# Chapter 23

# PLAGUE

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## INTRODUCTION

Plague is a zoonotic infection caused by *Yersinia pestis*, a Gram-negative bacillus, which has been the cause of three great pandemics of human disease in the common era: in the 6th, 14th, and 20th centuries. The naturally occurring disease in humans is transmitted from rodents and is characterized by the abrupt onset of high fever, painful local lymphadenopathy draining the exposure site (ie, a *bubo*, the inflammatory swelling of one or more lymph nodes, usually in the groin; the confluent mass of nodes, if untreated, may suppurate and drain pus), and bacteremia. Septicemic plague can sometimes ensue from untreated bubonic plague or, de novo, after a flea bite. Patients with the bubonic form of the disease may develop secondary pneumonic plague (also called plague pneumonia); this complication can lead to human-to-human spread by the respiratory route and cause primary pneumonic plague, the most severe and frequently fatal form of the disease.

During the last four millennia, plague has played a role in many military campaigns. During the Vietnam War, plague was endemic among the native population, but U.S. soldiers escaped relatively unaffected. This excellent protection of troops was largely due to our understanding of the rodent reservoirs and flea vectors of disease, the pathophysiology of the various clinical forms of plague, the widespread use throughout the war of a plague vaccine, and prompt treatment of plague victims with effective antibiotics. Mortality from endemic plague continues at low rates throughout the world despite the availability of effective antibiotics. People continue to die of plague, not because the bacilli have become resistant but, most often, because physicians do not include plague in their differential diagnosis (in the United States) or because treatment is absent or delayed (in underdeveloped countries).

To be best prepared to treat soldiers who are plague victims of endemic or biological agent attack by an enemy, military physicians must understand the natural mechanisms by which plague spreads between species, the pathophysiology of disease in fleas and humans, the minimal diagnostic information necessary to begin treatment with effective antibiotics, and the proper use and capabilities of the presently available plague vaccine.

The United States military's concern with plague is both as an endemic disease and as a biological warfare threat. A better understanding of the preventive medicine aspects of the disease will aid in the prompt diagnosis and effective treatment necessary to survive an enemy attack of plague.

Key terms in this chapter include *enzootic* and *epizootic*. These refer, respectively, to plague that is normally present in an animal community at all times but that occurs in only a small number of animals and in a mildly virulent form, and to widespread plague infections leading to death within an animal community (ie, equivalent to an *epidemic* in a human population). The death of a rodent pressures the living fleas to leave that host and seek other mammals, including humans. Understanding these two simple concepts will help us to understand how and when humans may be attacked, both in endemic and biological warfare scenarios.

## HISTORY

The biblical book of I Samuel records what may be the oldest reference to bubonic plague. In approximately 1320 BC, the Philistines stole the Ark of the Covenant from the Israelites and returned home. Then, I Samuel continues,

> [t]he Lord's hand was heavy upon the people of Ashdod and its vicinity; he brought devastation upon them and afflicted them with tumors. And rats appeared in their land, and death and destruction were throughout the city... [T]he Lord's hand was against that city, throwing it into a great panic. He afflicted the people of the city, both young and old, with an outbreak of tumors in the groin.[1]

After this time, plague became established in the countries bordering the eastern Mediterranean Sea.[2] In 430 BC, Sparta won the Peloponnesian War partly because of the plague of Athens.[3] Some scholars believe that this was the bubonic plague, but others suggest that it may have been due to other bacterial or viral diseases.[4]

### The First Pandemic

Procopius gave us the first identifiable description of epidemic plague in his account of the plague of the Byzantine empire during the reign of Justin-

ian I (AD 541–542),[5] which we now consider to be the first great pandemic of the common era. As many as 100 million Europeans, including 40% of the population of Constantinople, died during this epidemic.[6,7] Repeated, smaller epidemics followed this plague.[8]

**The Black Death (The Second Pandemic)**

The second plague pandemic, known as the Black Death, thrust this dread disease into the collective memory of western civilization.[8] Plague bacilli in fleas on the fur of marmots (a rodent of the genus *Marmota*) probably entered Europe via the trans-Asian silk road during the early 14th century. When bales of these furs were opened in Astrakhan and Saray, hungry fleas jumped from the fur seeking the first available blood meal, often a human leg.[8–10] In 1346, plague arrived in Caffa (modern Feodosiya, Ukraine), on the Black Sea. The large rat population there helped spread the disease as they stowed away on ships bound for major European ports such as Pera, a suburb of Constantinople, and Messina, in Sicily. By 1348, plague had already entered Britain at Weymouth.[5]

The Black Death took the lives of 24 million people between the years 1346 and 1352 and claimed perhaps another 20 million by the end of the 14th century.[6] However, the plague continued through 1720, with a final foray into Marseilles. Thirty percent to 60% of the populations of major cities such as Genoa, Milan, Padua, Lyons, and Venice succumbed during the 15th to the 18th centuries.[10]

Physicians of the time offered no effective treatment because they did not understand the epidemiology of plague. At the highly regarded University of Paris, physicians theorized that a conjunction of the planets Saturn, Mars, and Jupiter at 1:00 PM on March 20, 1345, caused a corruption of the surrounding atmosphere that led to the plague.[6] They recommended a simple diet; avoidance of excessive sleep, exercise, and emotion; regular enemas; and abstinence from sexual intercourse.[11] While some people killed cats and dogs, thinking them to be carriers of disease, no one ever thought to kill the rats.[6] Christians blamed the disease on Muslims, Muslims on Christians, and both Christians and Muslims on Jews or on witches.[8]

In 1666, a church rector in Eyam, Derbyshire, England, persuaded the whole community to quarantine itself when plague erupted there. This was the worst possible solution, since the people then stayed in close proximity to the infected rats. The city experienced virtually a 100% attack rate with 72% mortality (the average mortality for the Black Death was consistently 70%–80%).[8,12]

Accurate clinical descriptions of the Black Death were written by contemporary observers such as Boccaccio, who wrote in his *Decameron*:

> The symptoms were not the same as in the East, where a gush of blood from the nose was a plain sign of inevitable death, but it began both in men and women with certain swellings [buboes] in the groin or under the armpit. They grew to the size of a small apple or an egg, more or less, and were vulgarly called tumours. In a short space of time these tumours spread from the two parts named all over the body. Soon after this, the symptoms changed and black or purple spots appeared on the arms or thighs or any other part of the body, sometimes a few large ones, sometimes many little ones.[13(p646)]

Guy de Chauliac in Avignon added his own commentary, describing pneumonic plague and the axillary and groin forms of bubonic plague:

> Doctors dared not visit the sick for fear of infection; or, when they did, they helped little and gained nothing.[14(p646)]
>
> . . . .
>
> The disease is three fold in its infection; that is to say, firstly, men suffer in their lungs and breathing and whoever have these corrupted, or even slightly attacked, cannot by any means escape nor live beyond two days...and it is found that all those who have died thus suddenly have had their lungs infected and have spat blood. There is another form of the sickness, however, at present running its course concurrently with the first; that is, certain aposthumes appear under both arms and by these also people quickly die. A third form of the disease—like the two former, running its course at the same time with them—is that from which people of both sexes suffer from aposthumes in the groin. This is likewise quickly fatal.[15(p646)]

Some writers described bizarre neurological disorders, which gave rise to the term "Dance of Death," followed by anxiety and terror, resignation, blackening of the skin, and death. The sick gave off a terrible stench: "Their sweat, excrement, spittle, breath, [were] so foetid as to be overpowering"[; in addition, their urine was] "turbid, thick, black, or red."[6(p70)]

The second great pandemic slowly died out in Europe by 1720. Many reasons, including the following, have been suggested to explain its decline:

- The oriental rat flea, *Xenopsylla cheopis*, the main vector of the plague bacillus, could no longer exist in the cool European climate.[5]
- The black rat, *Rattus rattus*, was replaced by the brown rat, *Rattus norvegicus*, which was less likely to live in close proximity to man.[5,8]
- A new and less virulent species of *Y pestis*, or a related *Yersinia* species such as *Y pseudotuberculosis*, may have developed, causing natural immunization of infected rats and humans.[8]
- The European population was generally iron deficient, and iron is an essential factor for the bacterium's virulence.[12]
- Flea density on humans decreased as the use of soap became more widespread.[5]

### The Third Pandemic

The third, or modern, plague pandemic arose in 1894 in China and spread throughout the world via modern transportation.[12,16] It was also in 1894 that Alexandre J. E. Yersin discovered that *Yersinia pestis* satisfied Koch's postulates for bubonic plague.[17] The reservoir of plague bacilli in the fleas of the Siberian marmot was likely responsible for the Manchurian pneumonic plague epidemic of 1910–1911, which caused 50,000 deaths.[2] The modern pandemic arrived in Bombay in 1898, and during the next 50 years, more than 13 million Indians died of plague.[2,18]

The disease officially arrived in the United States in March 1900, when the lifeless body of a Chinese laborer was discovered in a hotel basement in San Francisco, California[19]; the disease appeared in New York City and Washington state the same year.[20] New Orleans, Louisiana, was infected in 1924 and 1926.[20] Rodents throughout the western United States were probably infected from the San Francisco focus, leading to more infected rodents in the western United States than existed in Europe at the time of the Black Death.[12] Therefore, human plague was initially a result of urban rat epizootics until 1925. After general rat control and hygiene measures were instituted in various port cities, urban plague vanished—only to spread into rural areas, where virtually all cases in the United States have been acquired since 1925.[21]

## PLAGUE AND WARFARE

It is an axiom of warfare that battle casualties are far fewer than casualties caused by disease and nonbattle injuries.[3] *Y pestis* can cause disease both through endemic exposure and as a biological warfare agent. Medical officers need to be able to distinguish likely from unlikely cases of endemic disease, and to keep the possible biological warfare threat in mind.

