Plague (disease)

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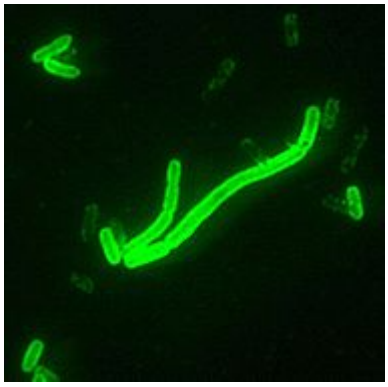
This article is about the disease caused by Yersinia pestis.



Plague
Classification and external resources

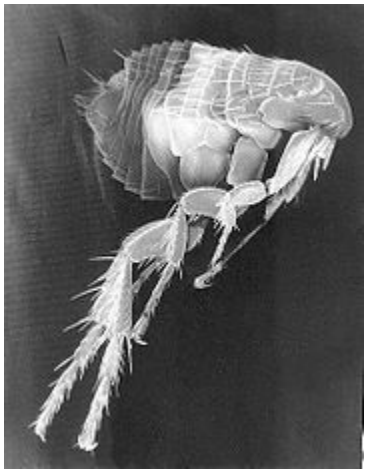
Yersinia pestis seen at 200× magnification with a fluorescent label. This bacterium, carried and spread by fleas, is the cause of the various forms of the disease plague.

Plague is a deadly infectious disease caused by the enterobacteria *Yersinia pestis (Pasteurella pestis)*. Plague is a zoonotic, primarily carried by rodents (most notably rats) and spread to humans via fleas. Plague is notorious throughout history, due to the unprecedented scale of death and devastation it brought. Plague is still endemic in some parts of the world.

Name

The epidemiological use of the term *plague* is currently applied to bacterial infections that cause *buboes*, although historically the medical use of the term plague has been applied to pandemic infections in general. Plague is often synonymous with "bubonic plague" but this only describes one of its manifestations. Other names have been used to describe this disease, such as "The Black Plague" and "The Black Death", the latter is now used primarily to describe the second, and most devastating pandemic of the disease.

Infection and transmission



Xenopsylla cheopis primary vector of Bubonic plague

Bubonic plague is mainly a disease in rodents and fleas (*Xenopsylla cheopis*). Infection in a human occurs when a person is bitten by a flea that has been infected by biting a rodent that itself has been infected by the bite of a flea carrying the disease. The bacteria multiply inside the flea, sticking together to form a plug that blocks its stomach and causes it to begin to starve. The flea then voraciously bites a host and continues to feed, even though it cannot quell its hunger, and consequently the flea vomits blood tainted with the bacteria back into the bite wound. The bubonic plague bacterium then infects a new victim, and the flea eventually dies from starvation. Serious outbreaks of plague are usually started by other disease outbreaks in rodents, or a rise in the rodent population.

In 1894, two bacteriologists, Alexandre Yersin of France and Shibasaburo Kitasato of Japan, independently isolated the bacterium in Hong Kong responsible for the Third Pandemic. Though both investigators reported their findings, a series of confusing and contradictory statements by Kitasato eventually led to the acceptance of Yersin as the primary discoverer of the organism. Yersin named it ***Pasteurella pestis*** in honor of the Pasteur Institute, where he worked, but in 1967 it was moved to a new genus, renamed ***Yersinia pestis*** in honor of Yersin. Yersin also noted that rats were affected by plague not only during plague epidemics but also often preceding such epidemics in humans, and that plague was regarded by many locals as a disease of rats: villagers in China and India asserted that, when large numbers of rats were found dead, plague outbreaks in people soon followed.

