Plague

Peste, Black Death, Bubonic Plague, Pneumonic Plague, Septicemic Plague, Pestis Minor

Last Updated: July 2023

Importance

Plague is a zoonotic, often flea-borne, bacterial disease that causes serious illnesses in both people and animals. Outbreaks in highly social species, such as prairie dogs, may kill nearly all of the animals in a colony. While clinical cases in less gregarious hosts are often sporadic, they are also frequently life-threatening. Pneumonic plague, a particularly deadly form of the disease, is usually fatal in all species if antibiotics are not started very soon after the symptoms appear. Bubonic plague, the most common form in people, is less fulminant, but still has a high mortality rate if left untreated.

At least three major plague pandemics occurred in humans before the development of antibiotics, together with improved sanitation and hygiene, made plague an uncommon cause of death in people. They included the Justinian plague in the 6th century AD, the Black Death starting in the 14th century, and a pandemic that began in China in the late 1800s. The organisms responsible for these events eventually became established in localized foci of small mammal reservoir hosts on most continents. Occasionally they still spill over from these reservoirs to affect various incidental hosts, including people. While most human cases occur in Asia and Africa, they are also seen sporadically in other regions, including western North America. Pneumonic plague outbreaks are particularly dangerous, as the organism can spread from person to person without the need for arthropod vectors. Human plague may reoccur after a long period when the disease seems to disappear, and outbreaks in some countries followed quiescent periods of 30-50 years.

Etiology

Plague results from infection by *Yersinia pestis*, a Gram negative, facultative intracellular bacillus in the family Enterobacteriaceae. There are three principal forms of plague – bubonic, pneumonic and septicemic. Bubonic plague, the most common form, usually results from the inoculation of *Y. pestis* into the skin, and is characterized by the development of a swollen, painful draining lymph node, called a bubo, in addition to other clinical signs. Pneumonic plague occurs after the inhalation of bacteria (primary pneumonic plague) or after blood–borne spread to the lungs (secondary pneumonic plague). The third form, septicemic plague, may develop without an obvious inoculation site and/or bubo (primary septicemic plague) or from the dissemination of the other two forms. Additional types of plague are also seen occasionally, such as a gastrointestinal form from ingestion.

Attenuated strains of *Y. pestis* have been developed for research purposes and are generally avirulent in humans; however, one attenuated strain, *Y. pestis* KIM, caused plague in a person who appeared to be unusually susceptible due to other illnesses and genetic conditions.

Species Affected

Small mammals including rodents, shrews and pikas (*Ochotona* spp.), which are lagomorphs, maintain and/or amplify *Y. pestis*. The principal hosts vary with the geographic region, and among rodents, can include prairie dogs (*Cynomys* spp.), ground squirrels/ susliks (*Spermophilus* spp.), antelope ground squirrels (*Ammospermophilus* spp.), chipmunks (*Tamias* spp.), rats (*Rattus* spp.), wood rats (*Neotoma* spp.), deer mice (*Peromyscus* spp.), Siberian marmots (*Marmota sibirica*), voles (*Microtus* spp.), jerboas, and certain gerbils (e.g., *Rhombomys opimus* and *Meriones* spp.). Some of these animals experience outbreaks of disease, but *Y. pestis* seems to circulate in others with little or no mortality. Whether a specific host maintains the organism between outbreaks or only amplifies it during an epidemic is sometimes unclear.

Many other mammals can be infected as incidental hosts, though some are more likely to have clinical signs than others. Clinical cases are seen regularly in cats and other felids, and have also been reported in dogs, camels, a llama, a horse, various cervids, pronghorn antelope (*Antilocapra americana*), black-footed ferrets (*Mustela nigripes*), coyotes, foxes, cottontail rabbits (*Sylvilagus* spp.) and a wild hare. Some dead goats were thought to have died of plague, though confirmatory testing was not done, and Tibetan sheep (*Ovis aries*) regularly become infected from marmot reservoirs in Asia.