### Endemic Disease

Just as plague befell armies of antiquity, so the disease has also afflicted armies in more recent times. Frederick the Great's troops were devastated by plague in 1745, as were Catherine the Great's in 1769–1771 when they returned from the Balkans with plague. In 1798, French military operations in Egypt were significantly impeded by plague, which even caused them to abandon their attack on Alexandria. The modern pandemic began in China, when Chinese troops were deployed in an epidemic plague area to suppress a Muslim rebellion. Military traffic is responsible for the rapid spread of disease to nearly every country in Asia.[2]

For the U.S. military since the mid 20th century, endemic plague has not been a source of disease and nonbattle injuries. During World War II and the Vietnam War, U.S. forces were almost entirely free of plague. However, the disease remains on and near our military bases because local mammal populations maintain reservoirs of infection.

#### *World War II*

Endemic plague has been established in Hawaii (on the islands of Hawaii and Maui) since December 1899. No evidence of the disease, however, in either rodents or humans, has been found on the islands of Oahu or Kauai since the first decade of this century. A "small outbreak"[22(p667)] occurred during World War II on the island of Hawaii (in 1943) but was contained by means of

> very strenuous rat control measures [that] were carried out in each of the endemic plague areas.... [T]hese measures were of sufficient thoroughness to prevent any spread of plague to military personnel during the war in the Pacific.[22(p667)]

Official policy during World War II was to vaccinate U.S. troops with a killed plague vaccine. No

U.S. troops contracted plague, although they served in known endemic areas.[22,23]

### *Vietnam War*

Plague entered Vietnam in Nha Trang in 1898[16] and several pneumonic epidemics have occurred since (in 1911, 1915, 1925, and 1941).[2,24] Cases have been reported from Vietnam every year since 1898 except during the Japanese occupation during World War II.[2] When French forces departed Vietnam after the Indochina War, public health conditions deteriorated and plague flourished. The reported plague incidence increased from 8 cases in 1961, to 110 cases in 1963, to an average of 4,500 cases from 1965 through 1969.[21,25–28] The mortality in clinically diagnosed cases was between 1% and 5%. In untreated individuals, it was much higher (60%–90%).[2,26] Only 8 American troops were affected (1 case per 1 million man-years) during the Vietnam War.[28] American success was attributed to

- the use of flea insecticide (*Xenopsylla cheopis* became resistant to the insecticide dichlorodiphenyltrichloroethane [DDT] during the war, but others were employed)[26];
- immunization of virtually all American troops with plague vaccine[2]; and
- a thorough understanding of the epidemiology of disease, which led to the use of insect repellents, protective clothing, and rat-proofed dwellings.[2]

It was during the 1960s that our knowledge of plague grew dramatically. This is due in great part to the work of two officers of the Medical Service Corps, U.S. Army, Lieutenant Colonel Dan C. Cavanaugh and Lieutenant Colonel John D. Marshall. These scientists studied plague ecology, related plague epidemics to weather as a function of flea physiology (epidemics virtually disappeared when the temperature rose above 28°C),[2] developed serologic tests for plague infection, and developed the data to demonstrate the efficacy of the whole-cell killed plague vaccine.[29]

### *Disease Threat on U.S. Military Installations*

Human exposure to plague on military installations may occur when pets bring home infected rodents, their fleas, or both; at recreation areas with sick or dead rodents and their infected fleas; or at field training and bivouac sites. The consequences of plague at a military installation include human illness, death, or both; pet or other animal illness, death, or both; lost use of training and bivouac sites; large expenditures of money, manpower, and equipment to eliminate the plague risk; and the lost use of recreation areas.[21] Plague risk has been identified on and near several U.S. military installations (Exhibit 23-1).

## Plague as a Biological Warfare Agent

The first attempt at what we now call "biological warfare" is purported to have occurred at the Crimean port city of Caffa on the Black Sea during the years 1346–1347.[2,6] During the conflict between Christian Genoese sailors and Muslim Tatars, the Tatar army was struck with plague. The Tatar leader catapulted corpses of Tatar plague victims at the Genoese sailors. The Genoese became infected with plague and fled to Italy. However, the disease was most likely spread by the local population of infected rats, not by the corpses, since an infected flea leaves its host as soon as the corpse cools.[6]

The 20th-century use of plague as a potential biological warfare weapon is the immediate concern of this chapter. Medical officers need to keep this use of plague in mind, particularly when the disease appears in an unlikely setting.

### *World War II*

During World War II, the Japanese army established a secret biological warfare research unit (Unit 731) in Manchuria, where epidemics of pneumonic plague had occurred in 1910–1911, 1920–1921, and 1927, and a cholera epidemic had spread in 1919. General Shiro Ishii, the physician leader of Unit 731, was fascinated by plague because it could create casualties out of proportion to the number of bacteria disseminated, the most dangerous strains could be used to make a very dangerous weapon, and its origins could be concealed to appear as a natural occurrence. Early experiments, however, demonstrated that dropping bacteria out of aerial bombs had little effect because air pressure and high temperatures that were created by the exploding bombs killed nearly 100% of the bacteria.[30]

One of Ishii's greatest achievements was his use of the human flea, *Pulex irritans*, as a stratagem to simultaneously protect the bacteria and target humans. This flea is resistant to air drag, naturally targets humans, and could also infect a local rat population to prolong an epidemic. Infected fleas may regurgitate up to 24,000 organisms in a single feeding. Spraying fleas out of compressed-air con-

**EXHIBIT 23-1**

**U.S. MILITARY INSTALLATIONS WITH IDENTIFIED PLAGUE RISKS***

Plague-infected animals on the installation; human case reported on post:

- Fort Hunter Liggett, California
- United States Air Force Academy, Colorado†

Human case reported in the same county:

- Edwards Air Force Base, Colorado‡
- F. E. Warren Air Force Base, Wyoming
- Kirtland Air Force Base, New Mexico§
- Peterson Air Force Base, Colorado

Plague-infected animals on the installation:

- Dugway Proving Ground, Utah
- Fort Carson, Colorado
- Fort Ord, California
- Fort Wingate Army Depot Activity, New Mexico
- Marine Corps Mountain Warfare Training Center, Bridgeport, California
- Navajo Army Depot Activity, Arizona
- Pueblo Army Depot Activity, Colorado
- Rocky Mountain Arsenal, Colorado
- Vandenberg Air Force Base, California
- White Sands Missile Range, New Mexico

Plague-infected animals or fleas are not on the installation but are in the same county:

- Bridgeport Naval Facility, California
- Camp Roberts, California
- Dyess Air Force Base, Texas
- Fort Bliss, Texas
- Fort Lewis, Washington
- Sierra Army Depot, California
- Tooele Army Depot, Utah
- Umatilla Army Depot Activity, Oregon
- Nellis Air Force Base, Nevada

Plague-infected animals or fleas are not on the installation or in the county, but susceptible animals are present:

- Fort Huachuca, Arizona

*Does not include military installations near Los Angeles and San Francisco, California, where urban plague cases and deaths were not uncommon in the first quarter of the 20th century; no plague cases have occurred in these urban areas since the mid-1920s.

†Fatality: 18-mo-old child died of pneumonic plague; rock squirrels and their fleas had taken up residence in the ducts of the on-base house.

‡Two human cases in the same county in 1995; animal surveillance on base began in 1996.

§Plague-infected animals in the county in 1995; last human case in the county in 1993; no animal surveillance on base since 1986.

Sources: (1) Harrison FJ. *Prevention and Control of Plague*. Aurora, Colo: United States Army Center for Health Promotion and Preventive Medicine, Fitzsimons Army Medical Center; September 1995: 3–8. Technical Guide 103. (2) Data collected from Preventive Medicine Officers on 30 military bases in the United States, March 1996.

tainers was not successful since aircraft had to fly too low for safety. High flying meant too much dispersion. Clay bombs solved these problems and resulted in an 80% survival rate of fleas.[30]

The Japanese apparently used plague as a biological warfare agent in China several times during World War II. At 0500 hours on a November morning in 1941, a lone Japanese plane made three low passes over the business center of Changteh, a city in the Hunan province. Although no bombs were dropped, a strange mixture of wheat and rice grains, pieces of paper, cotton wadding, and other unidentified particles were. Within 2 weeks, individuals in Changteh started dying of plague. This miniepidemic was thought to be of human origin for the following reasons[30]:

- Changteh and the whole surrounding area of China had never been afflicted by plague.
- Plague usually spreads with rice (because rats infest the grain) along shipping routes, but the nearest epidemic center was 2,000 km away by land or river. Changteh exported, not imported, rice. No individual who contracted plague had recently traveled outside the city.
- All reported instances of human plague occurred in the area of the city where the strange particles were dropped.
- No evidence of excessive rat mortality occurred until 2 months *after* the people began dying.
- The first six human cases occurred within 15 days of the aerial incident.

Applying the concepts implicit in these five points will help medical officers differentiate endemic plague from plague used as a biological warfare agent. In fact, these concepts are important in making a diagnosis of most forms of biological warfare.

In another incident, on October 4, 1940, a Japanese plane dropped rice and wheat grains mixed with fleas over the city of Chuhsien, in Chekiang province. A month later, bubonic plague appeared for the first time there, in the area where the particles had been dropped. There were 21 plague deaths in 24 days. Again, on October 27, 1940, a Japanese plane was seen releasing similar particles over the city of Ningpo, in Chekiang province. Two days later, bubonic plague occurred for the first time in that city, producing 99 deaths in 34 days. No epizootic or excessive mortality was found in the rat population.[30]

### *Since World War II*

An article[31] published in the popular press in 1993 stated that in the 1970s and 1980s the Soviet Union created lethal diseases that defied cures. This included a genetically engineered, dry, antibiotic-resistant form of plague. In this article, a defecting Soviet microbiologist was quoted as saying that producing this form of plague had been a top priority of the Soviets in the 5-year plan that started in 1984.