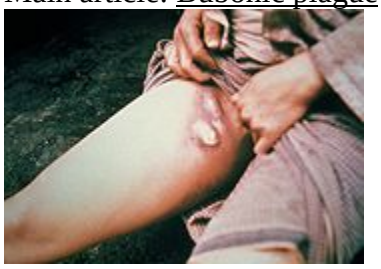
In 1898, the French scientist Paul-Louis Simond (who had also come to China to battle the Third Pandemic) established the rat-flea vector that drives the disease. He had noted that persons who became ill did not have to be in close contact with each other to acquire the disease. In Yunnan, China, inhabitants would flee from their homes as soon as they saw dead rats, and on the island of Formosa (Taiwan), residents considered handling dead rats a risk for developing plague. These observations led him to suspect that the flea

might be an intermediary factor in the transmission of plague, since people acquired plague only if they were in contact with recently dead rats, but not affected if they touched rats that had been dead for more than 24 hours. In a now classic experiment, Simond demonstrated how a healthy rat died of plague after infected fleas had jumped to it from a plague-dead rat.

Pathology

Bubonic plague

Main article: Bubonic plague



Buboes on the thigh of a person suffering from Bubonic plague

When a flea bites a human and contaminates the wound with regurgitated blood, the plague carrying bacteria are passed into the tissue. *Y. pestis* can reproduce inside cells, so even if phagocytosed, they can still survive. Once in the body, the bacteria can enter the lymphatic system, which drains interstitial fluid. Plague bacteria secrete several toxins, one of which is known to cause dangerous beta-adrenergic blockade.

Y. pestis spreads through the lymphatics of the infected human until it reaches a lymph node, where it stimulates severe haemorrhagic inflammation that causes the lymph nodes to expand. The expansion of lymph nodes is the cause of the characteristic "bubo" associated with the disease.

Septicemic plague

Main article: Septicemic plague

Lymphatics ultimately drain into the bloodstream, so the plague bacteria may enter the blood and travel to almost any part of the body. In septicemic plague, bacterial endotoxins cause disseminated intravascular coagulation (DIC), causing tiny clots throughout the body and possibly ischaemic necrosis (tissue death due to lack of circulation/perfusion to that tissue) from the clots. DIC results in depletion of the body's clotting resources, so that it can no longer control bleeding. Consequently, there is bleeding into the skin and other organs, which can cause red and/or black patchy rash and hemoptysis/haemoptysis (coughing up or vomiting of blood). There are bumps on the skin that look somewhat like insect bites; these are usually red, and sometimes white in the center. Untreated, septicemic plague is usually fatal. Early treatment with antibiotics

reduces the mortality rate to between 4 and 15 percent. [1][2][3] People who die from this form of plague often die on the same day symptoms first appear.

Pneumonic plague

Main article: Pneumonic plague

The pneumonic plague infects the lungs, and with that infection comes the possibility of person-to-person transmission through respiratory droplets. The incubation period for pneumonic plague is usually between two and four days, but can be as little as a few hours. The initial symptoms, of headache, weakness, and coughing with hemoptysis, vomiting blood, are indistinguishable from other respiratory illnesses. Without diagnosis and treatment, the infection can be fatal in one to six days; mortality in untreated cases is 50–90%.[4]

Other forms

There are a few other rare manifestations of plague, including asymptomatic plague and abortive plague. *Cellulocutaneous plague* sometimes results in infection of the skin and soft tissue, often around the bite site of a flea. *Plague meningitis* can occur in very rare cases of septicemic plague.

Treatments

Vladimir Havkin, a doctor of Russian-Jewish origin who worked in India, was the first to invent and test a bubonic plague vaccine,[5] on January 10, 1897.

The traditional treatments are:

- Streptomycin 30 mg/kg IM twice daily for 7 days
- Chloramphenicol 25–30 mg/kg single dose, followed by 12.5–15 mg/kg four times daily
- Tetracycline 2 g single dose, followed by 500 mg four times daily for 7–10 days (not suitable for children)

More recently,

- Gentamicin 2.5 mg/kg IV or IM twice daily for 7 days
- Doxycycline 100 mg (adults) or 2.2 mg/kg (children) orally twice daily have also been shown to be effective.[6]

History

Nicolas Poussin (1594-1665), French. The Plague of Ashdod, 1630. Oil on canvas, 148 x 198 cm. Musée du Louvre, Paris, France, Giraudon/Bridgeman Art Library.