The Center for Food Security & Public Health

Institute for International Cooperation in Animal Biologics

Iowa State University College of Veterinary Medicine

World Organisation for Animal Health Founded as OIE

USDA

In addition to these animals, serological surveys have found antibodies to *Y. pestis* in pigs and diverse wildlife species including African buffalo (*Syncerus caffer*), African elephants (*Loxodonta africana*), American badgers (*Taxidea taxus*), some species of skunks, black bears (*Ursus americanus*), North American beavers (*Castor canadensis*), raccoons (*Procyon lotor*), various canids and mustelids, and cottontail rabbits. Experimental infections in pigs, domestic ferrets, raccoons, striped skunks (*Mephitis mephitis*) and Siberian polecats (*Mustela eversmanni*) have confirmed their susceptibility to infection, though clinical signs were not seen in most species.

Zoonotic potential

Humans are susceptible to plague.

Geographic Distribution

Y. pestis can be found in parts of Africa, the Middle East, Asia, and North and South America, as well as Madagascar. The distribution of this organism is patchy. In North America, plague foci are limited to the western third of the continent, from Canada to Mexico, while in South America active foci have been identified mainly in Brazil and the Andes Mountain region of Bolivia, Peru and Ecuador. In Africa, this disease is most common in eastern and southern regions, though it can be seen elsewhere. Asian foci occur from the former U.S.S.R. east through China, and south to Southwest and Southeast Asia. Plague foci tend to be associated with arid or semi-arid locations in many areas, though they also occur in humid climates.

Transmission

Y. pestis is usually transmitted by fleas, which act as biological vectors. Transmission generally occurs in bites, but in some instances the organism might enter the body from flea feces inoculated into broken skin or mucous membranes. Certain species of fleas transmit *Y. pestis* more efficiently than others. Some rodent fleas, in particular the Oriental rat flea (*Xenopsylla cheopis)*, are good vectors, while dog and cat fleas (*Ctenocephalides* spp.) are relatively inefficient. Human lice, which excrete *Y. pestis* in their feces, also seem to be capable of transmitting this organism, and ticks have been suggested as possible mechanical vectors, though one experiment indicated this is probably rare and only occurs during the first day or two.

Y. pestis is occasionally transmitted directly between hosts when organisms in tissues, draining lesions or body fluids contact mucous membranes or broken skin. Human cases have occurred after close contact with infected animals, their carcasses or tissues, bites from animals (e.g., cats, prairie dogs) and the slaughter of an infected animal for food. Although direct person-to-person spread of bubonic plague is theoretically possible, it seems to be rare or nonexistent. However, people or animals with pneumonic plague can transmit *Y. pestis* in respiratory droplets. Pneumonic plague is most contagious during its final stages, when the number of bacteria in the sputum increases, and it does not seem to spread as readily early in the illness. Carnivores and omnivores can be infected by eating raw or undercooked tissues from infected animals, while herbivores are occasionally thought to have been exposed via rodent carcasses or their excretions in feed. Transplacental transmission has been reported in humans.

Y. pestis is not resistant to desiccation or heat, and it usually remains viable for less than 72 hours on surfaces such as glass and steel. However, there are reports of survival for up to 100 days in blood and as long as 9 months in human bodies, though one study could recover the organism from the carcasses of rodents buried for 10 but not 15 days. An attenuated *Y. pestis* strain (*Y. pestis* KIM5) persisted without growth in raw meat (ground pork) for at least 2 months at 4°C, and grew in this product at 10-30°C. Under laboratory conditions, *Y. pestis* can remain viable for many months, and possibly years, in sterilized (autoclaved) soil, and for long periods in water. Whether this is representative of natural conditions is unclear, as sterilized soil contains no competing microorganisms. However, *Y. pestis* was once recovered from ordinary soil that had been contaminated by the blood of a dead infected mountain lion 24 days earlier. The significance of soil as a reservoir for animals is unclear. Rodents have been infected experimentally by burrowing in or running over recently contaminated soil, but one study found transmission from heavily contaminated unsterilized soil was uncommon. An early study found that mud floors contaminated by cultures were only infectious to rodents for the first 12 hours, until they dried out.

Disinfection

Y. pestis is susceptible to a number of disinfectants including 1% sodium hypochlorite, 70% ethanol, 2% glutaraldehyde, formaldehyde, and iodine–based and phenolic products. It can also be inactivated by moist heat (121° C [250° F] for at least 15 minutes) or dry heat (160-170° C [320-338°F] for at least 1 hour).

Infections in Animals

Incubation Period

Though published information is limited, the incubation period in many animals is likely to be on the order of a few days, as in humans. However, there are also reports of prolonged incubation periods, for instance 3 or 4 weeks in a few experimentally infected grasshopper mice (*Onychomys leucogaster*).

