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Plague

Circular 1372

U.S. Department of the Interior
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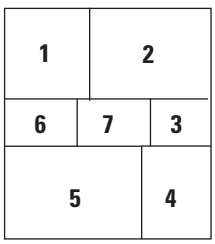

Cover Photos.

1. Plague warning sign (National Wildlife Health Center, NWHC).
2. Prairie dog on alert (U.S. Geological Survey, USGS).
3. Plague infected male *Xenopsylla cheopis* (Centers for Disease Control and Prevention, CDC/Dr. Pratt).
4. Cat carrying a mouse (Lxowle, Wikimedia Commons, CC BY SA).
5. Black-footed ferret (Ryan Hagerty, U.S. Fish and Wildlife Service, USFWS, Digital Library).
6. Rats (Chris Barber, Wikimedia Commons, CC BY SA).
7. Wright's stain of *Yersinia pestis* in a blood smear (Centers for Disease Control and Prevention, CDC).

Plague

By Rachel C. Abbott and Tonie E. Rocke

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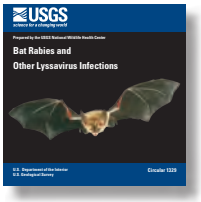

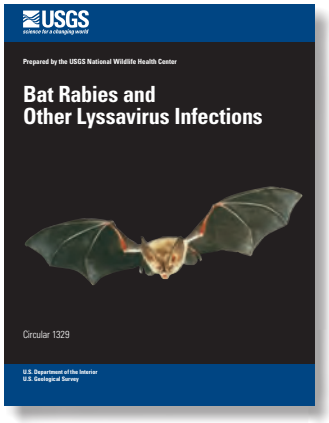

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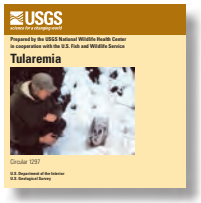

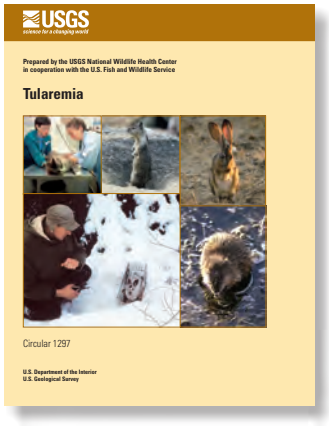

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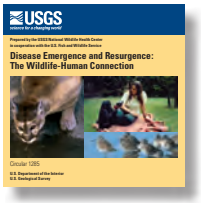

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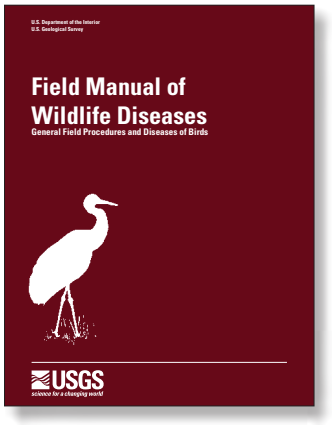

Field Manual of Wildlife Diseases—
General Field Procedures and Diseases of Birds
edited by Milton Friend and J. Christian Franson,
USGS Information and Technology Report 1999–001

Foreword

Plague has been described as "… one of the major calamities of history, not excluding wars, earthquakes, floods, barbarian invasions, the Crusades, and the last war [World War I]" (Zinsser, 1934). Despite this stark statement, there are many who consider plague to be a disease of the past. Still others, including many that reside in, or frequent, plague endemic areas have minimal concerns about plague. Contrasts in the number of human fatalities associated with modern plague outbreaks and those of the historic plague pandemics and advances in modern medicine for treatment of this disease are likely factors that influence current perspectives. Nevertheless, plague remains a serious global threat for modern society because of (1) its current stature as a naturally emerging infectious disease and (2) the potential for plague to be exploited for nefarious purposes. The latter situation was first attempted during the siege of Caffa in 1345 when plague-infected human corpses were catapulted into the city (see Box 1, this publication). Today, the catapult used may be a long-range ballistic missile or some other "advance" of modern technology. Further, plague poses a significant challenge for the long-term sustainability of some North American fauna, most notably the black-footed ferret.

Plague's "durability" over the ages as an infectious disease of major consequence for society stands in testimony to the ability of *Yersinia pestis* to convert changes within its established, time-specific, host-agent-environment relations into opportunities that favor agent perpetuation through disease persistence and geographic expansion. Clearly, the ecology of plague is highly complex, a factor that contributes to various aspects of its ecology not yet being fully understood. The authors of this publication have admirably addressed this complexity within the context of an extraordinarily rich, well-illustrated, easily read and highly insightful synopsis for one of the classic and intriguing diseases of humanity. There is much to be contemplated here, taken into consideration, and acted upon, especially as the further urbanization of society continues to enhance opportunities for sylvatic plague. This situation involves both the movement of animals into "metropolis" and the extension of "metropolis" into free-ranging animal habitats.

Advances in our knowledge of plague also provide insights for infectious diseases in general. These insights are important, as noted by Zinsser in his classic treatise on typhus fever:

> *"Infectious disease is one of the great tragedies of living things—the struggle for existence between different forms of life. … Incessantly, the pitiless war goes on, without quarter or armistice—a nationalism of species against species."*
>
> *(Zinsser, 1934, p. 7)*

Plague exemplifies the many facets of this battleground.

Milton Friend
September 11, 2011

[1]Zinsser, H., 1934, Rats, lice, and history: Boston, Massachusetts, Little, Brown and Company, 301 p.

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Topic Highlight Boxes

Figures

Tables

Words in **bold type** in the text, the topic highlight boxes, and the tables are defined in the Glossary.

Conversion Factors and Abbreviations

Inch/Pound to SI

Multiply	By	To obtain
	Length	
inch (in)	2.54	centimeter (cm)
foot (ft)	0.3048	meter (m)
mile (mi)	1.609	kilometer (km)
	Area	
acre	0.4047	hectare (ha)
	Mass	
pound, avoirdupois (lb)	0.4536	kilogram (kg)

Temperature in degrees Celsius (°C) may be converted to degrees Fahrenheit (°F) as follows:

°F=(1.8×°C)+32

Temperature in degrees Fahrenheit (°F) may be converted to degrees Celsius (°C) as follows:

°C=(°F-32)/1.8

Micrometer, µm

Milliliter, mL

Plague

By Rachel C. Abbott and Tonie E. Rocke

"Plague is not an extinct medieval monster, and epidemics still happen frequently." (Krasnov and others, 2006)

Synonyms

Black Death, bubonic plague, pneumonic plague, septicemic plague, pestis minor, peste, pestilential fever, pest

Overview

Plague is an **acute** infectious **zoonotic disease** caused by the highly virulent **bacteria** *Yersinia pestis*. **Infections** in humans most often result from the bites of **fleas** that feed on infected **rodents**, although person-to-person **transmission** can occur if the bacteria are inhaled. When someone is infected by *Y. pestis* and shows symptoms, the disease takes three main forms: bubonic, septicemic, and **pneumonic**. Without prompt antibiotic treatment, the **mortality rate** from **bubonic plague** can be as high as 60 percent, and the pneumonic form is nearly 100 percent lethal. Plague is broadly distributed around the world and is maintained by wild rodents and their fleas in natural **foci** or localized areas of infection. Outbreaks of plague develop periodically among **susceptible** rodents and can have severe impacts on the survival of threatened **species** of wild animals. **Epidemics** of plague continue among humans even in regions that have been unaffected for extended periods of time, prompting the World Health Organization (WHO) to identify plague as an **emerging disease**.

Background

Although the causative agent of plague, *Yersinia pestis*, was not identified until 1894, the disease is ancient, and the first descriptions of it may be found in the Bible. Passages in the book of Samuel describe a Philistine city in the 11th century afflicted by dying mice and numerous deaths of its residents who suffered swellings in the groin and thighs (Zietz and Dunkelberg, 2004). In the first century A.D., an outbreak of plague causing **buboes** and a high death rate may have occurred in Libya, Syria, and Egypt as described by Rufus of Ephesus (Zietz and Dunkelberg, 2004). Although it is difficult to definitively attribute plague as the cause of these early epidemics, it is generally accepted that there have been three **pandemics** of plague, the most infamous being the Black Death (Box 1).

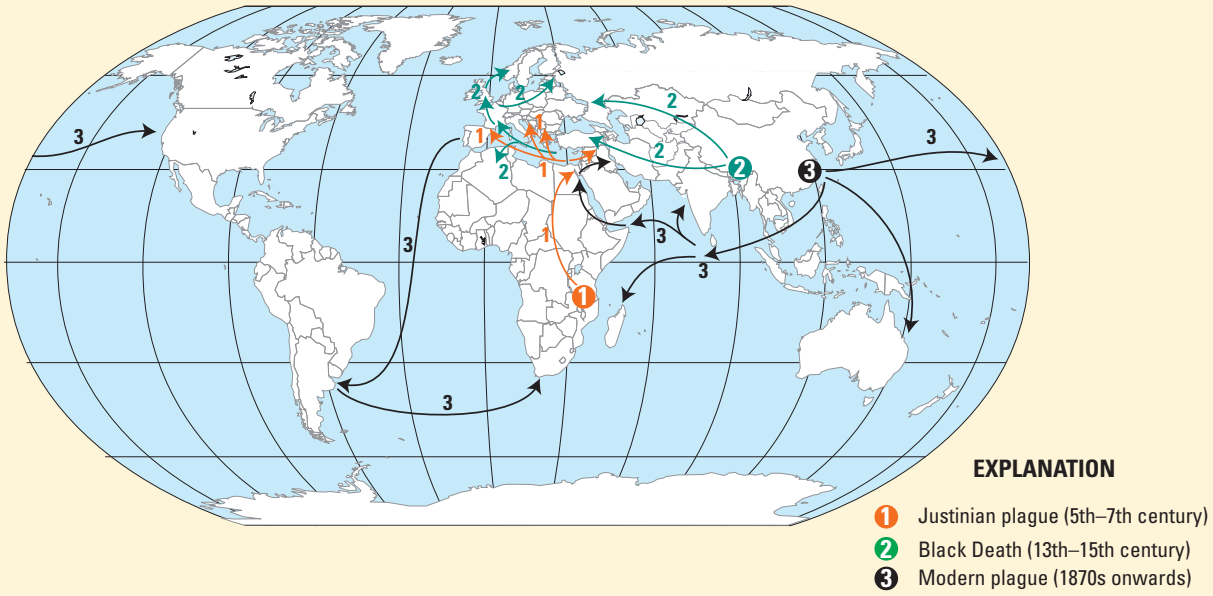
The 1894 discovery of the causative agent of plague at the onset of the plague epidemic in Hong Kong facilitated thorough research on this disease and resulted in rapid progress in the elucidation of the **epidemiology** of plague (table 1). Although the true cause of the Black Death and other ancient plagues may never be unequivocally determined, plague remains a real threat to both human and animal health. **Epizootics** of plague among threatened species of wildlife, epidemics causing numerous deaths and panic, and the threat of **bioterrorism** using the plague **bacillus** make *Y. pestis* not just a historical curiosity but a current menace.

Causative Agent

Plague is caused by *Yersinia pestis*, an oval-shaped bacteria that is unable to move on its own ("nonmotile") and that is shaped between the coccus, or spherical, and the bacillus, or rod-shaped, forms, thus making it a "coccobacillus" bacteria. Scientists can sometimes distinguish one kind of bacteria from another by applying a purple stain, the Gram stain, to samples that contain bacteria; another chemical that removes the Gram stain from some kinds of bacteria is applied to the sample, and those bacteria that retain the purple stain are "Gram positive" while those that do not retain the stain are "Gram negative." *Y. pestis* is Gram negative. A Wayson or Wright's stain can be used to diagnose plague, and when it is applied to a sample that contains *Y. pestis*, it tends to collect in either end of the *Y. pestis* structure, revealing the characteristic "safety pin" appearance of the bacterium (fig. 1).

Box 1 The Three Plague Pandemics

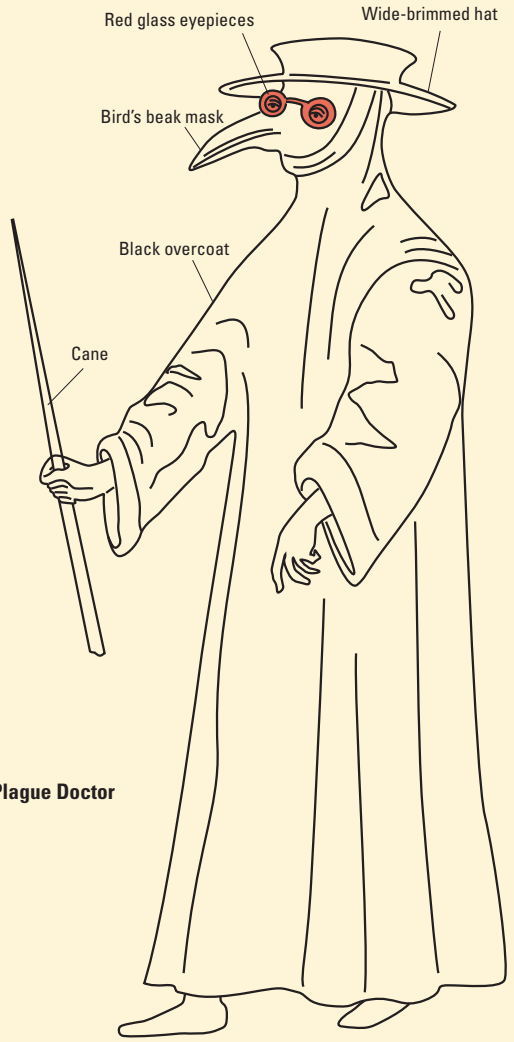
The first plague pandemic struck in the sixth century A.D., around the year 540 in the Byzantine Empire, and is known as the Plague of Justinian, after the reigning emperor. The pandemic probably originated in Ethiopia or Egypt and spread to Constantinople when ships loaded with grain also carried rats and their fleas. Primarily of the bubonic form, the disease spread through the Mediterranean region into Europe, Central and Southern Asia, and Arabia (see map). It has been estimated that 50–60 percent of the population in the region died between the years 541–700 (Perry and Fetherston, 1997; Gasper and Watson, 2001).



Routes followed by the three plague pandemic waves, labeled 1, 2, and 3. Circled numbers indicate the regions thought to be the origins of these pandemic waves. (Achtman and others, 1999)

The second pandemic is perhaps the most notorious. Known as the Black Death, the Great Pestilence, or the Great Plague, it arose in the 14th century and was responsible for killing one-quarter to one-third of Europe's population (Perry and Fetherston, 1997; Poland and others, 1994; Butler, 1998; Gage, 1998; Gasper and Watson, 2001). This pandemic probably began in Central Asia and spread through trade routes into the Crimea. It arrived in the port city of Caffa, in present day Ukraine, on the Black Sea in 1346. Caffa was an Italian walled city established by Genoa as a port for its merchant ships. In 1345, Mongol troops besieged the city, but they were severely hampered in their attack by an epidemic of plague. A witness described soldiers dying "as soon as the signs of disease appeared on their bodies: swellings in the armpit or groin caused by coagulating humors, followed by a putrid fever;" almost all soldiers "fell victim to sudden death after contracting this pestilential disease, as if struck by a lethal arrow which raised a tumor on their bodies." (Wheelis, 2002)
In an example of biological warfare, the survivors catapulted the corpses into the city of Caffa, thereby infecting the inhabitants of the city, whether by direct contact with infectious material or flea bites (Wheelis, 2002). The plague spread from Caffa and the Crimea into the Mediterranean region on rat-infested ships, and subsequently throughout Europe by land travel.

Outbreaks of plague, involving both the bubonic and pneumonic forms, continued sporadically throughout Europe for the next 300 years. One of the last major outbreaks was the Great Plague of London in 1665. Despite lack of knowledge about the cause and mode of transmission of plague, preventive measures were instituted to control these outbreaks and limit the spread of the disease. Forty-day restrictions on travel were imposed to decrease the spread of the disease, giving rise to the term "quarantine." Special protective clothing was developed for doctors to limit transmission. Because of its high mortality rate, plague had a lasting impact on European society. With the deaths of one-quarter to one-third of the population, most of who were peasants, the



The Plague Doctor

1. **The wide-brimmed black hat identified the wearer as a doctor and may have acted as a shield from infection.**
2. **Plague doctors wore bird's beak masks to draw plague, which was believed to be spread by birds at the time, away from the patient. The beak of the mask was filled with fragrant herbs to overcome the foul air associated with the spread of plague, as well as to mask the stenches of corpses and ruptured buboes.**
3. **Red glass eyepieces were attached to the mask to protect the wearer from evil.**
4. **Plague doctors wore a long black overcoat tucked around the mask to avoid exposing any skin. It was often coated with suet or wax to make it resistant to sputum and other bodily fluids.**
5. **A wooden cane was used to direct other people nearby to move patients or themselves. It may also have been used to examine the patient.**
6. **Leather breeches were worn under the overcoat to protect the legs and groin from infection.**

social structure changed dramatically, weakening the feudal system (Gage, 1998; Gasper and Watson, 2001). Culture, art, religion, and politics also changed because of plague (Stenseth and others, 2008).

The third pandemic, also known as the Modern Pandemic (Gage, 1998), began in China in 1855 in the south-central province of Yunnan and spread to Hong Kong and Canton by 1894, aided by movements of troops and refugees from a rebellion (Pollitzer, 1954; Perry and Fetherston, 1997). Steamships and trains spread the disease worldwide, reaching Bombay, India in 1896 and San Francisco in 1901 (see map). Many cities in Africa, Australia, Europe, Asia, North and South America were affected. *Y. pestis* disappeared from some areas, including Australia, after failing to become successfully established in maintenance cycles involving local fleas and animals (Poland and others, 1994).

Recently, the role of *Yersinia pestis* as the cause of the Black Death has been disputed (Duncan and Scott, 2005; Cohn, 2002; Twigg, 1984; Gilbert and others, 2004). Opponents believe other agents, such as anthrax (Twigg, 1984), a virus (Duncan and Scott, 2005), or typhus (Shrewsbury, 1970), were responsible for the pandemic based on what they see as significant inconsistencies in the epidemiology of the Black Death and present-day plague. They argue that the speed with which the disease spread across Europe, the lack of suitable rat species to spread the disease, the extremely high mortality, the long incubation period as evidenced by the successful 40-day quarantine period, and the directly infectious nature of the disease suggest the cause was an infectious agent other than *Y. pestis* (Duncan and Scott, 2005; Twigg, 1995). Others have pointed out that plague caused by *Y. pestis* can have different symptoms and that the organism may have evolved since the Black Death in such a way that current epidemics do not exactly replicate what was recorded during the Middle Ages (Wood and others, 2003; Stenseth and others, 2008; Raoult and Drancourt, 2002). Vectors other than fleas, such as lice, may have had a more prominent role in the transmission of ancient outbreaks of plague than is seen today (Drancourt and others, 2006; Houhamdi and others, 2006). In addition, the deoxyribonucleic acid (DNA) of *Y. pestis* has been identified by polymerase chain reaction (PCR) in the teeth of victims of the Black Death, leading researchers to conclude that these people suffered from septicemic plague, which probably caused their deaths (Drancourt and others, 1998; Raoult and others, 2000; Drancourt and Raoult, 2002). The anthrax bacillus was not found (Raoult and others, 2000). *Y. pestis* DNA has also been detected in the teeth (Drancourt and others, 2007; Drancourt and others, 2004) and skeletons (Wiechmann and Grupe, 2005) of victims of the Plague of Justinian. Subsequent testing of some of these bone and teeth samples by the use of a rapid diagnostic test (see Obtaining a Diagnosis) confirmed the presence of *Y. pestis* in skeletal remains (Bianucci and others, 2008; 2009).

Table 1. Timeline of important early events since the discovery of *Y. pestis.*

[Sources: Zietz and Dunkelberg, 2004; Gage, 1998; Butler, 1998; Olsen, 1981]

Year	Event
1894	Alexandre Yersin and Shibasaburo Kitasato independently find the plague bacterium in samples from humans and rats during the Hong Kong epidemic. Yersin is later credited with the discovery, because he correctly identified it as being Gram negative, whereas Kitasato described it as Gram positive. The organism is named *Bacterium pestis*.
1895	Wild rodents are confirmed as hosts of plague when wild marmots in Mongolia and Russia are found infected.
1896	Waldemar Haffkine develops a partially effective heat-killed vaccine and uses it during an outbreak in Bombay.
1897	Yersin proposes a link between rats and plague.
1897	Masanori Ogata in Taiwan suggests transmission of plague by flea bites.
1898	Paul-Louis Simond proposes the role of the flea in transmission of plague.
1900	The causative agent is renamed *Bacillus pestis*.
1900	The first human case in San Francisco occurs.
1902	The bacterium is found in commensal rats in the United States.
1905	William Glenn Liston provides proof of fleas as the vector of plague.
1908	Infected California ground squirrels are found in California.
1914	Charles James Martin and William Bacot describe transmission of *Y. pestis* by rat fleas, *Xenopsylla cheopis*, with blocked foreguts.
1923	The causative agent is renamed *Pasteurella pestis*.
1927	Ricardo Jorge identified wild living rodents as the reservoir of sylvatic plague.
1934	Ground squirrels and wood rats in United States are found to be infected in area outside of original focus. The first human case in the United States outside of California occurs and is associated with wild rodents.
1945	Insecticides (DDT) are used for first time to control an outbreak in Peru.
1946	Streptomycin is used for first time to treat cases of human plague and is shown to reduce the number of deaths caused by plague dramatically.
1963	Pierre Mollaret demonstrates experimental infection of animals in contact with contaminated soil.
1966–72	Killed vaccine used in soldiers in Vietnam is effective in preventing the bubonic form.
1970	The causative agent is renamed *Yersinia pestis*.

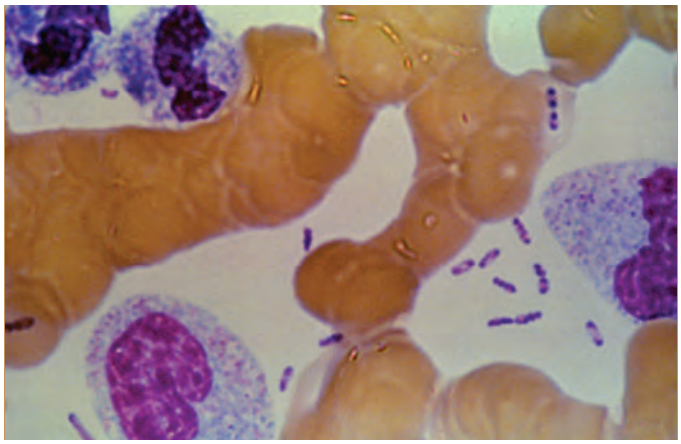


Figure 1. Wright's stain of *Y. pestis* in a blood smear showing its characteristic bipolar "safety pin" appearance. (Photo courtesy of the Centers for Disease Control and Prevention.)

Originally classified in the family Pasteurellaceae, *Y. pestis* is now considered to be a member of the family Enterobacteriaceae, based on similarities to *Escherichia coli* bacteria determined by studies of hereditary information contained in deoxyribonucleic acids (**DNA)** (table 2). The Enterobacteriacae are a large family of bacteria, and the Greek word "enteron" for "intestine," used in the family name, indicates the location in the body where some of the bacteria in the family are found. Although the **genus** *Yersinia* has 11 species, only 3 are **pathogenic** to humans: *Y. pestis*, *Y. pseudotuberculosis*, and *Y. enterocolitica* (table 3). Another species, *Y. ruckeri*, causes **enteric redmouth disease** in fish. Unlike *Y. pseudotuberculosis*, *Y. enterocolictica,* and other enterobacteria such as *Salmonella typhi* and *E. coli*, which are transmitted when feces are ingested in contaminated food and water (the **fecal-oral route**), *Y. pestis* has evolved the capability of transmission by **arthropods**, and it establishes infections in blood and **lymphoid tissues**.

Table 2. Taxonomy of *Yersinia* species

Kingdom	Eubacteria
Phylum	Proteobacteria
Class	Gammaproteobacteria
Order	Enterobacteriales
Family	Enterobacteriaceae
Genus	*Yersinia*
Species	*pestis, enterocolitica, pseudotuberculosis, frederiksenii, kristensenii, ruckeri, mollaretii, bercovieri, rohdei, aldovae, intermedia*

Table 3. *Yersinia* species pathogenic to humans.

Y. pestis	Plague	Flea bites, direct contact, airborne.
Y. enterocolitica	Yersiniosis	Foodborne.
Y. pseudotuberculosis	Pseudoappendicitis	Foodborne.

Genetic analysis has determined that *Y. pestis* is very closely related to *Y. pseudotuberculosis*, a bacterium that can cause symptoms similar to those of tuberculosis in animals but mimics appendicitis in humans. The two kinds of bacteria have identical **16S rRNAs** (Trebesius and others, 1998); they probably became separate species at least 12,000 years ago (Achtman and others, 1999, 2004; Achtman and Wagner, 2008). *Y. pestis* differs from *Y. pseudotuberculosis* by having two unique **plasmids**, pFra and pPla, that contain **genes** enabling *Y. pestis* to infect and spread within mammalian **hosts** and produce a transmissible infection in fleas (table 4). Different genes are expressed in the corresponding host, often according to the body temperature of the host, 98.6°F in **mammals** and 82.4°F or lower in fleas. The products of these genes enable the bacteria to survive and multiply in both mammals and fleas, thereby completing its life cycle. In particular, several genes located on the *Y. pestis* plasmids enable the bacteria to evade the host immune response as it establishes infection (Box 2).

Although fleas were considered to play a key role in the transmission of *Y. pestis* early in the history of plague (Simond, 1898), a mechanism was only first described in 1914, and it involved formation of a blockage in the flea's **foregut** (fig. 2) that would lead to **regurgitation** of infectious bacteria and transmission to the host (Bacot and Martin, 1914). Foregut blockage is reported to occur readily in the Oriental rat flea (*Xenopsylla cheopis*), considered the primary vector of plague in Asia and Africa (Poland and Barnes, 1979). However, not all species of fleas develop foregut blockage from *Y. pestis*, yet many are still able to transmit *Y. pestis* (Box 3). Some species, such as one of the ground squirrel fleas (*Oropsylla montana*), rarely develop foregut blockage, although they act as the primary vectors of *Y. pestis* to humans and certain **ground squirrels** in North America (Craven and others, 1993).

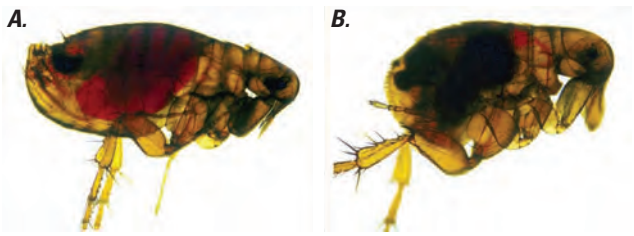
An alternative mechanism, called early-phase transmission (Eisen and others, 2006), does not involve blockage of the flea foregut. Although earlier studies had also documented transmission by fleas without foregut blockage, this mechanism was not initially considered important (Burroughs, 1947). Upon laboratory infection, a ground squirrel flea, *O. montana*, was able to immediately transmit the bacteria after becoming infected in the absence of blockage formation (Eisen and others, 2006). This early transmission of the bacteria, within 1–4 days of infection, by *O. montana* is in sharp contrast to fleas that transmit plague only after the formation of foregut blockage, which does not typically occur until at least 5 days after infection. The rat flea, *X. cheopis,* typically develops foregut blockage even later, 12–16 days after infection. In early-phase transmission, the **bacterial loads** decline over time, thus leading to decreased **transmission efficiency**, the rate at which a vector is able to transmit an infection to a host, expressed as the number of infections per the number of attempts. Subsequent blood meals on infected hosts, however, can boost the levels of bacteria in the fleas, such as the ground squirrel flea *O. montana*, to allow potential transmission after each subsequent infectious blood meal. Fleas with foregut blockage, on the other hand, will starve and generally die within 5 days of becoming blocked, limiting the period of transmission. Early-phase transmission by fleas without foregut blockage may explain the rapid spread of plague during epizootics in prairie dogs or other rodents (Eisen and others, 2006). Early-phase transmission by the human flea (*Pulex irritans*), which rarely develops foregut blockage, could also explain the rapid spread of plague in the Middle Ages in areas of Europe where the rat flea *X. cheopis* was rare (Eisen and others, 2006). Subsequent work revealed that the rat flea *X. cheopis* can transmit *Y. pestis* as early as 1 day after infection without foregut blockage, and it transmits *Y. pestis* in the early phase with the efficiency of blocked fleas (Eisen, Wilder, and others, 2007). In addition, the rat flea *X. cheopis* maintains a constant transmission efficiency until the formation of foregut blockage (Eisen, Wilder, and others, 2007).

Y. pestis has historically been classified into three **biovars** or **subspecies**, Antiqua, Mediaevalis, and Orientalis, according to biochemical characteristics (Devignat, 1951). Recently, a fourth biovar, Microtus, has been proposed (Zhou and others, 2004). **Strains** of *Y. pestis*, traditionally classified in the Mediaevalis biovar and obtained from plague foci associated with voles, rodents of the genus *Microtus*, in China, have been shown to have biochemical characteristics that distinguish them from other Mediaevalis strains (table 5). In addition, strains of *Y. pestis* within the Microtus biovar, although they are lethal to voles and other rodents, are not virulent in larger mammals including humans (Zhou and others, 2004). Other atypical strains of *Y. pestis* have been designated as Pestoides, and they differ from the other biovars biochemically (Anisimov and others, 2004). Molecular analyses of *Y. pestis* strains from around

Table 4. Virulence determinants of *Y. pestis*.