"Der Doktor Schnabel von Rom" (English: "Doctor Beak of Rome") engraving by Paul Fürst (after J Columbina). The beak is a primitive gas mask worn by physicians, stuffed with substances (such as spices and herbs) thought to ward off the plague.

The earliest (though unvalidated) account describing a possible plague epidemic is found in I Samuel 5:6 of the Hebrew Bible (Tanakh). In this account, the Philistines of Ashdod were stricken with a plague for the crime of stealing the Ark of the Covenant from the Children of Israel. These events have been dated to approximately the second half of the eleventh century B.C. The word "tumors" is used in most English translations to describe the sores that came upon the Philistines. The Hebrew, however, can be interpreted as "swelling in the secret parts".[*citation needed*] The account indicates that the Philistine city and its political territory were stricken with a "ravaging of mice" and a plague, bringing death to a large segment of the population.

In the second year of the Peloponnesian War (430 B.C.), Thucydides described an epidemic disease which was said to have begun in Ethiopia, passed through Egypt and Libya, then come to the Greek world. In the Plague of Athens, the city lost possibly one third of its population, including Pericles. Modern historians disagree on whether the plague was a critical factor in the loss of the war. Although this epidemic has long been considered an outbreak of plague, many modern scholars believe that typhus[7], smallpox, or measles may better fit the surviving descriptions. A recent study of the DNA found in

the dental pulp of plague victims, led by Manolis J. Papagrigorakis, suggests that typhoid was actually responsible. Other scientists dispute this conclusion, citing serious methodological flaws in the DNA study[*citation needed*].

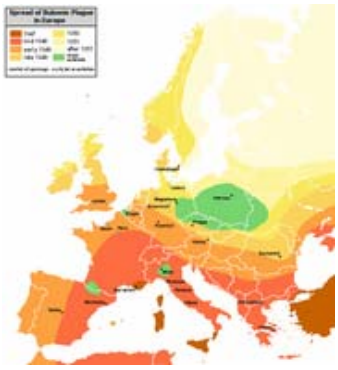
In the first century A.D., Rufus of Ephesus, a Greek anatomist, refers to an outbreak of plague in Libya, Egypt, and Syria. He records that Alexandrian doctors named Dioscorides and Posidonius described symptoms including acute fever, pain, agitation, and delirium. Buboes—large, hard, and non-suppurating—developed behind the knees, around the elbows, and "in the usual places." The death toll of those infected was very high. Rufus also wrote that similar buboes were reported by a Dionysius Curtus, who may have practiced medicine in Alexandria in the third century B.C. If this is correct, the eastern Mediterranean world may have been familiar with bubonic plague at that early date.[8][9]

First Pandemic: Plague of Justinian

The Plague of Justinian in A.D. 541–542 is the first known attack on record, and marks the first firmly recorded pattern of bubonic plague. This outbreak is thought to have originated in Ethiopia. The huge city of Constantinople imported massive amounts of grain, mostly from Egypt, to feed its citizens. The grain ships were the source of contagion for the city, with massive public granaries nurturing the rat and flea population. At its peak the plague was killing 10,000 people in Constantinople every day and ultimately destroyed perhaps 40% of the city's inhabitants. It went on to destroy up to a quarter of the human population of the eastern Mediterranean.

In A.D. 588 a second major wave of plague spread through the Mediterranean into what is now France. It is estimated that the Plague of Justinian killed as many as 100 million people across the world.[10][11] It caused Europe's population to drop by around 50% between 541 and 700.[12] It also may have contributed to the success of the Arab conquests.[13] [14] An outbreak of it in the A.D. 560s was described in A.D. 790 as causing "swellings in the glands...in the manner of a nut or date" in the groin "and in other rather delicate places followed by an unbearable fever". While the swellings in this description have been identified by some as buboes, there is some contention as to whether the pandemic should be attributed to the bubonic plague, *Yersinia pestis*, known in modern times.[15]