Clinical Signs

All three forms of plague - bubonic, septicemic and pneumonic – can be seen in animals. Septicemic and pneumonic plague can be difficult to diagnose, as they resemble a number of other diseases. Mild or asymptomatic infections are also possible, and can occur even in members of highly susceptible species such as cats and prairie dogs.

Cats, which account for most of the clinical cases described in domestic animals, mainly seem to develop

bubonic plague. Common clinical signs are fever and other nonspecific signs of illness (e.g., anorexia, lethargy, dehydration), together with an enlarged and sometimes abscessed or ulcerated lymph node (bubo) near the inoculation site. Because most cats are probably infected from their prey, the bubo often develops in a (sub)mandibular lymph node. Some animals also have cellulitis, abscesses in various locations, mouth lesions including ulcers, necrotic tonsillitis, gastrointestinal signs (vomiting, diarrhea), neurological signs and/or ocular discharge.

Bubonic plague can progress to pneumonic or septicemic plague; however, these forms can also be the primary presentation in a cat, in which case there is no bubo. Pneumonic plague is characterized by respiratory signs, which usually include dyspnea and hemoptysis as the disease progresses, while cats with septicemic plague have typical signs of sepsis, multiorgan dysfunction and, in some cases, disseminated intravascular coagulation (DIC) and/or respiratory distress. Both pneumonic and septicemic plague are rapidly fatal without treatment.

Dogs and other canids seem more likely to develop subclinical infections or mild illnesses than cats, and spontaneous recovery appears to be more common. Bubonic plague is the most common form reported in dogs, though pneumonic and septicemic plague are also seen occasionally. Most clinical cases resemble plague in cats, and bubos often develop in the mandibular lymph nodes, though other nodes can be affected. Some dogs with respiratory plague may initially have relatively mild signs that can resemble other respiratory illnesses, and atypical presentations have been reported. In one instance, a dog with respiratory plague presented with fever, pale mucous membranes, rigid jaw tone, drooling, and lameness of one foreleg, together with a lung opacity on x-ray, which initially resulted in a presumptive diagnosis of toxicity or trauma.

Wildlife with plague, such as wild felids, are often found dead or moribund. Although no significant clinical signs were seen in experimentally infected coyotes, there are a few reports of *Y. pestis* in dead coyotes, foxes and other canids. The outcome in rodents ranges from mostly subclinical infections and mild illnesses to severe, rapidly fatal disease, depending on the species. Prairie dogs are highly susceptible, and nearly all of the animals in a colony may die. Mule deer (*Odocoileus hemionus*) and black-tailed deer (*Odocoileus hemionus columbianus*) sometimes develop ocular plague, which appears as keratoconjunctivitis, endophthalmitis and panophthalmitis. Septicemia and pneumonia have also been seen infrequently in mule deer, either with or without ocular signs. Experimentally infected raccoons developed fever and lethargy in one study, though bacteremia was not seen, while some other studies reported that raccoons, striped skunks, domestic ferrets and some other mustelids, as well as pigs inoculated orally via contaminated meat, remained asymptomatic.

Post Mortem Lesions

Click to view images

Affected lymph nodes can be mildly to markedly swollen, with necrosuppurative inflammation, edema and hemorrhages. Necrotic foci or hemorrhages ranging from petechiae and ecchymoses to frank blood may be found in various internal organs. The liver may be pale and the spleen enlarged. Signs of diffuse interstitial pneumonia, focal congestion, consolidation, abscesses and hemorrhages may be found in the lungs. Suppurative and necrotic tonsillitis may also be seen in some animals.

Diagnostic Tests

Y. pestis may be found in blood, nasal or oral swabs, lower respiratory tract samples, aspirates from enlarged lymph nodes, swabs of draining lesions, and/or tissue samples from affected organs such as the liver, spleen and lung. A presumptive diagnosis can be made by observing the characteristic organisms in clinical samples, such as lymph node (bubo) aspirates or swabs of draining lesions. *Y. pestis* is a Gram negative coccobacillus or bacillus with bipolar staining, which is particularly evident when Wright-Giemsa or Wayson stains are used.

