# Factors Affecting the Spread and Maintenance of Plague

# 11

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## 11.1 Introduction

Plague is an exceptionally virulent flea-borne illness caused by the gram-negative bacterium *Yersinia pestis* (Prentice and Rahalison 2007). Humans are accidental hosts of this bacterium, which normally circulates among certain rodent species and their fleas, occasionally causing widespread plague epizootics with high mortality among its hosts. Most people have little knowledge of plague's status in the modern world, although many are aware that the disease causes outbreaks with high mortality and can spread very quickly within human populations. Some also remember that plague was the cause of the Black Death, an explosive epidemic that killed perhaps one-third of Europe's population over an approximately 4 years period in the mid-fourteenth century (Carniel 2008). Although the Black Death is the most widely recognized pandemic, plague also caused two other less well-known pandemics (Justinian's Plague and the Modern Pandemic) that killed millions, as well as innumerable regional epidemics, some of which caused the deaths of tens of thousands. In addition to causing high mortality, these outbreaks were characterized by the explosive spread of plague among its victims.

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Humans typically acquire plague through one of three routes of exposures: infectious flea bites, handling infected animals or inhaling infectious materials. The rarest source of exposure is inhalation of infectious materials, which typically results in primary pneumonic plague, a form of the disease that is characterized by very rapid onset, fever, and respiratory symptoms, including cough and frequently hemoptysis (expectoration of bloody sputum carrying viable *Y. pestis*). In most instances, primary pneumonic plague is acquired following exposure to another person who has pneumonic plague with associated cough and hemoptysis. Untreated cases of pneumonic plague are especially dangerous because they can lead to very rapid person to person spread and serious epidemics with exceptionally high mortality rates in the absence of appropriate control measures. Such outbreaks appear to have occurred regionally during the Black Death and others were confirmed early in the twentieth century in Manchuria during the Modern Pandemic, causing as many as 50,000–60,000 deaths (Meyer 1961; Pollitzer 1954). Factors promoting the spread of pneumonic plague include crowding of people within confined spaces, family members or others providing care to coughing patients without the use of appropriate respiratory protection, and cool and relatively humid conditions (Gabastou et al. 2000; Meyer 1961).

In other instances humans are exposed to plague through direct contact with the infectious body fluids and tissues of infected animals. Cases

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arising from contact with infectious animals typically occur singly or, rarely, in a small group of persons and under most circumstances present little risk of further human infection unless untreated cases progress to the pneumonic form of the disease (secondary pneumonic plague), a situation that poses the threat of person to person spread, and, perhaps, an outbreak of primary pneumonic plague.

Despite the threat posed by pneumonic plague outbreaks and occasional cases arising through animal contact, most humans acquire the disease through the bites of infectious fleas, an event that typically leads to the bubonic form of plague. If left untreated, this form of plague can progress rapidly to secondary septicemic or pneumonic plague. Such circumstances appear to have occurred frequently during the Black Death and also during some localized epidemics of modern times. Although not the most common pattern of flea-borne transmission, plague appears to be able to spread for at least brief periods from human to human through the bites of fleas not normally found on rodents or associated with the natural cycling of the disease in rodents. Specifically, some evidence suggests that the so-called human flea (*Pulex irritans*) can feed on a person who is dying from plague septicemia, ingest *Y. pestis* into its gut or contaminate its mouthparts with plague bacteria, and then, for at least brief periods, be able to pass viable *Y. pestis* to its next human host while feeding. Although the bites of *P. irritans* might have played an important role in spreading plague among the highly flea-infested population of Europe during the Black Death (Ell 1980), as well as during some local outbreaks in modern times (Blanc 1956), most cases of human plague today are acquired through the bites of infectious rodent fleas. In some plague foci, including those in North America, the primary vectors of human plague are wild rodent fleas. Human plague cases acquired from the bites of wild rodent fleas typically occur singly or in small clusters of cases. Far more threatening to humans are exposures to infectious rat fleas, particularly *Xenopsylla cheopis* (Oriental rat flea), which can effectively spread the disease not only among rats but also to humans (Pollitzer 1952). Indeed rat flea bite exposures represent the major source of infection for nearly all large outbreaks of bubonic plague reported in modern times.

Many factors contribute to the risk of humans acquiring flea-borne plague. It is generally accepted that certain human behaviors, low economic status, cultural ways, trading and travel activities, agricultural practices and changing land usage can influence human plague risk (Dennis 1998; Gage 1998; Kilonzo 1999; Stenseth et al. 2008), usually because these factors act to increase the likelihood that people will come into contact with infectious fleas or mammals. Living in close proximity to a known focus of plague is another factor that could obviously increase human risk, especially when persons living in these areas are poverty-stricken and inhabit homes heavily infested with commensal rats and rat fleas. Persons living in areas at risk for rat-associated plague often unknowingly encourage rat infestations by providing these animals with food and shelter, thereby increasing the odds that rats will acquire *Y. pestis* infections from plague-susceptible rodents living in the surrounding countryside. Although rat infestations are most common in poverty-stricken areas, poor rodent sanitation is hardly restricted to the poor and many relatively prosperous persons in the United States (U.S.) and elsewhere have home sites that provide favorable conditions for rats or other plague-susceptible rodents, some of which carry fleas capable of transmitting *Y. pestis* not only to these animals but also to the region's human residents (Barnes 1982; Gage et al. 1995).