During the Korean War, allied forces were accused of dropping on North Korea insects that were capable of spreading plague, typhus, malaria, Japanese B encephalitis, and other diseases. No evidence exists to support such claims.[32]

## THE INFECTIOUS AGENT

*Y pestis* is a Gram-negative, nonacid-fast, nonmotile, nonsporulating, nonlactose-fermenting, bipolar coccobacillus measuring 0.5–0.8 x 1.5–2.0 μm. The Yersinieae comprise Genus XI of the family Enterobacteriaceae, which includes the related enteropathogenic bacteria *Y enterocolitica* and *Y pseudotuberculosis*. Its bipolar appearance is best appreciated when Wright-Giemsa, Wayson's, and Gram's stains are used (Figure 23-1). *Y pestis* grows optimally at 28°C, producing tiny, 1- to 3-mm "beaten-copper" colonies after 48 hours on blood or MacConkey's agar. After 24 hours' growth in standard peptone broth, moderate growth with little or no turbidity is observed. Biochemically, the plague bacillus produces no hemolysins; is positive for catalase; and is negative for hydrogen sulfide, oxidase, urease, and fermentation of lactose, sucrose, rhamnose, and melibiose.[2]

The known virulence factors of *Y pestis* are encoded on the chromosome and its three plasmids. A chromosomal locus responsible for pigmentation phenotype, iron-inducible proteins, and iron uptake is necessary for virulence from a peripheral route of inoculation.[33] The pH 6 antigen (also encoded on the chromosome), a protein located on the surface of the bacterium, is necessary for complete virulence.[34] It is induced in vitro at low pH, perhaps in vivo at sites of inflammation and cellular necrosis, and within phagocytic cells.

The low calcium response (Lcr) plasmid of approximately 75 kilobase (kb), which is homologous in *Y pestis* and the other two *Yersinia* pathogens, *Y pseudotuberculosis* and *Y enterocolitica*, encodes for several secreted proteins, including *Yersinia* outer-membrane proteins (Yops), necessary for viru-

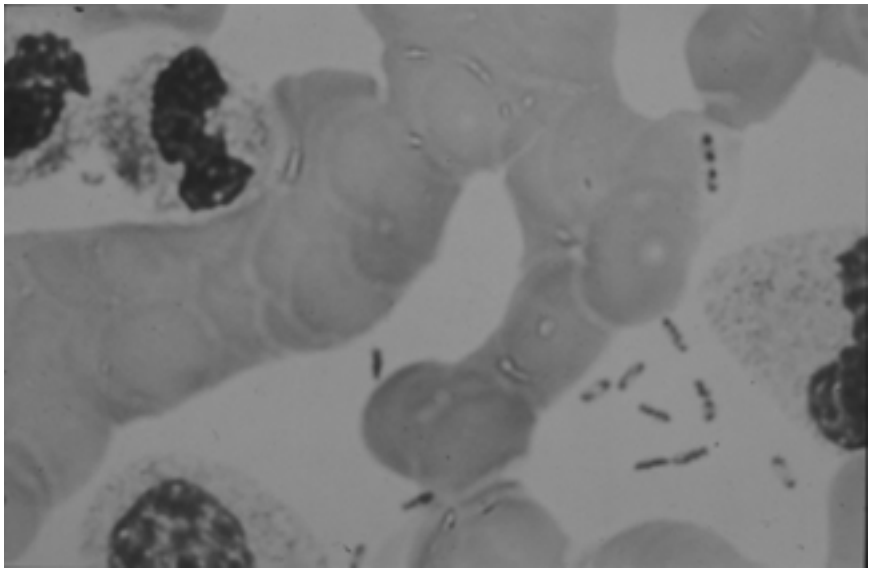

**Fig. 23-1.** This Wright-Giemsa stain of a peripheral blood smear from a patient with septicemic plague demonstrates the bipolar, safety-pin staining of *Yersinia pestis*. Gram's and Wayson's stains can also demonstrate this pattern. Photomicrograph: Courtesy of Ken Gage, Ph.D., Centers for Disease Control and Prevention, Fort Collins, Colo.

lence.[35] These proteins are produced in vitro in a low-calcium environment and, in some instances, by attachment to eucaryotic cells.[36] They include

- the V antigen, which is involved in regulation of growth and other plasmid-encoded secreted virulence proteins,[37] and which may also have a more direct role in virulence[33];
- Yop M, which binds thrombin, inhibits platelet aggregation, and may prevent an effective inflammatory response[38];
- Yops K and L, of unknown function[39]; and
- several proteins that interfere with phagocytic cell function, including Yop H, a tyrosine phosphatase,[40] and Yop E.[41]

Although additional virulence factors encoded on the Lcr plasmid have been described[35] for the other *Yersinia* species, confirmation of their importance in plague is not yet established.

*Y pestis* also possesses two additional plasmids not present in the other *Yersinia* species. First, a 9.5-kb plasmid encodes for a plasminogen activator protease, which is most active at temperatures higher than 30°C.[33] This proteolytic enzyme is necessary for systemic spread of infection from a peripheral subcutaneous site, perhaps by causing degradation of fibrin and extracellular matrix proteins, and by impairing the inflammatory response.[42] This same protease has predominantly coagulase activity at temperatures lower than 30°C.[33]

The second unique plasmid, of approximately 100 kb, codes for the protein capsule (fraction 1 antigen) of *Y pestis*. The capsule is antiphagocytic and necessary for full virulence in some animal species.[43] The 100-kb plasmid also encodes for an exotoxin that is active in the mouse and rat but not in primates.[33]

## EPIDEMIOLOGY

During the modern pandemic, W. G. Liston, a member of the Indian Plague Commission (1898–1914), made the association of plague with rats and incriminated the rat flea as a vector.[2] Subsequently, more than 200 species of animals and 80 species of fleas have been implicated in maintaining *Y pestis* endemic foci throughout the world.[21]

Throughout history, the oriental rat flea (*Xenopsylla cheopis*) has been largely responsible for spreading bubonic plague.[5] After the flea ingests a blood meal on a bacteremic animal, bacilli can multiply and eventually block the flea's foregut, or proventriculus, with a fibrinoid mass of bacteria (Figure 23-2).[2] When an infected flea with a blocked foregut attempts to feed again, it regurgitates clotted blood and bacteria into the victim's bloodstream, and so passes the infection on to the next mammal—whether rat or human. As many as 24,000 organisms may be inoculated into the mammalian host.[2] This flea desiccates rapidly in very hot and dry weather when away from its hosts, but flourishes at humidity just above 65% and temperatures

**Fig. 23-2.** The oriental rat flea (*Xenopsylla cheopis*) has historically been most responsible for the spread of plague to humans. This flea has a blocked proventriculus, equivalent to a human's gastroesophageal region. In nature, this flea would develop a ravenous hunger because of its inability to digest the fibrinoid mass of blood and bacteria. The ensuing biting of the nearest mammal will clear the proventriculus through regurgitation of thousands of bacteria into the bite wound, thereby inoculating the mammal with the plague bacillus. Photomicrograph: Courtesy of Ken Gage, Ph.D., Centers for Disease Control and Prevention, Fort Collins, Colo.

between 20°C and 26°C,[2] and can survive 6 months without a feeding.[21]

Although the largest outbreaks of plague have been associated with *X cheopis*, all fleas should be considered dangerous in plague endemic areas.[2] During the Black Death, the human flea, *Pulex irritans*, may have aided in human-to-human spread of plague; and during other epidemics, bedbugs (*Cimex lectularius*), lice, and flies have been found to contain *Y pestis*.[5] The presence of plague bacilli in these latter insects is associated with ingestion of contaminated blood from plague victims, however, and plays little or no role as a vector for the disease. The most important vector of human plague in the United States is *Diamanus montanus*, the most common flea on rock squirrels and California ground squirrels.[21]

Throughout history, the black rat, *Rattus rattus*, has been most responsible worldwide for the persistence and spread of plague in urban epidemics. *R rattus* is a nocturnal, climbing animal that does not burrow. Instead, it nests overhead and lives in close proximity to humans.[5] In the United Kingdom and much of Europe, the brown rat, *R norvegicus*, has replaced *R rattus* as the dominant city rat.[44] Unlike *R rattus*, *R norvegicus* is essentially a burrowing animal that lives under farm buildings and in ditches. However, *R norvegicus* may be involved in both rural and urban outbreaks of plague.[5]

Most carnivores, except cats, are resistant to plague infection, but animals such as domestic dogs, all rodents, and even burrowing owls may mechanically transmit fleas. Mammals that are partially resistant to plague infection serve as continuous reservoirs of plague. In the United States, deer mice (*Peromyscus* species) and ground squirrels (*Spermophilus* species) are thought to serve as the main reservoirs. Some susceptible mammals are only occasionally infected: chipmunks, tree squirrels, cottontail rabbits, and domestic cats (Figure 23-3).

Highly susceptible animals amplify both fleas and bacilli. Such epizootics occur in chipmunks, ground squirrels, and wood rats, but especially in prairie dogs, rock squirrels (*Spermophilus variegatus*), and California ground squirrels (*Spermophilus beechyi*). Although prairie dog fleas rarely bite humans, the infectious rodents can transmit plague to humans via direct contact (eg, handling a live or dead animal; stumbling into a nest while walking; or dissecting specimens [primarily laboratory personnel]). Rock squirrels and California ground squirrels both infect humans via direct contact and fleas.[5,21,45,46]

Many mammals in the United States harbor plague (Exhibit 23-2). Knowledge of this widespread harborage is important, because certain mammal–flea complexes found in the United States are dangerous: they contain both a susceptible mammal and a flea known to bite humans. These pairings include the following[21]:

- the rock squirrel (*S variegatus*) or California ground squirrel (*S beechyi*) and the fleas *Diamanus montanus* or *Hoplopsyllus anomalus*;
- the prairie dog (*Cynomys* species) and the flea *Opisochrostis hirsutus*; and
- Richardson's ground squirrel (*Spermophilus richardsoni*) or the golden-mantled ground squirrel (*S lateralis*) and the fleas *Oropsylla labis*, *O idahoensis*, or *Thrassus bacchi*.