Definitive identification is by culture, or by identification of the organism in clinical samples with PCR tests, rapid immunoassays to detect *Y. pestis* antigens, or immunofluorescence. *Y. pestis* will grow on ordinary media (e.g., blood agar, MacConkey), but *Yersinia*-specific agar is available, and particularly helpful when the sample is contaminated. The organism can be identified with routine biochemical tests and other methods; however, some automated systems may misidentify this bacterium due to its delayed/ weak biochemical reactions. *Y. pestis* colonies can also be identified by PCR, matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) or phage lysis. While animal assays are generally discouraged if there are other alternatives, *Y. pestis* can be recovered in laboratory animals such as mice.

Serological tests such as latex hemagglutination and passive hemagglutination are occasionally employed in diagnosis, though they are more often used in serosurveillance. A rising titer indicates a recent infection, but a single sample, together with consistent clinical signs, may be suggestive.

Treatment

Some affected animals have been treated successfully with antibiotics, particularly when treatment is begun early.

Control

Disease reporting

Veterinarians who suspect an animal has plague should follow their national and/or local guidelines for disease reporting. In addition to any other requirements, all suspected cases of animal or human plague in the U.S. should be reported to the local or state public health department. The state public health laboratory or U.S. Centers for Disease

Control (CDC) laboratory should be contacted before collecting or shipping any diagnostic samples.

Prevention

A good flea control program can help reduce the risk of transmission from flea bites in dogs and cats, and carnivores should be kept from hunting potentially infected animals or feeding on their carcasses. Animals that become ill should be examined by a veterinarian, using barrier precautions and good infection control measures, and they should be isolated during treatment. The most stringent measures are needed before antibiotics are begun and during the first few days, before fever abates and the clinical signs improve.

Vaccination has been used to protect endangered black-footed ferrets, which prey on prairie dogs, from epizootics in the latter species. Both vaccination and insecticide treatment have been employed in prairie dog colonies; however, severe epizootics are still observed in these colonies, and the cost effectiveness of these measures remains to be established. Vaccines are not available for domesticated animals.

Morbidity and Mortality

Y. pestis is normally maintained in various wild small mammals in endemic foci. Low level endemic transmission, where there is no noticeable effect on the population, can periodically transition into epizootics that may kill large numbers of animals. Various environmental factors can influence the development of epizootics, including rainfall, which can precede plague activity in some semi-arid areas. Whether *Y. pestis* circulates in its epizootic host(s) between outbreaks or is maintained in a different species is sometimes unclear. Some wild rodents have been reported to develop resistance to plague through repeated exposure, and this resistance appears to be heritable. Even in prairie dogs, mortality is lower in experimentally infected animals from areas where plague occurs regularly.

Plague epidemics in rodents, as well as other causes of population expansion followed by collapse, can result in their fleas seeking alternative hosts. This may result in increased transmission to domestic animals and humans. Antibodies in wildlife incidental hosts, including canids, felids and various other species, suggest that there is also ongoing exposure to incidental hosts during interepidemic periods, and that some of these animals survive.

Among domestic animals, most clinical cases have been reported in cats, probably due to their exposure to rodents as well as a relatively high susceptibility to plague. Studies in experimentally infected cats suggest a case fatality rate up to 60% in bubonic plague if left untreated, though transient, self-limited illnesses were also seen and a few cats remained asymptomatic. In naturally infected cats, one study estimated the case fatality rate to be about 14% in bubonic plague, which is more readily recognized and less rapidly progressive than the other two forms, 70% in septicemic plague and 83% in the pneumonic form. Dogs do not seem to be as susceptible to plague as cats, and most experimentally infected dogs have recovered unless they were inoculated via aerosols. Nevertheless, severe or fatal illnesses are seen occasionally in naturally infected dogs. Few studies have examined plague in other incidental hosts, but three camels orally exposed to *Y. pestis*, and 2 of 4 animals inoculated subcutaneously with the organism survived, while all 6 camels inoculated by the respiratory route died.

Infections in Humans

Incubation Period

The incubation period for bubonic plague is usually around 2-5 days, though it may be up to 10 days. Pneumonic plague typically develops within 1-4 days of exposure.