Second Pandemic: Black Death



Map showing the spread of bubonic plague in Europe

From 1347 to 1351, the Black Death, a massive and deadly pandemic originated in Central Asia, swept through Asia, Europe and Africa. It may have reduced the world's population from 450 million to between 350 and 375 million.[16] China lost around half of its population, from around 123 million to around 65 million; Europe around 1/3 of its population, from about 75 million to about 50 million; and Africa approximately 1/8th of its population, from around 80 million to 70 million (mortality rates tended to be correlated with population density so Africa, being less dense overall, had the lowest rate). This makes the Black Death the largest death toll from any known non-viral epidemic. Although accurate statistical data does not exist, it is thought that 1.4 million died in England (1/3 of England's 4.2 million people), while an even higher percentage of Italy's population was likely wiped out. On the other hand, Northeastern Germany, Bohemia, Poland and Hungary are believed to have suffered less, and there are no estimates available for Russia or the Balkans. It is conceivable that Russia may not have been as affected due to its very cold climate and large size, hence often less close contact with the contagion.

The Black Death contributed to the destruction of the feudal system in Medieval Time. As more slaves and workers died, there were fewer people to work for the nobles and they had to give higher wages to the workers willing to work on the nobles' lands. The Black Death also killed many great kings and nobles.[*dubious* – *discuss*] In its aftermath, the Black Death may also have favoured the use of more advanced farming tools as a smaller workforce was available and plots grew larger as a result of the population loss.

The plague continued to strike parts of Europe sporadically until the 17th century, each time with reduced intensity and fatality, suggesting an increased resistance due to natural selection.[15] Some have also argued that changes in hygiene habits and efforts to improve public health and sanitation had a significant impact on the falling rates of infection.[*who?*]

Nature of the disease

In the early 20th century, following the identification by Yersin and Kitasato of the plague bacterium that caused the late 19th and early 20th century Asian bubonic plague (the Third Pandemic), most scientists and historians came to believe that the Black Death was an incidence of this plague, with a strong presence of the more contagious pneumonic and septicemic varieties increasing the pace of infection, spreading the disease deep into inland areas of the continents. It was claimed that the disease was spread mainly by black rats in Asia and that therefore there must have been black rats in north-west Europe at the time of the Black Death to spread it, although black rats are currently rare except near the Mediterranean. This led to the development of a theory that brown rats had invaded Europe, largely wiping out black rats, bringing the plagues to an end, although there is no evidence for the theory in historical records. Some historians suggest that marmots, rather than rats, were the primary carriers of the disease.[17] The view that the Black Death was caused by *Yersinia pestis* has been incorporated into medical textbooks throughout the 20th century and has become part of popular culture, as illustrated by recent books, such as John Kelly's *The Great Mortality*.

Many modern researchers have argued that the disease was more likely to have been viral (that is, not bubonic plague), pointing to the absence of rats from some parts of Europe that were badly affected and to the conviction of people at the time that the disease was spread by direct human contact. According to the accounts of the time the black death was extremely virulent, unlike the 19th and early 20th century bubonic plague. Samuel K. Cohn has made a comprehensive attempt to rebut the bubonic plague theory.[18] In the Encyclopedia of Population, he points to five major weaknesses in this theory:

- very different transmission speeds — the Black Death was reported to have spread 385 km in 91 days in 664, compared to 12-15 km a year for the modern Bubonic Plague, with the assistance of trains and cars
- difficulties with the attempt to explain the rapid spread of the Black Death by arguing that it was spread by the rare pneumonic form of the disease — in fact this form killed less than 0.3% of the infected population in its worst outbreak (Manchuria in 1911)
- different seasonality — the modern plague can only be sustained at temperatures between 50 and 78 °F (10 and 26 °C) and requires high humidity, while the Black Death occurred even in Norway in the middle of the winter and in the Mediterranean in the middle of hot dry summers
- very different death rates — in several places (including Florence in 1348) over 75% of the population appears to have died; in contrast the highest mortality for the modern Bubonic Plague was 3% in Mumbai in 1903
- the cycles and trends of infection were very different between the diseases — humans did not develop resistance to the modern disease, but resistance to the Black Death rose sharply, so that eventually it became mainly a childhood disease

