage KL, Antolin MF. 2008. *Oropsylla hirsuta* (Siphonaptera: Ceratophyllidae) can support plague epizootics in black-tailed prairie dogs (*Cynomys ludovicianus*) by early-phase transmission of *Yersinia pestis*. *Vector-Borne Zoonotic Dis.* 8:359–67
128. Wilder AP, Eisen RJ, Bearden SW, Montenieri JA, Tripp DT, et al. 2008. Transmission efficiency of two flea species (*Oropsylla tuberculata cynomuris* and *Oropsylla hirsuta*) involved in plague epizootics among prairie dogs. *EcoHealth* 5:205–12
129. Williams SG, Sacci JB Jr, Schriefer ME, Andersen EM, Foujioka KK, et al. 1992. Typhus and typhuslike rickettsiae associated with opossums and their fleas in Los Angeles County, California. *J. Clin. Microbiol.* 30:1758–62
130. Winters AM, Staples JE, Ogen-Odoi A, Mead PS, Griffith K, et al. 2009. Spatial risk models for human plague in the West Nile region of Uganda. *Am. J. Trop. Med. Hyg.* 80:1014–22

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Contents

Indexes

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