Clinical Signs

Bubonic plague, the most common form in humans, usually begins with the sudden onset of fever, chills, headache, malaise, myalgia, arthralgia and other nonspecific signs of illness, together with the rapid development of the characteristic painful, swollen lymph node (the bubo) and occasionally a pustule, vesicle, eschar or papule at the site of the flea bite. The femoral and inguinal lymph nodes are the most common sites for the bubo, but other superficial nodes can be affected, and very rarely, it can occur in the abdominal cavity or retroperitoneal space. Variations in this pattern can be seen after exposure via food, which sometimes results in severe pharyngitis and tonsillitis, with swelling of a submandibular lymph node and the neck. Gastrointestinal signs, including vomiting, diarrhea and abdominal pain, were common in some outbreaks caused by *Y. pestis*-contaminated food, and can occur either with or without pharyngitis. Untreated bubonic plague in humans often progresses to septicemic and/or pulmonary plague. Some patients may also experience other complications, such as meningitis, abortion or postpartum hemorrhage.

Primary septicemic plague may begin similarly to bubonic plague, and sometimes includes gastrointestinal signs, but there is no bubo. The course of primary or secondary septicemic plague can be rapid, resembles other forms of septicemia, and may include multiorgan failure as well as hemorrhagic signs (e.g., epistaxis, hematuria, petechiae, ecchymoses), neurological signs and, in some cases, necrosis of the extremities due to coagulopathies. Patients occasionally develop meningitis, and various rare conditions including septic arthritis, multifocal osteomyelitis, pleuritis, myocarditis and endophthalmitis have been reported.

Pneumonic plague occurs after the inhalation of bacteria or after blood–borne spread to the lungs. The symptoms are acute and develop rapidly, with high fever, chills, headache (often severe), myalgia, malaise and an increased respiratory rate. The cough is initially dry but becomes productive, then bloodstained and/or purulent, and eventually foamy and pink or red from blood. Pneumonic plague is rapidly fatal, with dyspnea, stridor and cyanosis ending in respiratory failure and circulatory collapse.

Pestis minor is a benign form of bubonic plague, usually seen in regions where plague is common. It is characterized by fever, lymphadenitis, headache and prostration, which usually resolve spontaneously within a week.

Diagnostic Tests

The diagnosis of plague in humans is similar to animals; however, rapid immunoassays, such as F1 antigen tests and antigen-capture ELISAs, may also be available in some countries, and loop-mediated isothermal amplification tests have been published. Clinical samples from people include respiratory secretions, blood, lymph node (bubo) aspirates, cerebrospinal fluid, urine and postmortem tissue samples. *Y. pestis* consistently occurs in blood only during septicemia, but bacteria are sometimes released intermittently from lymph nodes into the blood, and a series of blood samples may be able to detect the organism. In pulmonary plague, PCR tests and culture are more likely to find *Y. pestis* in lower respiratory samples, such as bronchial/tracheal washings, than sputum.

Treatment

Plague can be treated with antibiotics; however, their efficacy is often limited in the pneumonic form unless the patient is treated quickly. Although antibiotic resistant strains of *Y. pestis* have been described, they seem to be rare.

Control

Measures to help reduce plague in endemic areas include rodent control around dwellings and the avoidance of contact with small mammals, their carcasses and burrows during occupational or recreational activities. Insect repellents can be applied to clothing and skin if exposure to rodent fleas is expected. Uncooked or undercooked tissues from game or livestock that may have been exposed to plague should be avoided. In some areas, authorities conduct control programs or surveillance for plague in its usual reservoir hosts. Concurrent insecticidal treatment is often necessary when these hosts die or are killed, as fleas leave the carcasses to seek new hosts. Flea control and other preventive measures in pets might reduce the transfer of infected fleas to households, in addition to reducing the risk the pet will become infected.

Good hygiene and infection control measures, with the use of personal protective equipment (PPE), can help prevent infections when caring for people or animals that are plague suspects. More stringent precautions are necessary when pneumonic plague is suspected or higher risk procedures such as necropsies are performed. Specific PPE recommendations are available from various public health agencies and other sources. People who have been exposed to *Y. pestis* are often treated prophylactically with antibiotics. Vaccines have occasionally been used in some countries or high risk groups, but there are concerns about the safety and efficacy of the current products, and their availability is limited.

Morbidity and Mortality

Bubonic plague is the most common form of plague in people, accounting for around 80-95% of cases worldwide. The case fatality rate in this form was estimated to be between 40% and 70% before the development of antibiotics, but it is now around 5-15%. Reported case fatality rates range from 25% to 50% or more in pneumonic plague, due to the narrow treatment window and difficulty in distinguishing this disease from other respiratory illnesses. However, most people survive if treated very soon after the onset of symptoms. Untreated pneumonic or septicemic plague is almost always fatal, often within a few days.