Cohn also points out that while the identification of the disease as having buboes relies on accounts of Boccaccio and others, they described buboes, abscesses, rashes and

carbuncles occurring all over the body, the neck or behind the ears. In contrast, the modern disease rarely has more than one bubo, most commonly in the groin, and is not characterised by abscesses, rashes and carbuncles.[15]

Researchers have offered a mathematical model based on the changing demography of Europe from 1000 to 1800 AD demonstrating how plague epidemics, 1347 to 1670, could have provided the selection pressure that raised the frequency of a mutation to the level seen today that prevent HIV from entering macrophages that carry the mutation (the average frequency of this allele is 10% in European populations).[19] It is suggested that the original single mutation appeared over 2,500 years ago and that persistent epidemics of a haemorrhagic fever struck at the early classical civilizations.

Third Pandemic

Main article: Third Pandemic

The Third Pandemic began in China in 1855, spreading plague to all inhabited continents and ultimately killing more than 12 million people in India and China alone. Casualty patterns indicate that waves of this pandemic may have come from two different sources. The first was primarily bubonic and was carried around the world through ocean-going trade, transporting infected persons, rats, and cargoes harboring fleas. The second, more virulent strain was primarily pneumonic in character, with a strong person-to-person contagion. This strain was largely confined to Manchuria and Mongolia. Researchers during the "Third Pandemic" identified plague vectors and the plague bacterium (see above), leading in time to modern treatment methods.

Plague occurred in Russia in 1877–1889 in rural areas near the Ural Mountains and the Caspian Sea. Efforts in hygiene and patient isolation reduced the spread of the disease, with approximately 420 deaths in the region. Significantly, the region of Vetlianka in this area is near a population of the bobak marmot, a small rodent considered a very dangerous plague reservoir. The last significant Russian outbreak of Plague was in Siberia in 1910 after sudden demand for Marmot skins (a substitute for Sable) increased the price by 400 percent. The traditional hunters would not hunt a sick Marmot and it was taboo to eat the fat from under the arm (the axillary lymphatic gland that often harboured the plague) so outbreaks tended to be confined to single individuals. The price increase, however, attracted thousands of Chinese hunters from Manchuria who not only caught the sick animals but ate the fat which was considered a delicacy. The plague spread from the hunting grounds to the terminus of the Chinese Eastern Railway and then followed the track for 2,700 km. The plague lasted 7 months and killed 60,000 people.

The bubonic plague continued to circulate through different ports globally for the next fifty years; however, it was primarily found in Southeast Asia. An epidemic in Hong Kong in 1894 had particularly high death rates, 90% [20]. As late as 1897, medical authorities in the European powers organized a conference in Venice, seeking ways to keep the plague out of Europe. Mumbai plague epidemic stuck the city of Mumbai (Bombay) in 1896. The disease reached the Republic of Hawaii in December 1899, and

the Board of Health's decision to initiate controlled burns of select buildings in Honolulu's Chinatown turned into an uncontrolled fire which led to the inadvertent burning of most of Chinatown on January 20, 1900 according to the Star Bulletin's Feature on the Great Chinatown Fire. Plague persisted in Hawaii on the outer islands of Maui and Hawaii (The Big Island) until it was finally eradicated in 1959.[21] Plague finally reached the United States later that year in San Francisco.

Although the outbreak that began in China in 1855 is conventionally known as the Third Pandemic, (the First being the Plague of Justinian and the second being the Black Death), it is unclear whether there have been fewer, or more, than three major outbreaks of bubonic plague. Most modern outbreaks of bubonic plague amongst humans have been preceded by a striking, high mortality amongst rats, yet this phenomenon is absent from descriptions of some earlier plagues, especially the Black Death. The buboes, or swellings in the groin, that are especially characteristic of bubonic plague, are a feature of other diseases as well.