Plague exists in one of two states in nature, enzootic or epizootic. An enzootic is the state of a stable rodent–flea infection cycle in a relatively resistant host population, without excessive rodent mortality. Importantly for humans, when the disease is in an enzootic state, the fleas have no need to seek less desirable hosts—such as ourselves. During an epizootic, on the other hand, plague bacilli have been introduced into moderately or highly susceptible mammals. High mortality occurs, most conspicuously in larger colonial rodents such as prairie dogs.[47]

Man is an accidental host in the plague cycle (Figure 23-4) and is not necessary for the persistence of the organism in nature. Humans usually acquire plague from

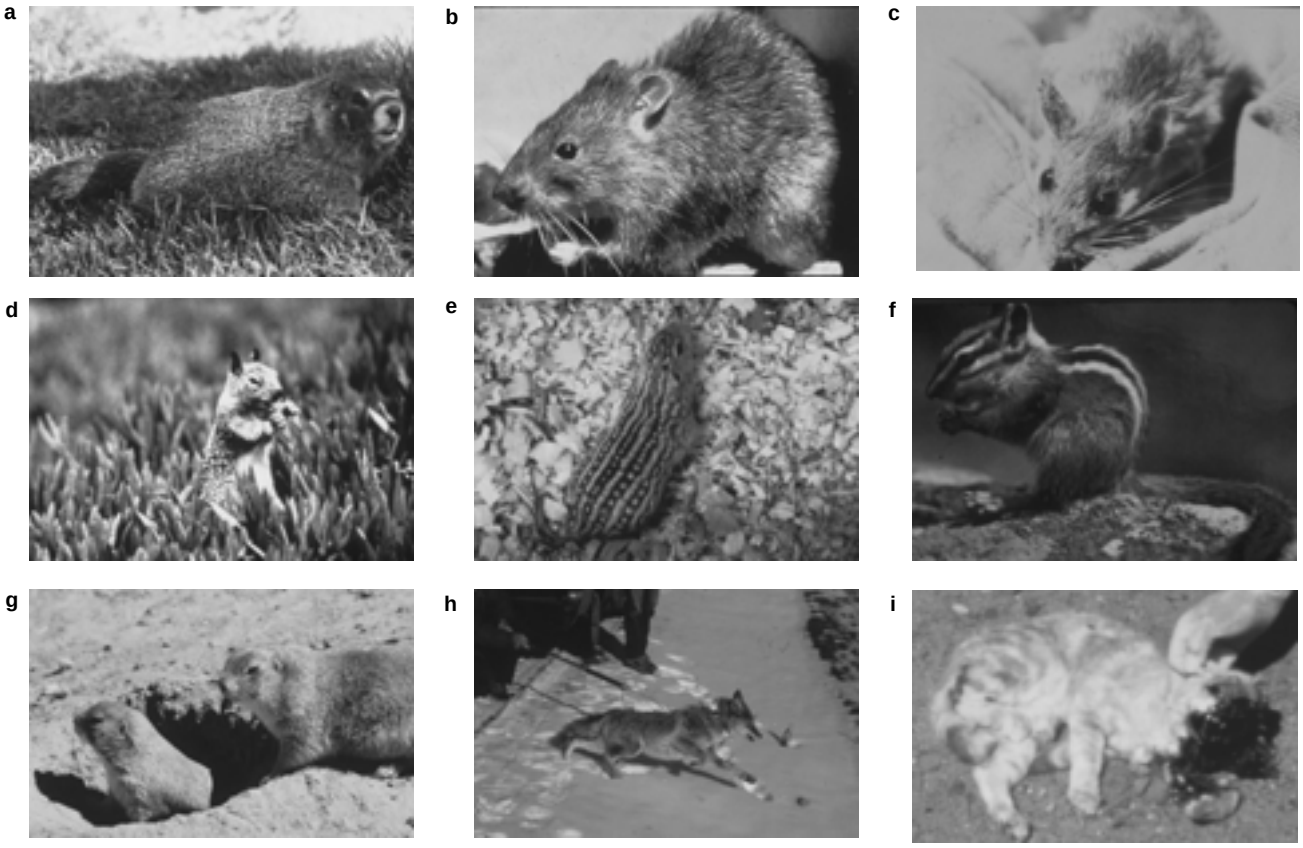


**Fig. 23-3.** Known mammalian reservoirs of plague in the United States (noninclusive). The common North American marmot (**a**) and the brown rat (*Rattus norvegicus*) (**b**), which has largely replaced the black rat, are considered to be reservoirs of plague (ie, hosts to infected fleas). Other reservoirs of plague during enzootics are thought to include the deer mouse (**c**), the California ground squirrel (**d**), and the 13-lined ground squirrel (**e**). Other infective mammals that can spread plague to humans include the chipmunk (**f**), prairie dogs (**g**), and the coyote (**h**). Domestic and nondomestic cats are also reservoirs of plague. This cat (**i**), which died of pneumonic plague, demonstrates a necrotic head. Photographs a, h: Courtesy of Denver Zoological Society, Denver, Colo. Photographs b–g, i: Courtesy of Centers for Disease Control and Prevention, Fort Collins, Colo.

**EXHIBIT 23-2**

**MAMMALS KNOWN TO HARBOR PLAGUE IN THE UNITED STATES**

Carnivores

Black bears, cats (including bobcats and mountain lions), coyotes, dogs, foxes, martens, raccoons, skunks, weasels, wolverines, wolves

Rodents

Chipmunks, gophers, marmots, mice, prairie dogs, rats, squirrels, voles

Lagomorphs

Hares, rabbits

Hooved Stock

Pigs, mule deer, pronghorn antelope

Adapted from Harrison FJ. *Prevention and Control of Plague*. Aurora, Colo: US Army Center for Health Promotion and Preventive Medicine, Fitzsimons Army Medical Center; September 1995: 25–28. Technical Guide 103.

Figure 23-4 is not shown because the copyright permission granted to the Borden Institute, TMM, does not allow the Borden Institute to grant permission to other users and/or does not include usage in electronic media. The current user must apply to the publisher named in the figure legend for permission to use this illustration in any type of publication media.

**Fig. 23-4.** Plague cycles in the United States. This drawing shows the usual, occasional, and rare routes by which plague is known to have spread between various mammals and humans. Reprinted with permission from Poland JD. Plague. In: Hoeprich PD, Jordan MC, eds. *Infectious Diseases: A Modern Treatise of Infectious Processes*. Philadelphia, Pa: Lippincott; 1989: 1297.

- fleas whose usual host is another mammal (eg, from flea bites, flea feces inoculated into skin with bites, and by directly biting the fleas [during the grooming behavior practiced in some cultures]);
- fleas whose usual host is a human;
- infected animals (eg, from aerosols, draining abscesses, eating infected tissue, and handling infected pelts); and
- other humans, via aerosol or direct contact with infected body substances.

The greatest risk to humans occurs when large concentrations of people live under unsanitary conditions in close proximity to large commensal or wild rodent populations that are infested with fleas that bite both humans and rodents.[2]

Human-to-human transmission of plague can occur from patients with pulmonary infection. However, understanding of the epidemiology of pneumonic plague is incomplete. Most epidemics have occurred in cool climates with moderate humidity and close contact between susceptible individuals. Outbreaks of pneumonic plague have been rare in tropical climates even during epidemics of bubonic disease. Respiratory transmission may occur more efficiently via larger droplets or fomites rather than via small-particle aerosols.[48]

## INCIDENCE

Worldwide cases of plague and mortalities are shown in Figure 23-5, and the known foci of plague in Figure 23-6. In 1992, most of the reported 1,582 cases occurred in Myanmar and Vietnam in Asia, and Zaire and Madagascar in Africa. Worldwide mortality was 8.7%. The outbreaks in 1994 of pneumonic and bubonic plague in India, and bubonic plague in Tanzania and Peru, highlight the potential for epidemics to arise from these foci.[49]

Plague has been endemic in the continental United States since at least 1900[20] and now is permanently established from the eastern slope of the Rocky Mountains westward—especially in pine–oak or piñon–juniper woodland habitats at altitudes of 5,000 to 9,000 ft, or on lower, dry grassland or desert scrub areas.[21] Between 1970 and 1990, 56% of all cases occurred in New Mexico, 14% in Arizona, and 10% in Colorado.[45]

In the first quarter of this century, virtually all 432 cases and 284 deaths (65.7% mortality) in the United States occurred in urban port cities. Epidemics occurred in San Francisco, California, during the years 1900–1904 (118 deaths) and 1907–1908 (78 deaths). The last time plague was transmitted between humans in the United States was during the 1924–1925 pneumonic plague epidemic in Los Angeles, California. Eighty percent of cases since 1925 have