[DNA, deoxyribonucleic acid. Temperatures are in degrees Celsius. Information obtained from Perry and Fetherston, 1997; Hinnebusch, 2005]

Genes specifically required to infect the vertebrate host:	
F1 capsular antigen (F1 or Caf1)	At 37°C, *Y. pestis* bacteria form large gel-like capsules to resist becoming engulfed and digested by the host's white blood cells. This reaction does not develop in fleas.
Plasminogen activator (Pla protease)	At 37°C, destruction of blood clots acting to trap the bacteria enables *Y. pestis* to spread from the site of the fleabite systemically.
Yersinia outer proteins (Yops)	Activities that kill host cells and prevent host white blood cells from attacking the bacteria are required for virulence and growth within the liver and spleen. Suppression of the host's immune system permits survival of *Y. pestis* within naïve host white blood cells during early infection.
V antigen (LcrV)	Immunosuppressive activity stimulates host production of IL–10, a potent anti-inflammatory protein that leads to prevention of the formation of a mass of immune cells to surround the bacteria and allows *Y. pestis* to maintain growth in visceral organs.
Yersiniabactin siderophore system (Ybt)	Part of the iron uptake system, it enables *Y. pestis* to acquire iron in blood, where availability is limited by the host's iron-binding molecules.
pH 6 antigen	Its fibrillar structure may facilitate entry of *Y. pestis* into naïve white blood cells and the delivery of Yops proteins into other white blood cells. These proteins help to prevent the host from developing an inflammatory response to infection.
Rough lipopolysaccharides (LPS)	A major component of the outer membrane of *Y. pestis*, they enable the bacteria to resist being destroyed by proteins found in the host's blood.
Endotoxin	A structural component of the bacteria that is released mainly when the bacteria are broken down; it causes signs and symptoms associated with septic shock.
Genes required to produce a transmissible infection in the flea:	
Murine toxin (ymt)	When first discovered, it was associated with the ability of the bacteria to cause disease in mammals, particularly mice (Ajl and others, 1955). Later, it was shown to enhance survival of *Y. pestis*, and other Gram-negative bacteria, in the flea midgut. It is not required for morbidity or mortality in mammals.
Pigmentation locus (Pgm)	Named for the appearance of densely pigmented colonies of *Y. pestis* grown at 28°C on media containing hemin or Congo red dye, which was correlated with virulence. This region of DNA contains genes required for the formation of blockage in the flea proventriculus and the genes involved in iron uptake.
Hemin storage locus (Hms)	It enables *Y. pestis* to synthesize a biofilm facilitating infection of the surface of spines in the proventriculus of the flea. This colonization allows *Y. pestis* to resist being swept into the midgut by the pumping action of the proventriculus and eventually block the proventriculus, thus permitting fleaborne transmission.



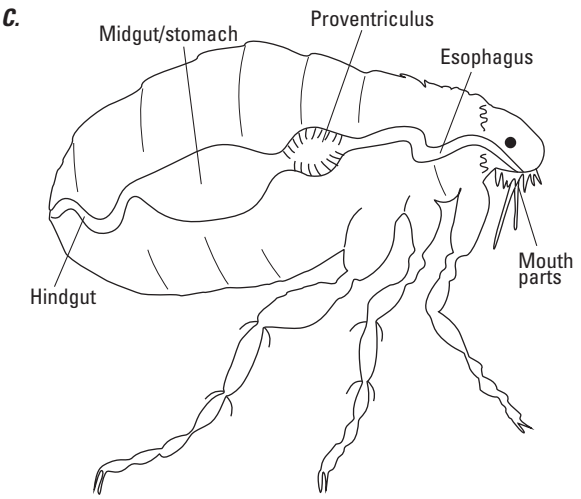


Figure 2. *X. cheopis* fleas immediately after feeding. ***A,*** uninfected flea and ***B***, infected, blocked flea. The blockage of the proventriculus prevents ingested blood from reaching the stomach and interferes with the valvular function of the proventriculus. As the starving flea repeatedly tries to feed, blood sucked from the mammalian host fills the esophagus, mixes with bacilli, and is regurgitated back into the mammalian host. Eventually, the blocked flea dies from starvation and dehydration. (Photos by permission; Hinnebusch, 2010) ***C,*** diagram of the digestive tract of the flea.

Box 2 Stealth and Deception by *Yersinia pestis*

"…the symptoms of plague…reflect the combination of stealth and deception effects, which cause the host to ignore the mortal danger of ongoing systemic invasion." (Brubaker, 2006)

Unlike other pathogens that do not kill their hosts to ensure transmission, *Y. pestis* is a highly virulent organism that can rapidly cause lethal disease in susceptible mammals. *Y. pestis* must reach high levels of bacteremia in the host, as much as 10 to 100 million organisms per milliliter of blood, for biting fleas to become infected (Hinnebusch, 2005). At the same time, *Y. pestis* must evade the host immune response to achieve these levels. Specific virulence factors (proteins which enable the bacteria to invade the host, elude the host immune response, and cause disease) allow *Y. pestis* to do just that.

As infected fleas feed, *Y. pestis* bacteria are deposited into the skin of the host. As few as 10 organisms can infect a susceptible host (Perry and Fetherston, 1997). The bacteria invade the lymphatic system and travel to regional lymph nodes, where severe inflammation results in the formation of buboes. This inflammatory response by the host may delay spread and multiplication of *Y. pestis*, but it generally does not block the disease process (Brubaker, 2006).

The bacteria then invade other host tissues. One virulence factor (Pla protease) facilitates the spread of *Y. pestis* from the site of the fleabite by breaking down components of blood clots that act to trap the bacteria (Sodeinde and others, 1992), while another (F1 protein) blocks phagocytosis (the ingestion and destruction) of bacteria by white blood cells during the initial spread of bacteria through host tissues (Friedlander and others, 1995). With this increased tissue invasiveness, the bacteria spread systemically and colonize visceral organs, especially the liver and spleen. Within these organs, other virulence factors act to prevent the host immune system from responding to the infection.

A major contributor to the stealth of *Y. pestis* is its use of several other virulence factors that inhibit or prevent the host from mounting a defense against disease. *Y. pestis* uses a needlelike appendage to target a host's white blood cells (Gendrin and others, 2010; Marketon and others, 2005). Using the needlelike appendage, *Y. pestis* injects proteins (Yops) directly into the host white blood cells. These proteins act to destroy immune functions of the host and prevent it from developing an inflammatory response that would inhibit or prevent further growth of the bacteria (Brubaker, 2006; Perry and Fetherston, 1997). *Y. pestis* can also inject into the host a different protein (V protein) that prevents the host from producing two of its own proteins that would be used to stimulate the formation of a mass of immune cells to surround the bacteria and prevent its growth (Nedialkov and others, 1997). In the case of plague, the host cells get a false message that tissue damage is under control, when, in fact, *Y. pestis* bacteria are rapidly taking over visceral organs, particularly the liver and spleen, leading to loss of function.

Eventually, as organs are destroyed, *Y. pestis* bacteria spill out into the bloodstream, causing septicemia. The structure of the outer membrane of *Y. pestis* confers some protection to the bacteria. The rough outer membrane allows the bacteria to resist destruction by proteins found in the host's blood (Porat and others, 1995). After the eventual death of the host from septicemia, infected fleas leave the carcass in search of new hosts for feeding. In this manner, the transmission cycle of *Y. pestis* is completed when these new hosts become infected.

Box 3 Fleaborne Transmission of *Y. pestis*

Day 0: Infection of the Flea

Fleas become infected by ingesting *Y. pestis* when they feed on a host mammal with at least 1 million bacteria per milliliter of blood (Engelthaler and others, 2000; Lorange and others, 2005).

Days 1–4: Early-Phase Transmission from Flea to Mammal

- Some species of fleas are able to transmit *Y. pestis* to a new mammal host as soon as 3 hours after becoming infected by what is now termed "early-phase transmission" (Eisen and others, 2006; Burroughs, 1947). Although the mechanism of this form of transmission is currently undetermined, mechanical transmission—that is, the bacteria do not invade the tissues of the flea or multiply—is unlikely because *Y. pestis* is unable to survive on the mouthparts of fleas for longer than 3 hours (Bibikova, 1977).

- The location of the bacteria within the flea's digestive tract is associated with the ability of the flea to transmit the infection to a host; esophageal infections are more readily transmitted than hindgut infections (Eisen and others, 2009; Eisen, Enscore, and others, 2007; Wilder, Eisen, Bearden, Montenieri, Gage, and Antolin, 2008; Wilder, Eisen, Bearden, Montenieri, and others, 2008).

- Early-phase transmission of *Y. pestis* to mammals continues in some fleas up to 4 days after they become infected (Eisen and others, 2006; Eisen, Wilder, and others, 2007; Eisen, Lowell, and others, 2007; Eisen, Holmes, and others, 2008; Eisen, Borchert, and others, 2008; Wilder, Eisen, Bearden, Montenieri, Gage, and Antolin, 2008; Wilder, Eisen, Bearden, Montenieri, and others, 2008). During this time, if the flea feeds on an uninfected host, the bacteria within the flea's digestive tract may be pushed further into its gut, leading to decreased infection transmission efficiency (Eisen, Lowell, and others 2007; Wilder, Eisen, Bearden, Montenieri, Gage, and Antolin, 2008; Wilder, Eisen, Bearden, Montenieri, and others, 2008).

- Some flea species, such as the cat flea (*Ctenocephalides felis*), rapidly eliminate *Y. pestis* in their feces making them poor transmitters (Eisen, Borchert, and others, 2008). In other fleas, *Y. pestis* multiplies within the digestive tract of the flea and forms dense clumps that are too big to pass into the hindgut.

Day 5 and Later: Transmission from Fleas with Blocked Foreguts to Mammals

- In some flea species, clusters of *Y. pestis* accumulate in the midgut and gradually extend into the proventriculus. The bacteria produce a biofilm to adhere to the surface of the spines lining the proventriculus, thus enabling them to resist being pumped into the midgut by the proventriculus (Jarrett, 2004; Hinnebusch and others, 2008).

- Between 3 and 9 days after the flea feeds on an infected host, the flea's proventriculus becomes blocked by the mass of bacilli that may extend into the esophagus. This blockage prevents ingested blood from reaching the flea's stomach and interferes with the valvular function of the proventriculus. Complete blockage of the proventriculus is not necessary for transmission of the bacteria from fleas to mammals; fleas with only partial obstruction can still transmit the bacteria.

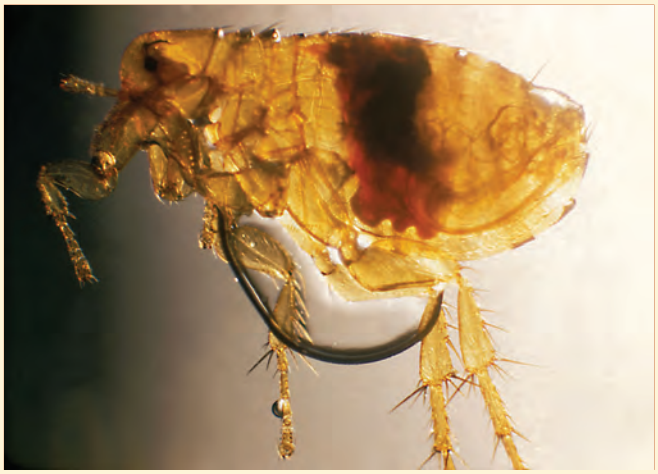
- As the starving flea repeatedly tries to feed, blood sucked from the mammalian host fills the esophagus, mixes with bacilli, and is regurgitated back into the mammalian host. As many as 11,000 to 24,000 bacilli may be regurgitated by the flea (Burroughs, 1947). Eventually, the blocked flea dies from starvation and dehydration, usually within 5 days (Burroughs, 1947).

Flea species that rarely develop foregut blockage, such as the ground squirrel flea *O. montana*, may continue to transmit the bacteria for long periods of time, especially after ingesting blood from additional infected hosts (Eisen, Lowell, and others, 2007).

For the rat flea *X. cheopis*, which can transmit *Y. pestis* both in the early-phase and after becoming blocked with equal efficiency, the period of potential transmission may be more than 1 month (Eisen, Wilder, and others, 2007; Engelthaler and others, 2000). Biofilm-induced blockages, or partial blockages, in fleas could be important for the maintenance of *Y. pestis* infections in fleas, allowing fleas to act as reservoirs of infection between transmission seasons (Gage and Kosoy, 2005; Vetter and others, 2010).

Transmission from Mammals to Fleas

- In a mammal, *Y. pestis* bacilli travel from the site of the flea bite to the regional lymph nodes, where they multiply rapidly and cause the formation of a bubo (swollen lymph node).
- The infection spreads into the bloodstream, and bacilli spread to the liver, spleen, and other organs, where they continue to multiply. The infection may progress to septicemic and pneumonic plague.
- High levels of bacilli in the blood increase the chances of infecting fleas that feed on the infected mammal. When the mammal dies, resident fleas depart to search for other hosts, including humans, thereby spreading the disease.



Plague infected male flea 28 days after feeding on an inoculated mouse. Photo from the Centers for Disease Control and Prevention (CDC).

the world have further subdivided the biovars and Pestoides into eight **populations** of *Y. pestis* (Achtman and others, 2004). However, these molecular groupings do not directly correspond to the biochemical characteristics associated with biovars, and different strains within a molecular grouping may have different biochemical characteristics. Historically, the original three biovars have been linked to the three plague pandemics. Recent evidence based on **genotyping** of strains indicates that the Orientalis biovar was involved in all three pandemics (Drancourt and others, 2004; Drancourt and others, 2007). Analysis of **rRNA gene restriction** patterns has divided strains of *Y. pestis* into 16 **ribotypes** (Guiyoule and others, 1994). Ribotypes B and O made up the majority of the strains studied and were associated with the biovars responsible for the three pandemics.

Geographic Distribution

Plague probably originated in Central Asia and has since spread worldwide. Natural foci of plague, "geographical areas in which **reservoir** and vector species coexist and in which the infection is common" (Biggins and Kosoy, 2001), occur on all inhabited continents, except Australia, in areas where populations of suitable rodent reservoirs and flea vectors are found (fig. 3). Appropriate climatic and landscape conditions must be present. In general, natural foci of plague occur between parallels 55°N and 40°S in **tropical** and **subtropical** regions as well as warmer parts of **temperate latitudes**. Tropical foci tend to be in cooler, relatively dry upland areas, for example, the central highlands in Vietnam and Madagascar and mountains of Tanzania. Areas such as **semideserts**, **steppes**, **savannas**, and **prairies** have low annual precipitation or prolonged dry seasons that limit the growth of thick woody vegetation, and plague is found in these areas because they are suitable habitat for rodents and their fleas. Plague is not found in **desert** areas, which have few or no rodents and are excessively hot and dry, or in large forested areas. Natural foci of plague in animals are found in North and South America, Africa, Asia, and limited areas of southeastern Europe, and they cover only 6–7 percent of Earth's dry land (Anisimov and others, 2004). In the United States, **sylvatic** plague is **enzootic** west of the 100th meridian (Cully and others, 2000), the historical boundary between the humid east and the dry west, where irrigation is required for successful agriculture (fig. 4). It is unclear why plague is nearly absent east of this line, because susceptible rodent species and flea vectors are present east of the line as well as west (Cully and Williams, 2001; Cully and others, 2006). Plague is most **prevalent** in the southwest (New Mexico, Arizona, Colorado, Utah) and the Pacific region (California, Oregon, Nevada). Species of rodents, and their fleas, within these foci vary according to geographic region (table 6).

During the period 1954–2003, plague in humans was reported from 39 countries (Tikhomirov, 1999; World Health Organization, 2004). In the 1970s, most cases of plague in humans were reported from Asia, particularly Vietnam. However, more recently most cases occur in African countries (fig. 5), especially Madagascar. In the United States, human cases are most frequent in the Southwest (New Mexico, Arizona, Colorado, Utah) and the Pacific regions (California, Oregon, Nevada).

Table 5. Classification systems of *Y. pestis* strains.

[In the classification of bacteria, strains with sufficiently distinct characteristics (for example, chemical or molecular) are biovars, or considered a subspecies of a taxonomic species (Devignat, 1951). A ribotype is a grouping of bacteria within a species based on similarities in ribosomal ribonucleic acid (rRNA) (Guiyoule and others, 1994). Blank cells indicate there is no corresponding biovar or ribotype for the molecular grouping.]

Molecular grouping[1]	Biochemical characteristics		Biovar	Biochemical characteristics			Corresponding ribotypes
	Ability to reduce nitrate	Ability to ferment glycerol		Ability to reduce nitrate	Ability to ferment glycerol	Ability to ferment arabinose[2]	
1.ANT	Yes	Yes	Antiqua	Yes	Yes	Yes	F to O
2.ANT	Varies	Yes	Antiqua	Yes	Yes	Yes	F to O
2.MED	No	Varies	Mediaevalis	No	Yes	Yes	O and P
1.ORI	Yes	Varies	Orientalis	Yes	No	Yes	A to G
0.PE4	No	Yes	Microtus[3]	No	Yes	No	
0.PE1	No	Yes					
0.PE2	Yes	Yes					
0.PE3	Yes	Yes					

[1]Achtman and others, 2004.

[2, 3] Zhou and others, 2004

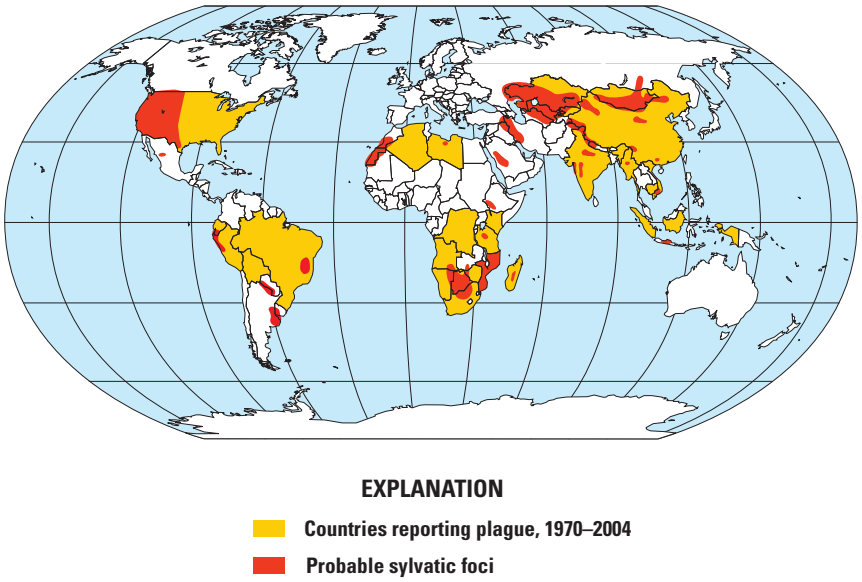


Figure 3. Global distribution and natural foci of plague. Natural foci of plague have become established in local rodent and flea populations on all inhabited continents except Australia. Sylvatic plague can act as a source of infection for humans. Since 1954, plague in humans has been reported from more than 35 countries. (From *http://www.cdc.gov/ncidod/dvbid/plague/resources/plagueFactSheet.pdf*)

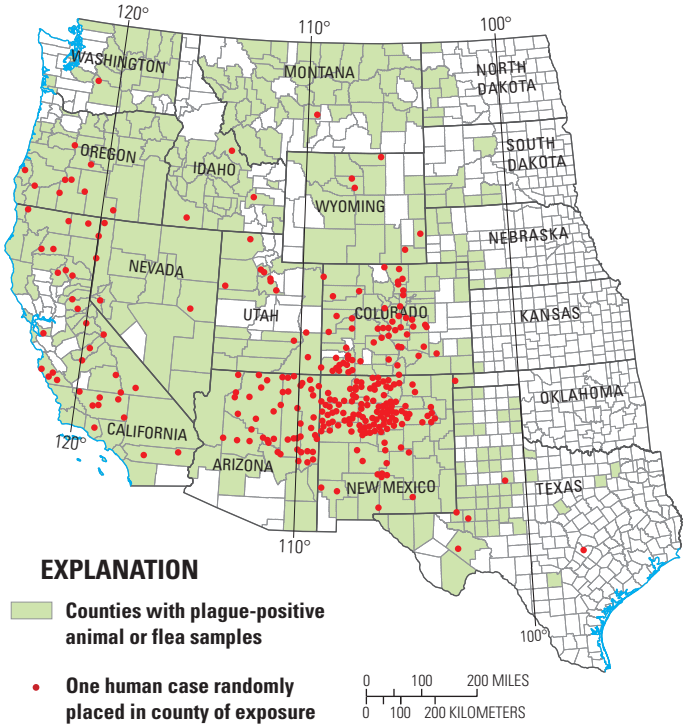


Figure 4. Areas in the United States where plague is found in animals, fleas, and humans. In the United States, most counties with plague-positive animal or flea samples (1970–2009; shaded areas) are located west of the 100th meridian, where the infection is enzootic. Cases of plague in humans (1970–2007; dots) are most prevalent in the southwest and Pacific regions. (Map based on information from Ken Gage, CDC)

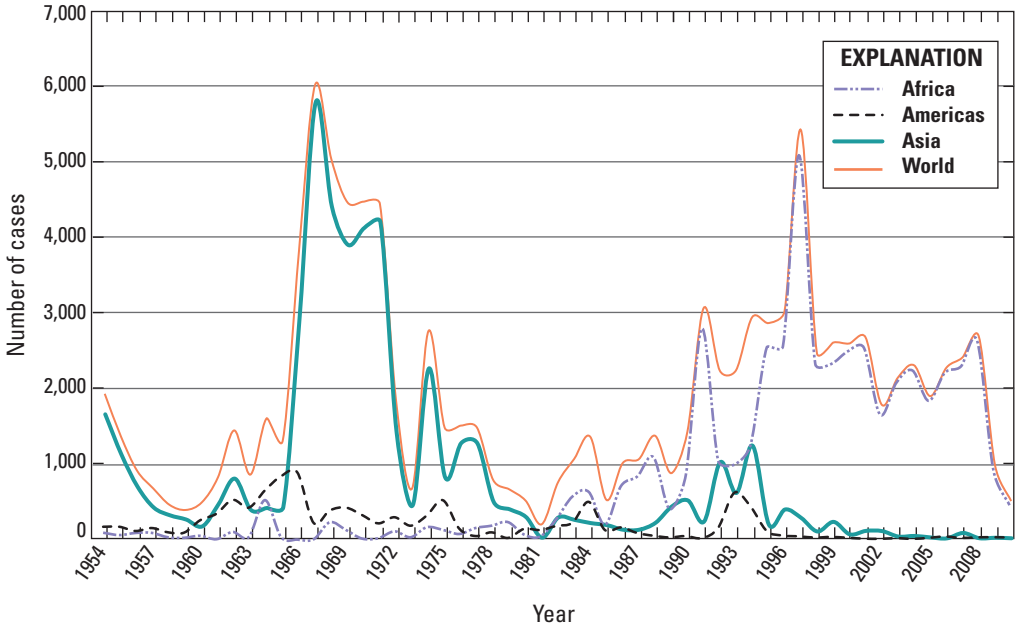


Figure 5. Human cases of plague, by region, 1954–2010. In the 1970s, most human cases of plague were reported from countries in Asia, particularly Vietnam. More recently, most cases are in African countries, especially Madagascar. War and political turmoil in Asian and African countries disrupted sanitation and medical services, contributing to the increased risk of transmission of *Y. pestis* from rodents to humans. (Data from World Health Organization, 2010; World Health Organization, 2000; World Health Organization, *www.who.ing/whosis/whostat/2011/en/index.html*)

Table 6. Major wild rodent hosts and flea vectors of natural plague foci.

[Sources: Gage, 1998; Gratz, 1999]

Region	Wild rodent hosts		Primary vectors	
	Common name	Scientific name	Common name	Scientific name
		North America		
Southwest	Prairie dog	*Cynomys* species	Prairie dog fleas	*Oropsylla* species
	Ground squirrel	*Spermophilus variegatus*	Ground squirrel fleas	*Oropsylla montana*
		Spermophilus spilosoma		*Thrassis* species
		Spermophilus lateralis		*Opisocrostis* species
	Antelope ground squirrel	*Ammospermophilus leucurus*		*Oropsylla idahoensis*
	Chipmunk	*Tamias* species		*Hoplopsyllus anomalus*
	Wood rat	*Neotoma albigula*	Chipmunk fleas	*Eumolpianus eumolpi*
		Neotoma mexicana	Wood rat fleas	*Orchopeas neotomae*
	Deer mouse	*Peromyscus maniculatus*		*Orchopeas sexdentatus*
		Peromyscus species	Mouse fleas	*Malaraeus* species
				Aetheca wagneri
				Orchopeas leucopus
Pacific Coast	Ground squirrel	*Spermophilus beecheyi*	Prairie dog fleas	*Oropsylla* species
		Spermophilus beldingi	Ground squirrel fleas	*Oropsylla montana*
		Spermophilus lateralis		*Thrassis* species
	Chipmunk	*Tamias* species		*Opisocrostis* species
	Wood rat	*Neotoma fuscipes*		*Oropsylla idahoensis*
		Neotoma cinerea		*Hoplopsyllus anomalus*
	Deer mouse	*Peromyscus maniculatus*	Chipmunk fleas	*Eumolpianus eumolpi*
	Vole	*Microtus californicus*	Wood rat fleas	*Orchopeas neotomae*
		Microtus montanus		*Orchopeas sexdentatus*
			Mouse fleas	*Malaraeus* species
				Aetheca wagneri
				Orchopeas leucopus
West	Ground squirrel	*Spermophilus elegans*	Prairie dog fleas	*Oropsylla* species
		Spermophilus armatus	Ground squirrel fleas	*Oropsylla montana*
		Spermophilus townsendi		*Thrassis* species
	Prairie dog	*Cynomys* species		*Opisocrostis* species
	Fox squirrel	*Sciurus niger*		*Oropsylla idahoensis*
				Hoplopsyllus anomalus

Table 6. Major wild rodent hosts and flea vectors of natural plague foci.—Continued

[Sources: Gage, 1998; Gratz, 1999]

Region	Wild rodent hosts		Primary vectors	
	Common name	Scientific name	Common name	Scientific name
		North America (continued)		
West (continued)			Chipmunk fleas	*Eumolpianus eumolpi*
			Wood rat fleas	*Orchopeas neotomae*
				Orchopeas sexdentatus
			Mouse fleas	*Malaraeus* species
				Aetheca wagneri
				Orchopeas leucopus
		South America		
	Commensal rat	*Rattus rattus*	Rat fleas	*Xenopsylla cheopis*
	Rice rat	*Oryzomys* species	Wild rodent fleas	*Polygenis* species
	Cotton rat	*Sigmodon* species		*Pleochaetis dolens*
	South American field mouse	*Akodon* species		
	Cane mouse	*Zygodontomys* species		
		Bolomys lasiurus		
		Oryzomys species		
	Leaf-eared mouse	*Phyllotis* species		
	Tree squirrel	*Sciurus stramineus*		
	Wild cavies and domestic guinea pig	*Cavia* species		
		Galea species		
		Africa		
	Multimammate mouse	*Mastomys* species	Gerbil fleas	*Xenopsylla philoxera*
	Unstriped grass mouse	*Arvicanthis* species	Rat fleas	*Xenopsylla brasiliensis*
	Swamp rat	*Otomys* species		*Xenopsylla cheopis*
	Gerbil	*Tatera* species	Wild rodent fleas	*Dinopsyllus* species
		Desmodillus species		
		Gerbillus species		
	Spring hare	*Pedetes capensis*		
	Groove-toothed cheek rat	*Pelomys* species		

Table 6. Major wild rodent hosts and flea vectors of natural plague foci.—Continued

[Sources: Gage, 1998; Gratz, 1999]

Region	Wild rodent hosts		Primary vectors	
	Common name	Scientific name	Common name	Scientific name
		Eurasia		
Central Asia	Gerbil	*Meriones* species	Gerbil fleas	*Xenopsylla* species
		Rhombomys opimus		*Nosopsyllus* species
	Marmot	*Marmota* species		*Coptopsylla* species
	Ground squirrel	*Spermophilus* species	Marmot fleas	*Oropsylla* species
	Voles	*Microtus* species		*Rhadinopsylla* species
		Eothenomys species		*Citellophilus* species
				Callopsylla species
			Ground squirrel fleas	*Citellophilus tesquorum*
				Neopsylla species
			Vole fleas	*Amphipsylla* species
				Rhadinopsylla species
Vietnam and Myanmar[1]	Black rat	*Rattus rattus*	Rat fleas	*Xenopsylla cheopis*
	Polynesian rat	*Rattus exulans*		*Xenopsylla astia*
	Norway rat	*Rattus norvegicus*		
	Bandicoot rat	*Bandicota indica*		
	Forest rat	*Rattus nitidus*		
	House shrew[2]	*Suncus murinus*		
India	Indian gerbil	*Tatera indica*	Gerbil fleas	*Xenopsylla astia*
	Rat	*Rattus* species		*Nosopsyllus punjabensis*
	Bandicoot rat	*Bandicota bengalensis*		
		Bandicota indica		
	Metad	*Millardia meltada*		
	Indian field mouse	*Mus booduga*		
	Spiny field mouse	*Mus platythrix*		
	Indian bush rat	*Golunda ellioti*		
	Palm squirrel	*Funambulus* species		
Java	Polynesian rat	*Rattus exulans*	Rat fleas	*Xenopsylla cheopis*
	Black rat	*Rattus rattus*		*Stivalius cognatus*
	White-bellied mountain rat	*Rattus niviventer*		
	Malayan wood rat	*Rattus tiomanicus*		
	House shrew[2]	*Suncus murinus*		

[1]Hosts in Vietnam and Myanmar are generally considered to be commensal rather than sylvatic.

[2]Nonrodent species, member of the Insectivora order.

Patterns and Trends

Since the 1950s, two peaks have been noted in the number of human plague cases in the world (fig. 5). The first peak was during the 1960s and 1970s, primarily in Asia, especially Vietnam (Tikhomirov, 1999). The second peak began in the 1980s in African countries, particularly Mozambique and Madagascar (Tikhomirov, 1999). During both time periods, war and political unrest in these countries contributed to increased poverty among inhabitants and the disruption of sanitation and medical services, including rodent and flea control and **surveillance**, which increased the risk of transmission of *Y. pestis* from wild rodents to commensal rodents to humans.

Complacency can also contribute to decreased surveillance and control programs in areas where human cases of plague have not occurred for many years. Several epidemics of plague have occurred in regions unaffected by plague for extended periods of time (table 7), indicating reactivation of established foci or importation of *Y. pestis* from outside sources. In several of these outbreaks, natural events, such as drought, flooding, and earthquakes, contributed to the spread of plague into urban areas. In the Madagascan city of Mahajanga, plague was probably reintroduced when infected rats were inadvertently transported from the highlands, where plague is endemic, to urban markets. *Y. pestis* infection then spread to Asian house shrews, the dominant small mammal, and to people (Chanteau and others, 1998; World Health Organization, 2006). The infection is now enzootic among shrews and has caused several subsequent outbreaks among people in the city (World Health Organization, 2006). Although the source of the 2003 epidemic in Algeria is unknown, *Y. pestis* was detected 2 years later in rat fleas, *X. cheopis*, from rodents captured in and around houses, and it suggests the establishment of an enzootic cycle (Bitam and others, 2006). The potential for spread of the disease internationally from the port cities involved in these reemergent epidemics highlights the importance of timely and vigilant surveillance of *Y. pestis* infections in rodents and fleas for controlling its reoccurrence.

New strains of *Y. pestis* have also recently been discovered. In Madagascar, all strains of *Y. pestis* were classified as the Orientalis biovar, ribotype B until 1982 (Guiyoule and others, 1997). Three other ribotypes, Q, R, and T, were obtained from human cases and rodents in the highlands of the country in 1982, 1983, and 1994, respectively (Guiyoule and others, 1997). The strain obtained in the outbreak of pneumonic plague in India in 1994 was identified as a new ribotype, designated S (Panda and others, 1996). The recent appearance of new biotypes may indicate evolution of *Y. pestis* over time. Whether or not these changes confer selective advantages to the bacteria remains unanswered.