Plague as a biological weapon

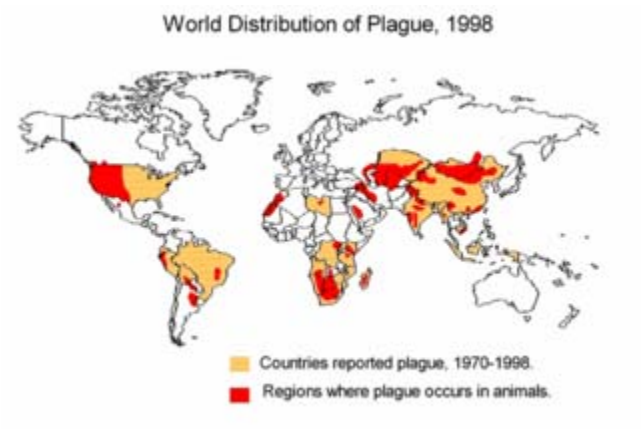
Plague has a long history as a biological weapon. Historical accounts from ancient China and medieval Europe detail the use of infected animal carcasses, such as cows or horses, and human carcasses, by the Xiongnu/Huns, Mongols, Turks, and other groups, to contaminate enemy water supplies. Han Dynasty General Huo Qubing is recorded to have died of such a contamination while engaging in warfare against the Xiongnu. Plague victims were also reported to have been tossed by catapult into cities under siege.

In 1347, the Genoese possession of Caffa, a great trade emporium on the Crimean peninsula, came under siege by an army of Mongol warriors of the Golden Horde under the command of Janibeg. After a protracted siege during which the Mongol army was reportedly withering from the disease, they decided to use the infected corpses as a biological weapon. The corpses were catapulted over the city walls, infecting the inhabitants. The Genoese traders fled, transferring the plague (Black Death) via their ships into the south of Europe, whence it rapidly spread.[22]

During World War II, the Japanese Army developed weaponised plague, based on the breeding and release of large numbers of fleas. During the Japanese occupation of Manchuria, Unit 731 deliberately infected Chinese, Korean, and Manchurian civilians and prisoners of war with the plague bacterium. These subjects, termed "maruta", or "logs", were then studied by dissection, others by vivisection while still conscious. Members of the unit such as Shiro Ishii were exonerated from the Tokyo tribunal by Douglas MacArthur but twelve of them were prosecuted in the Khabarovsk War Crime Trials in 1949 during which some admitted having spread Bubonic plague within a 36-km radius around the city of Changde. [23]

After World War II, both the United States and the Soviet Union developed means of weaponising pneumonic plague. Experiments included various delivery methods, vacuum drying, sizing the bacterium, developing strains resistant to antibiotics, combining the

bacterium with other diseases (such as diphtheria), and genetic engineering. Scientists who worked in USSR bio-weapons programs have stated that the Soviet effort was formidable and that large stocks of weaponised plague bacteria were produced. Information on many of the Soviet projects is largely unavailable. Aerosolized pneumonic plague remains the most significant threat. The plague can be easily treated with antibiotics, thus a widespread epidemic is highly unlikely in developed countries.



Worldwide distribution of plague infected animals 1998

1994 Epidemic in Surat, India

In 1994, there was a pneumonic plague epidemic in Surat, India that resulted in 52 deaths and in a large internal migration of about 300,000 residents, who fled fearing quarantine [24].

A combination of heavy monsoon rain and clogged sewers led to massive flooding which resulted in unhygienic conditions and a number of uncleared animal carcasses. It is believed that this situation precipitated the epidemic.[25]. There was widespread fear that the flood of refugees might spread the epidemic to other parts of India and the world, but that scenario was averted, probably as a result of effective public health response mounted by the Indian health authorities [26].

Much like the Black Death that spread through medieval Europe, some questions still remain unanswered about the 1994 epidemic in Surat[27].

Initial questions about whether it was an epidemic of plague arose because the Indian health authorities were unable to culture *Yersinia pestis*, but this could have been due to poor laboratory procedures[27]. Yet, there are several lines of evidence strongly suggesting that it was a plague epidemic: blood tests for Yersinia were positive, a number of individuals showed antibodies against Yersinia and the clinical symptoms displayed by the affected were all consistent with the disease being plague [28].