Human plague risks within endemic areas are also known to fluctuate over time, largely due to the irregular occurrences of plague epizootics among commensal or sylvatic (wild) rodents (Craven et al. 1993; Pollitzer 1954). In active foci these plague epizootics typically occur at irregular intervals of perhaps a few (3–4) to many (>10) years, sweeping rapidly through rodent populations and sometimes causing as much as 99% mortality among these animals (Cully and Williams 2001; Gage and Kosoy 2005, 2006), a factor that contributes to increased human plague risk when *Y. pestis*-infected fleas infest and feed

on new hosts to replace those killed by plague. Because most cases and epidemics of human plague occur in the wake of widespread epizootics in commensal rats and other rodents, it is important to understand what factors act as drivers to initiate, sustain and determine the rate of spread of these epizootics. This chapter reviews recently published research on this topic, including many studies done in the Flea-Borne Disease Activity at the Centers for Disease Control and Prevention (CDC) or in collaboration with scientists in other laboratories. Specifically, the chapter will concentrate on those advances that have improved our understanding of how host densities and abundance thresholds affect the spread of plague; how climate can influence rodent population dynamics and the likelihood epizootics and human cases will occur; and how certain fleas normally considered to be poor vectors of plague can, nevertheless, play important roles in the spread of plague during epizootics.

## 11.2 Factors Influencing the Occurrence of Plague Epizootics and the Spread of Plague

Once an epizootic begins, its ability to continue spreading is influenced by numerous factors, many of which have been reviewed by others (Eisen and Gage 2009; Gage and Kosoy 2005; Poland and Barnes 1979; Pollitzer and Meyer 1961). Among the most commonly cited factors are those related to seasonal changes in host populations, including the appearance of young susceptible animals and overcrowding of burrows by juvenile rodents during late spring and early summer, a time when transmission rates in temperate zone foci typically increase from a period of minimal transmission during the winter months (Pollitzer and Meyer 1961). The dispersal of young animals from their parent colonies during their juvenile year also has been suggested to significantly affect the spread of plague, as has the slow movement and spread of rodent populations in suitable habitat over time. Conversely, transmission rates will decrease markedly as certain temperate-zone species, such as ground squirrels, enter into hibernation in the fall.

Others have stressed the importance of flea-related factors in the spread of plague. In addition to being competent plague vectors, fleas must be able to locate and infest new hosts as their original ones die of plague. If a particular flea species is able to feed not only on their normal host species but also on other mammals, it is likely to contribute to the spread of a plague during epizootics. It also should be remembered that only the blood feeding adult flea is capable of becoming infected with and transmitting *Y. pestis* and the abundance of adult fleas is likely to peak on a seasonal basis, with most important vector species reaching greatest abundance during the peak of the plague transmission season, which in temperate areas occurs in the warmer months of the year (Craven et al. 1993) or after the rainy season in tropical lowland areas (Cavanaugh 1971). Krasnov et al. (2006) reported that flea species with high vector potentials for plague transmission occurred more abundantly on their hosts than did flea species with low vector potential. The rate of plague transmission by fleas also could be influenced by increased contact rates between infectious vectors and susceptible host individuals, with increased contact resulting in a concomitant increase in secondary infections as the disease spreads from an initial focal infection (Eisen and Gage 2009). Transmission rates also have been suggested to increase during epizootics as a result of infectious fleas becoming more and more concentrated on the decreasing number of surviving hosts (Poland and Barnes 1979; Tripp et al. 2009).

Predators of rodents, especially certain carnivores and birds of prey, are also believed to be agents for spreading plague between rodent populations. This is because in the course of capturing, killing and feeding on rodents, they acquire fleas from their prey, thus enabling these predators to carry these insects to new sites where they can hop off their accidental hosts and, perhaps, once again find new rodent hosts. The successful transport of *Y. pestis*-infected rodent fleas from one rodent population to another by predators is likely to occur only rarely, but if its frequency is

sufficiently high it is likely to play an important role in spreading the disease over moderately long distances. On a much larger scale, the transport of *Y. pestis*-infected rats and fleas across vast distances through human trade activities is well-known and believed to have been responsible for the spread of the three historical pandemics, as well as other outbreaks (Pollitzer 1954).

In addition to allowing the continued spread of epizootics and epidemics, the invasion of new areas can result in the establishment of new persistent plague foci, a process that was observed numerous times during the last pandemic in southern Africa, southern Asia, and both North and South America (Pollitzer 1954). Once plague invades an area and succeeds in becoming established in local rodent and flea populations, it is likely to pose an ongoing threat to the region's human populations, especially when epizootics occur among local rodents. It also should be noted that these persistent plague foci can serve as sources of infection for hosts living in surrounding areas that are normally unsuitable for the disease's maintenance but might under favorable conditions support plague transmission for brief periods, a situation that could lead to increased risks for humans living in these areas. The spatial distribution of suitable habitats also can affect the spread of plague, as can the occurrence of geographical barriers to spread, such as mountains, large rivers or very hot, dry deserts (Collinge et al. 2005a, b; Gage and Kosoy 2006; Pollitzer and Meyer 1961). Areas with high levels of habitat patchiness can provide refuges where rodent populations are able to escape a passing epizootic and, thus, provide hosts for repopulating nearby plague-affected habitat patches, a factor that could be important for plague maintenance. Habitat patchiness, especially when accompanied by geographic barriers, also can reduce the rate at which plague spreads between patches of rodent hosts, presumably because of the difficulties encountered in dispersing infected rodents or fleas to relatively isolated habitat patches. Although outside the scope of this chapter, such lags in spread might promote the stable persistence of plague in large metapopulations of some host species, such as prairie dogs or ground squirrels (Gage and Kosoy 2005, 2006; Salkeld et al. 2010).