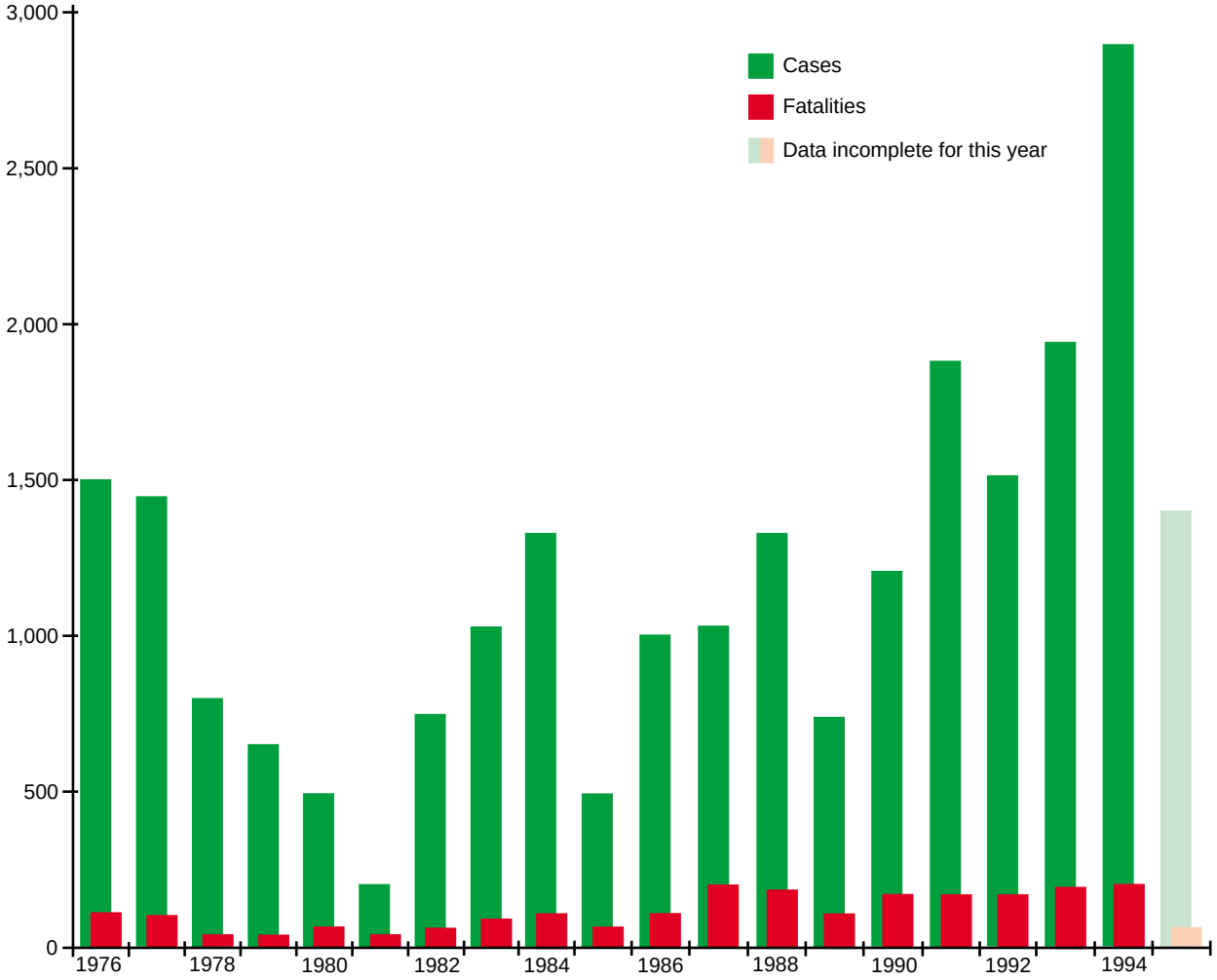


**Fig. 23-5.** Absolute numbers of annual worldwide plague cases, 1976–1994. Fatalities (a subset of the total cases) are shown in red, total cases in green. Data are as of 7 February 1996; reports for 1995 were not complete at that time. Note that the mortality rate continues between 5% and 12% despite the availability of effective antibiotics. Data sources: (1) Human plague in 1990. *WHO Weekly Epidemiological Record*. 1 Nov 1991;44:321–324. (2) Human plague in 1993. *WHO Weekly Epidemiological Record*. 17 Feb 1995;7:45–48. (3) Barkway J. World Health Organization, Geneva, Switzerland. Personal communication, 7 February 1996.

**Fig. 23-6.** Known worldwide foci of human plague infection. Data sources: (1) Human plague in 1990. *WHO Weekly Epidemiological Record*. 1 Nov 1991;44:321–324. (2) Human plague in 1993. *WHO Weekly Epidemiological Record*. 17 Feb 1995;7:45–48. (3) Barkway J. World Health Organization, Geneva, Switzerland. Personal communication, February 1996. (4) Ken Gage, Ph.D., Centers for Disease Control and Prevention, Fort Collins, Colorado. Personal communication, March 1996.

been sylvatic, involving contact with wild-rodent habitats.[20] Most cases (58%) are in men and occur within a 1-mile radius of home,[21] and half the victims in the United States have been younger than 20 years old.[20]

Between 1926 and 1960, the United States averaged only 1 case of plague per year. This number steadily rose to 3 per year during the 1960s, 11 during the 1970s, 18 during the 1980s, and then decreased to 9 per year since 1990.[45] The number of states reporting human plague cases has steadily increased over the last 5 decades, most likely because increasing encroachment of humans on previously wild areas brings people closer to infected animals and their fleas.[21]

In the United States, 93% of cases have occurred between April and November, peaking in July. During the last 25 years, pneumonic plague accounted for 11% of cases, and bubonic or septicemic plague, or both, for 89%. One case of meningitic plague also occurred.[45]

Epizootic cycles occur approximately every 5 years. The last large epizootic with a large die-off of rodents (1982–1984) was accompanied by the highest number of humans infected with plague since the urban epidemics of the first quarter of the century. The numbers of rodents slowly recovered to their characteristic levels by 1991, and the stage is now set for another epizootic, with the potential for increased human plague infections.[45,46]

## PATHOGENESIS

As few as 1 to 10 *Y pestis* organisms are sufficient to infect rodents and primates via the oral, intradermal, subcutaneous, and intravenous routes.[33] Estimates of infectivity by the respiratory route for nonhuman primates vary from 100 to 20,000 organisms.[50,51]

After being introduced into the mammalian host by a flea, where it had been at ambient temperature, the organism is thought to be initially susceptible to phagocytosis and killing by neutrophils. However, some of the bacteria may grow and proliferate within tissue macrophages.[52] Within the human host, several new environmental signals (including elevated temperature of 37°C, contact with eucaryotic cells, and perhaps the location within cells or in necrotic foci at low pH) are thought to induce the synthesis and activity of a multitude of factors contributing to virulence. These include the antiphagocytic fraction 1 capsule, pH 6 antigen, the antiphagocytic Yops H and E, V antigen, Yop M, and plasminogen activator. The bacteria in this state are now resistant to phagocytosis and they proliferate unimpeded extracellularly.

During the incubation phase, the bacilli most commonly spread to regional lymph nodes, where suppurative lymphadenitis develops, producing the characteristic bubo. Dissemination from the local site is thought to be related to the action of both plasminogen activator and Yop M. Infection will progress if untreated; septicemia will develop and the infection will spread to other organs. The endotoxin of *Y pestis* probably contributes to the development of septic shock, which is similar to the shock state seen in other causes of Gram-negative sepsis. The endotoxin also contributes to the resistance of the organism to the bactericidal activity of serum.[33] The acral cyanosis and necrosis seen in some cases of septicemic plague may also be related to the coagulase activity of the plasminogen activator, which occurs at temperatures lower than 37°C.[2]

Tissues most commonly infected include the spleen, liver, lungs, skin, and mucous membranes. Late infection of the meninges also occurs, especially if suboptimal antibiotic therapy has been given.

Primary pneumonic plague, the most severe form of disease, arises from inhalation of an infectious aerosol. Primary pneumonic plague is more rapidly fatal than secondary, because the inhaled droplets already contain phagocytosis-resistant bacilli, which have arisen from their growth at 37°C in the vertebrate host.[47]

Primary septicemic plague can occur from direct inoculation of bacilli into the bloodstream, bypassing initial multiplication in the lymph nodes. Asymptomatic pharyngeal carriage of plague has been reported to occur in contacts of patients with either bubonic or pneumonic plague.[53,54]

## CLINICAL MANIFESTATIONS

In the United States, most patients (85%–90%) with human plague present clinically with the bubonic form, 10% to 15% with the primary septicemic form, and 1% with the pneumonic form. Secondary septicemic plague occurs in 23% of patients who present with bubonic plague, and secondary pneumonic plague occurs in 9%.[46] If *Y pestis* were used as a biological warfare agent, the clinical mani-

festations of plague would be (*a*) epidemic pneumonia with blood-tinged sputum if aerosolized bacteria were used or (*b*) bubonic or septicemic plague, or both, if fleas were used as carriers.

### Bubonic Plague

Buboes manifest after a 1- to 8-day incubation period, with the regular onset of symptoms of sudden fever, chills, and headache often followed several hours later by nausea and vomiting. Presenting symptoms include prostration or severe malaise (75%), headache (20%–85%), vomiting (25%–49%), chills (40%), altered mentation (26%–38%), cough (25%), abdominal pain (18%), and chest pain (13%).[2] Six to 8 hours after onset of symptoms, buboes, heralded by severe pain, occur in the groin (90%, with femoral more frequent than inguinal), axillary, or cervical lymph nodes—depending on the site of bacterial inoculation (Figure 23-7). Buboes become visible within 24 hours; they are so intensely painful that even nearly comatose patients will attempt to shield them from trauma and will abduct their extremities to decrease pressure. Other manifestations of bubonic plague include bladder distention, apathy, confusion, fright, anxiety, oliguria, and anuria. Tachycardia, hypotension, leukocytosis, and fever are frequently encountered. Untreated, septicemia will develop in 2 to 6 days.[55] Approximately 5% to 15% of bubonic plague patients will develop secondary pneumonic plague and, as a result, the potential for airborne transmission.[56]

### Septicemic Plague

Septicemic plague may occur primarily, or secondarily as a complication of hematogenous dissemination of bubonic plague. Presenting signs and symptoms of primary septicemic plague are essentially the same as those for any Gram-negative septicemia: fever, chills, nausea, vomiting, and diarrhea. Later, purpura (Figure 23-8), disseminated intravascular coagulation (DIC), and acral cyanosis and necrosis (Figure 23-9) may be seen.

In New Mexico between 1980 and 1984, plague was suspected in 69% of patients who had bubonic plague, but in only 17% of patients who had the septicemic form. The mortality was 33.3% for septicemic plague versus 11.5% for bubonic, thus highlighting the difficulty of diagnosing septicemic plague. Diagnosis of septicemic plague took longer (5 vs 4 d) after onset, although patients sought physicians earlier (1.7 vs 2.1 d) and were hospitalized

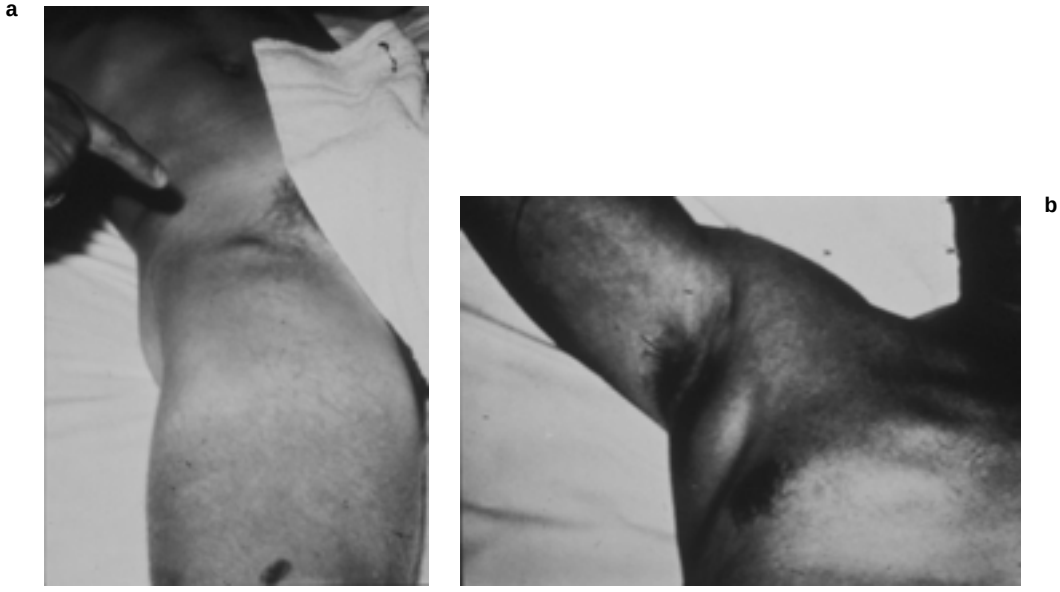


**Fig. 23-7.** A femoral bubo (**a**), the most common site of an erythematous, tender, swollen, lymph node in patients with plague. This painful lesion may be aspirated in a sterile fashion to relieve pain and pressure; it should not be incised and drained. The next most common lymph node regions involved are the inguinal, axillary (**b**), and cervical areas. Bubo location is a function of the region of the body in which an infected flea inoculates the plague bacilli. Photographs: Courtesy of Ken Gage, Ph.D., Centers for Disease Control and Prevention, Fort Collins, Colo.