In the United States, *Y. pestis* was first introduced on the west coast in San Francisco. A retrospective study of spatially and temporally unique plague cases sought to elucidate the route and speed at which plague initially spread eastward (Adjemian and others, 2007). Among cases of plague in humans, domestic animals, and wildlife from 1900 to 2005, cases representing the initial occurrence of plague in a specific region were found up until 1966. Thus, plague spread more

Table 7. Examples of the reemergence of human plague.

[Period of silence refers to time since last outbreak of plague]

Date	Country	Period of silence	Number of deaths per number of cases	Contributing factors	Reference
1989	Botswana	38 years	12/173	Increased rain led to rich harvest and an abundant rodent population that moved into villages.	Tikhmorov, 1999.
1991	Madagascar	More than 60 years	Not stated/41	Outbreaks were associated with Asiatic shrews.	Chanteau and others, 1998.
1994	India	About 30 years	54/876	Earthquake and flooding disrupted rat populations, causing increased rat contact with humans.	Tikhmorov, 1999.
1994	Mozambique	More than 15 years	3/226	Drought drove wild rodents into a village and increased hunting of rodents by villagers.	Barreto and others, 1995.
1996	Zambia	More than 30 years	26/319	Outbreak linked to flooding that drove rats into villages.	Tikhomorov, 1999; World Health Organization, 1997.
1997	Jordan	More than 80 years	Not stated/12	Outbreak of pharyngeal plague caused by consumption of camel meat.	Arbaji and others, 2005.
2003	Algeria	More than 50 years	1/18	Outbreak occurred at harvest time when rats entered a village searching for grain.	Bertherat and others, 2007.
2009	Libya	25 years	1/12	Outbreak from undetermined source in seminomadic community.	Tarantola and others, 2009.

than 1,395 miles (mi) in just over 40 years, travelling at a speed of 28–54 mi per year, but it has not continued its spread beyond the 103rd meridian in the subsequent 60 years (fig. 6) (Adjemian and others, 2007). It has become endemic in the southwest as well as in the Pacific region (fig. 4).

Plague has recently developed in new areas of the United States. In the 1990s, surveillance for *Y. pestis* infection or exposure in rodents and **carnivores** revealed the spread of the bacteria to Montana, Nebraska, and North Dakota, states that were previously thought to be free of plague (Centers for Disease Control and Prevention, 1994). Plague was also identified in two fox squirrels and a roof rat in Dallas, Tex. in 1993, a site far removed from the known plague foci in western Texas, although animals that had developed antibodies against *Y. pestis* (were seropositive) have occasionally been observed east of the 100th meridian in that state (Centers for Disease Control and Prevention, 1994). A **die-off** of black-tailed prairie dogs from plague occurred in 1997 in Kansas, an area where plague had not been documented since 1950 (Cully and others, 2000). A plague epizootic also broke out recently in 2008 among prairie dogs in South Dakota (U.S. Geological Survey, 2008a), a site where plague had not previously been documented. Similarly, the eastward spread of human plague can be seen from 1944 through 1993 (fig. 7) (Centers for Disease Control and Prevention, 1994; Perry and Fetherston, 1997). It is unknown if the distribution of plague will expand eastward in the future.

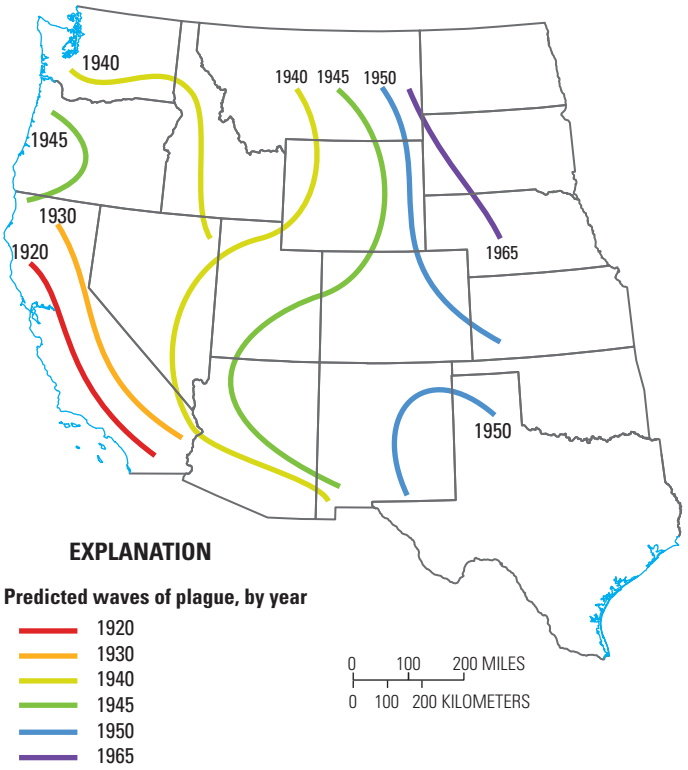


Figure 6. Predicted waves of plague movement from the west coast of the United States eastward into the Great Plains. (Based on Adjemian and others, 2007)

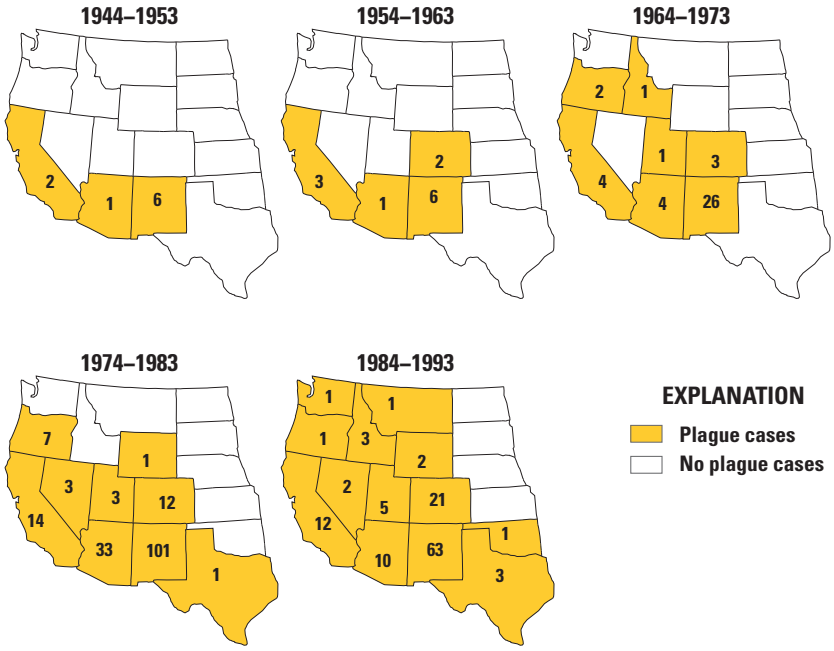


Figure 7. The spread of human cases of plague in the western United States, 1944–93. Similar to the expansion of sylvatic plague, cases of human plague in the United States have spread eastward. (From Centers for Disease Control, 1994)

Species Susceptibility

In considering species susceptibility to *Y. pestis*, it is important to differentiate between susceptibility to **infection** and susceptibility to **disease**. In this report, "plague" will be used to indicate clinical disease caused by infection with the bacteria *Y. pestis*.

Human Infections

Humans are extremely susceptible to plague, and most cases result from transmission by flea bites. People also can become infected when they inhale infectious respiratory droplets, eat infected animals, are bitten or scratched by infected animals, and come into direct contact with infected tissues or fluids (Box 4). Most human cases present as one of three main forms: bubonic, septicemic, and pneumonic plague. Other less common forms include **pharyngeal** and **meningeal** plague (Box 5). With appropriate and timely antibiotic treatment, most people usually recover. Forty to 60 percent of untreated cases of bubonic plague are likely to be fatal (Poland and Barnes, 1979), whereas untreated cases of septicemic and pneumonic plague are nearly 100 percent fatal and result from **septic shock**. In the United States, the average **fatality rate** is about 14 percent (Craven and others, 1993).

Wild and Laboratory Animal Infections

More than 200 species of mammals can be infected by *Y. pestis* (table 8), although not all species are susceptible to clinical disease (table 9). Susceptibility to **morbidity** and mortality caused by *Y. pestis* varies among both individuals and populations of a species.

Table 8. Animals naturally infected with *Y. pestis*.

[Data represent relative numbers of species in each group and may not include all species ever found to have been infected. Data from Poland and Barnes, 1979; Pollitzer, 1954]

Group	Number of species
Rodents	More than 200
Carnivores	20
Lagomorphs	14
Insectivores	4
Artiodactyla	3
Primates	2
Marsupials	2

Rodents

Rodents are the major group of animals infected by *Y. pestis*, and some species may act as reservoir or **amplifying hosts** for the organism. Some species, such as gerbils, marmots, deer mice, and California voles, demonstrate varied responses to infection by *Y. pestis*; some individuals suffer high **bacteremias** and death, while others survive after only mild illness. Within a population of hosts, certain individuals may be susceptible to disease while others are more **resistant**. Populations of the same species in different geographical locations may differ dramatically in their susceptibility to disease. Resistance within a population may be a result of genetic selection due to past exposure to plague. Northern grasshopper mice from Colorado, where plague is present, were much more resistant to disease than mice of the same species in a plague-free area of Oklahoma (Thomas and others, 1988). Deer mice and California voles also show differences in susceptibility to plague in different populations (Quan and Kartman, 1956, 1962).

Other rodent hosts are more uniformly susceptible to plague and undergo dramatic die-offs during epizootics of plague. These hosts are often referred to as "amplifying hosts." Colonies of prairie dogs, such as black-tailed prairie dogs and Gunnison's prairie dogs, may be completely decimated by plague (Lechleitner and others, 1968; Rayor, 1985; Cully and others, 1997; Pauli and others, 2006). Other highly susceptible species include California ground squirrels and rock squirrels, although mortality rates appear to be lower in these species than in prairie dogs (Meyer and others, 1943; Lang, 2004). Occasional epizootics also occur in other prairie dog species, chipmunks, wood rats, ground squirrels, deer mice, and voles.

Among laboratory animals, guinea pigs are susceptible to disease, but they survive longer than mice (Poland and Barnes, 1979; Gratz, 1999).

Shrews

The Asian house shrew, an insectivore, is susceptible to infection by *Y. pestis*, although it is moderately resistant to disease; none of 1,757 shrews examined for plague showed any gross abnormalities despite the presence of *Y. pestis* in their spleens (Marshall and others, 1967). In addition, serology revealed antibodies indicating prior exposure to *Y. pestis* (Marshall and others, 1967). In Mahajanga, Madagascar, 43 percent of house shrews caught after a plague epidemic in 1995 had antibodies against *Y. pestis* (Boisier and others, 2002). Other species of shrews, such as tree shrews, have also been found to be seropositive against *Y. pestis* (Suntsov and others, 1997). In plague-endemic areas of North America, shrews are rarely captured and tested for evidence of *Y. pestis* infection.

Lagomorphs

At least 14 species of **lagomorphs** have been shown to be naturally infected by *Y. pestis* (Pollitzer, 1954). Rabbits and hares are extremely susceptible to disease caused by *Y. pestis*. During rodent epizootics, they may suffer high mortality. **Pikas**, in central Asia, are also important reservoir hosts for *Y. pestis* (Gage and Kosoy, 2005).

Ferrets and Polecats

Ferrets and polecats vary in their susceptibility to plague. Domestic ferrets, like many other carnivores, are fairly resistant; experimental infection of domestic ferrets by **subcutaneous** injection of *Y. pestis* failed to produce **clinical signs** in eight of eight ferrets (Williams and others, 1991). Animals that received higher doses of **inocula** developed antibodies against *Y. pestis*, whereas those that received low doses did not develop antibodies, or "**seroconvert**." Similarly, two Siberian polecats also did not show clinical signs after experimental infection with low doses of *Y. pestis*; these animals did not seroconvert (Williams and others, 1991). In another experiment, 22 polecats were placed in pens where black-footed ferrets had either died of plague or were missing and presumed to be dead in underground burrows (Godbey and others, 2006). Only three polecats developed antibodies against *Y. pestis*; one of these animals died of plague. One animal that removed a plague-infected ferret carcass from its burrow did not develop antibodies to *Y. pestis*, a perhaps not surprising result considering very large numbers of plague bacteria typically appear to be required to infect animals by oral exposure (Butler and others, 1982).

In contrast, black-footed ferrets appear to be highly susceptible to plague. The first case was reported in 1993 in a captive animal in Wyoming after it was accidentally exposed to captive white-tailed prairie dogs (Williams and others, 1994). Approximately 3–4 days later, the ferret died of plague. It was presumed to have been orally exposed, possibly by ingestion of an infected rodent. In a similar incident in 1995, 30 captive ferrets were accidentally fed pieces of prairie dog meat infected with *Y. pestis* or meat that had come into contact with infected pieces (Godbey and others, 2006). Of these animals, 27 (90 percent) either died or went missing and were presumed to be dead in underground burrows; all the dead ferrets tested positive for plague and showed clinical signs, such as internal hemorrhages and congested lungs, consistent with plague (Godbey and others, 2006).

A subsequent study found that Siberian polecats are susceptible to plague following higher doses of *Y. pestis* in experimental infections; the mortality rate was 88 percent (or 29 of 33) (Castle and others, 2001). Only 6 of 33 polecats developed antibodies against *Y. pestis* and of these, 4 survived. Three of the surviving animals were reexposed to *Y. pestis* by ingestion of an infected mouse, and they did not develop clinical disease, suggesting at least partial protection by the antibodies (Castle and others, 2001). Thus, polecats are susceptible to disease caused by *Y. pestis*, but the outcome of infection depends on the dose of *Y. pestis* and the route of exposure (flea bite or oral).

Other members of the weasel family (**mustelids**), such as badgers, striped and spotted skunks, pine marten, and long-tailed weasels, appear to be resistant to plague. However, they can be infected as demonstrated by the presence of antibodies against *Y. pestis* (Salkeld and Stapp, 2006; Dyer and Huffman, 1999; Hopkins and Gresbrink, 1982; Messick and others, 1983).

Carnivores

Wild carnivores produce antibodies to *Y. pestis* after infection but, with the exception of **felids**, rarely show clinical signs (Poland and others, 1994; Gage, 1998; Gasper and Watson, 2001) (table 10). Wild felids, on the other hand, are highly susceptible to plague. Among Canada lynx reintroduced to Colorado, 6 of 52 lynx that died showed evidence of infection by *Y. pestis*; 5 of these lynx died as a direct result of plague pneumonia (Wild and others, 2006). A bobcat that was found dead in Texas died of acute plague before it could develop antibodies (Tabor and Thomas, 1986). Surveillance studies for plague in wild felids have found some animals that developed antibodies against *Y. pestis* **antigens**, so not all infections are fatal (Paul-Murphy and others, 1994; Biek and others, 2002; Wild and others, 2006; Bevins and others, 2009).

Wild carnivores have also been implicated in the transmission of plague to humans in several cases. Coyote, gray fox, badger, bobcats, and mountain lions were reportedly the source of infection in humans who had direct contact with infected tissues or who inhaled infectious droplets (Poland and others, 1973; von Reyn, Barnes, Weber, Quan, and Dean, 1976; Centers for Disease Control and Prevention, 1984; Gage and others, 1994; Wong and others, 2009).

Box 4 Routes of Transmission of *Y. pestis* to Humans Associated with Infected Animals

Most human cases of plague are transmitted from a bite from an infected flea. However, humans have become infected in other ways from contact with wild and domestic animals. In the United States, almost 20 percent of human cases with identified sources result from contact with infected animals (Gage, 1998; Gage and others, 2000).

Transmission by Direct Contact with Infected Animals

Humans have become infected with *Y. pestis* after contact with the tissues of infected animals. In most cases, infection was transmitted through a break in the skin of the person. A 19-year-old male developed bubonic plague after skinning an infected bobcat (Poland and others, 1973); he had many hangnails and raw areas around his fingers, allowing penetration by *Y. pestis*. His friends, who also participated in the skinning, did not have any skin abrasions and did not become infected despite contact with the blood and tissues of the bobcat (Poland and others, 1973). In another case, a man became infected after cutting his arm while skinning an infected bobcat (Centers for Disease Control and Prevention, 1984). Similarly, a young boy became infected with *Y. pestis* after skinning an infected coyote (von Reyn, Barnes, Weber, Quan, and Dean, 1976). The boy had a cut on his arm and a damaged nail bed that provided a route of entry for the bacteria. His friend, who had no cuts or abrasions, did not become infected. In all of these cases, *Y. pestis* was obtained from the wild animals, confirming their infection.

Numerous cases of bubonic plague in humans have resulted from contact with the tissues of infected rabbits, which are especially susceptible to plague. Most rabbit-associated cases occur in the winter, during hunting season when people become infected while skinning the rabbits and handling the tissues (Centers for Disease Control and Prevention, 2006; von Reyn, Barnes, Weber, and Hodgin, 1976; Centers for Disease Control and Prevention, 1984; Kartman, 1960; Link, 1950). Buboes most often form in the armpit or elbow regions. In the United States, cottontail rabbits are most often involved in these cases; wild hares are associated with cases in South Africa (von Reyn, Barnes, Weber, and Hodgin, 1976). In China and Mongolia, bubonic plague is commonly seen in marmot hunters who skin infected animals (Tikhomirov, 1999; Kool, 2005).

Cases of plague in people in South American countries have been associated with guinea pigs, a common food (Ruiz, 2001; Gabastou and others, 2000). In those cases, plague may have been transmitted by direct contact of infectious tissues, or fluid, or both with broken skin when an infected guinea pig was killed, skinned, and cooked (Ruiz, 2001; Gabastou and others, 2000). Similarly, people may become infected when slaughtering and preparing domestic livestock, such as camels, goats, and sheep, for food (Christie and others, 1980).

A child may have become infected with *Y. pestis* either by direct contact with an infected rabbit or by being licked around the face and mouth by a dog who had handled an infected rabbit (Kartman, 1960). The presence of cervical buboes implicated the mucous membranes of the mouth as the route of infection. However, a case-control study of dog-associated risk factors for human plague did not show any evidence supporting transmission by direct contact with an infected dog (Gould and others, 2008).

Transmission by Ingestion of an Infected Animal

Ingestion of meat from infected animals can cause pharyngeal plague in humans. In the Middle East, outbreaks of pharyngeal plague have occurred in people who ate raw camel meat (Arbaji and others, 2005; Bin Saeed and others, 2005; Christie and others, 1980). In Jordan, 12 people developed pharyngeal plague with enlarged lymph nodes in the neck and fever after eating meat from the same infected camel; 10 of the people had eaten the meat raw (Arbaji and others, 2005). In Saudi Arabia, four people in a group who ate raw liver from an infected camel contracted pharyngeal plague (Bin Saeed and others, 2005). A fifth case of plague associated with this sick camel was that of a man who cut his arm while slaughtering the animal. None of the 31 people who ate the liver or meat cooked contracted pharyngeal plague (Bin Saeed and others, 2005). In addition to the risk of becoming infected with *Y. pestis* by direct contact with infected meat, people who eat raw or undercooked meat from infected animals increase their risk of developing plague. An experimental study showed that thorough cooking of ground beef inoculated with *Y. pestis* would effectively decrease the probability and severity of disease in people who might eat it (Porto-Fett and others, 2009).

Probable modes of transmission in cases of plague in humans in the United States, 1970–95.

[Probable modes of transmission were identified for 294 of the 342 cases. Data from Gage, 1998]

Mode of transmission	Percentage of identified cases	Comment
Flea bite	79	Most of the people were probably exposed to infectious fleas from wild rodents, particularly rock squirrels and ground squirrels.
Direct contact with infected animals	19	Most of these people were hunters, trappers, and pet owners, and they were exposed to plague through contact with wild rabbits, domestic cats, wild carnivores, prairie dogs, and an Abert's squirrel.
Inhalation	2	Most of these people were cat owners or veterinary staff who were exposed to cats with pneumonic plague.
Commensal rats	0	No cases of human plague associated with commensal rats have occurred in the United States since the 1920s.
Human-to-human	0	The last case of human-to-human transmission of plague in the United States was in 1924.

People may also become infected with *Y. pestis* by ingesting infected fleas during grooming activities (Bin Saeed and others, 2005; Conrad and others, 1968; Pollitzer, 1954; McGovern and others, 1997); members of some native South American cultures catch fleas and lice and crush them with their teeth.

Transmission by Inhalation of Infectious Droplets from an Infected Animal

Y. pestis can be transmitted by inhalation of infectious droplets and cause primary pneumonic plague. Since the 1970s, numerous people have contracted pneumonic plague as a result of transmission from infected domestic cats (Gage and others, 2000; Centers for Disease Control and Prevention, 1994, 1992; Doll and others, 1994; Werner and others, 1984). The first wild carnivore-associated case of primary pneumonic plague was in 2007 in a wildlife biologist at Grand Canyon National Park, Ariz. (Wong and others, 2009). The biologist performed a necropsy examination of a dead mountain lion with his bare hands and, presumably, without protective gear, such as a respirator or coveralls. *Y. pestis* was most likely transmitted when the biologist inhaled infectious droplets that had become aerosolized during the necropsy. After developing fever, chills, and cough with bloody sputum, the biologist died 1 week after the necropsy. Tissue samples taken from the mountain lion's liver and the lymph nodes below its jaw were positive for *Y. pestis* by polymerase chain reaction (PCR) analysis.

Box 5 Forms of Plague in Humans

Bubonic Plague

Bubonic plague is the most common and well-known form of the disease. It most often results from the bite of an infected flea, but can also be contracted by exposure of open wounds to infective materials. Within 2 to 6 days after exposure to *Y. pestis*, patients develop symptoms of fever, headache, chills, muscle pain, and fatigue. Patients may also experience nausea, vomiting, and diarrhea. Lymph nodes near the site of exposure become swollen and extremely painful and are known as buboes, derived from "boubon," the Greek word for groin. Most often, buboes develop in the groin area, but they can also occur in the lymph nodes in the armpits and neck, depending on the site of the flea bite or other exposure. In a study of pediatric cases, 70 percent of the children had buboes in the groin, whereas 17 percent had buboes in the neck, and 13 percent had buboes in the armpits (Mann and others, 1982). Antibiotic treatment of bubonic plague reduces the case fatality rate from 60 percent to less than 5 percent. Without treatment, the disease progresses rapidly, and the bacteria enter the bloodstream and cause secondary plague septicemia.

Septicemic Plague

Plague septicemia can be either primary or secondary to bubonic plague. Primary septicemic plague results when bacteria are transmitted directly into the bloodstream; patients have positive blood cultures without obvious swollen lymph nodes. Patients experience fever, chills, headache, malaise, and gastrointestinal symptoms similar to septicemias caused by other bacterial infections. Cell and tissue death, or necrosis, and gangrene of the extremities may develop as a result of blood clots. Without antibiotic treatment, the mortality rate ranges from 30 to 50 percent. Septicemic plague may progress to secondary pneumonic plague as the bacteria spread through the body to the lungs.

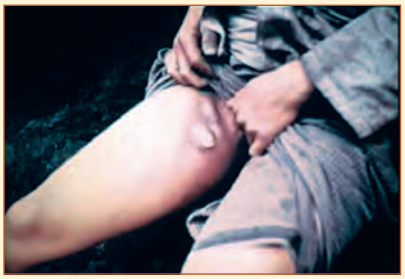
Pneumonic Plague

Primary pneumonic plague is the most uncommon form of plague in humans, accounting for only 2 percent of cases between 1970–95 in the United States (Gage, 1998). Between 1–3 days after infection, patients develop a flulike illness that progresses rapidly to pneumonia with coughing, chest pain, and bloody sputum. Pneumonic plague, primary or secondary, has a high mortality rate, even with treatment, due to respiratory failure and shock. When antibiotic therapy is delayed more than 24 hours after the onset of symptoms, pneumonic plague is always fatal.

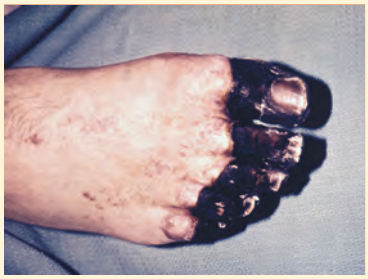
Patients become infected by inhaling bacteria found in respiratory droplets from infected individuals or animals. Person-to-person transmission of the disease requires prolonged, close contact at a distance of less than 6.5–10 feet with a person in the final stages of disease, when coughing produces profuse bloody sputum (Kool, 2005). In the United States, the last case of human-to-human transmission of pneumonic plague was in 1924. Instead, most cases of primary pneumonic plague in people result from contact with infected domestic cats, by inhalation of infectious droplets from a coughing or sneezing cat. In 2007, a wildlife biologist died of primary pneumonic plague after performing a necropsy exam on an infected mountain lion (Wong and others, 2009).

Pestis Minor

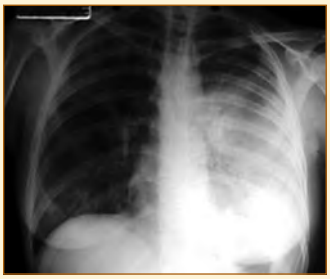
Pestis minor is a rare form of bubonic plague, most often seen in areas where plague is established. Symptoms of fever, inflamed lymph nodes, headache, and fatigue resolve without treatment within 1 week. This form is sometimes called "ambulatory" plague, because patients are generally not sick enough to need to lie down (Pollitzer, 1954).



Swollen, ruptured inguinal lymph node or bubo.



Gangrene.



Pneumonic plague.

Meningeal Plague

Acute meningitis caused by *Y. pestis* infection occurs rarely in 0.2–7.0 percent of cases (Becker and others, 1987). Most cases seem to be in children and are secondary to bubonic plague; buboes in the armpits or neck may increase the risk of developing plague meningitis (Pollitzer, 1954; Martin and others, 1967; Becker and others, 1987; Landsborough and Tunnell, 1947). Patients develop symptoms of acute meningitis including fever, headache, a painfully stiff neck, delirium, and confusion 9–17 days after the onset of illness (Martin and others, 1967; Becker and others, 1987; Landsborough and Tunnell, 1947; Pollitzer, 1954). Most patients have received some form of antibiotic treatment prior to developing meningitis, indicating that ineffective therapy due to choice of drug, duration, and dosage of treatment, and the onset of therapy may be important risk factors for plague meningitis (Pollitzer, 1954; Martin and others, 1967; Becker and others, 1987; Poland and Dennis, 1999). *Y. pestis* can spread to the central nervous system (CNS) during the intermittent presence of bacteria in the blood (Becker and others, 1987; Martin and others, 1967; Poland and Dennis, 1999). Commonly used antibiotics, such as tetracycline and streptomycin, do not cross the blood-brain barrier; thus, the amounts of antibiotics in the CNS are insufficient to inhibit the growth of *Y. pestis*. Chloramphenicol, which can cross the blood-brain barrier, is an effective treatment for plague meningitis.

Cutaneous Plague

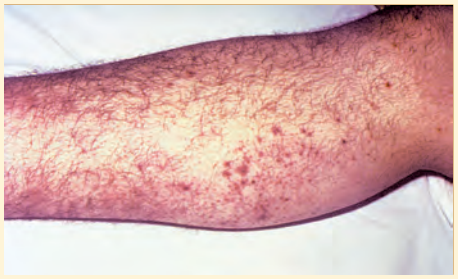
Skin lesions associated with plague include ulcers or pustules at the site of inoculation. The spread of the bacteria in the blood may result in hemorrhages and bruising of the skin. Gangrene with associated skin manifestations can develop in severe infections and is the source of the name "Black Death."

Pharyngeal Plague

Inflammation of the pharynx from plague, or plague pharyngitis, can develop after consumption of infected meat or inhalation of infectious droplets (Arbaji and others, 2005; Christie and others, 1980; Pollitzer, 1954; McGovern and others, 1997; Poland and Dennis, 1999; Laforce and others, 1971; Bin Saeed and others, 2005). Large droplets (more than 5 micrometers in size) tend to settle in the tonsils or pharynx, causing cervical buboes and pharyngitis, whereas smaller particles permeate into the lower respiratory tract to cause primary pneumonic plague (Laforce and others, 1971). Symptoms of plague pharyngitis include fever, infected lymph nodes in the neck or below the jaw, sore throat, weakness, and headache, and the symptoms resemble those of streptococcal or viral pharyngitis but with more severely painful lymph nodes (Poland and Dennis, 1999; McGovern and others, 1997).

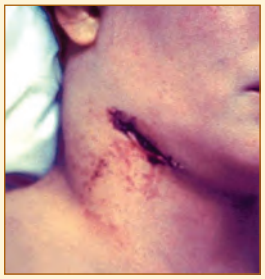
Pharyngeal plague broke out in the Middle East in people who ate raw camel meat (Arbaji and others, 2005; Bin Saeed and others, 2005; Christie and others, 1980). A group of six people in Nepal contracted pharyngeal plague when they inhaled infectious droplets from a patient with pneumonic plague (Laforce and others, 1971). Indians of Ecuador have also developed plague pharyngitis as a result of catching and killing fleas and lice with their teeth (Pollitzer, 1954; McGovern and others, 1997). Plague pharyngitis may progress to pneumonia if infectious material from abscesses is aspirated (Arbaji and others, 2005; McGovern and others, 1997; Pollitzer, 1954).

All images are from the Center for Disease Control (CDC) with the exceptions of pneumonic plague and cutaneous hemorrhages, which are from the Center for Biologic Counterterrorism and Emerging Disease (CBC-ED).



Cutaneous hemorrhages.

Gangrene, causing necrosis of the fingers.



Swollen, ulcerated cervical lymph node.

Table 9. Relative susceptibility of animal groups to infection and disease caused by *Y. pestis* and roles of animal groups as sources of human infection.

Animal	Susceptibility to		Source of human infection	Remarks
	Infection	Disease		
Rodents				
Rats 	Yes	High	Common	Source of infectious fleas in epidemics.
Mice 	Yes	Moderate	Sometimes	
Ground squirrels 	Yes	High	Common	Most common source of infectious fleas for isolated cases in humans in the United States.
Prairie dogs 	Yes	High	Rare	Epizootics in prairie dogs cause nearly 100 percent mortality.
Marmots 	Yes	High	Common	Transmission by direct contact with infected tissues of marmots is common in hunters.
Guinea pigs 	Yes	High	Sometimes	Transmission by human contact with or ingestion of infected guinea pig tissues.
Lagomorphs				
Rabbits, hares 	Yes	High	Common	Transmission by direct contact with infected tissues of rabbits and hares is common in hunters.
Pikas 	Yes	High	Rare	
Insectivores				
Shrews 	Yes	High	Common	Most common source of infectious fleas in epidemics in port cities of Madagascar.
Mustelids				
Black-footed ferret 	Yes	High	Not documented	
Domestic ferret 	Yes	Low	Not documented	
Polecats 	Yes	Moderate	Not documented	
Badgers 	Yes	Low	Not documented	
Skunks 	Yes	Low	Not documented	
Weasels 	Yes	Low	Not documented	
Carnivores				
Coyote 	Yes	Low	Rare	One case of transmission to a human by direct contact with infected tissues from a coyote.
Domestic dog 	Yes	Low	Sometimes	Source of infectious fleas to pet owners.
Bobcat 	Yes	High	Rare	Transmission by direct human contact with infected bobcat tissues.