The ability of plague to spread with populations and from one habitat patch to another also will be related to the severity (intensity) of the epizootic, a factor that will depend on host densities and the likelihood that at least some infected rodent hosts and fleas will be able to move from one habitat patch to another. Many authors have noted that rodent abundances are likely to be important for epizootic spread and persistence but few studies during the last century specifically addressed this issue and much of the evidence to support this suggestion was anecdotal (Gage and Kosoy 2005; Poland and Barnes 1979; Pollitzer and Meyer 1961). Studies done within the past decade, however, make it increasingly apparent that host abundance, expressed as either host densities or burrow occupancy, is important for the spread of plague. In Central Asia (Kazakhstan) the invasion and persistence of *Y. pestis* in great gerbil (*Rhombomys opimus*) populations (i.e., epizootic activity) was associated with periods when the abundance of these animals exceeded certain threshold levels (Davis et al. 2004). Statistical models generated during this work indicated that the abundance measurement most useful for determining the threshold value for invasion and persistence of plague epizootics was the level of burrow occupancy by gerbils rather than the actual numbers of gerbils per burrow. These same models indicated that current abundance levels were less predictive than abundance estimates from previous years, with a 2 year delay period providing the best abundance estimates for predicting epizootic spread in great gerbils during a given year. It should be noted that simple increases in gerbil abundance, as measured by burrow occupancy rates, to levels that according to the models should be sufficient for plague to invade and continue to spread were not always followed by documented epizootics, perhaps because data from the late stages of outbreaks resulted in erroneously lowering the estimated threshold required for invasion and spread, too few gerbils were tested, plague was locally extinct, flea abundance was too low, climate was unfavorable, or levels of resistance in gerbil populations were unfavorable for plague spread (Davis et al. 2007). Among these factors, insufficient sampling and local extinction

accounted for the most false positive predictions while low flea abundance or unfavorable climatic conditions appeared to exert little effect on the accuracy of the models' predictions. Nevertheless, the above work and further work by Samia et al. (2011) on plague dynamics in rodents and humans in Central Asia indicated that distinct threshold values were important in explaining the spread of plague in this system. In the last study two threshold values were found to be important, one related to the dynamics of plague transmission in the rodent reservoir and the other associated with the spillover of plague into human populations.

The spread of plague in great gerbils was further investigated using insights from percolation theory and it was found that the abundance threshold phenomenon could be explained by a percolation threshold that reflected the difference between small scale movements that result in the transport of infectious fleas from one gerbil family group to another and the much larger scale movements of plague into contiguous areas that have been colonized by gerbils and over which the disease can spread (Davis et al. 2008). Another study, which applied percolation theory to the spread of plague within black-tailed prairie dog (*Cynomys ludovicianus*) colonies on the High Plains of the western U.S., suggested that infected prairie dogs and their fleas acting alone could account for the limited spread of plague that might occur among adjacent coteries but not to more distant coteries. Interestingly, the presence of a second alternative host, the northern grasshopper mouse (*Onychomys leucogaster*), was proposed to increase connectivity between non-adjacent prairie dog coteries. When these mice were present in sufficiently high numbers, it also was suggested they could push the system above a percolation threshold that allowed plague to spread rapidly within a prairie dog colony, typically resulting in its demise within a few months (Salkeld et al. 2010). The effect of grasshopper mice on plague spread also is favored by their behavior which involves frequent exploration of prairie dog burrows and the free movement of these animals between the territories of adjacent and non-adjacent coteries that might be separated by considerable distances. The inquisitive nature and wide-ranging habits of grasshopper mice also favor transmission of plague in prairie dog colonies because they often result in these mice becoming at least temporarily infested with the fleas of many rodent species, including those found on prairie dogs. Grasshopper mice that encounter fleas in the burrows of prairie dog coteries that have succumbed to plague can act as temporary hosts for these fleas and spread them to other coteries, thus promoting the spread of the disease throughout the colony by increasing the connectivity between coteries. It seems likely other rodent species might play a similar role in increasing connectivity so that percolation thresholds can be reached and epizootic transmission can begin and continue. Clearly, grasshopper mice are not required for epizootic spread of plague within all prairie dog colonies, as prairie dog die-offs have been observed in colonies that lacked grasshopper mice. This includes colonies that experienced epizootics and were located within less than about 150 km of the sites studied by Salkeld et al. (2010) and Brinkerhoff et al. (2010). Unfortunately, insufficient data exist to examine how the dynamics of plague spread differ within prairie dog colonies at these two sites. Brinkerhoff et al. (2010) did note that although changes in the species assemblages of small rodent species were observed before and after epizootics, no relationship was found between the relative abundance of small mammals in years prior to, during or following plague epizootics in the prairie dog colonies they studied. The reasons for these apparently contradictory results remain unexplained but could be associated with the relatively close proximity of plague-affected prairie dog colonies in the Brinkerhoff et al. (2010) study to other nearby sites that previously had experienced plague and, therefore, might act as source sites for repeated invasions of *Y. pestis*-infected animals or fleas into other colonies.