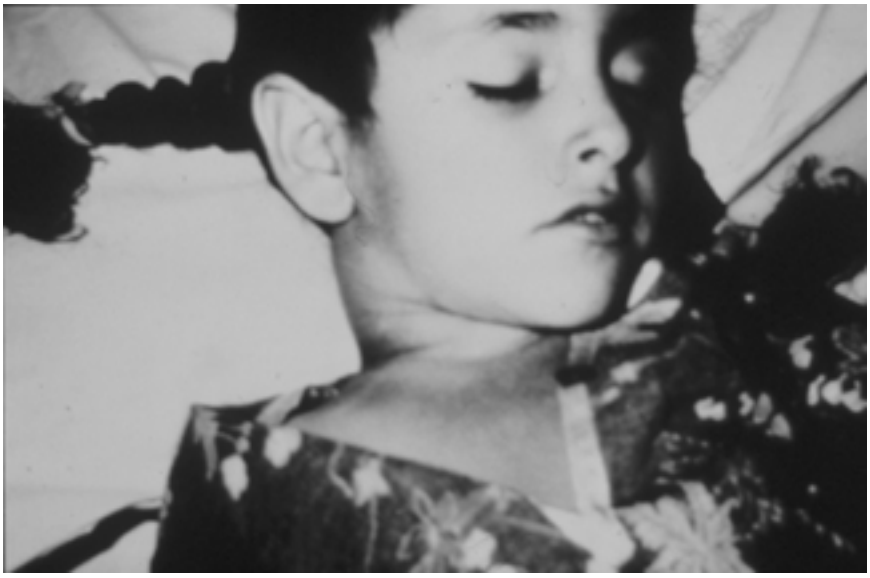

**Fig. 23-8.** Purpuric lesions can be seen on the upper chest of this girl with plague. The bandage on her neck indicates that a bubo has been aspirated. Photograph: Courtesy Ken Gage, Ph.D., Centers of Disease Control and Prevention, Fort Collins, Colo.

sooner (5.3 vs 6.0 d) than patients with bubonic plague. The only symptom present significantly more frequently in septicemic than in bubonic plague was abdominal pain (40% vs < 10%), probably due to hepatosplenomegaly.[57]

The risk of *developing* septicemic plague is higher for individuals older than 40 years of age, although the risk of *dying* from septicemic plague is higher for those younger than 30 years. This difference is most likely due to older undiagnosed patients

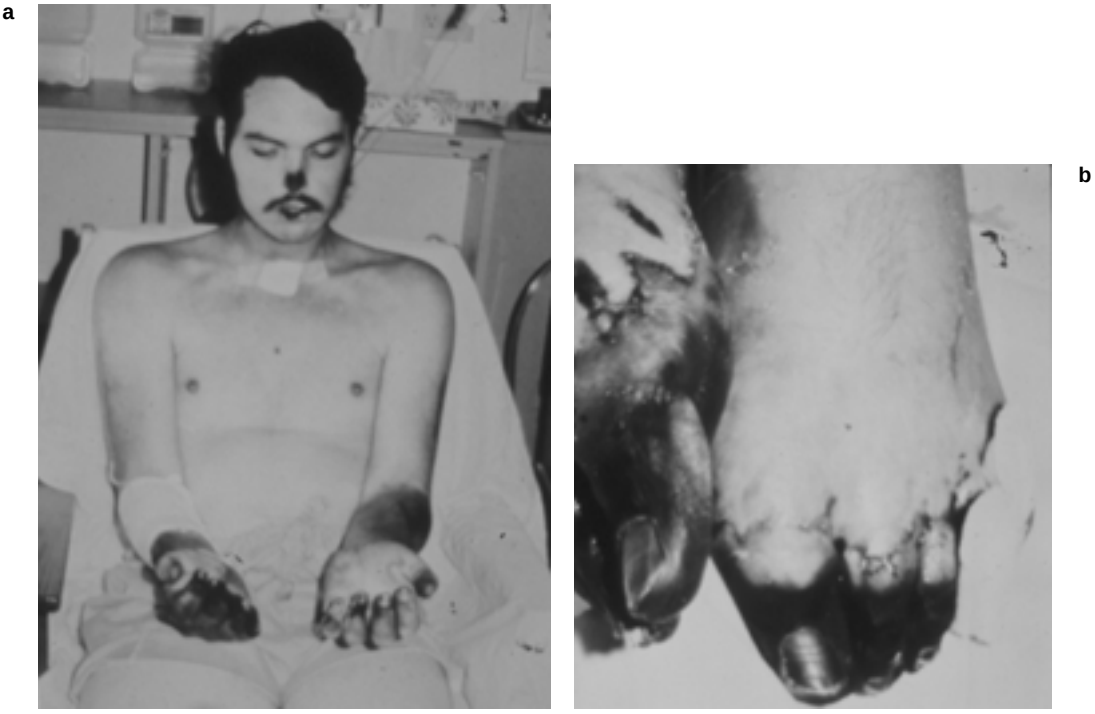


**Fig. 23-9.** This patient is recovering from bubonic plague that disseminated to the blood (septicemic form) and the lungs (pneumonic form). Note the dressing over the tracheostomy site. At one point, the patient's entire body was purpuric. Note the acral necrosis of (**a**) the patient's nose and fingers and (**b**) the toes. Photographs: Courtesy Ken Gage, Ph.D., Centers of Disease Control and Prevention, Fort Collins, Colo.

being treated empirically with antibiotics that kill *Y pestis*, and younger undiagnosed patients being treated with antibiotics (such as penicillin) that do not affect *Y pestis*. Earlier diagnosis and appropriate therapy, not newer antibiotics, will have the greatest effect on reducing mortality from septicemic plague.[57]

### Pneumonic Plague

Pneumonic plague may occur primarily, from inhalation of aerosols, or secondarily, from hematogenous dissemination. Patients typically have a productive cough with blood-tinged sputum within 24 hours after onset of symptoms.[2] The findings on chest roentgenography may be variable, but bilateral alveolar infiltrates appear to be the most common finding in pneumonic plague (Figure 23-10).[58,59]

### Plague Meningitis

Plague meningitis is seen in 6% to 7% of cases. The condition manifests itself most often in children after 9 to 14 days of ineffective treatment. Symptoms are similar to those of other forms of acute bacterial meningitis.[60]

### Pharyngeal Plague

Asymptomatic pharyngeal carriage has been reported to occur in contacts of plague patients.[53,54]

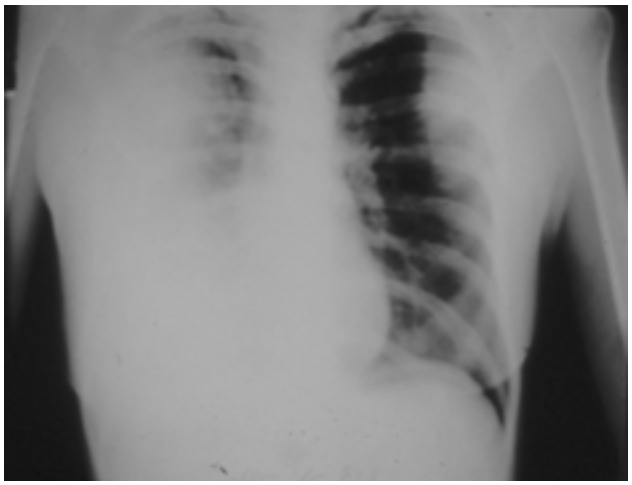

**Fig. 23-10.** This chest roentgenogram shows right middle- and lower-lobe involvement in a patient with pneumonic plague. Photograph: Courtesy Ken Gage, Ph.D., Centers for Disease Control and Prevention, Fort Collins, Colo.

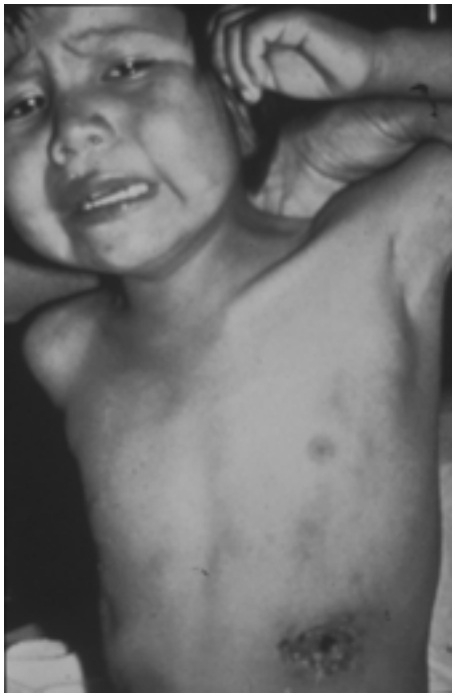

**Fig. 23-11**. This child has left axillary bubonic plague. The erythematous, eroded, crusting, necrotic ulcer on the child's left upper quadrant is located at the presumed primary inoculation site. Photograph: Courtesy of Ken Gage, Ph.D., Centers for Disease Control and Prevention, Fort Collins, Colo.