Table 9. Relative susceptibility of animal groups to infection and disease caused by *Y. pestis* and roles of animal groups as sources of human infection.—Continued

Animal	Susceptibility to		Source of human infection	Remarks
	Infection	Disease		
Carnivores (continued)				
Mountain lion 	Yes	High	Rare	First case of primary pneumonic plague from wildlife in a biologist who performed necropsy exam on an infected mountain lion carcass in 2007.
Domestic cat 	Yes	High	Common	Numerous cases of bubonic and primary pneumonic plague in humans who had contact with infected cats.
Ungulates				
Camel 	Yes	Moderate	Sometimes	Transmission by direct human contact with or ingestion of infected camel tissues.
Goat 	Yes	Moderate	Sometimes	
Sheep 	Yes	Moderate	Sometimes	
Swine 	Yes	Low	Not documented	
Deer 	Yes	Low	Not documented	
Primates				
Nonhuman 	Yes	High	Not documented	
Humans 	Yes	High	Sometimes	Pneumonic plague can be transmitted human-to-human.
Other				
Birds 	No	No	No	

Ungulates

Plague is relatively rare in wild **ungulates**. Deer, in general, are probably not highly susceptible to the disease, although several cases of fatal plague have been reported in mule deer (Edmunds and others, 2008; Thorne and others, 1987) and in black-tailed deer (Jessup and others, 1989). One of the mule deer showed evidence of blood poisoning (**septicemia**), pneumonia, and inflamed lymph nodes (**lymphadenitis**) (Thorne and others, 1987). In three mule deer and one black-tailed deer, **ocular** lesions developed as a result of infection with *Y. pestis* (Edmunds and others, 2008; Jessup and others, 1989). The deer appeared to be blind and, in some cases, had bulging eyes. Examination of the eyes at necropsy showed widespread, severely inflamed tissue and dead tissue in both eyes and numerous *Y. pestis* bacteria (Edmunds and others, 2008; Jessup and others, 1989). The bacteria probably entered the eyes by the bloodstream.

One human case of plague was acquired from an infected pronghorn antelope during butchering (Poland and others, 1994).

Wild boar can be infected by *Y. pestis,* as demonstrated by the presence of antibodies, but they do not suffer clinical disease. The infection is most likely acquired by ingestion of an infected rodent or other animal (Nelson and others, 1985).

Antibodies to *Y. pestis* were found in African buffalo (26 of 391 animals tested, or 6.6 percent) within 1 year of a plague epizootic among rodents in Zimbabwe Rhodesia (Gordon and others, 1979). Elephants (1 of 330 animals tested, or 0.3 percent) in the area were also found to be seropositive. No seropositive zebras or sable antelopes were found, although the numbers sampled were low (15 and 5, respectively).

Table 10. Prevalence of antibodies to *Y. pestis* in blood specimens from carnivores and omnivores in the western United States.

[The western United States includes California, Oregon, Arizona, Colorado, New Mexico, Utah, Wyoming, Idaho, Kansas, Texas, North Dakota, and South Dakota. These combined data from many studies are listed individually in Salkeld and Stapp, 2006]

Animal	Number of animals with *Y. pestis* antibodies per number of animals tested for *Y. pestis* antibodies	Percentage of tested animals with *Y. pestis* antibodies
Coyote 	2458/17,403	14
Swift fox 	54/117	46
Gray fox 	10/81	12
Kit fox 	0/1	0
Badger 	621/1125	55
Raccoon 	58/438	13
Fisher 	0/1	0
Long-tailed weasel 	19/339	6
American marten 	29/91	32
Striped skunk 	9/92	10
Spotted skunk 	2/2	100
Ringtail cat 	6/26	23
Bobcat 	142/959	15
Canada lynx 	2/39	5
Mountain lion 	24/64	38
Black bear 	117/523	22
Wild boar 	18/23	74

Nonhuman Primates

Nonhuman primates are highly susceptible to plague and exhibit symptoms similar to those seen in humans (Gage, 1998).

Birds

Although **birds** are not susceptible to infection by *Y. pestis*, **raptors** may spread the organism by carrying infected fleas or prey to new areas (Poland and others, 1994).

Domestic Animal Infections

Cats

Domestic cats are highly susceptible to plague, and as many as 75 percent die if they are not treated (Eidson and others, 1991). Infected cats suffer from bubonic, septicemic, and pneumonic forms of plague, and they develop signs earlier than humans (Box 6).

Dogs

Domestic dogs are susceptible to infection by *Y. pestis*, although they are relatively resistant to clinical disease. Dogs show a brief, self-limiting, nonspecific, feverish illness after infection (Orloski and Eidson, 1995; Rust, Cavanaugh, and others, 1971). Dogs with plague may occasionally have oral lesions or infected lower jaw lymph nodes, or both, presumably as a result of ingesting infected rodents or rabbits (Orloski and Eidson, 1995). *Y. pestis* has been obtained from the throats of dogs experimentally infected by the oral route (Rust, Cavanaugh, and others, 1971); some dogs may briefly develop bacteremia, enabling the bacteria to be found in blood samples (Rust, Cavanaugh, and others, 1971). Infected dogs demonstrate an antibody response within 8 days that can last at least 11 months (Rust, Cavanaugh, and others, 1971).

Livestock

Camels, llamas, goats, and sheep are susceptible to plague, and they may be infected by fleas, or more rarely ticks, or by eating forage contaminated by infected rodents (Christie and others, 1980; Fedorov, 1960; Arbaji and others, 2005). In experimental infections of camels with *Y. pestis*, susceptibility to plague was low; some animals injected with high doses of *Y. pestis* recovered after mild illness featuring buboes (Federov, 1960). Individual differences in susceptibility to disease were noted among the camels, and some animals died after infection. Presumably, more camels contract plague during rodent epizootics, when they are more frequently exposed to infected rodents (Federov, 1960). Camels often bed down for the night in soil loosened by rodent burrowing, thereby increasing their exposure to rodent fleas (Federov, 1960). Llamas, another camelid species, have been found infected with plague in the United States, and at least one llama in New Mexico apparently died of the disease (Centers for Disease Control and Prevention, unpublished data).

Domestic pigs have been experimentally infected with *Y. pestis* by ingestion of mice dead from plague (Marshall and others, 1972). All seven pigs in this study developed high levels of antibody against *Y. pestis*, indicating infection, but none developed clinical disease.

Horses and donkeys appear to be resistant to infection with *Y. pestis*.

Vector Infections

Fleas are the primary vector for the transmission of *Y. pestis* among rodents. Numerous **genera** and species of fleas have been demonstrated to be competent vectors, although their efficiency of transmission varies (table 6). The human flea (*Pulex irritans*) can also transmit *Y. pestis* (Blanc and Baltazard, 1941a; Gratz, 1999). At least two other arthropod groups have been found to transmit *Y. pestis* under experimental conditions, although neither has been shown to be important vectors under natural conditions.

The human body **louse** (*Pediculus humanus corporis*) has been shown experimentally to transmit plague (Houhamdi and others, 2006; Ayyadurai and others, 2010). Lice became infected with *Y. pestis* after feeding on rabbits whose blood contained bacteria. *Y. pestis* multiplied within the lice and were excreted in the lice feces. Infected lice were then able to infect naïve rabbits, completing the transmission cycle. Body lice were also able to transmit *Y. pestis* to guinea pigs (Blanc and Baltazard, 1941b). The human head louse (*Pediculus humanus capitis*) has also been shown experimentally to transmit *Y. pestis* (Blanc and Baltazard, 1941b).

Ixodid (*Hyalomma asiaticum asiaticum*) and **argasid** (*Ornithodorus tartakovskyi*) **ticks** were successfully used to infect camels with *Y. pestis* experimentally (Federov, 1960). Other species of *Ornithodorus* ticks became infected with *Y. pestis* after feeding on infected mice. Although they maintained viable *Y. pestis* up to 1 year after the initial infectious blood meal, none of the ticks transmitted the infection to mice (Thomas and others, 1990).

Box 6 Plague and Cats

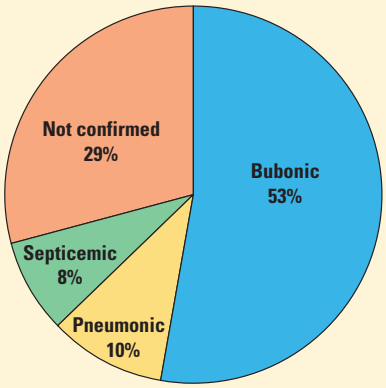
Cats are the most common pet in the United States (American Veterinary Medical Association, 2007). Thirty-three percent of U.S. households own at least 1 cat, totaling 81 million owned cats (Conrad and others, 2005; Robertson, 2008). Unlike most other carnivores, cats are highly susceptible to plague and typically present with symptoms similar to those seen in infected humans. This increased susceptibility results from the lack of a strong immune response following infection by *Y. pestis* to block the development of observable signs. The microscopic examination of lesions in experimentally infected cats shows that the lesions are remarkably similar to those found in humans, suggesting a comparable mechanism of disease development (Watson and others, 2001). Several species of wild cats (lynx, mountain lion, and bobcat) are also known to be highly susceptible to plague (Wild and others, 2006; Tabor and Thomas, 1986).

Plague lesions in carnivores following experimental challenge with *Y. pestis* compared with human lesions.

[Watson and others, 2001]

Form of plague	Humans	Cats	Other carnivores[1]
Pneumonic	Occurs	Occurs	Does not occur.
Septicemic	Occurs	Occurs	Does not occur.
Bubonic	Occurs	Occurs	Does not occur.
Death	Yes	Yes	No.

[1]Excluding black-footed ferrets, a carnivore that is highly susceptible to plague.



Forms of feline plague in New Mexico, 1977–85 (from Eidson and others, 1991). The 35 (29 percent) unconfirmed cases did not have buboes or pneumonia, and blood cultures were not performed to confirm septicemia.

Like humans, domestic cats may suffer from bubonic, septicemic, and pneumonic plague, and the bubonic form is the most common. Although the disease is probably is transmitted to some cats by flea bites, it is thought that most transmission of *Y. pestis* to cats is through ingestion of infected rodents or rabbits. Cats experimentally exposed to *Y. pestis* by ingestion of an infected rodent had inflamed cranial and neck lymph nodes, similar to what is seen in naturally infected cats (Watson and others, 2001; Rust, Cavanaugh, and others, 1971). *Y. pestis* also may invade cuts in the oral mucosa, and then spread to the local lymph nodes below the lower jaw and in the neck (Eidson and others, 1988; Orloski and Lathrop, 2003). Experimentally infected cats have developed severe inflammation of the lymph nodes, leading to complete disruption of the normal structure of the nodes and the escape of the bacteria into the bloodstream (Watson and others, 2001). Once *Y. pestis* enters the blood, septicemic plague occurs, and it may lead to secondary pneumonic plague.

Cats with primary and secondary septicemic plague exhibit severe observable signs. Primary pneumonic plague has not been documented in cats (Orloski and Lathrop, 2003), but secondary pneumonic plague is the second most common form in cats (Eidson and others, 1988, 1991). Similar to humans, plague causes high mortality among cats; 33–38 percent die (Gage and others, 2000; Eidson and others, 1991; Gasper and others, 1993), and the greatest risk of death is among cats with pneumonic plague (Eidson and others, 1991).

Plague in cats, particularly the pneumonic form, presents a serious risk of infection to humans associated with these cats, that is, their owners and veterinarians. Prior to 1977, no human case of feline-associated plague had been confirmed in the United States, although at least one case was suspected to have been acquired by contact with a cat (Kaufmann and others, 1981). From 1977 to 2006, 29 people in 8 western States (New Mexico, Colorado, California, Arizona, Nevada, Oregon, Utah, and Wyoming) were diagnosed with cat-associated plague; at least 5 (17 percent) of these patients developed primary pneumonic plague (Gage and others, 2000; Hinckley and Gage, written communication). Cats with pneumonic plague present the most serious risk to humans because of the threat of acquiring primary pneumonic plague, the most lethal form, by inhaling infectious droplets from a coughing or sneezing cat. From 1993 to 1994, the proportion of human cases of primary pneumonic plague was significantly higher among cases acquired from cats than among cases from other sources (Centers for Disease Control and Prevention, 1994). People can also be infected by scratches and bites of infected cats, contacting infectious

bodily fluids while examining or caring for sick cats, and burying dead cats (Gage and others, 2000). The claws of an infected cat may become contaminated with *Y. pestis* from contact with saliva or abscesses that contain the bacteria, either from itself or another cat (Weniger and others, 1984). In addition, claws may be contaminated with *Y. pestis* from recent contact with an infected rodent (Weniger and others, 1984), as could easily happen during hunting activities. Cats develop significant bacteremias, enabling them to infect fleas, which could, in turn, infect people or other animals (Rust, Cavanaugh, and others, 1971). Although most cases of cat-associated plague have occurred in the United States, a few cases have been reported in South Africa (Thornton and others, 1975; Simpson, 1905), Argentina (Mall and O'Leary, 1945), and Brazil (Mall and O'Leary, 1945).

Cats that hunt and eat wild rodents or rabbits, especially in endemic areas, are at greatest risk of developing plague. Other risk factors for cats include exposure to dead rodents or rabbits and flea infestation (Orloski and Lathrop, 2003; Eidson and others, 1988). Because cat fleas (*Ctenocephalides felis)* are uncommon in plague endemic areas, the presence of fleas on a cat in these areas should alert the owner or veterinarian to the possibility of plague; the fleas would most likely be from a rodent and could potentially transmit plague (Eidson and others, 1988; Orloski and Lathrop, 2003). Cats may bring infected rodents—and their fleas—back to their homes, presenting a source of infection for people who then come into contact with these animals. Taking care of cats with plague poses a significant risk of infection to the attending veterinarian and staff, as well as their owners. Cat caretakers who take precautions, such as using a respirator, gloves, and eye protection; disinfecting equipment; and isolating infected cats, are taking effective measures to prevent disease transmission to themselves, other people, and other animals. Owners who prevent their cats from roaming and hunting are helping to prevent the potential transmission of diseases to people and other animals. Additional measures include not handling wild rodents and discouraging rodent nesting around homes by reducing food and shelter. Insecticides can be used to control fleas on pets.

Observable signs in cats with plague.

Form	Signs
Bubonic	Fever.
	Lethargy.
	Anorexia.
	Enlarged lymph nodes (underneath the jaw and in the neck).
Septicemic	Vomiting.
	Diarrhea.
	Elevated heart rate.
	Weak pulse.
	Respiratory distress.
	Disseminated intravascular coagulopathy (DIC), a severe, potentially fatal, response to septicemia in which excessive clotting and bleeding develops.
Pneumonic	Fever.
	Lethargy.
	Anorexia.
	Respiratory signs:
	dyspnea or shortness of breath;
	nasal discharge;
	coughing;
	sneezing.

Routes of exposure for cat-associated human plague cases in the United States, 1977–98.

[Adapted from Gage and others, 2000]

Type of exposure	State	Form of plague	Outcome
Bite or scratch	New Mexico	Bubonic	Recovered.[1]
	New Mexico	Bubonic	Recovered.
	New Mexico	Bubonic	Recovered.
	New Mexico	Bubonic	Recovered.
	New Mexico	Bubonic	Recovered.
	Colorado	Bubonic	Recovered.[1]
	Oregon	Bubonic	Recovered.
	California	Bubonic	Recovered.[1]
Inhalation	California	Pneumonic	Died.
	Wyoming	Pneumonic	Recovered.[1]
	Colorado	Pneumonic	Recovered.[1]
	Utah	Pneumonic	Recovered.
Face-to-face contact	Colorado	Pneumonic	Died.
	Arizona	Bubonic	Recovered.
Cared for sick cat	Nevada	Septicemic	Died.
	Colorado	Bubonic	Died.
	Colorado	Bubonic	Recovered.[1]
	Colorado	Bubonic	Recovered.
	New Mexico	Bubonic	Recovered.
	California	Bubonic	Recovered.
Handled sick cat	California	Bubonic	Died.[2]
	New Mexico	Bubonic	Recovered.
	Arizona	Bubonic	Recovered.

[1]Person infected was a veterinarian or veterinary technician.

[2]Person buried a dead cat that had been sick.

Obtaining a Diagnosis

Human cases of plague are classified as suspect, presumptive, or confirmed, depending on published guidelines of diagnostic criteria (table 11). An initial diagnosis of plague can be made based on the symptoms and the exposure history of the person or animal. Tissue and fluid samples (blood, **sputum**, lymph node **aspirates**, and **nasopharyngeal swabs**) can be used for visual identification of the bacteria as well as **culture** for definitive diagnosis. The organism can be seen in smears of these samples stained with Wayson or Giemsa stains or with Gram's stain. Smears can also be analyzed using **direct fluorescent antibody testing** (anti-F1 antibody). Tissues from the liver, spleen, bone marrow, and swollen lymph nodes also can be analyzed following the death of the host by using autopsy or necropsy samples. A definitive diagnosis of plague can be made when *Y. pestis* colonies grow in specimen growth media that have been inoculated with tissue or body fluid from the patient. Colonies of *Y. pestis* are slow growing and take about 2 days to become visible. They are opaque and smooth with irregular edges, and they have been described as having a "hammered-metal" appearance (Perry and Fetherston, 1997). The colonies can be presumptively identified as *Y. pestis* using biochemical tests and fluorescent antibody assays. Conclusive identification is made by **lysis** by a specific **bacteriophage**. Unfortunately, although biochemical testing can be done in many microbiological laboratories, the reagents required for fluorescent antibody assays and bacteriophage lysis tests often are available only in certain public health reference laboratories, such as the one at the Centers for Disease Control and Prevention (CDC). Polymerase chain reaction (**PCR**) testing, which targets multiple genes within a single sample, has also been used for identification of *Y. pestis* in patient and environmental specimens within 3–5 hours (Tomaso and others, 2003; Melo and others, 2003; Loïez and others, 2003; Woron and others, 2006; Riehm and others, 2011).

Plague can be diagnosed retrospectively by serological testing. A fourfold or greater change in the concentration of antibodies developed against *Y. pestis* F1 antigen detected by **passive hemagglutination testing** of paired **serum** samples indicates infection. The enzyme-linked immunosorbent assay (ELISA) is also commonly used to detect anti-F1 antibodies in serum.

Rapid diagnostic tests to detect F1 antigen in fluid samples drawn from buboes, serum, sputum, and urine are being developed (Chanteau and others, 2000; 2003; Ratsitorahina and others, 2000). These tests, known as "dipstick assays," have been field tested in Madagascar and are at least as sensitive and specific as the standard ELISA and culture methods of diagnosis for humans. The dipstick test has the advantage of being able to be used at the bedsides of patients under field conditions and of giving a reliable result in 10–15 minutes. The dipstick assay can also be used with samples that have deteriorated, been contaminated, or that were obtained after antibiotic treatment was started in a patient.

Table 11. Standard case definitions of plague.

[PCR, polymerase chain reaction. World Health Organization, 2006]

Case definition	Criteria
Suspect plague	Compatible observable signs *and*
	Features consistent with possible exposure or infection by *Y. pestis*, such as contact with infected animals or humans, evidence of flea bites, living in or travelling to area with known plague.
Presumptive plague	Meets the definition for a suspect case *plus*
Putative new or reemerging focus:	*At least two of the four following:*
	Gram-negative or bipolar coccobacilli in stained material from a bubo, blood, sputum;
	F1 antigen detection in a patient specimen;
	Single blood sample is positive for anti-F1 antibodies without prior infection or vaccination;
	PCR detection of *Y. pestis* in a patient specimen.
Known endemic focus:	*At least one of the following:*
	Gram-negative or bipolar coccobacilli in stained material from a bubo, blood, sputum;
	Single blood sample is positive for anti-F1 antibodies without prior infection or vaccination;
	PCR detection of *Y. pestis* in a patient specimen.
Confirmed plague	Meets the definition for suspect case *plus*:
	Bacteria identified as *Y. pestis* by physical appearance and *two of the four following*: phage lysis (destruction of the bacteria by specific viruses), F1 antigen detection, PCR, biochemical profile;
	Fourfold change in concentration of antibodies to F1 antigen in paired blood samples;
	Positive rapid diagnostic test to detect F1 antigen (in endemic areas when no other confirmatory test available).

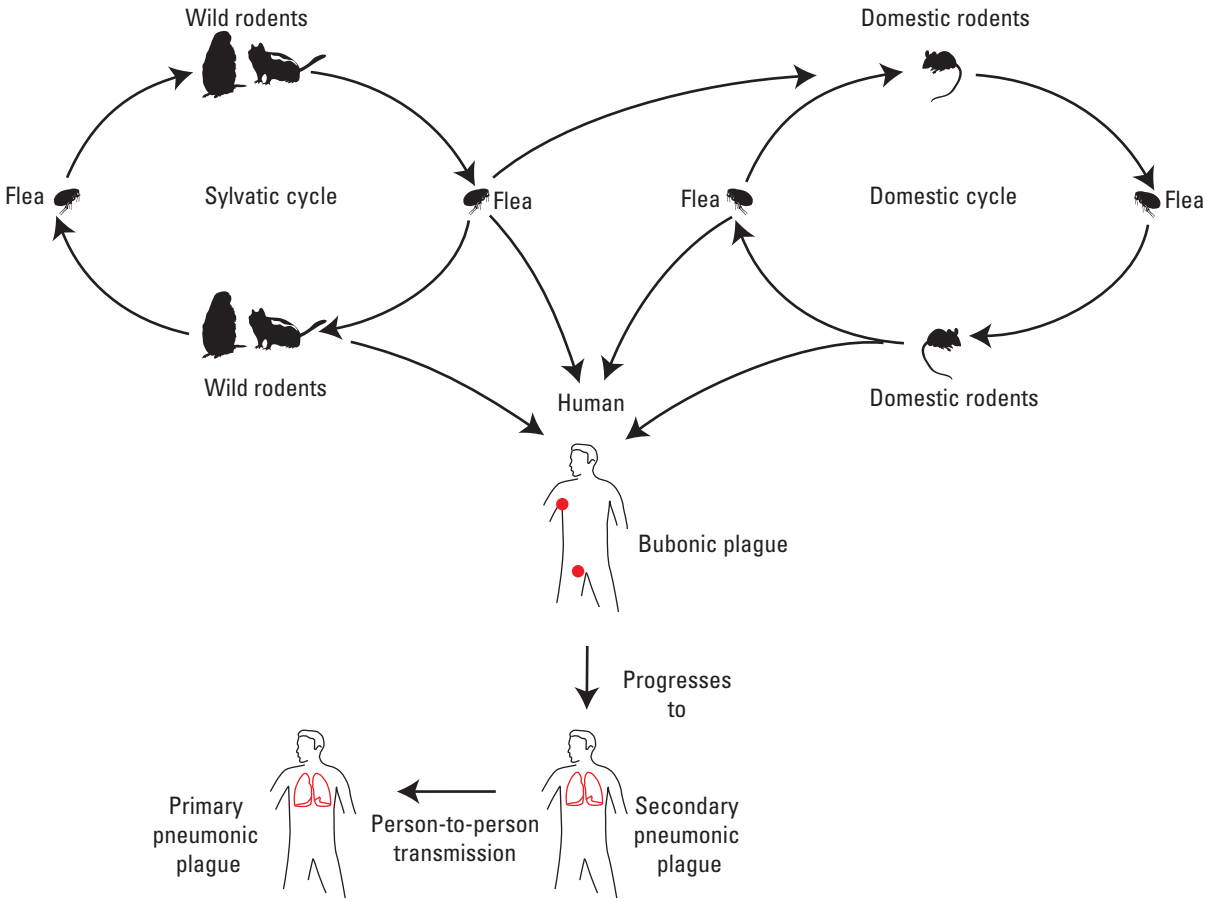


Figure 8. The *Y. pestis* transmission cycle and the progression from bubonic plague to pneumonic plague in humans. *Y. pestis* is transmitted between rodent hosts and flea vectors in two cycles: domestic and sylvatic. Humans can become infected by flea bites or by direct contact with infected rodents and other animals. Pneumonic plague can be transmitted person-to-person.

Similar rapid dipstick assays are being developed to detect anti-F1 antibodies in serum for use in the field as alternate tests to ELISA (Thullier and others, 2003; Rajerison and others, 2009); these tests are designed for use in humans and other mammals.

All human cases of suspected plague should be reported to the local public health department which will then notify the CDC and, if necessary, the WHO.

Disease Ecology

The basic life cycle of *Y. pestis* involves transmission between rodent hosts and flea vectors (fig. 8). Within this cycle, different species of rodents play different, although sometimes overlapping, roles depending on their susceptibility to disease. The specific rodent hosts involved in these cycles vary with geographic location. Rodents that suffer high mortality during epizootics present the greatest risk for human exposure. Nonrodent hosts are generally either susceptible or resistant to disease and can act to spread the infection to other locations or animals, although they are rarely thought to play a primary role in maintaining the disease in nature (table 12). For epidemiologic purposes, the cycle of plague can be divided into domestic and sylvatic cycles.

Domestic Cycle

The domestic cycle of plague involves the transmission of *Y. pestis* among rodents living with humans and can lead to outbreaks of disease in both human and animal populations (fig. 9).

Commensal Rats

The traditional epidemiological model of plague, thought to be responsible for the three pandemics, involves the transmission of *Y. pestis* among commensal rats by rat fleas and the accidental infection of humans by these same vectors. The primary species are the roof or black rat and the Norway or brown rat along with their fleas (Gage, 1998).

Table 12. Roles of hosts in maintaining plague in natural populations.

Enzootic or maintenance rodent hosts	Relatively resistant to disease	California vole.
	Low mortality	Northern grasshopper mouse.
	Long multiestrus breeding season with multiple litters	Rock squirrel.
	Successive multiple litters	
	High reproductive potential	
	Short natural life span	
	High replacement rate of individuals	
	Vector flea activity year round	
Epizootic or amplification rodent hosts	Low to moderate resistance to disease	Prairie dogs.
	High mortality	Ground squirrels.
	High density population to sustain outbreak	
Resistant nonrodent hosts	Robust immune response	Ungulates (deer).
	Illness rare	Canids.
Susceptible nonrodent hosts	High morbidity and mortality	Humans.
	Rapid proliferation of *Y. pestis*	Primates.
	Bubonic, pneumonic, septicemic plague	Felids.
		Ferrets.

The movement of these infected rats and their fleas had spread plague from central Asia or Africa throughout the world, causing the three pandemics. Although the Norway rat has largely displaced the black rat in many urban and port areas as a result of its aggressive nature, the black rat remains the dominant species in most rural areas of developing countries and is still, along with the rat flea, *X. cheopis*, the major source of infection in most of the world's bubonic plague outbreaks (Gage, 1998). In the United States, no humans have contracted plague as a result of transmission from commensal rats since the 1920s (Gage, 1998).

Although commensal rats and their fleas have been responsible for causing epidemics (and pandemics) of bubonic plague among people, it has been generally accepted that, by themselves, rats are not able to maintain plague in an area indefinitely. Wild rodents that are relatively resistant to plague, as well as fleas that are able to transmit the bacteria, are thought to maintain the infection in established foci of plague from which commensal rodents can become periodically infected (Gage, 1998). However, modeling studies of plague in urban rats suggest the disease can also be maintained in their populations without introduction from another source (Keeling and Gilligan, 2000a, b; Durham and Casman, 2010). According to these models, plague circulates within rat populations when the proportion of susceptible rats is between 25 and 50 percent, and these circumstances pose little risk of causing an epidemic among humans (Keeling and Gilligan, 2000a, b). When the proportion of susceptible rats is greater than 80 percent, an epizootic occurs among the rats and human cases may result. Thus, plague may exist in an enzootic state within interconnected populations of rats for many years, allowing the disease to persist and surface among humans without introduction from an external source (Keeling and Gilligan, 2000a, b). Another modeling study concluded that enzootic plague in rats of a specified area depends on the "critical flea index," a statistical tipping point related to the rat population. When flea density of the area is greater than the critical flea index, plague will become enzootic in urban rats (Durham and Casman, 2010).

Urban Epidemics

Human infections typically follow rodent acquisition of plague. When susceptible rodents die from plague, their fleas leave the carcasses in search of new hosts. Upon finding a new rodent or human host, the infection can be transmitted during the blood meal. Urban epidemics are generally preceded by numerous rodent deaths, often described as a "rat-fall," because in ancient times dead rats would fall from the ceilings of houses, a phenomenon still observed in certain villages with thatched roof huts. The disease may be further transmitted from person to person by coughing and inhalation of infectious droplets, resulting in pneumonic plague.