## 11.3 Environmental Drivers of Plague Epizootics and Associated Increases in Human Plague Risk

Based on the above studies, it seems reasonable to accept that rodent abundances must exceed certain thresholds for plague epizootics to occur and

be sustained in susceptible rodent populations. If we also accept that most human cases occur in the wake of epizootics, it becomes important for public health reasons to determine what environmental drivers lead to increased rodent abundance and heightened risk of epizootic activity. Clearly, it is possible that human behaviors, cultural beliefs, agricultural and food storage practices, or local landscape usage patterns could result in conditions, particularly increased local availability of food and shelter, that are likely to be favorable for rodents and, thus, result in the populations of these animals increasing in abundance to the point where if plague invades the area, epizootics are likely to occur and humans might temporarily experience increased plague risk. Indeed, this scenario might explain many small-scale plague outbreaks that remain localized and cause small numbers of human cases but quickly disappear before spreading more than a few kilometers from their point of origin.

Of much more interest, however, are those instances when plague outbreaks begin in specific sites and then spread widely or arise simultaneously in many areas over widespread distances with no evidence that any one outbreak site was the origin. An example of the latter is provided by the widespread epizootic activity that occurred in the southwestern U.S. in 1983 and resulted in an unusually high number of human cases in the region (Craven et al. 1993). Multi-locus variable number tandem repeat analysis (MLVA) of archived samples from human cases that occurred during this outbreak clearly indicated that these cases were acquired from multiple *Y. pestis* variants rather than from a single clone that spread widely across this region (Lowell et al. 2005). The widespread nature of this epizootic activity also suggested that one or more environmental drivers existed to raise rodent abundances above key threshold values and these drivers operated simultaneously, or nearly simultaneously, over large geographic areas. Increasingly, these drivers appear to be climatic in nature (Gage et al. 2008).

The possible role of climate in the epidemiology and ecology of plague has been the subject of speculation for many decades (Gage and Kosoy 2005) and some more recent evidence even suggests that each of the major plague pandemics were preceded by climatic anomalies (Keys 1999; Stenseth et al. 2006; Zhang et al. 2007; Xu et al. 2011). Following the arrival of the Modern Pandemic in India, it was noted that plague outbreaks in that country were associated with seasonal changes, particularly those related to rainfall and temperature. As precipitation levels peaked during the monsoon, the numbers of human cases would dwindle only to increase again as warmer and drier conditions returned after the monsoon season. It was also noted the numbers of cases began to decrease as temperatures exceeded 26.7°C (80°F) and epidemics virtually stopped once temperatures exceeded 29.4–32.2°C (85–95°F) (Pollitzer 1954). In another study (Brooks 1917) reported that epidemics ceased when temperatures exceeded 27°C and saturation deficits, a measure of the "dryness" of air that accounts for both temperature and humidity (Randolph and Storey 1999), exceeded 0.76 cm (0.3 in.). Similar effects were observed during the Vietnam War (Cavanaugh and Marshall 1972; Cavanaugh and Williams 1980). Much of the impact of climate on plague transmission in these last two studies was attributed to the effect of these relatively high temperatures on the ability of fleas to remain blocked and, therefore, efficient transmitters of *Y. pestis* (see below for further discussion of transmission by blocked fleas), although it must be noted that hot, dry conditions also decrease flea survival (Krasnov et al. 2002; Gage et al. 2008).

A more recent study noted that the numbers of human cases of plague in the state of New Mexico in the U.S. were positively correlated with greater than average cool season (October–May) precipitation (Parmenter et al. 1999). The proposed mechanism underlying this observation was a trophic cascade, where increased precipitation leads to increased plant growth and insect reproduction, both of which enhance food availability for rodents. As food becomes more plentiful, rodent reproduction and survival will increase, thereby increasing the abundance of these animals to a threshold value where the appearance of plague in their populations is likely to lead to epizootic spread of the disease. A number of other

studies have found that increases in precipitation are associated with heightened plague transmission in rodent, human and even pet (dog and cat) populations in relatively arid regions, such as the American West or Central Asia (Brown et al. 2010; Collinge et al. 2005a, b; Enscore et al. 2002; Kausrud et al. 2007; Stenseth et al. 2006; Xu et al. 2011). Although investigations in relatively arid temperate regions have tended to support variants of the trophic cascade hypothesis, at least one study noted that the responses of rodent populations to increased precipitation might depend on the characteristics of local rodent communities and other factors that could act differently in wetter tropical regions, such as China's Yunnan province, where increased precipitation was expected to be negatively associated with occurrences of plague (Xu et al. 2011).

Other studies have indicated that not only precipitation but also temperature is likely to be important in determining how widely and for how long plague will spread during epizootics. Enscore et al. (2002) found that both time-lagged late winter precipitation and summertime threshold temperatures were associated with the frequency of human plague cases in the southwestern U.S. A positive relationship was observed between human plague frequency and both time-lagged late winter precipitation and the number of days above lower threshold values for maximum daily summer temperatures. Conversely, an elevated number of days above high-threshold temperatures had a strong negative effect on the occurrence of human plague in the region. The negative effect of an increased number of hot days was proposed to be related to the negative effects of high temperatures on flea survival because extended periods of high temperatures can reduce flea survival (Burroughs 1953; Krasnov et al. 2001; Pollitzer 1954; Pollitzer and Meyer 1961; Rust and Dryden 1997), although these temperatures also will affect the ability of fleas to become blocked and retain infection. This can be particularly true when periods of elevated temperatures are accompanied by dry summer conditions. It should be pointed out that although low humidity and high temperatures negatively impact flea survival, excessive humidity (90%) can lead to fatal fungal infections in larval fleas, a fact that has been proposed to explain the restricted persistence of rat-associated plague in hot humid lowland areas in the tropics and reinforces the concept that plague foci and epizootic plague are likely to occur only within certain boundary values for key environmental variables, such as temperature, precipitation and humidity (Buxton 1938; Gage et al. 2008; Olson 1969).