Rarely, pharyngitis—resembling tonsillitis and associated with cervical lymphadenopathy—has been reported.[17,55] A plague syndrome of cervical buboes, peritonsillar abscesses, and fulminant pneumonia has also been reported to occur among Indians of Ecuador, who are known to catch and kill fleas and lice with their teeth. It is thought, although not proven, that endobronchial aspiration from peritonsillar abscesses leads to fulminant pneumonia. A similar syndrome may have occurred in Vietnam.[55]

### Cutaneous Manifestations

Approximately 4% to 10% of plague patients are said to have an ulcer or pustule at the inoculation site (Figure 23-11).[59,61] The flea typically bites the lower extremities; therefore, femoral and inguinal buboes are the most common. Infection arising from the skinning of infected animals typically produces axillary buboes. Buboes may point and drain spontaneously or, rarely, they may require incision and drainage because of pronounced necrosis.

Petechiae and ecchymoses may occur during hematogenous spread to such an extent that the signs mimic severe meningococcemia, and the microscopic lesions are almost indistinguishable. The pathogenesis of these lesions is probably that of a generalized Shwartzman reaction (DIC secondary to the *Y pestis* endotoxin). Purpura and acral gangrene may also be due to the activities of the plasminogen activator/coagulase enzyme, and prognosis is poor when these signs occur.[2,62] Patients in the terminal stages of pneumonic and septicemic plague often develop large ecchymoses on the back. Lesions like these are likely to have given rise to the medieval epithet "the Black Death."

Ecthyma gangrenosum has been reported in several patients.[53,62] The only case cultured grew *Y pestis*, which suggests that the skin lesions were the result of septicemic seeding of the organism.[62]

## DIAGNOSIS

### Signs and Symptoms

A patient with a typical presentation of bubonic plague (eg, with a painful bubo in the setting of fever, prostration, and possible exposure to rodents or fleas in an endemic area) should readily suggest the diagnosis of plague. However, if the medical officer is not familiar with the disease or if the patient presents in a nonendemic area or without a bubo, then the diagnosis can be most difficult. When a bubo is present, the differential diagnosis should include tularemia, cat scratch disease, lymphogranuloma venereum, chancroid, tuberculosis, streptococcal adenitis, and scrub typhus (Figure 23-12). In both tularemia and cat scratch disease, the inoculation site will usually be more evident and the patient will usually not be septic. In chancroid and scrofula, the patient has less local pain, the course is more indolent, and there is no sepsis. Patients with chancroid and lymphogranuloma venereum will have a recent history of sexual contact and genital lesions. Those with the latter disease may be as sick as patients with plague. Streptococcal adenitis may be difficult to distinguish initially, but the patient is usually not septic, and the node is more tender when plague is present.

The implications of the absence of a bubo were clearly demonstrated in a review of 27 cases of plague seen in New Mexico.[59] There were no deaths among 10 patients with typical bubonic plague. However, 3 of 5 patients died who presented with an upper respiratory infection syndrome of fever, sore throat, and headache. Similarly, 3 of 5 patients died who presented with fever, chills, and anorexia. The other 7 patients presented with nonspecific gastrointestinal and urinary tract symptoms without a bubo. Thus, other causes of lymphadenitis, upper respiratory tract infection, gastrointestinal disease including appendicitis, and nonspecific febrile illnesses, must all be considered.

The differential diagnosis of septicemic plague also includes meningococcemia, Gram-negative sepsis, and the rickettsioses. The patient with pneumonic plague who presents with systemic toxicity, a productive cough, and bloody sputum suggests a large differential diagnosis. However, demonstration of Gram-negative rods in the sputum should readily suggest the correct diagnosis, because *Y pestis* is perhaps the only Gram-negative bacterium that can cause extensive, fulminant pneumonia with bloody sputum in an otherwise healthy, immunocompetent host.

### Laboratory Confirmation

In patients with lymphadenopathy, a bubo aspirate should be obtained by inserting a 20-gauge needle attached to a 10-mL syringe containing 1 mL of sterile saline. Saline is injected and withdrawn several times until it is tinged with blood. Repeated, sterile bubo aspiration may also be done to decompress buboes and relieve pain. Drops of the aspirate should be air-dried on a slide for one of the following stains: Gram's, Wright-Giemsa, or Wayson's. If available, a direct fluorescent antibody (DFA) stain of bubo aspirate for the presence of *Y pestis* capsular antigen should be performed; a positive DFA result is more specific for *Y pestis* than are the other listed stains (Figure 23-13).[63,64]

Both Wright-Giemsa stain and DFA stain for *Y pestis* should also be performed on peripheral blood smears and sputum specimens, when applicable. Although a bipolar, safety-pin staining morphology has been reported to be specific for *Y pestis*, it is not. Other bacteria such as *Pasteurella* species, *Escherichia coli*, *Klebsiella* species, and diplococci (*Streptococcus*) may also exhibit this morphology. None of the listed stains is better than any other for demonstrating the bipolar, safety-pin morphology. In fact, even *Y pestis* will sometimes not exhibit this morphology.[64]

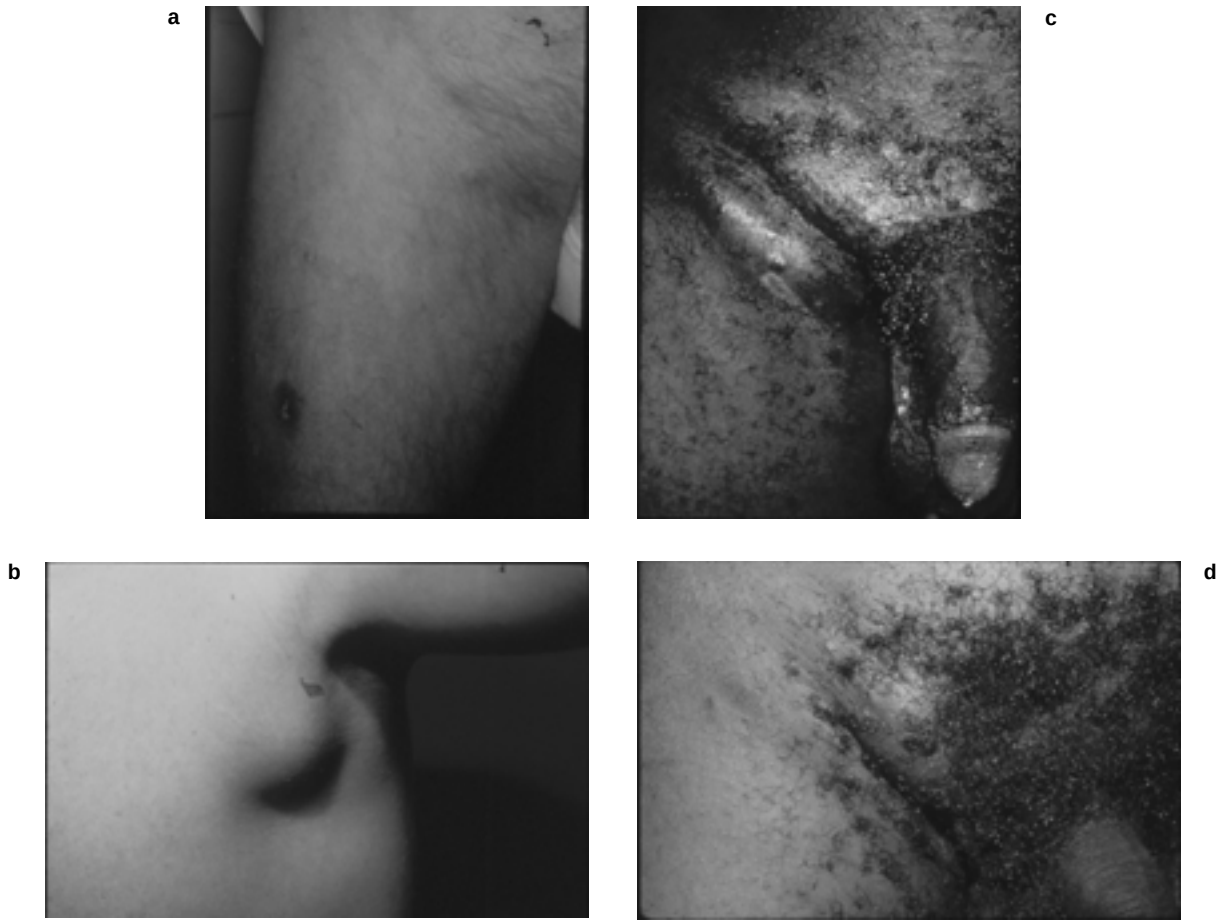


**Fig. 23-12.** (**a**) Small femoral bubo and presumed inoculation site (on the inferior thigh) in a patient with tularemia. This Gram-negative bacterial infection (with *Francisella tularensis*) may closely mimic bubonic plague and is successfully treated with the same antibiotics. (**b**) Axillary bubo seen in child with cat scratch disease. (**c**) Greenblatt's sign of ipsilateral femoral and inguinal buboes with intervening depression over the inguinal ligament, seen in a patient with lymphogranuloma venereum caused by *Chlamydia trachomatis*. (**d**) Large inguinal bubo seen in a patient with chancroid caused by *Haemophilus ducreyi*. Photographs: Courtesy of Dermatology Service, Fitzsimons Army Medical Center, Aurora, Colo.