A modern epidemic involving commensal rodents occurred in India in 1994 (Perry and Fetherston, 1997; Tikhomirov, 1999). According to one story of the outbreak, as a result of an earthquake, storage buildings for grain were damaged, attracting wild, plague-infected rodents into villages in the Maharashtra State. People complained of increased

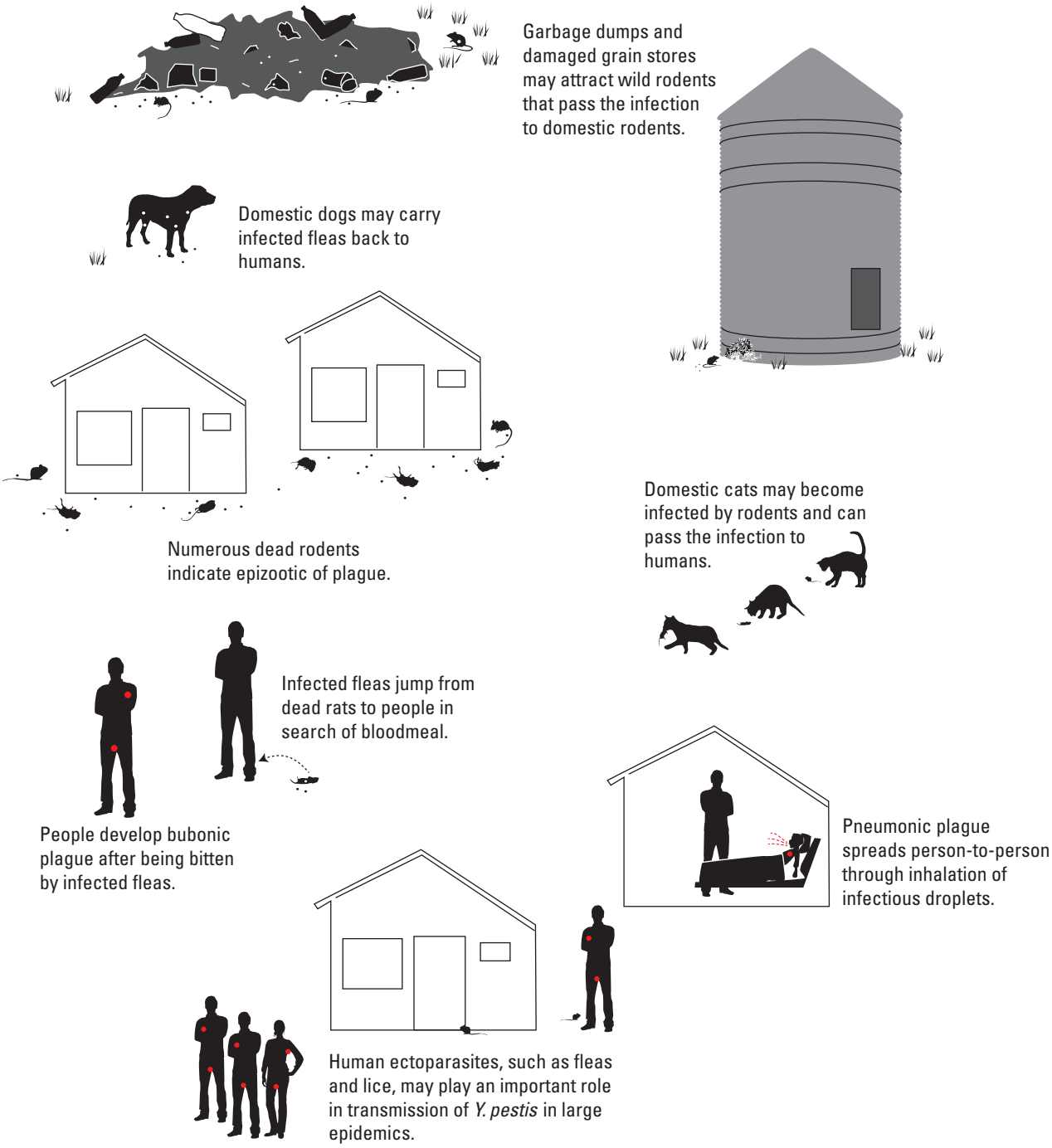


Figure 9. General pathways of plague transmission for the domestic cycle. Rats are the main rodent host in the domestic cycle of plague, although shrews are involved in some regions. Human cases are generally preceded by many dead rodents or "rat-fall."

numbers of fleas and "rat fall" as susceptible local rats became infected and died. The disease spread to humans, who developed bubonic plague, and in some cases, it progressed to pneumonic plague. The disease was believed to then be spread by persons who traveled during the **incubation period** of their illness to another region, Surat. As the infected person(s) who had traveled to Surat became ill, they developed pneumonic plague and spread their infection to others. Transmission from infected rodents was also possible because previous flood damage had led to an increase in rodents attracted to the accumulation of garbage. Subsequent panic and flight among the residents of the city had the potential to spread the disease to a much wider region in India. Fortunately, the epidemic was contained with **insecticides** and **prophylactic** antibiotics, and it resulted in only 54 deaths (Perry and Fetherston, 1997; Tikhomirov, 1999).

In Vietnam, fleas are scarce among wild rodents because of the humid tropical climate. Populations of the rat flea *X. cheopis* are able to survive on commensal rodents that live indoors where they are sheltered from rain. Because the density of rodents and their fleas required to maintain plague transmission is found only in human settlements, nearly all cases of human plague in Vietnam result from the domestic cycle (Suntsov and others, 1997) and are highly seasonal, depending on temperature and other climatic factors (Cavanaugh and Marshall, 1972).

In Madagascar, a series of outbreaks of plague among humans occurred from 1995 to 1998 in the port city of Mahajanga. In the central highlands of Madagascar, plague has been present since its introduction by boats from India in 1898 (Chanteau and others, 1998), and the black rat is the primary reservoir (Boisier and others, 2002). Although the black rat is also found in Mahajanga, the Asian house shrew is the predominant small mammal in the city and is a common host for the rat flea, *X. cheopis* (Boisier and others, 2002). Most cases of plague in these outbreaks were a result of transmission from commensal rats and shrews in the crowded and unsanitary conditions in some areas of the city (Boisier and others, 2002).

Human Skin Parasites as Vectors

Although most epidemics are generally blamed upon rat fleas, other human parasites that live on the skin (ectoparasites) can act as vectors (Blanc and Baltazard, 1941a, b; Houhamdi and others, 2006; Laforce and others, 1971). In 1967, bubonic plague broke out in Nepal; the disease probably was transmitted by the bites of human fleas. There was no evidence of a rodent epizootic, and strict quarantine measures resulted in distinct clustering of cases within households (Laforce and others, 1971). The human flea was also strongly associated with plague frequency among humans in specific areas of Tanzania, suggesting a role in plague epidemiology (Laudisoit and others, 2007). Human ectoparasites, such as fleas and lice, may have played a prominent role in the transmission of *Y. pestis* in large epidemics in the past, and they could possibly become a factor today in homeless or refugee populations and in bioterrorism events (Drancourt and others, 2006; Ayyadurai and others, 2010).

Pneumonic Plague

Progression of bubonic plague to the secondary pneumonic form can result in person-to-person transmission of the disease. Despite the common perception of being highly **contagious**, transmission of pneumonic plague actually requires prolonged, close contact of less than 6.4–9.6 feet (ft) (2–3 meters (m)) with a person in the final stage of disease who produces profuse bloody sputum when coughing (Kool, 2005; Gage, 1998; Perry and Fetherston, 1997). Pneumonic plague is transmitted by inhalation of infectious respiratory droplets, which cannot travel as far as finer **aerosols**; particles less than 5 micrometers in diameter pass into the lungs to cause primary pneumonic plague (Laforce and others, 1971).

In the early 1900s, two epidemics of pneumonic plague occurred in Manchuria among marmot hunters (Kool, 2005). The hunters became infected with *Y. pestis* after contact with infected marmot tissues, and they developed secondary pneumonic plague. Subsequent travel in crowded, poorly ventilated trains allowed person-to-person transmission, resulting in many cases of primary pneumonic plague. The epidemics followed the paths of the railroad tracks. Pneumonic plague broke out in the United States in 1919 and 1924 in which secondary pneumonic plague spread to 12 and 32 other people, respectively (Kool, 2005; Gage, 1998). No cases of person-to-person transmission of plague in the United States have been documented since that time, although cases of primary pneumonic plague have occurred as a result of transmission from infected cats (domestic and wild), dogs, and laboratory accidents (Kool, 2005; Gage, 1998; Gage and others, 2000; Burmeister and others, 1962; Wong and others, 2009).

Modern epidemics of pneumonic plague have occurred in India (Tikhmorov, 1999; Perry and Fetherston, 1997; Gupta 2007), the Democratic Republic of Congo (World Health Organization, 2005; Bertherat and others, 2011), Uganda (Begier and others, 2006), Madagascar (Ratsitorahina and others, 2000), and China (World Health Organization, 2009) (table 13). These outbreaks demonstrated the risk of spread is not as high as often perceived; the infection rate among people who had close contact with infected patients was only about 8 percent (Ratsitorahina and others, 2000; Begier and others, 2006). Modeling studies suggest the spread of pneumonic plague can be easily interrupted by public health interventions, such as by isolating ill people and treating them with antibiotics (Gani and Leach, 2004). In areas with limited resources and unsophisticated hospital facilities, transmission from infected patients to health care workers can be minimized by such simple procedures as examining the patient from behind to avoid face-to-face contact, limiting the contact time with infected patients, and providing well-ventilated wards (Kool, 2005).

Table 13. Modern outbreaks of pneumonic plague.

Date	Country	Number of cases	Number of deaths	Comments	Source
1994	India	Hundreds	Numerous	An epidemic of bubonic plague developed into an outbreak of pneumonic plague, causing panic. The number of cases was poorly documented.	Tikhomirov, 1999; Perry and Fetherston, 1997.
1997	Madagascar	18	8	A healer, who cared for a person with bubonic plague that progressed to secondary pneumonic plague, developed primary pneumonic plague. Person-to-person transmission of plague among family members and attendees of funeral occurred.	Ratsitorahina and others, 2000.
2002	India	16	4	The first documented case was bubonic plague in a person who had skinned a wild cat. This person developed secondary pneumonic plague and passed the infection to relatives.	Gupta and Sharma, 2007.
2004	Uganda	4	3	Two patients with secondary pneumonic plague transmitted infection to two caregivers.	Begier and others, 2006.
2005, 2006	Democratic Republic of the Congo	292	102	Pneumonic plague spread through workers at two separate diamond mines and caused mass panic.	World Health Organization, 2005; Bertherat and others, 2011.
2009	China	12	3	The source of the outbreak was a marmot that had contact with the dog owned by the primary case.	World Health Organization, 2009.

Sylvatic Cycle

The ecology of plague among wild rodents is complex and not completely understood. Sylvatic plague, or the transmission of *Y. pestis* among "wild" rodents and their fleas (fig. 10), is present worldwide in what are known as natural foci of plague. Within these foci, numerous species of rodents and their fleas are infected with *Y. pestis* (fig. 11; table 6). Wild rodents can serve as sources of infection for other groups of wild and domestic animals, as well as commensal rodents and humans. In the US, between 1970 and 1991, most cases (46 percent) of human plague were associated with ground squirrels and their fleas (Craven and others, 1993). Prairie dogs and rabbits were also important sources of infection (fig. 12).

Classification of the Role of Wild Rodents

Wild rodents have been classified in several ways, depending on their roles in the ecology of plague. In one system, wild rodents can be characterized as primary or secondary hosts of plague (Fenyuk, 1940). Primary hosts and their fleas are able to maintain plague in a focus without contributions from other hosts; secondary rodent hosts and their fleas are unable to maintain plague without the assistance of primary hosts, although they may act to disseminate the disease (Gage and Kosoy, 2005). Factors affecting whether or not a rodent species acts as a primary or secondary host include susceptibility to plague, population size and distribution, behavior, and habitat (Gage and Kosoy, 2005).

Related to primary and secondary hosts is the categorization of foci according to the number of rodent hosts involved in the maintenance of plague. Single species of rodents maintain plague in **monohostal** foci; **polyhostal** foci involve more than one species of host. While there are clearly polyhostal foci, such as susliks and pikas in Mongolia and susliks, gerbils, and jerboas in central Asia (Gage and Kosoy, 2005), the designation of monohostal foci is more difficult. Although it is generally accepted that introduction of *Y. pestis* from a wild rodent to commensal rats often precedes an epizootic in the rats, plague may be maintained in commensal rats in some areas without involvement of other hosts. In Madagascar, for example, rats in the rural areas are considered to be the primary host in a monohostal focus (Gratz, 1999).

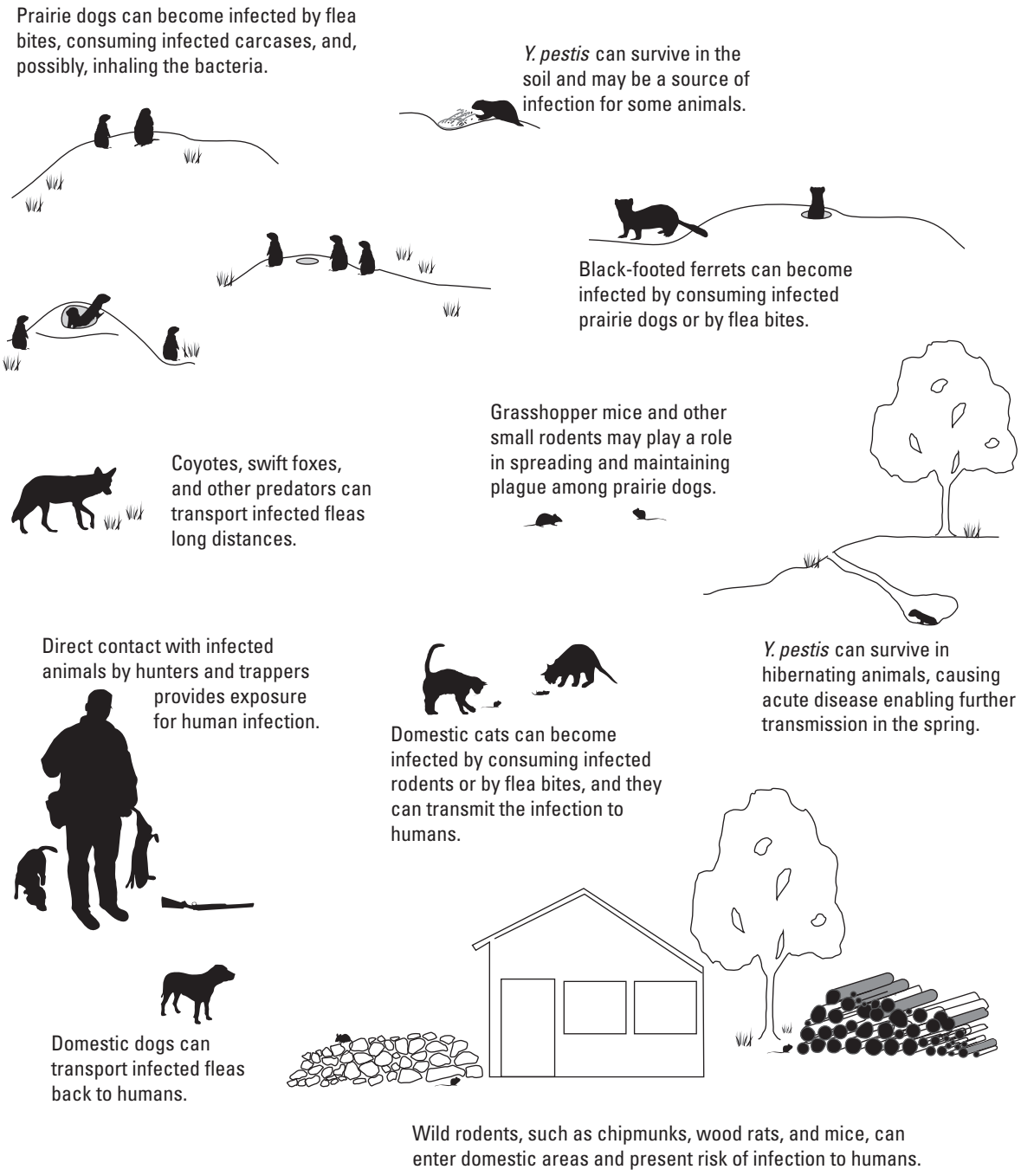


Figure 10. General pathways of transmission for sylvatic cycle in North America. Many species of wild rodents are involved in the sylvatic cycle of plague.

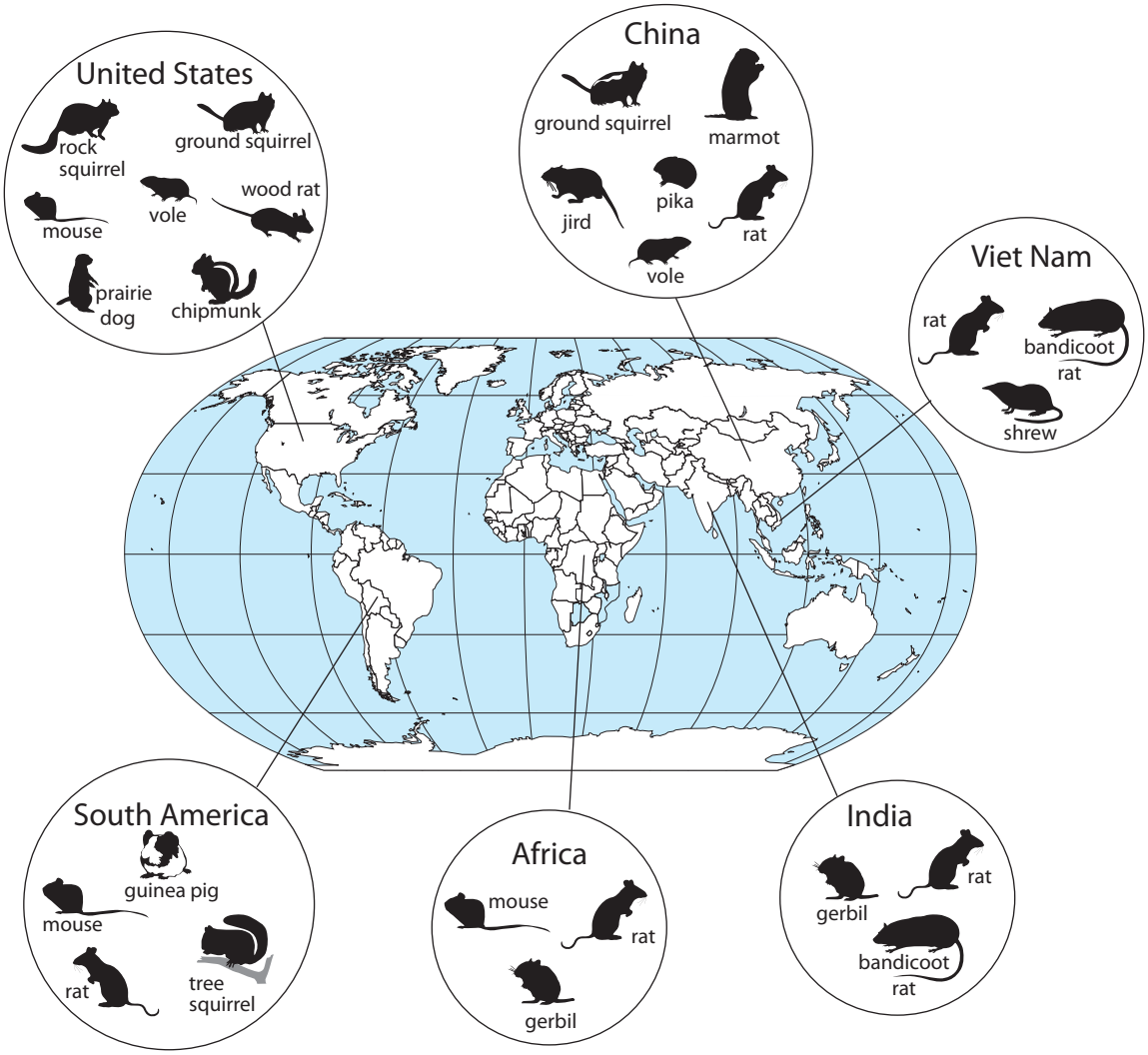


Figure 11. Areas where rodents are infected with *Y. pestis* and serve as sources of infection for other groups of wild and domestic animals and humans. The species of rodents involved in natural foci of plague vary by geographic region.

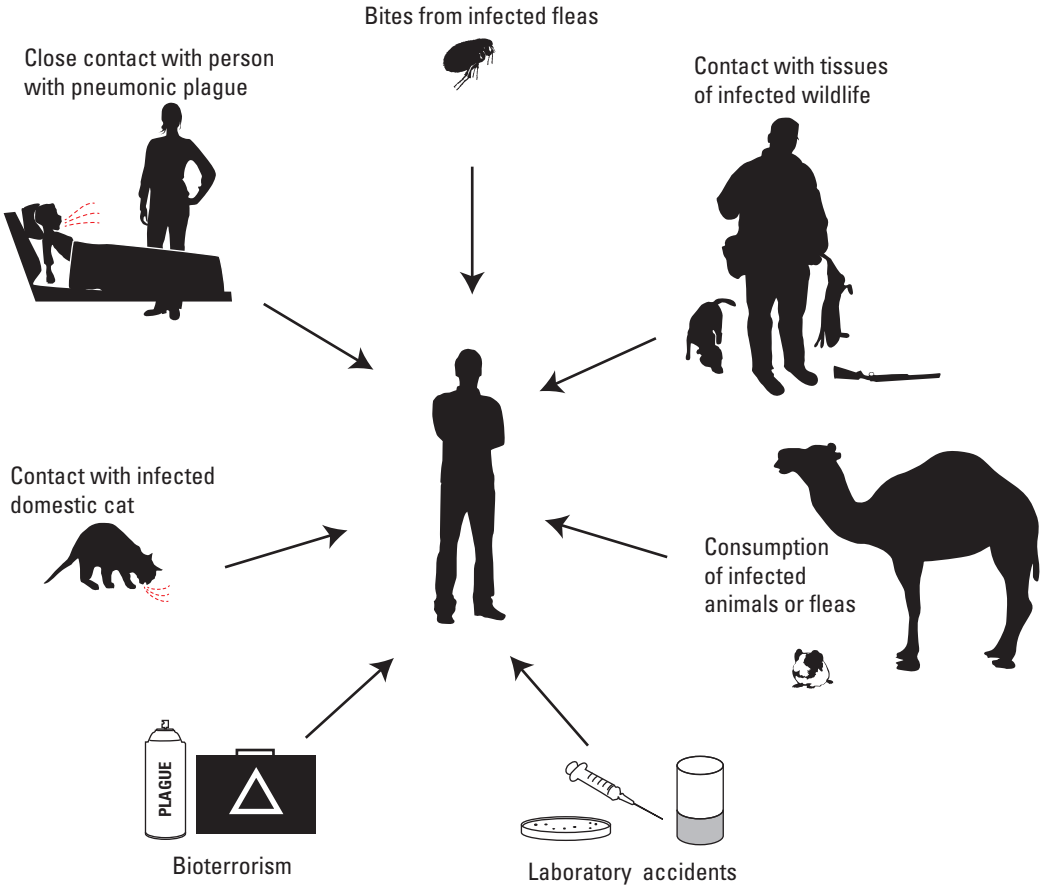


Figure 12. Routes of human exposure to *Y. pestis*. Humans can become infected with *Y. pestis* from many sources.

Enzootic and Epizootic Cycles

In the United States, plague in wild rodents has traditionally been divided into two cycles affecting different rodent hosts: the enzootic cycle involving **maintenance hosts** and the epizootic cycle involving amplifying hosts (Gage and Kosoy, 2005; Poland and others, 1994). Enzootic, or maintenance, hosts are characterized as having a **heterogeneous** response to plague; some individuals are susceptible while others are resistant. Deer mice and voles have typically been classified as being enzootic hosts. Epizootic, or amplifying, hosts, on the other hand, are highly susceptible to plague and experience sporadic outbreaks resulting in high mortality. Prairie dogs, ground squirrels, chipmunks, and wood rats have been classified as epizootic hosts.

Enzootic Hosts

Despite the persistence of this classification system, there has been little evidence to support the existence of enzootic hosts (Gage and Kosoy, 2005; Eisen and Gage, 2009; Stapp and others, 2008). A study of small rodents commonly occurring on prairie dog colonies found no evidence that they acted as long-term enzootic hosts of *Y. pestis* (Stapp and others, 2008). Northern grasshopper mice, thirteen-lined ground squirrels, deer mice, and kangaroo rats were trapped on prairie dog colonies in Colorado before, during, and after epizootics in prairie dogs. Only grasshopper mice were found to be seropositive during epizootics; other rodents were seropositive only after epizootics. There was no evidence of plague in rodents prior to epizootics.

Although grasshopper mice have many of the characteristics of an enzootic host (table 12), the evidence to validate their role in the maintenance of *Y. pestis* infections between epizootics is insufficient (Stapp and others, 2009; Stapp and others, 2008). Grasshopper mice do appear to be involved in the spread of plague epizootics among prairie dog colonies as revealed by a study of small rodents residing within and around prairie dog complexes in northern Colorado (Stapp and others, 2009). Epizootics in prairie dogs were more likely following years that grasshopper mice were more abundant (Stapp and others, 2009). Grasshopper mice harbored a wide range of flea species including *O. hirsuta*, a common prairie dog flea. Infestation of grasshopper mice by *O. hirsuta* increased dramatically during plague outbreaks, probably as fleas left dead prairie dogs in search of new hosts. The authors concluded high levels of *O. hirsuta* on grasshopper mice may be a predictor of an impending outbreak of plague among prairie dogs. No other small rodents acted as hosts of *O. hirsuta*. Another flea species, *Pleochaetis exilis*, found almost exclusively on grasshopper mice, was found to be infected with *Y. pestis* by PCR analysis. This finding demonstrated that grasshopper mice develop sufficient bacteremia to infect fleas (Stapp and others, 2009). Typically, this level of bacteremia is lethal to the mice, and it occurs 4–9 days after infection (Thomas and others, 1988). During this time period, grasshopper mice would have the opportunity to travel to other burrows and family groups (coteries) within the prairie dog colony, thereby spreading the disease by transporting infected fleas. Involvement of multiple coteries within a colony would result in a noticeable epizootic. These findings were supported by the results of a modeling study: the abundance of grasshopper mice on a prairie dog colony determined whether or not plague developed into an epizootic or remained at an enzootic level among prairie dogs (Salkeld and others, 2010).

Other studies have corroborated the suggestion that deer mice are not directly involved in maintenance of an enzootic cycle and transmission of *Y. pestis* to prairie dogs (Salkeld and Stapp, 2008a; Eisen, Holmes, and others, 2008). Deer mice often do not harbor enough of their primary flea species (*A. wagneri*) to be able to sustain the level of transmission needed for enzootic maintenance (Eisen, Holmes, and others, 2008). In addition, deer mice appear to be an uncommon host for the prairie dog flea, *O. hirsuta*, and show little indication of exposure to infected fleas in this system (Salkeld and Stapp, 2008a), although they might play a more significant role in areas where prairie dogs do not live or these mice carry more fleas. Thus, despite the search for enzootic hosts, no rodent species has been definitively identified as playing this role.

Epizootic Hosts

On the other hand, certain rodent species are clearly epizootic hosts of plague. In the western United States, several species of prairie dogs undergo sporadic epizootics of plague and suffer nearly 100 percent mortality (Rayor, 1985; Cully and others, 1997; Pauli and others, 2006; Lechleitner and others, 1968; Ubico and others, 1988). Other rodent species that experience epizootics with significant die-offs include wood rats, California ground squirrels, and thirteen-lined ground squirrels (Barnes, 1982).

Enzootic Plague

An alternative view is that the enzootic and epizootic cycles involve the same species of rodents but differ in other factors, such as rates of transmission of *Y. pestis* and the numbers of hosts infected depending on area, current environmental conditions, and the densities of rodent hosts and flea vectors (Eisen and Gage, 2009; Stapp and others, 2009). Under certain conditions, *Y. pestis* may exist in a rodent population in an enzootic state, but under other conditions, the level of infection transforms into an epizootic.

Indirect evidence for enzootic plague in prairie dog colonies was obtained in a recent study of survival rates of black-footed ferrets at two reintroduction sites in Montana (Matchett and others, 2010). Ferret survival at these sites was poor, even in the apparent absence of epizootic plague in prairie dogs (Matchett and others, 2010). To determine if enzootic plague was present, prairie dog burrows were dusted with deltamethrin to control fleas at some locations but not others. Also, half the ferrets released at each location were vaccinated with F1–V **vaccine** to decrease their risk of plague infection (see Disease Prevention and Control below); the other half received a placebo. Survival rates of ferrets were higher on dusted locations than nondusted locations. Likewise, survival rates were higher in vaccinated ferrets compared to unvaccinated ferrets on nondusted locations, but there was no difference on dusted locations. The results of this study suggest that the presence of enzootic plague decreased ferret survival. The positive effects of flea control as well as vaccination on survival of ferrets suggest that fleas are required for transmission or maintenance, or both, of enzootic plague. Similarly, survival rates of prairie dogs were higher at dusted sites than nondusted sites in the absence of plague epizootics (Biggins and others, 2010).

Climate

Despite evidence of the maintenance of plague within populations of rodents, the factors that transform plague from an enzootic to an epizootic state and that act to maintain *Y. pestis* in an area during the period between epizootics are not well understood (Eisen and Gage, 2009; Gage and Kosoy, 2005). One factor that may influence plague dynamics is climate, which can impact both host and flea populations, as explained by the **trophic cascade** model (fig. 13) (Collinge and others, 2005a; Enscore and others, 2002; Parmenter and others, 1999). An increase in rainfall provides the necessary moisture for increased **primary productivity** of the region, that is, plants become more abundant. The plentiful food supplies allow rodents to increase their populations, thereby

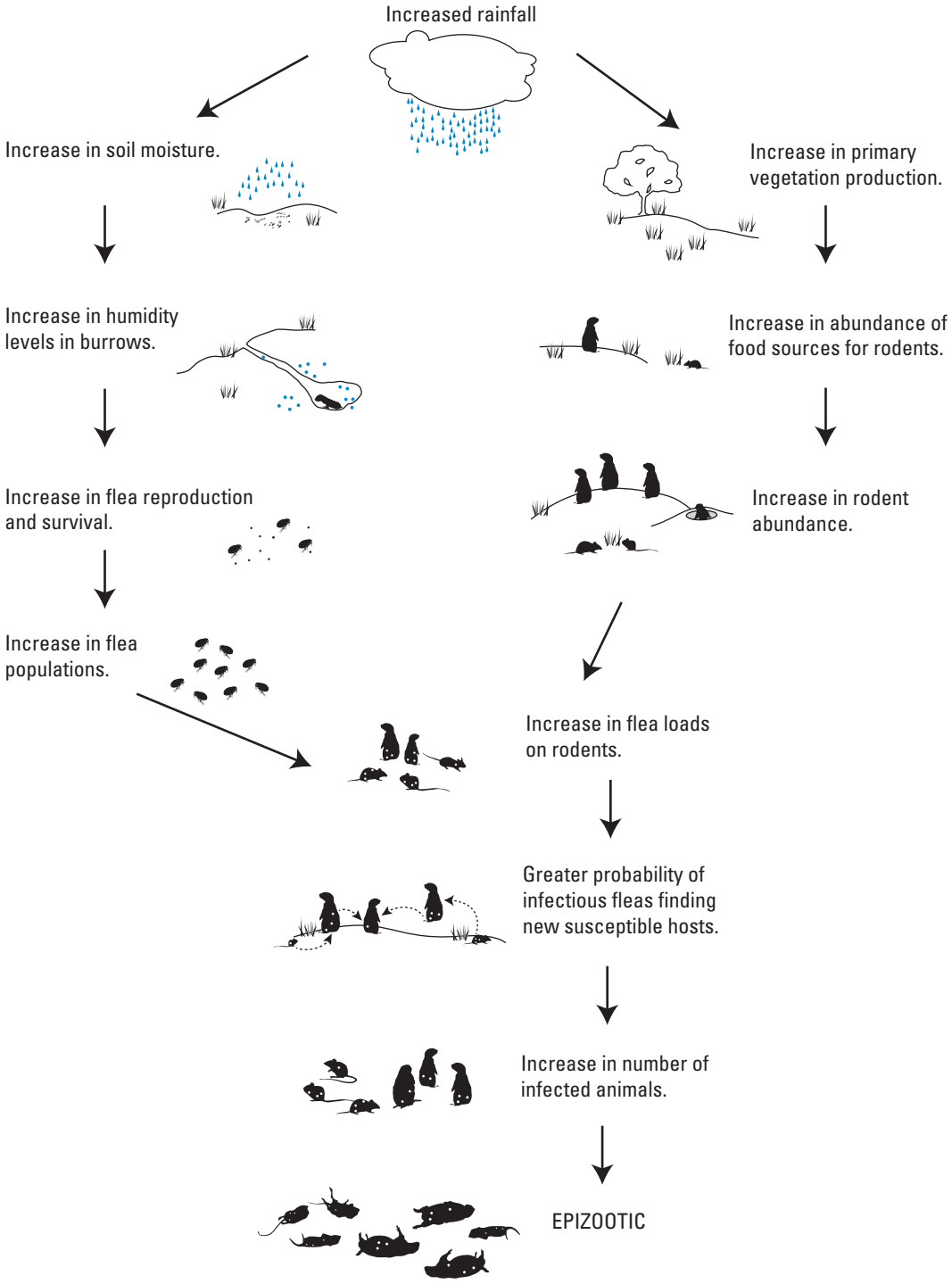


Figure 13. Trophic cascade model of plague. Climate may influence the incidence of plague by its influence on rodent and flea populations, as explained by the trophic cascade model.

increasing the numbers of potential plague hosts. The additional moisture in the soil also could have an effect on the local flea population. Because fleas are susceptible to desiccation, in moist years they are more successful in reproducing and surviving. The increase in flea numbers allows for increased transmission of *Y. pestis* when host densities are above a certain threshold (Davis and others, 2004), leading to a greater **incidence** of plague in the rodents and, possibly, an epizootic of plague. With the larger rodent populations comes an increased risk of human exposure to plague through direct contact with infected animals or their fleas. Domestic animals would be similarly at increased risk, presenting a further risk to their owners and caretakers.