Elsewhere in the U.S., precipitation and temperature appeared to exert largely similar effects on plague in prairie dogs in Phillips County, MT (Collinge et al. 2005a, b), as indicated by the fact that the occurrence of plague in these animals was positively associated with time-lagged precipitation and the number of warm days in a year. Hot temperatures were negatively correlated with the appearance of plague in these animals, a finding that agrees with the effects of temperature on the occurrence of plague in humans (Enscore et al. 2002). Similar results were not observed among prairie dog colonies in Boulder County, CO, however, and it was suggested that the differences between the Montana and Colorado study areas might be explained by the fact that precipitation patterns in Montana exhibited strong seasonal peaks that occurred regularly each year, whereas peak precipitation in the Colorado study area showed no consistent pattern, with the month of peak precipitation likely to occur in different seasons in different years. Plague activity in gerbils in Kazakhstan also was found to be positively associated with precipitation and temperature, specifically with warmer springs and wetter summers (Stenseth et al. 2006). In this region the prevalence of plague in gerbils can be expected to increase when spring temperatures are warmer than normal, providing that gerbil abundance at a relevant time lag is above a threshold value. Presumably, this increased plague prevalence in gerbils during years with warmer than normal springs is related to increased flea abundance and higher than normal vector to host ratios during the spring, factors that should lead to increased opportunities for plague to spread by flea bite during a given year. Stenseth et al. (2006) also reported that increased summer precipitation is associated with increased prevalence in gerbils during the fall.

Based on the above-described studies, it would be reasonable to expect that the occurrence of El Nino events would be associated with increased epizootic activity in the American Southwest because these events typically result in increased precipitation in this plague-endemic region. Parmenter et al. (1999) found that cool season precipitation (October to May) was positively associated with the numbers of human cases of plague in New Mexico, which has more human plague than any other state in this country, but the occurrence of El Nino events was not correlated with increased numbers of human cases. By contrast, Stapp et al. (2004) suggested that plague epizootics among prairie dogs were more likely to occur after El Nino events, although other factors, including colony size and proximity to other plague-affected prairie dog colonies, influenced the likelihood that epizootics would occur in individual colonies. More recent research reveals that the relationship between El Nino and other climatic cycles to human plague is more complex than originally imagined (Ben Ari et al. 2011). Ben Ari et al. (2008) used statistical modeling and a 56-year time series of human cases of plague from the western U.S. to analyze how the occurrence of human cases in a given year were associated with the numbers of human cases that occurred in previous years, precipitation, and temperature, as well as the index values for two climatic cycles that are responsible for predictable climatic anomalies in this region. The first of these cycles is the well-known and previously mentioned El Nino Southern Oscillation (ENSO) and the other is the Pacific Decadal Oscillation (PDO), both of which are known to exert considerable influence on ecological processes in western U.S. The results indicated that variability in human plague across this vast region could be explained largely by interactions between previous levels of human plague, above normal temperatures as indicated by the number of days above 37°C for 100 weather stations located throughout the western United States, and March index values for the PDO. It should be noted that use of the March PDO index values reflects earlier studies indicating that late winter and early spring temperatures were positively correlated with the frequency of human plague in the southwestern states of New Mexico and Arizona (Enscore et al. 2002). Based on these findings and the other studies discussed above, the authors proposed that the observed impact of the PDO was due to the influence of precipitation and temperature on the rodent hosts and flea vectors of plague. Interestingly, no association was noted in this initial study between occurrences of human plague and index values for the ENSO (Ben Ari et al. 2008). In a follow-up study using wavelet analysis, it was found that the ENSO actually does exert an influence on the dynamics of human plague in the western United States by acting at certain times in concert with the PDO cycle (Ben Ari et al. 2010). Specifically, the co-occurrence of ENSO events and elevated PDO values also corresponded to increased precipitation, increased vegetative growth as measured by satellite-derived data expressed as normalized difference vegetative indices (NDVI), and greater numbers of human plague cases. These climatic effects on human plague were thought to be due to the impacts of elevated precipitation and suitable temperatures on the wild rodent hosts and flea vectors of the disease, a finding that agrees in principle with the trophic cascade hypothesis. Not surprisingly, the model indicated that low PDO values accompanied by La Nina events had the opposite effects on precipitation, NDVI values and the occurrence of human plague, presumably because lower precipitation across the western U.S. will decrease food availability for rodents and, therefore, drive rodent abundances to levels below the threshold levels where the epizootic spread of plague can occur.

## 11.4 The Role of Fleas in Epizootic and Epidemic Spread of Plague

More than a century ago, Simond convincingly demonstrated that rat fleas could act as vectors of plague (Simond 1898). Within the next few decades the abilities of certain other fleas to transmit plague, including those species found on wild rodents, also became apparent (Eisen et al. 2009; Eskey and Haas 1940; McCoy 1910; Pollitzer