The incidence of plague is highest in Asia and Africa, but sporadic cases and outbreaks can be seen in any endemic region. On average, fewer than 20 cases of plague are reported annually in the U.S., while Madagascar, which is among the countries with the highest incidence, usually has around 90 cases each year, mostly of the bubonic form. Bubonic plague does not seem to spread readily from person to person in the absence of ectoparasites, but pneumonic plague can cause outbreaks. In some areas, plague transmission can also result from traditional burial practices that involve close contact with the body. There are some indications that genetic background might influence susceptibility to plague in humans, though this is still controversial.

Internet Resources

U.S. CDC. Plague Resources

eMedicine.com. Pediatric Plague

Nelson et al. Antimicrobial Treatment and Prophylaxis of Plague: Recommendations for Naturally Acquired Infections and Bioterrorism Response

Public Health Agency of Canada. Pathogen Safety Data Sheets

The Merck Manual

The Merck Veterinary Manual

United States Geological Survey. National Wildlife Health Center. Sylvatic Plague

World Health Organization (WHO). Plague

Acknowledgements

This factsheet was written by Anna Rovid Spickler, DVM, PhD, Veterinary Specialist from the Center for Food Security and Public Health. The U.S. Department of Agriculture Animal and Plant Health Inspection Service (USDA APHIS) provided funding for this factsheet through a series of cooperative agreements related to the development of resources for initial accreditation training.

The following format can be used to cite this factsheet. Spickler, Anna Rovid. 2023. *Plague*. Retrieved from http://www.cfsph.iastate.edu/DiseaseInfo/factsheets.php.

References

Acha PN, Szyfres B [Pan American Health Organization (PAHO)]. Zoonoses and communicable diseases common to man and animals. Volume 1. Bacterioses and mycoses. 3rd ed. Washington DC: PAHO; 2003. Scientific and Technical Publication No. 580. Plague; 207-18.

Aiello SE, Moses SA, editors. The Merck veterinary manual [online]. Whitehouse Station, NJ: Merck and Co; 2012. Plague. Available at: http://www.merckvetmanual.com/mvm/index.jsp?cfile=htm/bc/51900.htm.* Accessed 16 September 2013.

Anonymous. Fatal laboratory-acquired infection with an attenuated *Yersinia pestis* strain - Chicago, Illinois, 2009. MMWR Morb Mortal Wkly Rep. 2011;60(7):201-5.

Ayyadurai S, Houhamdi L, Lepidi H, Nappez C, Raoult D, Drancourt M. Long-term persistence of virulent *Yersinia pestis* in soil. Microbiology. 2008;154(Pt 9):2865-71.

Ayyadurai S, Sebbane F, Raoult D, Drancourt M. Body lice, *Yersinia pestis* orientalis, and black death. Emerg Infect Dis. 2010;16(5):892-3.

Baeten LA, Pappert R, Young J, Schriefer ME, Gidlewski T, Kohler D, Bowen RA. Immunological and clinical response of coyotes (*Canis latrans)* to experimental inoculation with *Yersinia pestis*. Wildl Dis. 2013;49(4):932-9.

Barbieri R, Signoli M, Chevé D, Costedoat C, Tzortzis S, Aboudharam G, Raoult D, Drancourt M. *Yersinia pestis*: the natural history of plague. Clin Microbiol Rev. 2020;34(1):e00044-19.

Bevins SN, Chandler JC, Barrett N, Schmit BS, Wiscomb GW, Shriner SA. Plague exposure in mammalian wildlife across the western United States. Vector Borne Zoonotic Dis. 2021;21(9):667-74.

Bevins SN, Tracey JA, Franklin SP, Schmit VL, Macmillan ML et al. Wild felids as hosts for human plague, western United States. Emerg Infect Dis. 2009;15(12):2021-4.

Bhaduri S, Phillips JG. Growth of a pYV-bearing *Yersinia pestis* KIM5 in retail raw ground pork. Foodborne Pathog Dis. 2013;10(5):467-71.

Biberstein EL, Holzworth J. Bacterial diseases. Plague. In: Holzworth J, editor. Diseases of the cat. Philadelphia, PA: W.B. Saunders; 1987. p. 294, 660.