The effects of climate on the occurrence of plague have been documented in populations of wild rodents as well as in humans. Among black-tailed prairie dogs studied in Montana, time-lagged precipitation was strongly associated with the number of colony die-offs; high precipitation in April to July of the previous year was positively associated with the number of cases of plague (Collinge and others, 2005a; Snäll and others, 2008). Temperature was also important, and the optimal temperature range for plague transmission was 80–95°F (Collinge and others, 2005a). Outside of this range, the temperature presumably had a negative effect on the fleas, which are susceptible to desiccation in hot weather. In addition, the ability of fleas to transmit *Y. pestis* is temperature related (Cavanaugh, 1971; Hinnebusch and others, 1998). Climatic variations associated with El Niño have been associated with **extirpations** of black-tailed prairie dog colonies in Colorado (Stapp and others, 2004). From 1969 to 2000, 75 percent of plague epizootics among prairie dogs happened during years of warmer and wetter winters attributed to El Niño events (Stapp and others, 2004). The 25 percent of extirpations not associated with El Niño events indicated that other factors may be important in the occurrence of epizootics of plague among prairie dogs (Stapp and others, 2004).

Similar results were obtained in studies assessing climate effects on the number of human cases in Arizona and New Mexico (Enscore and others, 2002; Parmenter and others, 1999; Ben Ari and others, 2008, 2010). Increased late-winter precipitation was associated with a higher number of human cases of plague two years later (Enscore and others, 2002). In years following winter-spring precipitation of above-average levels in New Mexico, 60 percent more cases of human plague resulted (Parmenter and others, 1999). An optimal temperature range of 80–90°F in New Mexico or 85–95°F in Arizona was associated with increased numbers of cases in humans (Enscore and others, 2002). The use of broader regional climatic indices, the Pacific Decadal Oscillation (PDO) and El Niño Southern Oscillation (ENSO), for 13 western States showed that during 1950–2005, positive phases of the PDO, characterized by warmer and wetter conditions, corresponded to periods of increased numbers of cases of plague in humans, particularly when coincident with El Niño events (Ben Ari and others, 2008; 2010).

Climate effects on plague occurrence can also be seen in central Asia among great gerbils (Stenseth and others, 2006; Kausrud and others, 2007). Warmer springs and wetter summers increase the fall **prevalence** of plague in the gerbils. Spring temperature is a primary environmental factor affecting plague prevalence in gerbils in Kazakhstan; a 1.8°F (1°C) increase in spring temperature may lead to a more than 50 percent increase in the number of plague cases in gerbils the following spring (Stenseth and others, 2006). It has been proposed that climate influences plague in gerbils through its effects on fleas. The colder the spring, the lower the **flea load** on gerbils and, with higher relative humidity in the summer, flea loads are higher on gerbils in the fall (Stenseth and others, 2006). Thus, warmer springs and wetter summers provide a basis for higher incidence of plague in gerbils (Stenseth and others, 2006; Kausrud and others, 2007).

It should be kept in mind that the effects of climate on plague occurrence are regional and not, in general, broadly applicable for making predictions about the incidence of plague. The optimal temperatures for transmission of *Y. pestis* may vary by latitude, with northern areas having a range of temperatures that are slightly lower than the range of temperatures in southern areas (Collinge and others, 2005a). The combined effects of El Niño and positive PDO events are stronger in the southwestern Unites States than in the western and northern areas (Ben Ari and others, 2010). Other factors, such as landscape features, regional variations in climate, and the timing and abundance of precipitation, can affect the plausibility of the trophic cascade model (Collinge and others, 2005a; Cavanaugh and Marshall, 1972). For example, in areas of Vietnam with already high humidity, increased rainfall can decrease the incidence of plague in humans owing to flooding of rodent burrows and subsequent decreases in flea populations (Cavanaugh and Marshall, 1972). In Colorado, no association was detected between climate and the occurrence of plague in prairie dogs, possibly because the study site did not exhibit predictable seasonal precipitation patterns (Collinge and others, 2005a).

Metapopulations of Rodents

Related to the trophic cascade hypothesis of plague occurrence is the idea that abundance of rodents is a factor in influencing the transformation of enzootic plague into an epizootic. The concept of **metapopulations** of rodents has been used to model plague in populations of prairie dogs, gerbils, and rats (Davis and others, 2004, 2007, 2008; Keeling and Gilligan, 2000a, b; Stapp and others, 2004). A metapopulation can be defined as a group of distinct populations of the same species that interact at some level but are separated by unoccupied or unsuitable areas of habitat. Although individual populations may go extinct, the metapopulation is considered to be stable because of migration between populations. Seemingly isolated populations may, in fact, be connected.

In the natural foci of plague in central Asia, the great gerbil acts as the primary host of the disease and lives in family groups within distinct, permanent burrow systems that do not change appreciably in number, location, and size over time. In Kazakhstan, the gerbil population can be considered to be a metapopulation, and each burrow system is a distinct family grouping within the larger gerbil population (Davis and others, 2007, 2004). The occupancy rate of these burrows varies considerably over time (Davis and others, 2004; Kausrud and others, 2007). One study determined that at least 30 percent of the burrows must be occupied for an epizootic of plague to occur (Davis and others, 2008). Evidently, this level of occupancy is enough to allow transportation of infectious fleas between burrow systems, which must occur to continue transmission of *Y. pestis*. This **abundance threshold** may be the consequence of what is termed a "percolation phenomenon"; as the **critical threshold** is reached, isolated patches of burrow systems with their fleas become connected to form a continuous area in which infection can more readily be transmitted. This phenomenon results from the difference in scale between movements of infectious fleas between burrow systems and the immense size of the habitats used by the gerbils (Davis and others, 2008), and it reflects the significance of the spatial structure and abundance of the host population for predicting epizootic transmission (Eisen and Gage, 2009). A percolation phenomenon involving abundance of grasshopper mice may also be important in promoting epizootic spread of plague among prairie dogs. Results of a modeling study demonstrated that when the number of grasshopper mice reaches a critical threshold within a prairie dog colony where enzootic plague is present, the mice can act to spread plague between infected and susceptible coteries (Salkeld and others, 2010).

The concept of metapopulations can also be applied to black-tailed prairie dogs (Stapp and others, 2004). In a study of the patterns of **extinction** of prairie dog colonies due to plague, the likelihood of extinction of a colony depended on the size and outcome of neighboring colonies, but it was not related to the distance between colonies (Stapp and others, 2004). Although colonies may appear to be isolated from distant neighbors, reduced vulnerability to the effects of plague was not seen, indicating that spatially separated colonies interacted (Stapp and others, 2004). However, the precise mechanisms of interaction among colonies that act to maintain and spread plague are unknown (Stapp and others, 2004).

Landscape features have been found to influence plague occurrence among black-tailed prairie dogs in areas of urban Colorado and rural Montana (Collinge and others, 2005b). Roads, lakes, and streams were found to decrease the occurrence of plague. These features may act as barriers to the spread of plague either by limiting the movement of hosts, or fleas, or both or by decreasing the quality of the habitat for these animals (Collinge and others, 2005b). Interestingly, urbanization by itself was not associated with the incidence of plague in prairie dogs (Collinge and others, 2005b), although increasing prairie dog density within colonies is associated with increases in adjacent urbanization (Johnson and Collinge, 2004).

Comparison of plague dynamics in different species of prairie dogs has revealed factors that may influence the spread of plague and the survival of colonies (Cully and Williams, 2001). All five species of prairie dogs (black-tailed, white-tailed, Gunnison's, Utah, and Mexican) are each highly susceptible to plague, but on a population basis, the responses to epizootics of plague differ among the species. These differences may possibly be explained by their varying social systems and colony densities (Cully and Williams, 2001). White-tailed prairie dogs are the least social species and live in low-density colonies. As a result of fewer contacts within their own species, the spread of *Y. pestis* through a white-tailed prairie dog colony is slower than in some other species, which could allow surviving prairie dogs to reproduce to replace the dead at a rate high enough to maintain the population. In contrast, black-tailed and Gunnison's prairie dogs are more social and live in colonies up to 10 times as dense as those of white-tailed prairie dogs. The resulting increased transmission of *Y. pestis* by higher rates of flea exchange and direct contact may lead to an increased probability of black-tailed and Gunnison's prairie dog colony extinction. In the Cimarron National Grasslands in Kansas, colonies of black-tailed prairie dogs infected with *Y. pestis* are widely scattered and are interspersed with uninfected colonies, indicating that a metapopulation structure may be important in this landscape; the rate of recolonization of extinct colonies is roughly equal to the rate of colony extinction caused by plague (Cully and Williams, 2001).

Reservoirs of Plague

Modeling studies on the relative importance of various modes of transmission of *Y. pestis* during epizootics in prairie dogs suggested that transmission from a short-term (2–3 weeks) infectious reservoir may be important in driving epizootics (Webb and others, 2006). Transmission by fleas with foregut blockage was apparently not efficient enough to sustain epizootics at flea loads typically seen on prairie dogs. Aerosol transmission appeared unlikely to drive epizootics because of the presumed rapid mortality of animals infected by this route; the number of infectious prairie dogs would not reach high enough levels to sustain the outbreak. In addition, based on experimental studies in guinea pigs (Meyer, 1961), aerosol transmission resulting in pneumonic plague appears to be unlikely in prairie dogs. However, no data to test these hypotheses are currently available. Possible short-term reservoirs of *Y. pestis* include resistant rodent species, infected carcasses, tissues, soil, and fleas without foregut blockage (Webb and others, 2006). These reservoirs may also be important in maintenance of *Y. pestis* in a focus during the periods between epizootics (Eisen and Gage, 2009; Drancourt and others, 2006).

Table 14. Relative efficiency of early-phase transmission of *Y. pestis* by fleas found on epizootic and enzootic hosts.

Flea species	Early-phase transmission efficiency	Primary host	Role of host	Reference
Xenopsylla cheopis	High	Rat	Epizootic	Eisen, Wilder, and others, 2007; Eisen, Netter, and others, 2008.
Oropsylla montana	High	California ground squirrel Rock squirrel	Epizootic	Eisen and others, 2006; Eisen, Lowell, and others, 2007; Eisen, Netter, and others, 2008.
Oropsylla hirsuta	High	Prairie dog	Epizootic	Wilder, Eisen, Bearden, Montenieri, Gage, and Antolin, 2008; Wilder, Eisen, Bearden, Montenairi, Trip, and others, 2008a.
Oropsylla tuberculata cynomuris	High	Prairie dog	Epizootic	Wilder, Eisen, Bearden, Montenairi, Trip, and others, 2008.
Aetheca wagneri	Low	Deer mouse	Enzootic	Eisen, Holmes, and others, 2008.
Ctenocephalides felis	Low	Cat	Other	Eisen, Borchert, and others, 2008.

Fleas

Early-phase transmission of *Y. pestis* by fleas without foregut blockage may play an important role in driving epizootics of plague (Eisen and others, 2006; Eisen, Lowell, and others, 2007; Eisen and Gage, 2009; Webb and others, 2006; Wilder and others, 2008a, b), because unblocked fleas may be able to remain infectious for the requisite 2–3 week period of a short-term reservoir (Eisen and Gage, 2009). Many of the flea species that are efficient early-phase transmitters are commonly found on rodent hosts that suffer high mortality during epizootics (table 14). Conversely, flea species that are inefficient early-phase transmitters are commonly found on hosts that do not experience epizootics or that suffer low mortality due to plague. Fleas have been proposed to be reservoirs of *Y. pestis* during enzootic periods (Gage and Kosoy, 2005; Salkeld and Stapp, 2008b; Hanson and others, 2007; Wilder and others, 2008a; Wimsatt and Biggins, 2009). Among colonies of black-tailed prairie dogs in Montana, PCR analysis of fleas found an unexpectedly high prevalence of *Y. pestis* infection (57–63 percent of colonies) during a period of time without evidence of epizootic activity of plague, that is, decreasing colony size or increased flea activity (Hanson and others, 2007). Although an intriguing finding, this result and the use of PCR to detect *Y. pestis* in fleas have yet to be validated. Experimental studies of early-phase transmission by *O. hirsuta*, a major flea of black-tailed prairie dogs, found that these fleas are most efficient at transmitting *Y. pestis* 24 hours postinfection; they are relatively inefficient in the late phase after developing foregut blockage (Wilder and others, 2008a). Based on this early-phase efficiency, modeling studies predicted that a flea load of 11.6 fleas per host would be adequate to maintain plague at an enzootic level; a level of 23.1 fleas per host would be sufficient to produce an epizootic of plague among the prairie dogs. Based on the natural level of about 12 fleas per prairie dog on average (Brinkerhoff and others, 2006), the authors concluded that plague may be maintained at an enzootic level among prairie dogs and their fleas (Wilder and others, 2008a). As more prairie dogs become infected and die, fleas will accumulate on the remaining prairie dogs until the threshold flea load is reached to cause an epizootic. A subsequent study of fleas on black-tailed prairie dogs in Colorado found the average number of fleas (*O. hirsuta* and *P. simulans*) per prairie dog increased from 10.4 before epizootics to 18.9 during epizootics (Tripp and others, 2009). In addition, the greatest increases were seen on prairie dogs infested with *Y. pestis*-infected fleas compared to prairie dogs with uninfected fleas. These results support the idea that flea abundance may be important in the dynamics of plague epizootics.

Ecological characteristics of fleas are associated with their potential efficiency as vectors of *Y. pestis*. Using the percentage of fleas with foregut blockage in experimental infections as a measure of a flea's ability to transmit *Y. pestis* to a host, one study found flea species that are more abundant than others, which was expressed as the number of fleas per individual host, tend to be more efficient transmitters (Krasnov and others, 2006). Presumably, a high abundance of fleas can compensate for the high mortality of blocked fleas. This high abundance may not be needed by efficient early-phase transmitters, because they generally survive longer than blocked fleas (Eisen, Wilder, and others, 2007; Eisen, Lowell, and others, 2007). In the case of the rat flea, *X. cheopis*, which is able to transmit *Y. pestis* with equal efficiency both in the early phase and after becoming blocked (Eisen, Wilder, and others, 2007), abundance may influence its role in triggering epizootics (Eisen, Wilder, and others, 2007). When flea abundance and host density are high, epizootics may be propagated by early-phase transmission (Eisen, Wilder, and others, 2007).

Flea vectors that are considered to be efficient transmitters of *Y. pestis*, based on the likelihood of developing foregut blockage, were also shown to have a narrower taxonomic range of hosts (Krasnov and others, 2006), tending to feed from only closely related species, and ensuring the persistence and transmission of disease to suitable hosts. Fleas that live only on a specific host animal, such as the prairie dog flea, *O. hirsuta*, which rarely forms blockages, may be important in the long-term persistence of *Y. pestis* in enzootic cycles within specific hosts, such as black-tailed prairie dogs (Krasnov and others, 2006; Wilder and others, 2008a). Switching hosts may affect the ability of a flea species to maintain its infection and transmit the bacteria to a new host (Eisen, Vetter, and others, 2008). In an experimental study, a ground squirrel flea (*O. montana)* and a rat flea (*X. cheopis)* showed a higher prevalence of infection and higher bacterial loads after feeding on infected rat blood, compared to either rabbit or mouse blood (Eisen, Vetter, and others, 2008). If feeding on the blood of natural hosts also affects the duration of infection in fleas and their ability to transmit the bacteria, the range of hosts used by a flea species may affect the dynamics of plague epizootics (Eisen, Vetter, and others, 2008). As an epizootic progresses and fleas move to alternative hosts, the rate of disease transmission may be affected.

Resistant Hosts

Resistant hosts are unlikely to act as the short-term reservoir of *Y. pestis* infection (Eisen and Gage, 2009). For a host to be able to transmit the bacteria to fleas during a blood meal, the number of bacteria in its blood must reach a level of at least 10 million colony forming units per milliliter (Engelthaler and others, 2000). Colony forming units are a measure of the number of bacteria in blood that are able to survive and multiply. This high level of bacteremia is likely to favor survival and transmission to successive hosts of highly virulent strains of *Y. pestis*. However, animals with this many bacteria in their blood would not be able to survive as long as 2–3 weeks. Thus, resistant hosts having lower numbers of bacteria in their blood are not a source of infection for fleas, although they could potentially act as a vehicle for infectious fleas and transport the disease between disparate areas (see discussion below).

Although prairie dogs are highly susceptible to outbreaks of plague on a population level, individual animals do survive infection with *Y. pestis*. Studies of epizootics among black-tailed and Gunnison's prairie dogs have found serological evidence of infection in surviving animals (Pauli and others, 2006; Cully and others, 1997). Among the 5 percent of black-tailed prairie dogs that survived plague during an epizootic in Wyoming, half of them had antibodies to *Y. pestis*; of the 1 percent surviving Gunnison's prairie dogs affected by a plague epizootic in New Mexico, more than 40 percent of them were seropositive for *Y. pestis*. Acquired immunity to infection, rather than avoidance of infection, contributed to their survival (Pauli and others, 2006). Surviving prairie dogs can contribute to repopulation of colonies and may be important in the evolution of resistance to plague (Pauli and others, 2006). Among grasshopper mice experimentally infected with *Y. pestis*, a lower mortality rate was seen in mice descended from mice originating from a plague-endemic area in Colorado than those descended from mice obtained from a plague-free area in Oklahoma (Thomas and others, 1989), supporting the idea that populations may develop resistance to plague under natural conditions (Thomas and others, 1988).

In Central Asia, where the plague bacillus probably originated more than 12,000 years ago, *Y. pestis* has coevolved with rodents to produce distinct strains that occur in specific rodent species or geographic areas. Selective pressure has led to a balance between virulence of *Y. pestis* and resistance among rodent hosts. Rodent species that are less social or that have higher resistance to disease would be more likely to survive. The relationship between sociality of certain rodent species and their acquired resistance is evident. Marmots, the most social sciurid in Asia, are the most resistant to plague (Biggins and Kosoy, 2001). Similarly, populations of great gerbils, another highly social rodent, contain a high proportion of resistant animals (Biggins and Kosoy, 2001). In North America, where *Y. pestis* has been present for only about 100 years, highly social prairie dogs are extremely susceptible to plague. With time, North American prairie dogs may develop resistance to plague as they coevolve with *Y. pestis*, similar to what has taken place in their Asian counterparts.

Soil

Another possible short-term reservoir of *Y. pestis* is soil. In 1894, Yersin reportedly obtained viable *Y. pestis* from soil in a house in which the residents had died of plague (Yersin, 1894). *Y. pestis* was also obtained from the burrow of a gerbil that died of plague; the burrow had been unoccupied by other rodents or fleas for 10–11 months (Karimi, 1963). Experimental work demonstrated survival of *Y. pestis* in autoclaved soil for 16 months (Mollaret, 1963). Transmission of *Y. pestis* to animals in contact with contaminated soil has also been successful in experimental situations (Indian Plague Commission, 1906; Mollaret, 1963). More recent experimental work showed that *Y. pestis* inoculated into sterilized soil, kept moist, survived and remained virulent for 40 weeks (Ayyadurai and others, 2008). *Y. pestis* has also survived in soil under natural conditions for at least 24 days (Eisen, Petersen, and others, 2008). In this case, blood from a plague-infected mountain lion contaminated soil in a sheltered location in Grand Canyon National Park, Ariz. Soil samples were collected 3 weeks after the mountain lion's death, and virulent *Y. pestis* was obtained from the soil samples by **mouse inoculation** and cell culture. Although it is unclear how *Y. pestis* might survive long term in soils, several mechanisms have been proposed, including adherence to **invertebrates** in the soil, invasion of single celled organisms, and survival within host tissues (Eisen and Gage, 2009). If virulent *Y. pestis* is capable of long-term persistence in soil, it may be able to infect animals that burrow or forage in contaminated soil either by ingestion or inhalation, and soil may act as a

reservoir of *Y. pestis* (Gage and Kosoy, 2005; Drancourt and others, 2006). Humans have contracted pneumonic plague by excavating plague corpses in Madagascar suggesting survival of *Y. pestis* in the soil (Ayyadurai and others, 2008).

Carcasses and Tissues of Infected Animals

Carcasses and tissues of animals infected with *Y. pestis* may also serve as short-term reservoirs of *Y. pestis*. *Y. pestis* can be transmitted by the ingestion of infected animals by **predation**, **scavenging**, and **cannibalism**. Northern grasshopper mice are omnivores, and they frequently kill and eat other rodents (Thomas and others, 1989). In an experimental study, grasshopper mice were fed white mice infected with *Y. pestis*, and 35 percent of the grasshopper mice became infected (Thomas and others, 1989). Grasshopper mice naturally consume rodent carcasses on inhabited prairie dog colonies that may or may not be infected with *Y. pestis*. If the carcasses are infected, the mice may act to spread plague among neighboring prairie dog colonies (Boone and others, 2009). *Y. pestis* has survived for more than 2 months in carcasses of black-footed ferrets in burrows, subsequently infecting and causing the death of a Siberian polecat that scavenged the carcasses (Godbey and others, 2006). *Y. pestis* may also be transmitted by cannibalism among rodents. Healthy rats were housed with infected rats dying of plague; rats that consumed the infected animals died of plague within 2–5 days (Rust and others, 1972). Mice have also become infected experimentally by drinking water containing *Y. pestis* (Butler and others, 1982) further demonstrating infection by ingestion of *Y. pestis*.

Role of Carnivores

The role of carnivores in the ecology of plague remains unclear. Based on serological studies, many species of North American carnivores are exposed to *Y. pestis* and are able to survive the infection (table 10). Carnivores can be infected by bites of infected rodent fleas or by consumption of infected prey during predation or scavenging (Perry and Fetherston, 1997; Gasper and Watson, 2001; Poland and others, 1994). Carnivores that spend time in rodent burrows or colonies during hunting or scavenging may pick up infected fleas and transport them to distant rodent colonies. Evidence for such transport was found in a study of **genotypes** of *Y. pestis* in colonies of Gunnison's prairie dogs in Arizona (Girard and others, 2004). The existence of similar genotypes in colonies separated by more than 6 mi (10 km) by habitat unsuitable for prairie dogs suggests distribution of plague-infected fleas by animals other than prairie dogs, such as **predators** or **scavengers** or both (Girard and others, 2004). Swift foxes and coyotes have been found to harbor flea species commonly found on prairie dogs: *Pulex simulans* and *O. hirsuta* (McGee and others, 2006; Harrison and others, 2003; Salkeld and others, 2007). A sizable proportion (24 percent) of swift foxes sampled in Colorado had antibodies to *Y. pestis* and harbored *P. simulans*, although none of the fleas were positive for *Y. pestis* when tested by PCR (Salkeld and others, 2007). Exposure of the foxes to *Y. pestis* was strongly associated with recent epizootics of plague among black-tailed prairie dogs in the area (Salkeld and others, 2007). Similarly, *P. irritans* (commonly known as the human flea but abundant on swift foxes) and *P. simulans* and *O. hirsuta* (prairie dog fleas) were collected from swift foxes in Texas following an epizootic in black-tailed prairie dogs; none of the fleas were positive for *Y. pestis* by mouse inoculation (McGee and others, 2006). Oral transmission by consumption of infected prairie dogs probably plays an important role in exposing foxes and other carnivores to *Y. pestis*. In an experimental study, coyotes and foxes scavenged guinea pig carcasses from inhabited prairie dog colonies and from prairie dog colonies that had experienced a recent plague outbreak, most often within 2 days of being laid out (Boone and others, 2009). As a result of this behavior, carnivores could become infected with *Y. pestis* as well as pick up infected fleas and transport them to distant colonies. Infected fleas were regularly found on prairie dog carcasses 1–2 days after the death of the animal (Boone and others, 2009; Salkeld and others, 2007).

Humans have become infected with *Y. pestis* by direct contact with various carnivores, including coyotes, foxes, bobcats, mountain lions, and badgers, primarily while skinning animal carcasses (Gage and others, 1994; Wong and others, 2009), suggesting carnivore-to-carnivore transmission may also be possible. Felids are highly susceptible to plague, but other carnivores mount a strong immune response to *Y. pestis*, as evidenced by surveillance studies (Hopkins and Gresbrink, 1982; Thomas and Hughes, 1992; Messick and others, 1983; Clover and others, 1989; Biek and others, 2002; Dyer and Huffman, 1999; Ryan and others, 1992; Gese and others, 1997). Nonfelid carnivores appear relatively resistant to disease, and they probably do not develop bacteremia high enough to infect fleas (Rust, Cavanaugh, and others, 1971). The presence of virulent *Y. pestis* in the throats of experimentally infected dogs (Rust, Cavanaugh, and others, 1971) suggests the possibility of transmission to other carnivores, including members of the same species, through close contact during grooming, food begging, fighting, predation, and scavenging (Salkeld and Stapp, 2006). However, in a study assessing dog-associated risk factors for plague in humans, there was no evidence that direct contact, such as being licked by an infected dog, increased the risk of plague for humans (Gould and others, 2008). Transmission by inhalation is another possibility among social carnivores that share dens (Salkeld and Stapp, 2006). The differences between nutritional and health status of domestic dogs that were naturally or experimentally infected and wild carnivores may affect the susceptibility to infection and ability to transmit *Y. pestis*. It has been suggested that slower transmission among resistant hosts or hosts of lower population density, like carnivores, may contribute to the persistence of plague (Girard and others, 2004; Salkeld and Stapp, 2006), but further studies are needed to clarify their role in the ecology of plague.

Survival of *Y. pestis*

Y. pestis may be able to survive for prolonged periods of time in fleas. Infected prairie dog fleas (*O. labis* and *O. tuberculata cynomuris*) were collected from burrows in Colorado more than 1 year after an epizootic of plague had wiped out the colony (Lechleitner and others, 1968; Kartman and others, 1966). Apparently, the infected fleas overwintered and maintained the infection into the following spring.

Y. pestis may also be able to survive in the tissues of hibernating rodents and cause disease in the spring (Bižanov and Dobrokhotova, 2007; Pollitzer, 1954; Anisimov and others, 2005; Kartman and others, 1966). Experimental inoculation of ground squirrels (Bižanov and Dobrokhotova, 2007; Pollitzer, 1954; Kartman and others, 1966), marmots (Pollitzer, 1954), and susliks (Pollitzer, 1954) during **hibernation** produced inapparent or **latent** infections with *Y. pestis*. Infected animals survived for several months during hibernation, but upon awakening in the spring, most animals developed bacteremias and died. In addition, a much higher (20x) experimental dose of *Y. pestis* was required to kill hibernating animals than normal experimental control animals (Kartman and others, 1966). Experimental studies of the effects of temperature on the virulence of *Y. pestis* have revealed a **symbiotic** relationship between the bacteria and the rodent host or flea host or both that enable the bacteria to persist asymptomatically while the host hibernates (Anisimov and others, 2005). During hibernation, marmots and ground squirrels typically have body temperatures of about 41°F (Ortmann and Heldmaier, 2000; Kauffman and others, 2004). When *Y. pestis* is grown at this temperature, the main virulence factors (Caf1, PsaA, Yops, Yscs, and Pla) become inhibited, making the organism less pathogenic (Han and others, 2005). At the same time, the host immune response is also muted during hibernation (Maniero, 2002; Prendergast and others, 2002), facilitating survival of *Y. pestis*. When spring arrives, the temperature increases and the rodents awaken; they can then develop acute disease, thus enabling further transmission of *Y. pestis*.

Y. pestis may utilize many avenues of persistence to survive in enzootic foci and produce epizootics. These reservoirs likely vary geographically and seasonally and depend on numerous intertwining factors related to the host, vector, and environment. There exists a "…delicate balance between the enzootic and epizootic state …[in which there is] … a complex interaction of host and parasite within the framework of the environment, creating a dynamic equilibrium wherein minor changes in any of a multitude of influencing factors can tip the balance one way or the other" (Olsen, 1981).

Points to Ponder

> "Plague has not been, and will not be soon, eradicated, despite the major advances made since the beginning of this century in the knowledge of the disease, in public health, and in therapy." (Guiyoule and others, 1994)

Numerous factors, including environmental and human-created changes, have contributed to the reemergence of human cases of plague as well as increased activity within established foci of sylvatic plague. Regional as well as broader climatic trends have been used to predict plague activity in both rodents and humans (Enscore and others, 2002; Parmenter and others, 1999; Ben Ari and others, 2008, 2010; Stenseth and others, 2006; Kausrud and others, 2007). Global warming has been predicted to have varying effects on plague in the United States and Asia. In one study, climate change is apparently shifting the northern and southern limits of human plague cases in a northerly direction in the United States, with the result of increasing the potential for transmission in Wyoming and Idaho (Nakazawa and others, 2007). At the same time, global warming may decrease cases of human plague in the Southwest by decreasing soil moisture and increasing temperatures that will negatively impact fleas and rodents as hypothesized in the trophic cascade model (Ben Ari and others, 2010). Plague prevalence in prairie dog colonies may decrease if global warming causes temperatures to increase above a level that would be detrimental to fleas (Snäll and others, 2009) or to transmission of *Y. pestis* by fleas (Cavanaugh, 1971; Hinnebusch and others, 1998). However, increases in the spring temperatures in central Asia are predicted to cause an increase in both the abundance of the primary host for plague, the giant gerbil, as well as the number of cases of infection in this host (Stenseth and others, 2006). Combined with changes in political structures and public health resources, these increases could lead to increased risk of plague among humans (Stenseth and others, 2006).