1954). Arguably the most important of these ensuing studies were those of Bacot and Martin (1914) who investigated the development of plague bacteria in *X. cheopis* and the factors influencing the ability of this flea to transmit plague bacteria. In this work we first encounter a description of proventricular blocking in fleas, a condition that results from the blockage of the proventriculus with masses of *Y. pestis* embedded in an extracellular matrix now known to consist of a polysaccharide-containing biofilm expressed by the plague bacterium (Hinnebusch and Erickson 2008). In a much later but equally elegant series of experiments, it was clearly demonstrated that blockage depends on expression of genes within the chromosomally located *hms* locus of *Y. pestis* (Hinnebusch and Erickson 2008; Hinnebusch et al. 1996). The presence of a blockage in the proventriculus of a flea, which is described in greater detail below, typically increases its ability to efficiently transmit *Y. pestis* and the strong evidence for this conclusion from the work of Bacot and Martin led many to believe that transmission of *Y. pestis* by blocked fleas represents the primary, if not almost exclusive, means by which flea-borne plague transmission occurs, a concept that is often referred to as the proventricular blockage model or classical transmission model. Although the importance of nearly complete blockage of the proventriculus for efficient plague transmission was widely accepted among past plague researchers, it should be noted that Bacot (1915) later stressed that partially blocked fleas transmitted plague bacteria more effectively than completely blocked fleas (Hinnebusch 2005). Partially blocked fleas also remain capable of feeding effectively, thus allowing them to avoid starvation and probably have more opportunities to transmit *Y. pestis* than starving fully blocked fleas.

In order to understand how the spread of plague epizootics might be influenced by proventricular blockage or other factors related to *Y. pestis* transmission by fleas, it is best to first briefly describe how fleas acquire infection, how plague bacteria colonize and develop in different flea species, and what factors influence the blocking process in these insects. In many ways, fleas are surprisingly inefficient vectors, with some flea species being prone to losing infection soon after becoming infected and others retaining infection for a few days but failing to ever become infectious. It should be noted that fleas ingest only tiny amounts of blood during each feeding and that feedings are likely to occur at intervals of 1 or more days, facts that probably explain why fleas must feed on heavily bacteremic hosts ($10^6$–$10^9$ CFU/mL) in order to reliably become infected (Eisen et al. 2009; Engelthaler et al. 2000). Plague bacteria contribute significantly to the development of these overwhelming, fatal bacteremias in their hosts through expression of a variety of virulence factors that promote the initial dissemination of *Y. pestis* within the host, suppression of the host immune system, early survival of plague bacteria within phagocytes, and their eventual resistance to phagocytosis by host cells (Carniel 2003; Huang et al. 2006; Perry and Fetherston 1997). Collectively, these factors allow *Y. pestis* to establish an infection in its host and then escape into its bloodstream where they will multiply in sufficient numbers to cause the heavy bacteremias that can result in the infection of blood feeding fleas. It also should be emphasized that the development of these high level, fatal bacteremias in the fleas' hosts, force fleas to leave the carcasses of their suddenly dead hosts and find new hosts that can provide the blood meals needed by fleas to survive and reproduce. Obviously, this process of host transfer provides infectious fleas with the opportunity to transmit *Y. pestis* to other susceptible mammals and contribute to the further spread of plague epizootics.

Once a flea ingests *Y. pestis* while feeding on a highly bacteremic and dying animal, the bacteria begin to multiply within the flea gut and express so-called transmission factors that promote their establishment and survival in fleas and later transmission by these insects (Hinnebusch 2005; Hinnebusch and Erickson 2008). In some species, such as *X. cheopis*, this colonization and rapid multiplication occurs both in the midgut and the proventriculus, the latter being a spine-filled structure that lies at the end of the foregut and next to the front of the flea's midgut ("stomach") (Bacot and Martin 1914; Engelthaler

et al. 2000; Hinnebusch et al. 1996). In other species, such as the North American ground squirrel flea, *Oropsylla montana*, development of the bacteria appears to be restricted almost exclusively to the midgut (Engelthaler et al. 2000). Although it remains to be determined why *Y. pestis* initially fails to colonize the proventriculus in some species, it has been found that survival within the flea midgut requires expression by *Y. pestis* of a factor that is coded on the pFra plasmid of this bacterium (Hinnebusch et al. 1998) and referred to as Ymt. Coincidentally, this factor originally was found to be toxic for murines, hence its common name murine toxin. More recent research has revealed Ymt to be a phospholipase D (Hinnebusch 2005). The means by which Ymt protects *Y. pestis* from digestion and death in the flea's midgut remains to be determined.

Flea species, such as *X. cheopis*, that support rapid colonization of the proventriculus by plague bacteria are the ones most likely to develop the *Y. pestis*-induced masses that completely occlude this structure and result in blockage. As noted above, blockage requires expression of genes in the *hms* locus in order for biofilm formation by *Y. pestis* to occur (Jarrett et al. 2004; Hinnebusch 2005; Hinnebusch and Erickson 2008). Complete blockage of the proventriculus with this biofilm, which consists of a polysaccharide-containing extracellular matrix within which the plague bacteria are embedded, prevents ingested blood from passing through the flea's foregut to the midgut, thus leading to starvation of the flea. Typically, starving blocked fleas will repeatedly attempt to clear the blockages in their guts through multiple attempts to imbibe blood through the foregut, a process that results in a reflux action as the muscles along the foregut eventually tire and relax, releasing tension in the esophagus and elsewhere in the foregut and causing bacteria to be flushed from the blockage into the feeding site. Unfortunately for the flea, the blockages appear to be quite stable and only disappear after the flea dies or is held at temperatures in excess of 27°C. This last observation can be explained by the fact that accumulation of the biofilm that forms the blockage requires temperature-dependent expression of chromosomal genes in the *hms* locus of *Y. pestis* (Kartman 1969; Hinnebusch 2005; Hinnebusch and Erickson 2008). Thus, at temperatures in excess of approximately 27°C biofilms will fail to form or be maintained in the flea's gut, resulting in decreased efficiency of transmission and perhaps actual clearance of *Y. pestis* infection from the flea.