Other Contemporary cases

Two non-plague Yersinia - *Yersinia pseudotuberculosis* and *Yersinia enterocolitica* - still exist in fruit and vegetables from the Caucasus Mountains east across southern Russia and Siberia, to Kazakhstan, Mongolia, and parts of China; in Southwest and Southeast Asia, Southern and East Africa (including the island of Madagascar); in North America, from the Pacific Coast eastward to the western Great Plains, and from British Columbia south to Mexico; and in South America in two areas: the Andes mountains and Brazil. There is no plague-infected animal population in Europe or Australia.

- On August 31, 1984, the Centers for Disease Control and Prevention reported a case of pneumonic plague in Claremont, California. The CDC believes that the patient, a veterinarian, contracted plague from a stray cat. This could not be confirmed since the cat was destroyed prior to the onset of symptoms.[29]
- From 1995 to 1998, annual outbreaks of plague were witnessed in Mahajanga, Madagascar as per a study done by Pascal Boisier and other scientists and publish in Emerging Infectious Diseases journal in March 2002.

- In the U.S., about half of all food cases of plague since 1970 have occurred in New Mexico. There were 2 plague deaths in the state in 2006, the first fatalities in 12 years.[30]

- In February 2002, a small outbreak of pneumonic plague took place in the Shimla District of Himachal Pradesh state in northern India.[31]

- In Fall of 2002, a New Mexico couple contracted the disease, just prior to a visit to New York City. They both were treated by antibiotics, but the male required amputation of both feet to fully recover, due to the lack of blood flow to his feet, cut off by the bacteria.

- On April 19, 2006, CNN News and others reported a case of plague in Los Angeles, California, lab technician Nirvana Kowlessar, the first reported case in that city since 1984.[32]

- In May 2006, KSL Newsradio reported a case of plague found in dead field mice and chipmunks at Natural Bridges about 40 miles (64 km) west of Blanding in San Juan County, Utah.[33]

- In May 2006, AZ Central reported a case of plague found in a cat.[34]

- One hundred deaths resulting from pneumonic plague were reported in Ituri district of the eastern Democratic Republic of the Congo in June 2006. Control of the plague was proving difficult due to the ongoing conflict.[35]

- It was reported in September 2006 that three mice infected with *Yersinia pestis* apparently disappeared from a laboratory belonging to the Public Health Research

Institute, located on the campus of the University of Medicine and Dentistry of New Jersey, which conducts anti-bioterrorism research for the United States government.[36]

- On May 16, 2007, an 8-year-old hooded capuchin monkey in the Denver Zoo died of the bubonic plague. Five squirrels and a rabbit were also found dead on zoo grounds and tested positive for the disease.[37]

- On June 5, 2007 in Torrance County, New Mexico a 68 year old woman developed bubonic plague, which progressed to pneumonic plague.[38]

- On November 2, 2007, Eric York, a 37 year old wildlife biologist for the National Park Service's Mountain Lion Conservation programPDF (144 KB) and The Felidae Conservation Fund, was found dead in his home at Grand Canyon National Park. On October 27, York performed a necropsy on a mountain lion that had likely perished from the disease and three days afterward York complained of flu-like symptoms and called in sick from work. He was treated at a local clinic but was not diagnosed with any serious ailment. The discovery of his death sparked a minor health scare, with officials stating he likely died of either plague or hantavirus, and 49 people who had come in to contact with York were given aggressive antibiotic treatments. None of them fell ill. Autopsy results released on November 9, confirmed the presence of *Y. pestis* in his body, confirming plague as a likely cause of death.[39][40]

- In January 2008, at least 18 people died of bubonic plague in Madagascar.[41]

- On January 19, 2009, British newspaper The Sun reported an Al-Qaeda training camp in Algeria had been wiped out by the plague, killing approximately 40 Islamic extremists[42]