Humans may put themselves at risk of becoming infected with *Y. pestis* by encroaching on the sylvatic cycle of plague through expanded housing developments or recreational activities. In the western United States, ground squirrels and rock squirrels are common hosts of plague and suffer high mortality. These rodents readily adapt to human presence, often making their homes in rock walls, outbuildings, and refuse dumps, and their distribution corresponds to areas of higher risk of human exposure to *Y. pestis* (Eisen, Enscore, and others, 2007). These normally sylvatic species become peridomestic, thereby increasing the risk of transmission of *Y. pestis* to humans through direct contact with these rodents or their fleas.

The recent reemergence of plague in humans after prolonged periods of absence (table 7) highlights the importance of maintaining surveillance systems for monitoring plague activity in rodent populations. War and political unrest, natural disasters, as well as climatic trends affecting rodent

and flea populations, can underscore the need to be alert to increasing plague activity within specific areas. In addition, attention to controlling human ectoparasites, such as body lice or human fleas, may be warranted to limit outbreaks of plague among infested groups of refugees and homeless people (Drancourt and others, 2006; Ayyadurai and others, 2010). This may become particularly important in the event of deliberate use of *Y. pestis* as a biological weapon (Box 7).

The effects of plague have serious impacts on the conservation of many wildlife species. Numerous rodent species designated as conservation concerns by the International Union for Conservation of Nature live in areas in the western United States that experience periodic outbreaks of plague. The black-tailed prairie dog, renominated for addition to the endangered species list in 2007, has recently suffered devastating epizootics of plague. The resulting population declines in prairie dogs have repercussions for the endangered black-footed ferret, which is also highly susceptible to plague and which preys almost solely on prairie dogs for food (Box 8).

Disease Prevention and Control

Wild carnivores are routinely used in surveillance programs as **sentinels** of plague activity, because they produce antibodies to *Y. pestis* after infection but, with the exception of felids, rarely suffer mortalities. A primary route of infection for carnivores is through ingestion of infected prey species, either by predation or scavenging. Thus, the antibody status of carnivores reflects the infection status of the rodent prey and helps to determine the level of plague infections in rodent populations, especially when the probability of new infections is low (Barnes, 1982). Sampling only a few rodent-eating carnivores is equivalent to testing hundreds of rodents for infection (Gage and others, 1994). Carnivores used in surveillance programs include coyotes, badgers, raccoons, striped skunks, bobcats, and black bears (Hopkins and Gresbrink, 1982; Thomas and Hughes, 1992; Messick and others, 1983; Clover and others, 1989; Biek and others, 2002; Dyer and Huffman, 1999; Ryan and others, 1992; Gese and others, 1997). Wild boar and domestic dogs may also be useful as sentinel animals in plague surveillance systems (Nelson and others, 1985; Barnes, 1982; Rust, Miller, and others, 1971; Archibald and Kunitz, 1971). Surveillance of carnivores has been useful in documenting the spread of plague throughout the western United States and has detected the emergence of plague in previously unaffected areas (Gage and others, 1994). Knowledge about the presence of plague is useful for predicting the level of risk to humans living in the area.

Monitoring the abundance of rodents in relation to climate variations may also be useful for predicting epizootics among particular species of rodents as well as increases in the expected number of human cases based on modeling studies (Enscore and others, 2002; Parmenter and others, 1999; Stenseth and others, 2006; Davis and others, 2008).

Residents of enzootic areas can minimize their risk of developing plague by controlling rodents and fleas (Centers for Disease Control and Prevention, 1996). Sources of food and shelter for rodents around homes can be eliminated, and access to homes by rodents can be prevented. People can avoid direct contact with sick or dead rodents. Domestic dogs and cats could potentially act as sources of infection for humans by transporting infected fleas into homes (Orloski and Eidson, 1995; Gould and others, 2008; Pollitzer, 1954; Poland and Barnes, 1979); regularly treating pets with flea controlling preparations and preventing their eating rodents can decrease the risk of infection. Severely ill cats may survive—and the risk to their owners may be mitigated—if they are seen promptly by a veterinarian. Veterinarians working in enzootic areas need to be aware of the risk of acquiring plague from infected cats. Gloves, eye protection, and respirators or masks are prudent precautions for veterinarians when examining potentially infected cats. Hunters and campers in enzootic areas can reduce their risk of infection by avoiding rodent nest areas and using insect repellents. Wearing gloves when handling dead animals, regardless of species, also reduces the risk of infection.

Prophylactic treatment with tetracycline of people in close contact (within 6.5 ft or 2 m) (Centers for Disease Control and Prevention, 1996) with pneumonic plague patients, as well as people who have been exposed to infected fleas or who have had direct contact with body tissues and fluids of infected animals, is warranted within 6 days to minimize the risk of infection. Sulfonamides and trimethoprim-sulfa combinations can also be used for prophylaxis.

Control of outbreaks of plague among rodents living near humans is important for preventing human infections. The first step is the dusting of burrows with insecticides to kill the fleas transmitting the bacterium. Next, rodent control is useful for reducing the numbers of infected and susceptible animals. It is important to kill the fleas first; otherwise infected fleas may leave dying rodents and bite humans. Depending on the species of rodents involved and the location, trapping and **rodenticides** can be used.

Outbreaks among animals involving endangered species may have different considerations and may require different methods of control. Flea control is important and the use of vaccines may be helpful. Vaccines for use in prairie dogs and black-footed ferrets are being developed (Box 9).

Plague vaccines for humans were first used in the late 1890s when a killed whole cell vaccine was used during on outbreak in Bombay. From 1946 until 1999, when the manufacturer discontinued production, an inactivated whole cell vaccine was available for use in the United States (Center for Infectious Disease Research and Policy, 2005). It appeared to be protective against bubonic plague, based on positive results among U.S. military personnel in the Vietnam War (Cavanaugh and others, 1974). The incidence of plague among soldiers was dramatically lower compared to the incidence among Vietnamese civilians, despite roughly equal rates of murine typhus, which was also transmitted by

Box 7 Plague as a Biological Weapon

"…the intentional release of an infectious particle, be it a virus or bacterium, from the confines of a laboratory or medical practice must be formally condemned as an irresponsible threat against the whole human community." (Lederberg, 1999)

Yersinia pestis has been used as a biological weapon since the 14th century when Tartar forces heaved plague-infected corpses into the walled city of Caffa in 1346 (Koirala, 2006; Kirby, 2005; McGovern and others, 1997). Similar use of plague-infected bodies was employed by Russian forces against Sweden in the 18th century (Koirala, 2006; Kirby, 2005). During World War II, Japan expanded the use of plague as a biological weapon by exploiting the human flea, *P. irritans*, as a vector (McGovern and others, 1997; Kirby, 2005). Unit 731 was formed as a secret biological warfare unit under the pretense of being a water purification unit (Kirby, 2005) to devise a bomb that could disseminate plague-infected fleas. The Uji bomb was designed to hold 30,000 plague-infected fleas along with grain and rice to attract rodents. Upon detonation of the bomb in the air, the fleas and grain were dispersed over cities where they would eventually land with 80 percent survival of fleas (McGovern and others, 1997; Kirby, 2005) In 1940, 2 of these bombs were dropped onto two Chinese cities, causing epidemics of bubonic plague among the inhabitants that killed 120 people in one city and 24 in the other (Kirby, 2005; Inglesby and others, 2000).

Further development of plague as a bioweapon by the United States and the U.S.S.R. in the 1950s and 1960s exploited aerosol transmission of *Y. pestis* to cause cases of primary pneumonic plague (Inglesby and others, 2000). The World Health Organization estimated that if 110 pounds of *Y. pestis* were released as an aerosol over a city of 5 million people, 150,000 people would develop pneumonic plague and 36,000 of them would die; *Y. pestis* could remain viable in an aerosol form for 1 hour and disperse up to 6.2 mi (World Health Organization, 1970). Testimony from a Soviet defector alleged that the U.S.S.R. continued to develop plague as a bioweapon in the 1970s and 80s, attempting to genetically engineer antibiotic resistant forms of *Y. pestis* (Barry, 1993). Today, *Yersinia pestis* is classified as a Category A bioweapon based on its global distribution, ease of mass production, and potential to cause epidemics with high mortality, as well as incite panic among the populace.

Aerosol transmission of *Y. pestis* causes primary pneumonic plague associated with a high fatality rate, as well as subsequent person-to-person transmission that could spread the disease to a broader geographic range by secondary cases. Symptoms of pneumonic plague caused by use of a bioweapon would resemble those of other severe respiratory illnesses, and fever, dyspnea, and cough would develop 1–6 days after exposure (Inglesby and others, 2000; Koirala, 2006). The illness would progress to production of copious amounts of bloody sputum and sepsis, resulting in high mortality rates.

Rapid diagnosis of pneumonic plague is crucial to limiting the risk of deaths; when antibiotic therapy is delayed more than 24 hours after the onset of symptoms, pneumonic plague is always fatal. Unfortunately, early diagnosis of plague requires a large amount of suspicion, which authorities and medical personnel may not have in nonendemic areas. In addition, there are currently no effective warning systems for detecting aerosols of *Y. pestis* (Inglesby and others, 2000). When plague is suspected, appropriate samples (blood, sputum, and nasopharyngeal swabs) should be taken for diagnostic testing. In addition to standard diagnostic methods, use of a newly developed onsite, rapid diagnostic test (RDT), based on antibodies to an antigen of *Y. pestis*, may help health workers diagnose cases of pneumonic plague in a timely manner to limit fatalities (Chanteau and others, 2003). Contacts who may need prophylactic antibiotics could then be identified, limiting spread of the disease

Although streptomycin is the drug of choice for treating plague, supplies of this antibiotic are limited in the United States. Alternative drugs that may be more appropriate for a widespread outbreak include gentamicin, which is widely available and cheap, as well as tetracycline and doxycycline (Inglesby and others, 2000). Unfortunately, standard antibiotics may not be effective if *Y. pestis* strains that are resistant to multiple antibiotics are genetically engineered for use as bioweapons. Antibiotic susceptibility testing of the *Y. pestis* strain during early

Characteristics and examples of diseases that can be used as bioterrorism agents.

[From Centers for Disease Control and Prevention, 2009]

Characteristics of diseases in category	Examples of diseases in category
Category A	
Easily disseminated or transmitted person-to-person Causes high mortality with potential for major public health impact Might cause public panic and social disruption Requires special action for public health preparedness	Anthrax, botulism, plague, smallpox, tularemia, viral hemorrhagic fevers.
Category B	
Moderately easy to disseminate Causes moderate morbidity and low mortality Requires specific enhancements of Center for Disease Control and Prevention's diagnostic capacity and surveillance	Q fever, brucellosis, glanders, ricin toxin, epsilon toxin, staphylococcal enterotoxin B.
Category C	
Emerging pathogens that could be engineered for mass dissemination Ease of production and dissemination Potential for high morbidity and mortality and major health impact	Nipah virus, hantavirus, tickborne encephalitis viruses, yellow fever, multidrug-resistant tuberculosis.

response to the epidemic would enhance effectiveness of treatment (Inglesby and others, 2000). In large outbreaks, preventive antibiotics are recommended for people who develop a fever of more than 101.3°F or new cough (Koirala, 2006). Basic methods to control person-to-person spread of the infection include the use of masks, gloves, gowns, and eye protection; isolation of cases for the first 48 hours of antibiotic treatment; and thorough disinfection of rooms, bedding, and clothing of patients (Inglesby and others, 2000).

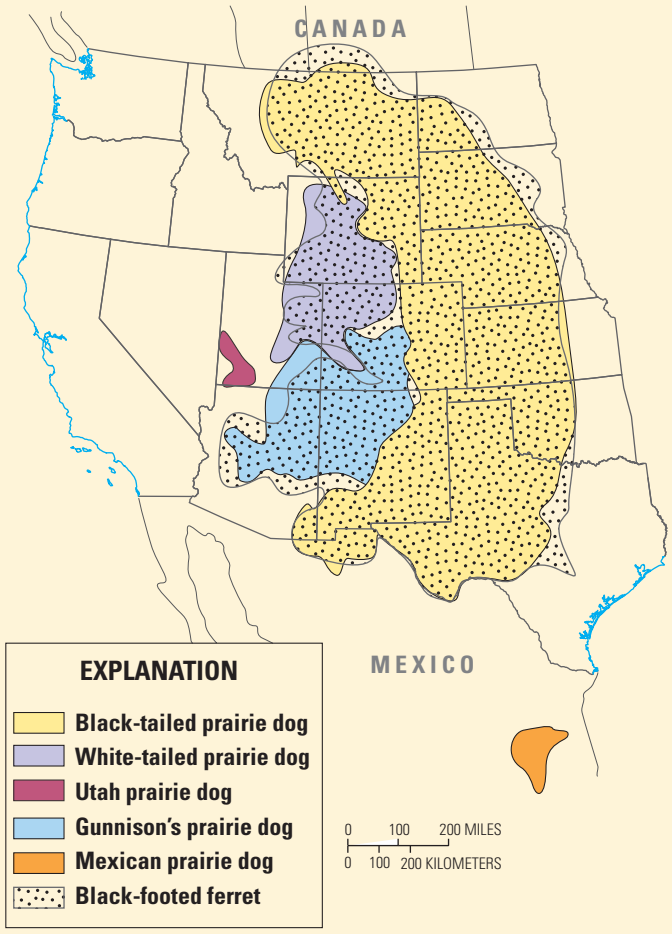
Distinguishing a naturally occurring epidemic of pneumonic plague from one resulting from a bioweapon is important for assessing the potential for continued exposure from an identified source. Forensic analysis of *Y. pestis* obtained from human cases can link these cases of plague to environmental sources of *Y. pestis* (Lowell and others, 2005; Colman and others, 2009). Epidemiological clues pointing to plague as the result of a bioattack include an epidemic occurring in a nonenzootic location, lack of a previous epizootic among local rodents, and occurrence in people lacking the usual risk factors (Inglesby and others, 2000; Koirala, 2006). The size of an outbreak would depend on the virulence of the strain of *Y. pestis* used, the amount of bacteria released and method of release, as well as environmental conditions (Inglesby and others, 2000).

Box 8 Plague and the Conservation of Prairie Dogs and Ferrets

Five species of prairie dogs live in western North America, and their ranges extend from Canada to Mexico and from the Rocky Mountains to eastern Nebraska. Of these five, the black-tailed prairie dog is the most numerous and the only one to inhabit the Great Plains. In the early 1900s, when plague first arrived in North America, black-tailed prairie dogs occupied 98 million acres of grasslands in the Great Plains area, possibly numbering as many as 5 billion animals (Wuerthner, 1997; Hoogland, 2006b). Increasing use of these lands by ranchers and farmers led to the perception of prairie dogs as pests that competed with domestic livestock for forage or fed on grain crops. Programs for eradicating and controlling prairie dogs by the use of poisons were implemented, and recreational shooting of the animals became popular. Combined with loss of habitat to increasing human populations and agriculture, these programs led to drastic declines in prairie dog populations. Compounding human impacts on prairie dogs is the natural threat of plague, to which prairie dogs are highly susceptible, and they often suffer nearly 100 percent mortality during outbreaks (Rayor, 1985; Cully and others, 1997; Pauli and others, 2006; Lechleitner and others, 1968; Ubico and others, 1988).

Utah prairie dog (NWHC).

Gunnison's prairie dog (Andrew Hollander).



Historical ranges of prairie dogs and the black-footed ferret in the western United States. (From Miller and Cully, 2001; blackfootedferret.org/reintroduction)

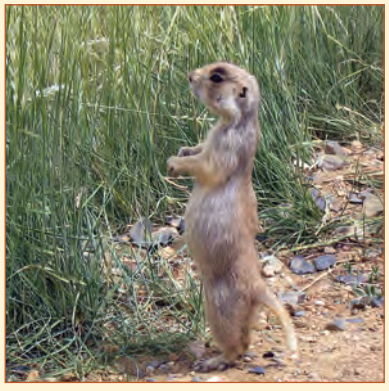
Today, it is estimated that prairie dogs occupy only 1–2 percent of their former range (Proctor and others, 2006). Colonies are now much smaller and more widely dispersed than they were before human intervention, making individual colonies more vulnerable to extinction (Miller and Ceballos, 1994; Antolin and others, 2002; Proctor and others, 2006). The black-tailed prairie dog is thought to have been extirpated in Arizona sometime between 1930 and 1960 (Underwood and Van Pelt, 2008), and it is currently being reintroduced to its original site in Arizona (Arizona Game and Fish Department, 2008). Of the five species of prairie dogs in North America, currently only one is listed as endangered, although petitions have been filed for listing others under the Endangered Species Act.

Prairie dogs play an important ecological role in grassland ecosystems and have been called "keystone species," because they significantly influence ecosystems in ways that are not entirely replicated by other species and are disproportionate to their abundance (Power and others, 1996). Although the status of prairie dogs as keystone species has been debated, it is generally agreed that prairie dogs play a vital role in the grassland ecosystem by supporting a different set of species than those in areas that are not colonized (Stapp, 1998; Miller and Ceballos, 1994; Miller and others, 2000, 2007; Kotliar and others, 1999; Kotliar, 2000). Many species prey upon prairie dogs or use their burrows for shelter and protection from predators. Others take advantage of the effects of prairie dog grazing for nesting sites or feeding on nutritious young grasses. Prairie dog colonies serve various functions for several animals, including the highly endangered black-footed ferret, which depends on prairie dogs for almost 90 percent of its prey.

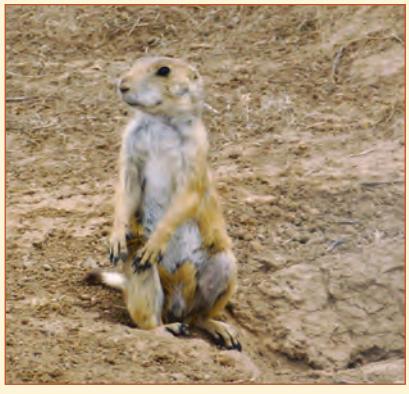
Status of prairie dogs under the Endangered Species Act.

[From U.S. Fish and Wildlife Service, 2010]

Common name	Status	Current distribution
Black-tailed prairie dog	Not listed, although it has repeatedly been petitioned for listing under the Endangered Species Act	Colorado, Arizona, Kansas, Montana, North Dakota, Nebraska, New Mexico, Oklahoma, South Dakota, Texas, Wyoming.
Gunnison's prairie dog	Candidate in montane region	Colorado, New Mexico, Arizona, Utah.
White-tailed prairie dog	Not listed, although it has repeatedly been petitioned for listing under the Endangered Species Act	Wyoming, Colorado, Utah, Montana.
Utah prairie dog	Threatened; it had been listed as an endangered species from 1973 to 1983	Utah.
Mexican prairie dog	Endangered since 1970	Mexico.



White-tailed prairie dog (Rhonda Foley).



Black-tailed prairie dog (J. Chipault, NWHC).

continued

Box 8 Plague and the Conservation of Prairie Dogs and Ferrets (*continued*)

Animals that are dependent on prairie dog colonies.

[From Kotliar and others, 1999. Obligate: almost totally dependent on prairie dogs for survival; strongly facultative: use one or more features of prairie dog colonies that have limited availability outside of colonies; weakly facultative: use features of prairie dogs colonies that are also abundant outside of colonies, use of colonies varies over time and area. Prey: prairie dogs serve as food source for predator; burrows: prairie dog burrows are used for shelter and protection from predators; nesting: short grass at colony sites is used as nesting ground; foraging: colony sites are used by animals feeding on vegetation and prey other than prairie dogs.]

Common name	Dependency on prairie dog colonies	Function
Black-footed ferret	Obligate	Prey, burrows.
Mountain plover	Strongly facultative	Nesting, foraging.
Burrowing owl	Strongly facultative	Burrows, foraging.
Golden eagle	Weakly facultative	Prey.
Ferruginous hawk	Weakly facultative	Prey.
Horned lark	Weakly facultative	Nesting, foraging.
Deer mouse	Weakly facultative	Nesting, foraging.
Northern grasshopper mouse	Weakly facultative	Nesting, foraging.
Swift fox	Weakly facultative	Prey.

The black-footed ferret was declared an endangered species when the Endangered Species Act was passed in 1973, and it had disappeared from the wild by the late 1970s (Biggins and Godbey, 2003). However, a wild population was found on white-tailed prairie dog colonies in Meeteetse, Wyo. in 1981. These animals were carefully monitored until distemper spread through the colony and threatened its existence in 1985 (Williams and others, 1988). At the same time, plague broke out in the prairie dog colony (Ubico and others, 1988). The remaining ferrets were captured in 1987 and placed in a captive breeding facility as part of a conservation plan. Since then, the population has expanded from the original 18 ferrets, and over 7,000 kits have been born in six North American breeding centers. Ferrets have been reintroduced into 19 sites in 8 States, Mexico, and Canada, and several populations are now self-sustaining (Jachowski and Lockhart, 2009; World Wildlife Fund, 2009). Unfortunately, plague is a major impediment to these conservation programs. In addition to losing nearly all of their prey during an outbreak, ferrets are themselves highly susceptible to plague and suffer high mortality (Williams and others, 1994). The most recent outbreak of plague that threatened ferrets was in 2008 in prairie dogs in the Conata Basin in South Dakota, a region that had previously been free of plague and was the most successful reintroduction site for black-footed ferrets (U.S. Geological Survey, 2008a; U.S. Fish and Wildlife Service, 2008). At sites where plague is thought to be enzootic, survival of reintroduced ferrets has been very poor (Matchett and others, 2010). Conservation of black-footed ferrets depends on protecting both prairie dogs and ferrets from the effects of plague.

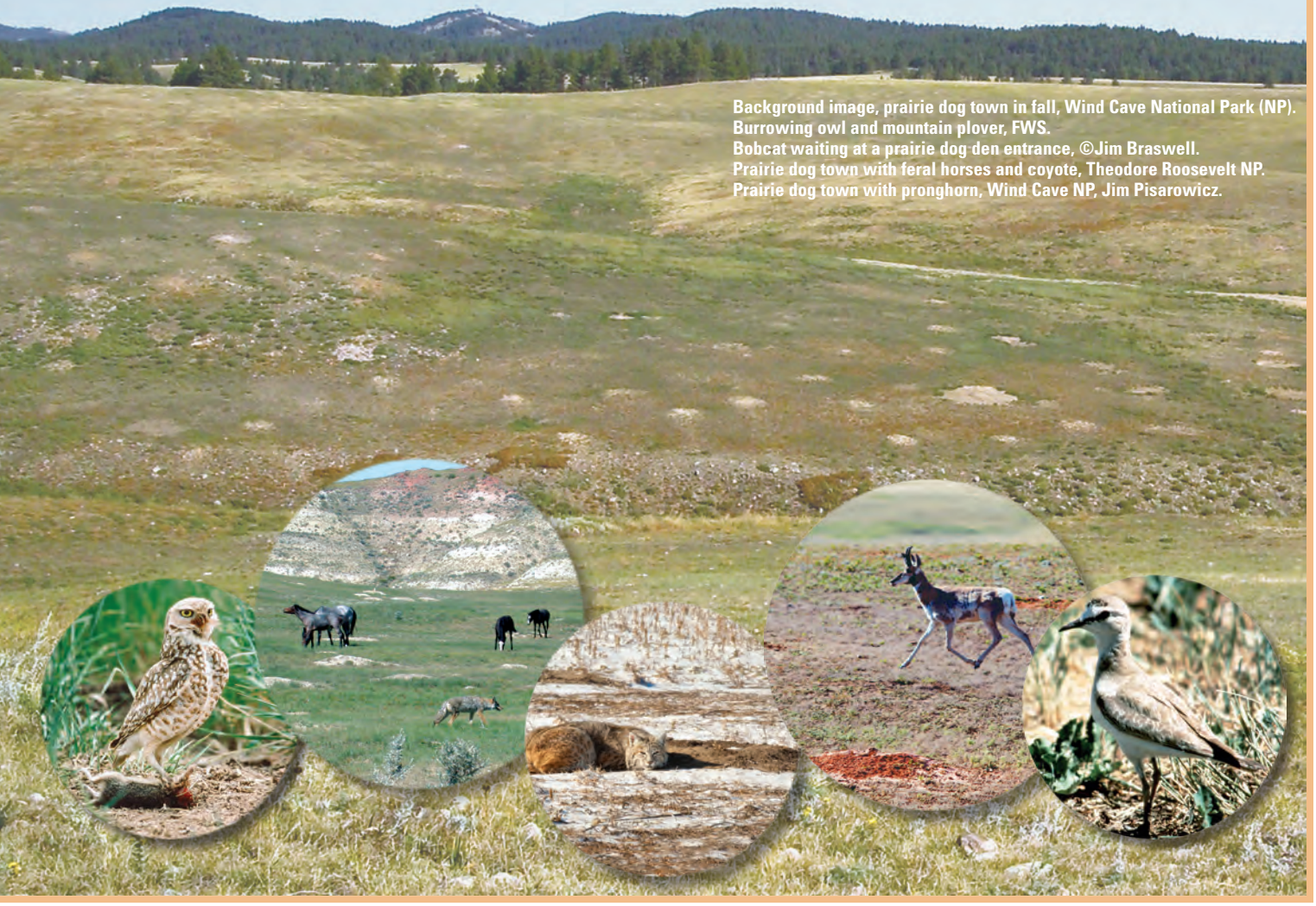
Efforts to battle plague in areas where ferrets have been reintroduced have focused on the use of insecticides to kill fleas. Dusting of burrows with deltamethrin has been shown to significantly reduce numbers of fleas both within burrows and on prairie dogs for at least 84 days after application (Seery and others, 2003). Because deltamethrin is waterproof, it can potentially remain active up to 8 months after application (Seery and others, 2003). Use of Pyraperm® in burrows killed fleas in a colony of Utah prairie dogs and immediately stopped epizootics of plague in 1998 and 2001 (Hoogland and others, 2004). If plague can be controlled in prairie dogs, ferrets will also benefit. Another method of combating plague is vaccination;

U.S. Fish and Wildlife Service (FWS)

vaccines are currently being developed to protect both prairie dogs and ferrets from infection by *Y. pestis* (Box 9). **Translocation** of prairie dogs is also used to recolonize depleted areas or establish new colonies (Long and others, 2006).

Conservationists have argued that designation of prairie dogs as a keystone species is important in ensuring their conservation (Kotliar and others, 1999; Kotliar, 2000; Miller and Ceballos, 1994) and would emphasize the critical role prairie dogs play in the grassland ecosystem. Conservation of prairie dogs would have a beneficial influence on the preservation of other dependent species, particularly the black-footed ferret, which has shown significant population declines as a result of declines in prairie dog populations (Kotliar and others, 1999; Wuerthner, 1997). Although preserving prairie dogs in small widely distributed colonies may preserve them as a species, ecologically they will be functionally extinct (Miller and others, 2007; Proctor and others, 2006). Their persistence as a species depends on establishing equilibrium between extinction and recolonization (Roach and others, 2001; Antolin and others, 2002). Effective management includes consideration of the ability of prairie dogs to repopulate colonies that become extinct (Roach and others, 2001; Antolin and others, 2002; Wuerthner, 1997); the optimal distance between colonies has been estimated to be about 1.2–1.9 miles (Roach and others, 2001; Milne, 2004). Appropriate distances for ferret dispersal are also a factor for consideration (Bevers and Hof, 1997). Landscape features that provide accessible dispersal routes around prairie dog colonies aid in the repopulation of colonies (Roach and others, 2001; Wuerthner, 1997; Antolin and others, 2002). In addition, prairie dog colonies that are large enough to act as sustainable prey bases benefit black-footed ferrets; to maintain a population of 200 adult ferrets requires a prairie dog complex covering 16,000 acres (Bevers and Hof, 1997).

"By surviving 200 years of poisoning, plague, loss of habitat, and recreational shooting, prairie dogs have demonstrated that they can overcome formidable obstacles. With prudent conservation, the preservation of prairie dogs for future generations is eminently feasible" (Hoogland, 2006b, p. 52). The only factor not under human control in this statement is plague. Understanding the dynamics of plague will be vital for the conservation of both prairie dogs and black-footed ferrets.

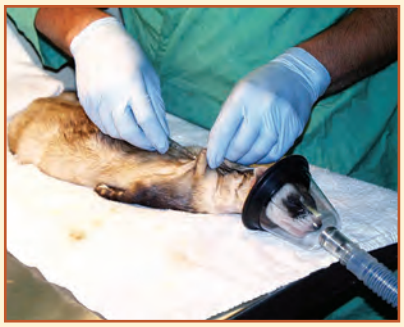


Background image, prairie dog town in fall, Wind Cave National Park (NP).
Burrowing owl and mountain plover, FWS.
Bobcat waiting at a prairie dog den entrance, ©Jim Braswell.
Prairie dog town with feral horses and coyote, Theodore Roosevelt NP.
Prairie dog town with pronghorn, Wind Cave NP, Jim Pisarowicz.

Box 9 Using Vaccines to Fight Plague in Prairie Dogs and Black-Footed Ferrets

Black-footed ferret (NWHC).

FWS scientist sprays pesticide on a prairie dog burrow to kill plague-carrying fleas (Randy Matchett, FWS).



USGS scientist injects a vaccine into a black-footed ferret (NWHC).

Conservation of prairie dogs and black-footed ferrets depends on the ability to control the effects of plague on these species, both of which suffer high mortality rates from the disease (Lechleitner and others, 1968; Rayor, 1985; Cully and others, 1997; Pauli and others, 2006; Ubico and others, 1988; Williams and others, 1994; Rocke and others, 2004, 2006; Rocke, Smith, Marinari, and others, 2008; Rocke, Smith, Stinchcomb, and others, 2008; Rocke, Pussini, and others, 2010). Although insecticides to control fleas, which are the vectors of *Y. pestis*, are useful in stopping plague outbreaks in prairie dog colonies, this practice is labor intensive, time consuming, and has detrimental effects on other insects (Cully and others, 2006). Preemptive methods to prevent infection may be more effective. Because the ecology of plague is so complex and incompletely understood, the only measure—other than pesticides—with potential prophylactic use is vaccination. Vaccines are being developed for use in prairie dogs and ferrets and have shown promise in successfully protecting these animals from infection with *Y. pestis* (Rocke and others, 2004, 2006; Rocke, Smith, Marinari, and others, 2008; Rocke, Smith, Stinchcomb, and others, 2008; Rocke, Pussini, and others, 2010; Rocke, Iams, and others, 2010; Mencher and others, 2004).