As noted above, blockage formation is considered extremely important because flea species that are capable of becoming blocked also transmit *Y. pestis* at higher efficiencies than those that fail to block. This observation often has led to the assumption that the only important plague vectors are those species that frequently become blocked. Support for this conclusion might be provided by the observation that the primary flea vector in rat-associated plague outbreaks is usually *X. cheopis*, the species first studied by Bacot and Martin (1914) and the one that still remains the primary vector in most rat-associated plague outbreaks of modern times. Despite this observation, the question of how essential blocking is to the epizootic spread of plague in nature remains open (Eisen et al. 2009; Gage and Kosoy 2005; Webb et al. 2006). One issue is the fact that *X. cheopis* is often absent from plague-endemic regions and epidemiological or ecological observations frequently suggest that the most likely plague vectors in these *X. cheopis*-free regions are species of local wild rodent fleas that rarely become blocked. For example, most epidemiological evidence suggests that the ground squirrel flea *O. montana* is the primary vector of human plague in the U.S., a finding that is hard to explain in terms of the classical blocked flea model because this particular flea species rarely becomes blocked or does so only many weeks after becoming infected (Eisen et al. 2006; Engelthaler et al. 2000). Similarly, black-tailed prairie dog colonies frequently experience explosive die-offs that result in the almost complete annihilation of affected colonies within a few weeks after plague is first detected (Cully and Williams 2001). Past studies indicate that flea species commonly found on prairie dogs, including *Oropsylla hirsuta*, seldom become blocked (Eskey and Haas 1940; Webb et al. 2006). Furthermore, laboratory studies on a wide variety of other flea species have demonstrated that most

*Y. pestis*-infected fleas found on wild rodents fail to form blockages or rarely do so (Eisen et al. 2009), a fact that is hard to reconcile with the blocked flea model, especially when plague transmission, including detectable epizootics, occurs in areas that apparently lack fleas capable of becoming blocked. Even among those relatively few flea species that occasionally become blocked following infection, many require periods of several weeks to months before blockages eventually develop in their guts (Eisen et al. 2009). According to a relatively strict interpretation of the blocked proventriculus model of transmission, such a finding should indicate these fleas will not be able to transmit efficiently for considerable periods after first becoming infected. The period of time between when a vector first becomes infected until it actually can transmit a particular pathogen to a new host is referred to as the extrinsic incubation period and prolonged extrinsic incubation periods, such as described above, would be expected to greatly slow the epizootic spread of plague.

Recently, the importance of blocked flea transmission for the spread of plague epizootics has gained increased attention. In one study Webb et al. (2006) constructed an ordinary differential equation model that included two subordinate susceptible-exposed-infected (SEI) models, one of which described plague dynamics within fleas and the other which described disease dynamics within the prairie dog hosts. The results of this modeling study indicated transmission by blocked fleas is insufficient to explain the epizootic spread of plague within prairie dog colonies and that continued epizootic spread depended on the existence of what was termed a "short-term reservoir." It was speculated this short-term reservoir could involve some combination of other small mammal host species, infectious prairie dog carcasses or transmission of *Y. pestis* by fleas that had not become blocked.

Although sources of infection other than flea bites, including consumption of infectious carcasses, contact with contaminated soils, or close contact (respiratory or direct body contact) with infected hosts, have been proposed by some to be important for the spread of plague, data to support the widespread importance of these alternative modes of transmission have been minimal. Conversely, the evidence for fleas as important sources of infection in natural plague cycles, including periods of epizootic activity, is much stronger. In addition to the frequent recovery of *Y. pestis*-infected fleas from hosts, burrows or other sites during epizootics and the transmission of plague bacteria in laboratory experiments by locally important flea species, others have reported that epizootic activity can be halted or greatly diminished by insecticide applications, a treatment that can be expected to virtually eliminate local flea populations but should have little direct effect on consumption of infectious host carcasses or the possible contamination of soils by plague bacteria (Biggins et al. 2010).

Because of the widespread acceptance over the past century of the blocked flea or classical transmission model as the dominant mechanism for plague transmission during both epizootic and inter-epizootic periods, few studies were initiated to examine the potential importance of plague transmission by unblocked or partially blocked fleas. Although no one doubts that the ability of *X. cheopis* to become blocked is associated with its role as an important plague vector, Bacot (1915) himself, as noted above, was careful to suggest that partially blocked fleas might be even more dangerous vectors than blocked fleas because they not only transmitted with reasonably high efficiency but also could continue to feed successfully, thus allowing these fleas to prolong their survival and continue to transmit (Hinnebusch 2005). Others have noted that mechanical transmission might explain the "mass transmission" results reported from some experiments where transmission is observed only when large numbers of fleas are placed on hosts (Burroughs 1947; Kartman et al. 1958a, b; Quan et al. 1953). These investigators also suggested such "mass transmission" could play an important role during epizootics, especially when flea densities on hosts are exceptionally high. Although the term mechanical transmission has been used in different ways in the medical entomology literature, in the context of this discussion it means contamination of the flea's mouthparts with viable

*Y. pestis* in such a way that these bacteria will be injected into the feeding site when the flea takes its next blood meal. Others have discounted the potential importance of mechanical transmission because of their belief that *Y. pestis* can survive on flea mouthparts for only 3 h (Bibikova 1977), an opinion that appears to be somewhat at odds with other investigations reporting the survival of *Y. pestis* suspended in BHI on the surfaces of stainless steel, polyethylene and glass for up to 72 h and on paper surfaces for as long as 120 h (Rose et al. 2003). In other experiments, transmission by unblocked fleas was observed in the first few days after fleas consumed an infectious blood meal but the results were considered anomalous or attributed to the above-mentioned "mass action" phenomenon and considered to be insignificant (Burroughs 1947; Wheeler and Douglas 1945).