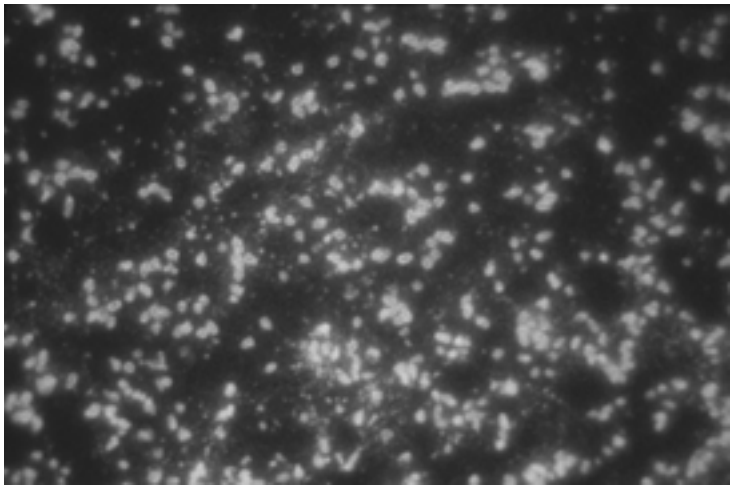

**Fig. 23-13**. These *Yersinia pestis* fluorescent cells are from infected mouse spleen. Notice how the outlines of the coccobacilli "light up" in this direct fluorescent antibody (DFA) test. The DFA test is specific and therefore better than the other stains discussed in this chapter (original magnification x 1,000). Photograph: Courtesy of M. C. Chu, Centers for Disease Control and Prevention, Fort Collins, Colo.

Cultures of blood, bubo aspirate, sputum, and cerebrospinal fluid (if indicated) should be performed. Tiny, 1- to 3-mm "beaten-copper" colonies will appear on blood agar by 48 hours, but it is important to remember that cultures may be negative at 24 hours. In a recent study, 24 (96%) of 25 blood cultures of patients with bubonic plague were positive on standard supplemented peptone broth.[59]

Complete blood counts often reveal leukocytosis with a left shift. Leukemoid reactions with up to 100,000 white blood cells per microliter may be seen, especially in children. Platelet counts may be normal or low, and partial thromboplastin times are often increased. When DIC is present, fibrin degradation products will be elevated. Because of liver involvement, alanine aminotransferase, aspartate aminotransferase, and bilirubin levels are often increased.

Serologic assays measuring the immune response to plague infection are mainly of value retrospectively, since patients present clinically before they develop a significant antibody response. Enzyme-linked immunosorbent assay (ELISA) tests and the older, less-sensitive passive hemagglutination assay (PHA) both measure antibodies to the fraction 1 capsule. They are available from the Centers for Disease Control and Prevention, Fort Collins, Colorado, and the U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland. Rapid diagnostic tests are available on an investigative basis.

An immunological assay to detect circulating fraction 1 antigen in the serum of acutely infected patients can detect levels as low as 0.4 ng/mL serum.[65] During plague infection, fraction 1 antigenemia may reach levels of 4 to 8 μg/mL serum. During a plague outbreak in Namibia, 38 cases of plague were confirmed: 50% by culture, 34% by antibody response, and 16% by antigenemia.[66] Because fraction 1 antigen and antibody do not occur simultaneously in serum, and because neither may be present early in infection, titers for both should be performed on several sequential blood specimens.

A polymerase chain reaction (PCR) test, using primers for the plasminogen activator gene, can detect as few as 10 *Y pestis* organisms, even in the presence of flea tissue. This test may be useful in surveillance of rats and could be adapted to aid in the diagnosis of human infection.[67]

## TREATMENT

### Isolation

All patients with plague should be isolated for the first 48 hours after the initiation of treatment. Special care must be taken in handling blood and bubo discharge. If pneumonic plague is present, then strict, rigidly enforced respiratory isolation procedures must be followed, including the use of gowns, gloves, and eye protection. Patients with pneumonia must be isolated until they have completed at least 4 days of antibiotic therapy. If patients have no pneumonia or draining lesions at 48 hours, they may be taken out of strict isolation.

### Antibiotics

Since 1948, streptomycin has remained the treatment of choice for bubonic, septicemic, and pneumonic plague. It should be given intramuscularly in a dose of 30 mg/kg/d in two divided doses. In cases of suspected meningitis or in patients who are hemodynamically unstable, intravenous chloramphenicol (50–75 mg/kg/d in four divided doses) should be added. Gentamicin has had much less clinical usage but can be used as an alternative to streptomycin or given together with chloramphenicol. Treatment should be continued for a minimum of 10 days or 3 to 4 days after clinical recovery. If clinically indicated, oral tetracycline can be used to complete a 10-day course of treatment after at least 5 days of systemic therapy. In patients with very mild bubonic plague who are not septic, tetracycline can be used orally at a dose of 2 g/d in 4 divided doses for 10 days. Doxycycline should be an acceptable alternative, although there are no published data on its efficacy in humans. Doxycycline, ofloxacin, and ceftriaxone have all been shown to be effective in experimental animal models of septicemic plague.[68]

In pregnant women, streptomycin or gentamicin should be used unless chloramphenicol is specifically indicated. Streptomycin is also the treatment of choice in newborns.

If treated with antibiotics, buboes typically recede in 10 to 14 days and do not require drainage. Patients are unlikely to survive primary pneumonic plague if antibiotic therapy is not initiated within 18 hours of the onset of symptoms. Without treatment, mortality is 60% for bubonic plague and 100% for the pneumonic and septicemic forms.[53]

## PREVENTION

All plague-control measures must include insecticide use, public health education, and reduction of rodent populations with chemicals such as cholecalciferol.[2,25] Fleas must *always* be targeted before rodents, because killing rodents may release massive amounts of infected fleas.[56] Use of insecticides in rodent areas is effective because rodents pick up dust on their feet and carry it back to their nests, where they distribute it over their bodies via constant preening.[2] Plague must be reported to the World Health Organization as an internationally quarantinable disease for which travelers may be detained up to 6 days.

### Postexposure Prophylaxis

Not only contacts of patients with pneumonic plague but also individuals who have been exposed to aerosols (eg, in a biological warfare attack) should be treated with tetracycline 15 to 30 mg/kg/d (1–2 g/d) administered in four divided doses for 7 days. Doxycycline 100 mg administered twice daily is probably an effective alternative if tetracycline is not available. Pregnant women and children under 8 years of age should receive trimethoprim/sulfamethoxazole (40 mg sulfa/kg/d) administered orally in two divided doses for 7 days.

Hospital personnel who are observing recommended isolation procedures do not require prophylactic therapy, nor do contacts of patients with bubonic plague. However, people who were in the same environment and who were potentially exposed to the same source of infection as the contact case should be given prophylactic antibiotics. In addition, previously vaccinated individuals should receive prophylactic antibiotics if they have been exposed to a plague aerosol.

### Immunization

The first plague vaccine, consisting of killed whole cells, was developed by Russian physician Waldemar M. W. Haffkine, working in India in 1897. In 1942, Karl F. Meyer, D.V.M., began developing an immunogenic and less-reactogenic vaccine for the U.S. Army from an agar-grown, formalin-killed, suspension of virulent plague bacilli. With minor modifications, this is the same procedure used to prepare the licensed vaccine we have available today. Live-attenuated vaccines have been unsuccessful, since they are much more reactogenic than the present killed vaccine.[23]

Only individuals at high risk for plague should be immunized—such as military troops and other field personnel working in plague endemic areas in which exposure to rats and fleas cannot be controlled. Laboratory personnel working with *Y pestis*, people who reside in enzootic or epidemic plague areas, and those whose vocations bring them into regular contact with wild animals, particularly rodents and rabbits, should also be vaccinated.[69]

The dose schedule for adults is 1.0 mL initially, with 0.2 mL at 1 to 3 months, followed by a third dose 5 to 6 months later. Booster doses of 0.2 mL are given every 6 months for 1.5 years, and then every 1 to 2 years thereafter if risk for exposure continues. If an accelerated schedule is essential, then 0.5 mL at 0, 7, and 14 days has been recommended, although no supporting data exist.[69]

Approximately 92% to 93% of vaccinees will produce antibody titers after the initial series of three injections.[69–71] Local side effects include erythema, soreness, or swelling, in any combination, in 11% of vaccinees and 6% of injections. Systemic side ef fects include headache, malaise, and myalgias in 4% of vaccinees and 1% of injections. Rarely, sterile abscesses, necrotic lesions, or anaphylaxis may occur.[72]

Data from animal and human investigations suggest that the killed plague vaccine is effective for preventing or ameliorating bubonic but *not pneumonic* plague.[50,51,73–75] A recombinant vaccine candidate that protects laboratory animals from inhalational challenge is being studied.

## SUMMARY

Plague is a zoonotic infection caused by the Gram-negative bacillus *Yersinia pestis*. Three great human pandemics have been responsible for more deaths than any other infectious agent in history. Plague is maintained in nature, predominantly in urban and sylvatic rodents, by a flea vector. Humans are not necessary for persistence of the organism, and we acquire the disease from animal fleas, contact with infected animals, or, rarely, from other humans, via aerosol or direct contact with infected secretions.

To be able to differentiate endemic disease from plague used in biological warfare, medical officers must understand the typical way in which

humans contract plague in nature. First, a die-off of animals in the mammalian reservoir that harbors bacteria-infected fleas will occur. Second, troops who have been in close proximity to such infected mammals will become infected. By contrast, in the most likely biological warfare scenario, plague would be spread via aerosol. A rapid, person-to-person spread of fulminant pneumonia, characterized by blood-tinged sputum, would then ensue. If, on the other hand, an enemy force were to release fleas infected with *Y pestis*, then soldiers would present with classic bubonic plague before a die-off in the local mammalian reservoir occurred.

The most common form of the disease is bubonic plague, characterized by painful lymphadenopathy and severe constitutional symptoms of fever, chills, and headache. Septicemic plague without localized lymphadenopathy occurs less commonly and is difficult to diagnose. Secondary pneumonia may follow either the bubonic or the septicemic form. Primary pneumonic plague is spread by airborne transmission, when aerosols from an infected human or animal are inhaled.

Diagnosis is established by isolating the organism from blood or other tissues. Rapid diagnosis may be made with fluorescent antibody stains of sputum or tissue specimens. Patients should be isolated and treated with aminoglycosides, preferably streptomycin, plus chloramphenicol when meningitis is suspected or shock is present. A licensed, killed, whole-cell vaccine is available to protect humans against bubonic, but not against primary pneumonic, plague.

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