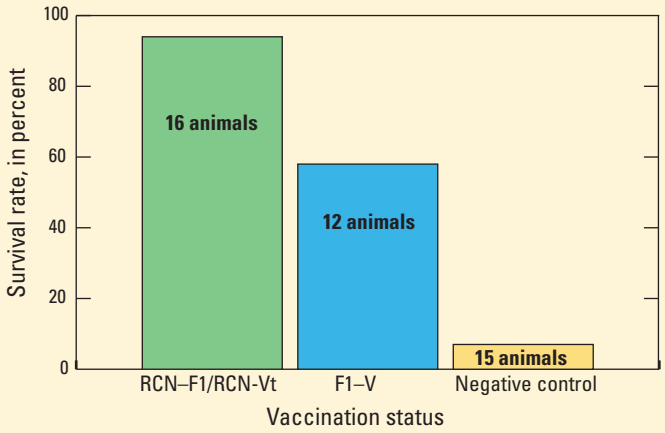
An injectable vaccine using proteins of *Y. pestis* virulence factors (proteins which enable the bacteria to invade the host, elude the host immune response, and cause disease), F1 and V, developed for use in humans by the U.S. Army Medical Research Institute for Infectious Disease (Heath and others, 1998), has been tested in black-footed ferrets (Rocke and others, 2004, 2006; Rocke, Smith, Marinari, and others, 2008). In initial studies with older animals, 69–86 percent of vaccinated animals survived infection with virulent *Y. pestis* injected under their skin, which mimics flea bites (Rocke and others, 2004, 2006). Subsequently, vaccination of ferret kits at 60 and 120 days of age was shown to fully protect animals (8 of 8 animals) against infection by the oral route, that is, ingestion of *Y. pestis*-infected mice (Rocke, Smith, Marinari, and others, 2008), which is the most likely route of exposure in the field. Vaccinated ferrets developed significant numbers of antibodies to combat F1 and V antigens, and their antibodies persisted for at least 3 years, indicating the potential for long-lasting immunity (Rocke, Smith, Marinari, and others, 2008).

The F1–V vaccine may be useful in captive-breeding facilities for protecting animals against inadvertent exposure to *Y. pestis* from infected prairie dogs used as food (Williams and others, 1994; Castle and others, 2001). Beginning in 2008, all captive-born ferrets released into the wild have been given two doses of the F1–V vaccine to protect them against plague. Most recently, the vaccine has been used as an emergency intervention method to limit ferret infections during the plague outbreak in the Conata Basin of South Dakota (U.S. Geological Survey, 2008b). However, vaccination of wild ferrets in the field is difficult and time consuming. Management of the disease in prairie dogs may be easier and more effective for prevention of plague in ferrets.

Development of vaccines for use in prairie dogs has focused on an oral vaccine for use in the field; these vaccines use raccoon poxvirus (RCN) as a vector for infecting oral mucosa with antigens of *Y. pestis*. Initial studies used F1 antigen to stimulate a protective immune response in mice (Osorio and others, 2003). Subsequently, RCN–F1 vaccine was incorporated into sweet potato baits that were voluntarily consumed by prairie dogs (Mencher and others, 2004; Rocke, Smith, Stinchcomb, and others, 2008). Ingestion of a series of two RCN–F1 vaccine-laden baits provided prairie dogs with 40–50 percent protection against experimental infections with virulent *Y. pestis* injected under the skin (Mencher and others, 2004; Rocke, Smith, Stinchcomb, and others, 2008). The vaccinated prairie dogs developed

significant amounts of anti-F1 antibodies after vaccination, with higher numbers of antibodies in prairie dogs that survived the disease (Rocke, Smith, Stinchcomb, and others, 2008; Mencher and others, 2004).

In an effort to increase the effectiveness of the oral vaccine, the V gene was also incorporated into the viral vector. A truncated version of the gene (Vt) was used to avoid the immune impairment associated with the full V protein (Rocke, Iams, and others, 2010; Rocke, Pussini, and others, 2010). Both RCN–F1 and RCN–Vt vaccines were incorporated into sweet potato baits that were voluntarily consumed by prairie dogs. Survival rates of prairie dogs orally vaccinated with the RCN–F1/RCN–Vt combination were directly compared to rates in prairie dogs inoculated by injection with the F1–V vaccine previously studied in ferrets (Rocke, Pussini, and others, 2010). Although the numbers of antibodies against F1 and V were higher in the animals vaccinated by injection with the F1–V vaccine than in the animals that ingested the RCN–F1/RCN–Vt vaccine, 94 percent of the animals vaccinated with the RCN–F1/RCN–Vt vaccine survived compared to the 58 percent of animals vaccinated with the F1–V protein vaccine that survived (Rocke, Pussini, and others, 2010). Thus, the oral RCN–F1/RCN–Vt vaccines provided nearly full protection against injections of virulent *Y. pestis* replicating numerous flea bites. More recently a single vaccine containing both genes (RCN F1–Vt) has been shown to be equally effective even after prairie dogs consumed the baits one time (T. Rocke, unpub. data, 2010).



Survival rates in prairie dogs challenged with subcutaneous *Y. pestis*.

Work continues in the development of suitable bait for vaccine delivery in the field that could be distributed by plane or vehicle. Protection of prairie dogs against plague would have several benefits. In addition to reducing mortality of the prairie dogs themselves, the source of bacteria for flea transmission to unvaccinated animals could be reduced. Use of an oral vaccine in the field could have the added benefit of immunizing small rodents that may be important in maintaining *Y. pestis* during periods between epizootics (Creekmore and others, 2002). Human exposure to *Y. pestis* could also be reduced. The ultimate goal would be to distribute the vaccine-laden baits in areas where black-footed ferrets are present. By preserving the prey of black-footed ferrets, as well as decreasing the source of infection for these animals, conservation of this species would be enhanced.

Black-tailed prairie dog (Dean Biggins, USGS Photo Gallery).

A variety of vaccine-laden oral baits (NWHC).

the vector of *Y. pestis*, the rat flea *X. cheopis*. Protection by the vaccine against the pneumonic form was not apparent. Currently, development of vaccines based on virulence factors of *Y. pestis*, F1 antigen and V antigen, is ongoing (Center for Infectious Disease Research and Policy, 2005; Titball and Williamson, 2001). Particular emphasis is being placed on protection against pneumonic plague for combatting potential bioterrorism events using airborne *Y. pestis*. Because the efficacy of potential vaccines cannot be rigorously tested in humans, other preventive measures can be employed to continue to minimize the risk of plague to vaccinated people.

Treatment

Prompt treatment of patients suspected of having plague infection is important because of the high mortality associated with delayed treatment. Untreated bubonic plague causes death in 40–60 percent of patients, and pneumonic plague is fatal within 48 hours of the first symptoms (Poland and Barnes, 1979). Early treatment with antibiotics can reduce the mortality rate to less than 15 percent. Treatment for pneumonic plague is most effective when it is started within 24 hours of the first symptoms. Streptomycin is the drug of choice for treatment of plague (Poland and Dennis, 1999; Butler, 2009), and other effective antibiotics include gentamicin, chloramphenicol, tetracycline, and sulfonamides. Chloramphenical is especially useful in treating plague when it spreads to the meninges, (the membranes covering the brain and spinal cord), the pleura (the membrane surrounding the lungs), and the tissues surrounding the eyes, in conditions known as **meningitis**, **pleuritis**, and **endophthalmitis**, respectively (Poland and Barnes, 1979).

Recently, two strains of *Y. pestis* that are resistant to multiple drugs were obtained from cases of bubonic plague in humans in Madagascar (Galimand and others, 1997; Guiyoule and others, 2001); both patients recovered after treatment with trimethoprim-sulfamethoxazole. These strains of *Y. pestis* may have come into contact with other bacteria in the flea midgut that were resistant to multiple drugs. The *Y. pestis* then acquired DNA from the other bacteria through a process called "**horizontal gene transfer**"; the acquired DNA carried the genes for multidrug resistance, which was then conferred on the *Y. pestis* bacteria (Galimand and others, 2006). If additional drug-resistant strains emerge, current antibiotic therapies to treat plague will become less effective, thus contributing to a major public health problem. Thorough surveillance of strains of *Y. pestis* can help to combat this threat, especially in light of the reemergence of plague.

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Glossary

Bolded terms within the definition of a term are in the glossary.

16S rRNA A small portion of the ribosomal **RNA** of bacteria used in studies of the evolution of a **species**, because it is nearly identical among members of a species of **bacteria**.

A

abundance threshold The minimum population of a species of rodent above which an epizootic of plague may occur.

acute Sharp or severe, such as an illness with a sudden onset and a relatively short course.

aerosol Fine mist of microscopic solid or liquid particles suspended in air or gas.

amplifying host A **host** in which disease agents, such as viruses, increase in number.

antibody A protein formed in the body of a vertebrate that is used by the immune system to identify and neutralize the effects of foreign invading proteins, called **antigens**, such as **bacteria** and viruses.

antigen Any foreign substance (generally proteins) to which the body reacts by producing **antibodies**. **Antigens** may be soluble substances such as toxins, particulate matter such as pollen, or microorganisms such as **bacteria** and viruses.

argasid ticks Eight-legged **arthropods** of the family Argasidae characterized by their soft, membranous external shells; also called "soft ticks."

aspirate The substance or material obtained by suctioning of fluids from a cavity.

arthropod An **invertebrate** belonging to the phylum Arthopoda, including insects, spiders, and crustaceans. Arthropods are covered by a hard exoskeleton and are characterized by a segmented body, jointed legs, and many pairs of limbs.

B

bacillus (bacilli, plural) Any rod-shaped **bacteria** that can be found in many different taxonomic groups of bacteria.

bacteria (bacterium, singular) Microscopic, unicellular organisms that have distinct cell membranes and lack a distinct nucleus surrounded by a nuclear membrane.

bacteremia The presence of **bacteria** in the blood.

bacterial load The number of **bacteria** within the **vector**; the number of *Y. pestis* within a flea.

bacteriophage A virus that infects a bacterium.

biofilm A mass of microorganisms in which cells are adhered to each other, or to a surface, or both.

bioterrorism The use of biological agents, such as **pathogenic** organisms or agricultural pests, for terrorist purposes.

biovar In the classification of **bacteria**, **strains** with sufficiently distinct characteristics (for example, chemical, molecular) to be considered a **subspecies** of a taxonomic **species**.

bioweapon Any weapon usable in biological warfare and **bioterrorism**.

birds Warm-blooded **vertebrates** with wings and feathers, although the wings are poorly developed in some flightless **species**. Birds belong to the taxonomic class Aves.

bubo An enlarged and inflamed lymph node, particularly in the armpit or groin, due to infection with *Y. pestis* or other organisms, such as those causing gonorrhea, tuberculosis, or syphilis.

bubonic plague A severe bacterial **disease** of humans due to infection by *Y. pestis*; acute regional enlargement and inflammation of lymph nodes (buboes) is typical of this most common form of plague in humans.

C

cannibalism The act of any **species** consuming members of its own kind.

carnivore **Mammals** with teeth and other body adaptations for feeding on flesh; primarily **species** belonging to the order Carnivora such as wolves, bears, raccoons, weasels, civets, hyenas, and tigers.

clinical signs Readily observable indications of a disease or injury.

coccobacillus A type of rod-shaped **bacteria** intermediate between the coccus (spherical) and bacillus (elongated) forms.

commensal Living with or near people and depending on humans, at least partially, for food and shelter.

contagious Capable of being transmitted from animal to animal.

critical threshold The level, such as numbers or density of animals, above which a particular event, such as an **epizootic** of plague, occurs suddenly. Below the threshold, the event does not occur.

culture The growing of **bacteria**, other microorganisms, or cells in a specially prepared nutrient medium.

D

desert An area that receives almost no precipitation, less than 10 inches (250 millimeters) per year, or that loses more than is received; vegetation is sparse to almost nonexistent.

die-off A sudden dramatic decline of a population of animals or plants caused by natural events such as weather or disease.

direct fluorescent antibody test A laboratory test using **antigen**-specific **antibodies** labeled with fluorescent dye to detect the presence of microorganisms.

disease An abnormal condition of an animal or plant that causes specific signs or symptoms.

DNA (deoxyribonucleic acid) A nucleic acid found mainly in the **chromosomes** that contains the hereditary information of organisms and some viruses.

domestic Pertaining to an environment managed by humans.

E

emerging disease A **disease** that has newly appeared or increased in frequency of occurrence, or both, within the past three decades, or threatens to increase in the near future relative to populations affected, geographic distribution, or magnitude of effects.

endemic A **disease** that commonly is present within a human population or a geographical area or pertaining to such a disease.

endophthalmitis Inflammation involving the eye cavities and their adjacent structures.

enteric redmouth disease A bacterial infection of fish caused by *Yersinia ruckeri*. Infected fish have bleeding under the skin around the mouth, fins, and eyes. Bleeding also occurs on internal organs, such as the intestine and swim bladder. The disease can cause severe economic losses in the trout farming industry.

enzootic An animal **disease** that commonly is present within a population or a geographical area or pertaining to such a disease.

epidemic An outbreak of **disease** affecting a disproportionately large number of humans within a population, community, or region during a period of time or pertaining to such an outbreak.

epidemiology The study of factors affecting the frequency and distribution of **disease** within populations.

epizootic An outbreak of **disease** affecting a greater number of animals than normal, typically involving many animals in the same region at the same time or pertaining to such an outbreak.

extinction The end of a **species** or other taxon when there are no surviving members of the group.

extirpation Local extinction; a **species** (or other taxon) ceases to exist in a particular area, but survives elsewhere.

F

fatality rate The ratio of deaths within a designated population with a particular **disease**, over a specified period of time.

fecal-oral route A route of **transmission** of **disease**, in which **pathogens** are passed from individual to individual by ingestion of feces.

felid **Mammals** within the family Felidae (for example, domestic cats, lion, tiger, leopard, lynx, cheetah, and many other wild cats).

flea Small, wingless, bloodsucking insect within the order Siphonaptera with laterally compressed body and legs adapted for jumping.

flea load The number of **fleas** infesting an animal.

fluorescent antibody test A laboratory test utilizing fluorescent dyes as stains for the detection of **antibody** against specific **pathogens**.

foci (**focus**, singular) A geographically localized area in which plague is maintained indefinitely by specific **rodents** and their **fleas**.

foregut The esophagus and **proventriculus** of the **flea**.

G

gene The biologic unit of heredity consisting of a specific sequence within a **DNA** molecule that determines a particular characteristic of an organism by controlling production of a specific protein.

genera (**genus**, singular) (plural of genus) A low-level taxonomic rank used in the classification of living and fossil organisms.

genotype The genetic makeup of a cell, an organism, or an individual, usually with reference to a specific character under consideration.

genotyping The process of determining the **genotype** of an individual by the use of biological tests, including **PCR** and **DNA** sequencing.

genus A **taxonomic** group of similar **species**; similar **genera** are grouped into families.

Gram-negative Referring to the inability to retain the purple dye when treated by Gram's stain for differentiating **bacteria** into two major groups (Gram-negative and Gram-positive).

ground squirrels Typically, burrowing small **rodents** of the family Sciuridae, but this term often also includes species in other genera such as chipmunks and prairie dogs. Ground squirrels in the United States include the thirteen-lined ground squirrel, rock squirrel, and antelope ground squirrel.

H

heterogeneous Made up of parts with dissimilar characteristics or properties.

hibernation A state of inactivity and metabolic depression in animals, characterized by lower body temperature, slower breathing, and lower metabolic rate to conserve energy, especially during winter when food is scarce.

horizontal gene transfer Any process in which an organism incorporates genetic material from another organism without being the offspring of that organism.

host An organism that harbors or nourishes microbes, viruses, and parasites on or in itself.

I

incidence The probability of a new case of a specific **disease** developing in a population at risk during a specified time period.

incubation period The time interval required for the development of **disease**; the time between the invasion of the body by a disease agent and the appearance of the first **clinical signs**.

infection The invasion by and reproduction of microorganisms in body tissues.

inguinal Related to the groin, the junction between the abdomen and thighs.

inocula (**inoculum**, singular) The antigenic material introduced into an animal to produce immunity or **disease**.

insecticide A pesticide used against insects.

insectivore An animal that feeds primarily on insects.

ixodid ticks Arthropods of the family Ixodidae that are important for **disease transmission**; includes ticks of the genera *Dermacentor*, *Amblyomma*, *Ixodes*, and *Haemaphysalis*; also known as "hard ticks."

J

K

L

lagomorph **Mammal** within the order Lagomorpha (rabbits, hares, and **pikas**).

latent Dormant or concealed; a latent **infection** refers to the situation in which a **disease** condition is not apparent.

latitude The location of a place on Earth north or south of the equator.

louse Small, wingless, usually flattened insect that is parasitic on animals, or plants, or both and derives its nutrition by feeding on **host** blood or other body components; true lice infest animals, including humans, and transmit several important **diseases**.

lymphadenitis Inflammation of lymph nodes.

lymphadenopathy **Disease** (**infection**, autoimmune disease, or tumor) of the lymph nodes, often used synonymously with "swollen/enlarged lymph nodes."

lymphoid tissues Immune system tissues, such as bone marrow, thymus, lymph nodes, tonsils, and spleen

lysis Refers to the death of a cell by breaking of the cellular membrane, causing the contents to spill out.

M

maintenance host An organism that keeps a **disease** agent in existence in nature and provides a source of infections to susceptible **hosts**. (*See* **reservoir**.)

mammal Warmblooded vertebrate animal that possesses hair during some part of its life and suckles it young.

mandibular Related to the mandible or lower jaw bone.

meningeal Related to the meninges, the membranes covering the brain and spinal cord.

meningitis Inflammation of the meninges, the membranes covering the brain and spinal cord.

metapopulation A group of spatially separated populations of the same **species** that interact at some level.

monohostal Describing maintenance of plague in a **focus** by a single **rodent species**.

morbidity A diseased condition, or the severity or incidence of a **disease**.

mortality Susceptible to death; death.

mortality rate The ratio of deaths (in general or due to a specific cause) in a specific population over a particular period of time.

mouse inoculation Injection of material suspected of containing a **disease**-causing agent into a mouse; development of disease in the mouse confirms the presence of the **pathogen** in the sample.

mustelid A member of the weasel family (Mustelidae), carnivorous animals such as weasel, wolverine, otter, marten, badger, ferret, and mink.

N

nasopharyngeal swab A sample of fluid obtained by passing a sterile instrument up the nostril to the portion of the pharynx above the soft palate.

necrotizing panophthalmitis Severe inflammation of all the eye structures leading to death of the tissues.

O

ocular Related to the eye.

P

pandemic An **epidemic** of infectious **disease** that is spreading through human populations across a large region, such as a continent or worldwide.

parasitism An association between two **species** in which one (the parasite) benefits from the other (the **host**), often by obtaining nutrients and shelter.

passive hemagglutination testing A laboratory test in which red blood cells are coated with soluble **antigen**; the red blood cells then clump in the presence of **antibodies** specific for the antigen.

pathogen Typically, a microorganism capable of inducing **disease**, but broadly including all disease-inducing agents.

pathogenic The ability to cause **disease**.

PCR (polymerase chain reaction) A laboratory technique used to generate millions or more copies of a particular **DNA** sequence.

peridomestic Pertaining to living in and around human habitations.

pharyngeal Pertaining to the pharynx, the musculomembranous passage between the mouth and the larynx and esophagus.

pika Short-eared, small rabbit-like **mammals** within the order Lagomorpha; also referred to as coney or rock rabbit.

plasmid A piece of **DNA** found in **bacteria** independent of the chromosomal DNA.

pleuritis Inflammation of the pleura, the membrane surrounding the lungs and lining the thoracic cavity.

pneumonic Pertaining to the lungs or pneumonia.

polyhostal Describing maintenance of plague in a **focus** by more than one **rodent species**.

population A group of organisms inhabiting a specific area or possessing a specific trait.

prairie Mainly in North America, the part of the **temperate latitude** grasslands characterized by level-to-rolling terrain, deep fertile soil, moderate rainfall, and a predominance of grasses, herbaceous plants, and shrubs, rather than trees.

predation The characteristic of preying on other animals as a source of food.

predator An animal that preys on other animals as a source of food.

prevalence The total number of cases of a **disease** in a population at a given time.

prevalent Widely or commonly occurring.

primary productivity The rate at which sunlight is used by plants to convert carbon dioxide (CO_2) to organic compounds used by animals as food.

prophylactic Preventing the spread of **disease**.

protozoa One-celled animals with recognizable nucleus, cytoplasm, and cytoplasmic structures, such as amoebas, ciliates, flagellates, and sporozoans.

protein An essential component of living cells that is made of chains of amino acids and contains carbon, hydrogen, nitrogen, oxygen, and sometimes sulfur.

proventricular blockage Obstruction of the **proventriculus** by the aggregation and adherence of *Y. pestis* within its interior space.

proventriculus The valve that connects the midgut to the esophagus of a **flea**.

Q

R

raptor Synonymous with **birds** of prey; including hawks, owls, falcons, and eagles, that feed on flesh.

regurgitation The flow of stomach contents back into the esophagus and mouth.

reservoir The **host** that maintains the **disease** agent in nature and provides a source of **infection** to susceptible hosts. (*See* **maintenance host**.)

resistant Pertaining to the ability of a microorganism to remain unaffected by an antimicrobial agent or the ability of an animal to remain either uninfected by a **disease**-causing organism or disease-free despite becoming infected.

ribotype A grouping of **bacteria** within a **species** based on similarities in rRNA. (*See also* **116 rRNA**.)

RNA (ribonucleic acid) A nucleic acid found mainly in the cytoplasm of cells that functions principally in the production of **proteins**. It differs from **DNA** by having a single chain rather than a double chain of nucleotides and containing the sugar ribose instead of deoxyribose.

rodent A diverse group of **mammals** characterized by incisor teeth that grow throughout life and that must be worn away by cutting and gnawing hard materials. **Species** within the order Rodentia include squirrels, mice, rats, voles, chipmunks, gophers, lemmings, beaver, porcupines, and many others.

rodenticide Toxic substances used to kill rodents.

rRNA gene restriction pattern A molecular tool used to type strains of **bacteria** by analyzing the number and size of fragments of rRNA obtained after enzymatic digestion. (*See also* **116 rRNA** and **RNA**.)

S

savanna A tropical grassland characterized by small, widely spaced trees, where most rain falls during one season of the year.

scavenging Feeding on dead or decaying matter.

scavenger An animal that feeds on dead carcasses, other carrion, and refuse (such as vultures, crows, hyenas, and jackals).

semidesert An extremely dry area characterized by sparse vegetation.

sentinel A susceptible animal or population that is monitored for the appearance or recurrence of a **pathogen** or antibodies against the pathogen as part of a **disease surveillance** system.

septicemia Blood poisoning; persistence of **pathogenic** microorganisms, or their toxins, or both in the blood.

septic shock A sudden drop in blood pressure caused by severe **infection**, especially with gram-negative **bacteria**, and marked by low blood pressure, coldness of the skin, increased heart rate, anxiety, and death in some cases.

seroconvert To develop detectable specific antibodies in the blood **serum** in response to immunization or **infection**.

serological testing The diagnostic identification of antibodies in the **serum**, the liquid portion of blood.

serum The pale liquid that separates from the blood when it is allowed to clot completely.

species A population of organisms whose members are able to breed among themselves and produce fertile offspring. More precise determinations of species are based on similarity of **DNA**. (*See also* **strain**.)

sputum Material, such as mucus or phlegm, that is coughed up from the lungs, bronchi, and trachea, into the mouth.

steppe A vast semiarid grass-covered plain, found in southeast Europe and Siberia.

strain A genetically or biochemically distinguishable subtype of a microorganism.

subcutaneous Under the skin.

subspecies A taxonomic category subordinate to a **species**, whose members differ morphologically from other members of the species but remain capable of interbreeding with them.

subtropical The region in each hemisphere between the **tropical** and **temperate** regions.

surveillance The systematic collection, analysis, and interpretation of data pertaining to the occurrence of specific diseases for the purpose of monitoring **morbidity** and **mortality** trends.

susceptible Pertaining to the ability of an animal to become infected by a **disease**-causing organism or to develop disease after becoming infected.

sylvatic Existing normally in the wild, not in the human environment.

symbiotic Living together in symbiosis, the close association of two unlike organisms with varying degrees of benefit, or harm, or both to the participants.

T

taxonomy The systematic principles and procedures of grouping and arranging organisms into a hierarchical order.

temperate latitudes Latitudes of the globe that lie between the tropics and the polar circles that exhibit seasonal temperature patterns.

translocation Human capture of wildlife at one geographic area and its transportation and release at a different geographic area.

transmission The spread of infectious agents from one individual to another by direct and indirect means, such as through contaminated environment or inanimate objects.

transmission efficiency The rate (**infections** per number of attempts) at which a **vector** is able to transmit an infection to a **host**.

trophic cascade Trophic level refers to an animal's position in the food chain. In plague ecology, precipitation and temperature have a cascading effect on plague occurrence by influencing the plant productivity of an area, which in turn affects the populations of **rodents** and **fleas** that further affect the **transmission** of plague.

tropical Geographically, the zone on either side of the equator, bounded by the Tropic of Cancer (23°27' North latitude) and the Tropic of Capricorn (23°27' South latitude); climatically hot and humid for most of the year.

U

ungulate **Mammals** having hooves. The even-toed hoofed **species** (Artiodactyla) include deer, antelope, cattle, and sheep; the odd-toed hoofed mammals (Perissodactyla) include horses, tapirs, and rhinoceroses.

V

vaccine A biological preparation containing an **antigen**, a molecule that stimulates the immune system, that is used to establish immunity to a **disease**.

vector An insect or other living organism that carries and transmits a **disease** agent from one animal to another.

vertebrate An animal that has a backbone, such as **mammals**, **birds**, amphibians, and fish.

virulence The degree or ability of a **pathogenic** organism to cause **disease**. The disease-producing ability of a microorganism, generally indicated by the severity of the **infection** in the **host** and the ability of the agent to invade or cause damage or both to the host's tissues.

W

X

Y

Z

zoonotic Pertaining to a disease that can be transmitted from animals to humans, and vice versa.

Appendix 1. Common and Scientific Names for Species Cited

Common name	Scientific name
Abert's squirrel	*Sciurus aberti*
African buffalo	*Syncerus caffer*
American marten	*Martes americana*
Antelope ground squirrel	*Ammospermophilus leucurus*
Asian house shrew	*Suncus murinus*
Badger (American)	*Taxidea taxus*
Bandicoot rat	*Bandicota indica*
	Bandicota bengalensis
Black bear	*Ursus americanus*
Black-footed ferret	*Mustela nigripes*
Black rat	*Rattus rattus*
Black-tailed deer	*Odocoileus hemionus*
Black-tailed prairie dog	*Cynomys ludovicianus*
Bobcat	*Lynx rufus*
Burrowing owl	*Athene cunicularia*
California ground squirrel	*Spermophilus beecheyi*
California vole	*Microtus californicus*
Camel	*Camelus* species
Canada lynx	*Lynx canadensis*
Cane mouse	*Zygodontomys* species
	Bolomys lasiurus
	Oryzomys species
Chipmunk	*Tamias* species
Cotton rat	*Sigmodon* species
Cottontail rabbit (mountain)	*Sylvilagus nuttallii*
Coyote	*Canis latrans*
Deer mouse	*Peromyscus* species, including *P. maniculatus*
Domestic cat	*Felis catus*
Domestic dog	*Canis lupus familiaris*
Domestic ferret	*Mustela putorius furo*
Domestic guinea pig	*Cavia porcellus*
Domestic pig	*Sus scrofa*
Donkey (ass, burro)	*Equus asinus*
Elephant (African)	*Loxodonta africana*
Ferruginous hawk	*Buteo regalis*
Fisher	*Martes pennanti*
Forest rat	*Rattus nitidus*
Fox (red, kit)	*Vulpes* species
Fox squirrel	*Sciurus niger*
Gerbil (jird, great gerbil)	*Meriones* species
	Rhombomys opimus
	Tatera species
	Desmodillus species
	Gerbillus species

Common name	Scientific name
Goat	*Capra hircus*
Golden eagle	*Aquila chrysaetos*
Gray fox	*Urocyon cinereoargenteus*
Great gerbil	*Rhombomys opimus*
Groove-toothed cheek rat	*Pelomys* species
Ground squirrel	*Spermophilus* species including
	S. variegatus
	S. spilosoma
	S. beecheyi
	S. lateralis
	S. beldingi
	S. elegans
	S. armatus
	S. townsendi
	Citellus species
Guinea pig	*Cavia porcellus*
Gunnison's prairie dog	*Cynomys gunnisoni*
Hare	*Lepus species*
Horned lark	*Eremophila alpestris*
Horse	*Equus caballus*
House shrew	*Suncus murinus*
Indian bush rat	*Golunda ellioti*
Indian field mouse	*Mus booduga*
Indian gerbil	*Tatera indica*
Jerboa	Family *Dipodidae*
Kangaroo rat (Ord's)	*Dipodomys ordii*
Kit fox	*Vulpes macrotis*
Leaf-eared mouse	*Phyllotis* species
Llama	*Lama glama*
Long-tailed weasel	*Mustela frenata*
Lynx (Canada)	*Lynx canadensis*
Malayan wood rat	*Rattus tiomanicus*
Marmot	*Marmota* species
Metad or soft-furred field rat	*Millardia meltada*
Mexican prairie dog	*Cynomys mexicanus*
Mountain lion	*Puma concolor*
Mountain plover	*Charadrius montanus*
Mule deer	*Odocoileus hemionus*
Multimammate mouse	*Mastomys* species
Northern grasshopper mouse	*Onychomys leucogaster*
Norway or brown rat	*Rattus norvegicus*
Palm squirrel	*Funambulus* species
Pika	*Ochotona* species

Common name	Scientific name
Pine marten	*Martes martes*
Polynesian rat	*Rattus exulans*
Prairie dog	*Cynomys* species
Pronghorn antelope	*Antilocapra americana*
Rabbit (cottontail, Old World)	*Sylvilagus* species
	Oryctolagus species
Raccoon	*Procyon lotor*
Rat	*Rattus* species
Rice rat	*Oryzomys* species
Ringtail cat	*Bassariscus astutus*
Rock squirrel	*Spermophilus variegatus*
Roof or black rat	*Rattus rattus*
Sable antelope	*Hippotragus niger*
Sheep	*Ovis aries*
Siberian polecat (Steppe)	*Mustela eversmanii*
South American field mouse	*Akodon* species
Spiny field mouse	*Mus platythrix*
Spotted skunk	*Spilogale putorius*
Spring hare	*Pedetes capensis*
Striped skunk	*Mephitis mephitis*
Suslik	*Spermophilus species*
Swamp rat	*Otomys* species
Swift fox	*Vulpes velox*
Thirteen-lined ground squirrel	*Spermophilus tridecemlineatus*
Tree shrew (common)	*Tupaia glis*
Tree squirrel	*Sciurus stramineus*
Unstriped grass mouse	*Arvicanthis species*
Utah prairie dog	*Cynomys parvidens*
Vole	*Microtus* species, including
	M. californicus
	M. montanus
	Eothenomys species
White-bellied mountain rat	*Rattus niviventer*
White-tailed prairie dog	*Cynomys leucurus*
Wild boar	*Sus scrofa*
Wild cavies	*Cavia* species
	Galea species
Wood rat	*Neotoma* species, including
	N. albigula
	N. mexicana
	N. fuscipes
	N. cinerea
Zebra	*Equus* species

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