An alternative to the blocked flea model was proposed recently to explain the rapid spread of plague by fleas and address the issues raised by Webb et al. (2006) and others regarding the role of the classical model (blocked proventriculus model) in epizootics. This alternative model, which is referred to as early phase transmission (EPT), differs from the classical model in that it does not describe the state of the flea vector's gut (blocked or unblocked) or have an identified molecular mechanism for its action, such as biofilm formation in the proventricular blockage model. Rather, EPT simply represents "transmission by unblocked fleas during the time period prior to the earliest time point during which a complete blockage is able to form" (Eisen and Gage 2011). In this sense, EPT represents an ecological mechanism that describes the efficiency of transmission by unblocked fleas and its potential impacts on sustaining host to host transmission, particularly during epizootics. The actual physical, physiological or molecular mechanism underlying transmission during the early phase period has yet to be determined and it is possible that a combination of factors are involved, such as mechanical transmission and regurgitation of infectious bacteria into the bite wound by unblocked fleas. Although the actual means by which EPT occurs has yet to be discovered, recent experiments using biofilm-deficient *Y. pestis* mutants clearly indicate that biofilm is not required for EPT and fleas infected with mutants that overexpress biofilm actually transmitted plague less frequently by EPT than wild type *Y. pestis* or mutants that completely lack this substance or are deficient in its production (Vetter et al. 2010).

Regardless of the underlying mechanisms, the significance of EPT lies in the fact that until recently transmission by unblocked fleas generally was assumed to be minimal and relatively unimportant compared to transmission by blocked fleas. Eisen et al. (2006) recently demonstrated that this assumption is erroneous for *O. montana*, the aforementioned ground squirrel flea that is the primary vector of human plague in the North America. It should be noted that this flea's apparent role as an important plague vectors was always considered somewhat anomalous because it rarely became blocked and most laboratory experiments suggested it was a very inefficient vector. In their investigation, Eisen et al. (2006) fed *O. montana* fleas through mouse skin membranes covering an artificial feeder that was filled with blood containing *Y. pestis* at a concentration similar to what would be encountered by a flea feeding on a heavily bacteremic host ($10^9$ CFU/mL). Following the initial infectious feeding, the fleas were allowed to feed each successive day on susceptible laboratory mice and these mice were then monitored for evidence of *Y. pestis* infection for up to 21 days post-flea feeding. The results of the experiment indicated that *O. montana* fed highly bacteremic blood could transmit efficiently during their next blood meal (as soon as 3 h post-infection) and could continue to transmit for as long as 4 days after first becoming infected. Even more importantly, the efficiency of transmission by *O. montana* during this early phase period rivaled that seen for blocked *X. cheopis* and further analysis of the experimental results using a transmission model modified from Lorange et al. (2005) indicated that the level of EPT observed for *O. montana* is sufficient to sustain epizootic transmission in host populations and requires infestation rates less than those normally observed for these fleas on their natural hosts (California ground squirrels and rock squirrels). In addition to the high level of transmission observed, the ability of this flea to maintain epizootic spread in

the transmission model also depended on the notably brief extrinsic incubation time, which was as short as the time required for an infected flea to be able to take its next blood. This length of time, which in this experiment was as short as 3 h but not more than 1 day, resulted in an extrinsic incubation period much shorter than that required for even *X. cheopis* to become blocked. Later studies revealed that the ability of *O. montana* to transmit during early phase was not unique but shared by many other flea species, including *X. cheopis* (Eisen et al. 2007a, 2008a, b; Wilder et al. 2008a, b). This last finding is significant because it suggests that many flea species, including those that rarely, if ever, become blocked, could be important vectors for spreading plague during epizootics. The observation that *X. cheopis* can transmit efficiently by EPT, as well as by becoming blocked, further explains why this flea is such a dangerous plague threat to humans and its rat hosts. Another interesting finding is that fleas can be fed more than once on infected hosts and when provided with a second infectious feeding (booster feeding) after the 4 day period when EPT by *O. montana* normally ceases, these fleas typically experience a second period of EPT (Eisen et al. 2007b). Presumably, such booster feedings could occur in nature as fleas leave hosts that have died of plague, transmit *Y. pestis* to their new hosts by EPT, and then continue to feed on their new hosts until they become infected and can act as a second source of an infectious blood meal for the feeding flea, thereby renewing its ability to undergo another round of EPT. Obviously, such an event could increase the likelihood that plague epizootics will continue to spread among susceptible hosts, a process that is likely to endanger nearby humans and other accidental hosts.

## 11.5 Conclusions

In conclusion, research completed over the last decade or so has greatly improved our understanding of the factors influencing the spread of plague among rodents during epizootics. The lines of inquiry that have been particularly productive include: the role of host abundance and threshold densities in the initiation and persistence of epizootics; the impacts of climate on rodent host and flea vector populations, as well as the abilities of fleas to transmit *Y. pestis*; and the ability of unblocked fleas to transmit *Y. pestis* efficiently through EPT. The information gained from these studies is especially important because human risks of acquiring plague through the bites of infectious rodent fleas or other means typically increase markedly following the occurrence of plague epizootics among rodents. These same studies also can be useful to wildlife biologists and others who work with species, such as prairie dogs and black-footed ferrets, which are of conservation interest and highly susceptible to plague.

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