Bin Saeed AA, Al-Hamdan NA, Fontaine RE. Plague from eating raw camel liver. Emerg Infect Dis. 2005;11(9):1456-7.

Boegler KA, Graham CB, Montenieri JA, MacMillan K, Holmes JL, Petersen JM, Gage KL, Eisen RJ. Evaluation of the infectiousness to mice of soil contaminated with *Yersinia pestis*-infected blood. Vector Borne Zoonotic Dis. 2012;12(11):948-52.

Butler T. Plague gives surprises in the first decade of the 21st century in the United States and worldwide. Am J Trop Med Hyg. 2013;89(4):788-93.

Butler T. Yersiniosis and plague. In: Palmer SR, Soulsby EJL, Simpson DIH, editors. Zoonoses. New York: Oxford University Press; 1998. p. 281-93.

Cabanel N, Leclercq A, Chenal-Francisque V, Annajar B, Rajerison M, Bekkhoucha S, Bertherat E, Carniel E. Plague outbreak in Libya, 2009, unrelated to plague in Algeria. Emerg Infect Dis. 2013;19(2):230-6.

Centers for Disease Control and Prevention (CDC). Plague [Web site]. CDC; 2013 Jun. Available at: http://www.cdc.gov/plague/.* Accessed 16 September 2013.

Collins FM. *Pasteurella*, *Yersinia*, and *Francisella*. In: Baron S., editor. Medical microbiology. 4th ed. New York: Churchill Livingstone; 1996. Available at: http://www.ncbi.nlm.nih.gov/books/NBK7798/* Accessed 20 Nov 2002.

Colman RE, Brinkerhoff RJ, Busch JD, Ray C, Doyle A, Sahl JW, Keim P, Collinge SK, Wagner DM. No evidence for enzootic plague within black-tailed prairie dog (*Cynomys ludovicianus*) populations. Integr Zool. 2021;16(6):834-51.

Dai R, Qi M, Xiong H, Yang X, He J, et al. Serological epidemiological investigation of Tibetan sheep (*Ovis aries*) plague in Qinghai, China. Vector Borne Zoonotic Dis. 2019;19(1):3-7.

Dai R, Wei B, Xiong H, Yang X, Peng Y, et al. Human plague associated with Tibetan sheep originates in marmots. PLoS Negl Trop Dis. 2018;12(8):e0006635.

Dhawan VK. Plague. eMedicine.com; 2021 Aug. Available at: http://emedicine.medscape.com/article/967495-overview. Accessed Jul 2023.

Drancourt M, Houhamdi L, Raoult D. *Yersinia pestis* as a telluric, human ectoparasite-borne organism. Lancet Infect Dis. 2006;6(4):234-41.

Edmunds DR, Williams ES, O'Toole D, Mills KW, Boerger-et al. Ocular plague (*Yersinia pestis*) in mule deer (*Odocoileus hemionus*) from Wyoming and Oregon. J Wildl Dis. 2008;44(4):983-7.

Eisen RJ, Gage KL. Adaptive strategies of *Yersinia pestis* to persist during inter-epizootic and epizootic periods. Vet Res. 2009;40(2):1.

Eisen RJ, Petersen JM, Higgins CL, Wong D, Levy CE et al. Persistence of *Yersinia pestis* in soil under natural conditions. Emerg Infect Dis. 2008;14(6):941-3.

Feng N, Zhou Y, Fan Y, Bi Y, Yang R, Zhou Y, Wang X. *Yersinia pestis* detection by loop-mediated isothermal amplification combined with magnetic bead capture of DNA. Braz J Microbiol. 2018;49(1):128-37.

Fleck-Derderian S, Cooley KM, Nelson CA. Plague in disguise: the discovery of occult buboes on surgical procedure or autopsy. Vector Borne Zoonotic Dis. 2022;22(4):225-31.

Fleck-Derderian S, Nelson CA, Cooley KM, Russell Z, Godfred-Cato S, Oussayef NL, Oduyebo T, Rasmussen SA, Jamieson DJ, Meaney-Delman D. Plague during pregnancy: a systematic review. Clin Infect Dis. 2020;70(70 Suppl 1):S30-S36.

Frank KM, Schneewind O, Shieh WJ. Investigation of a researcher's death due to septicemic plague. N Engl J Med. 2011;364(26):2563-4.

Gage KL, Kosoy MY. Natural history of plague: perspectives from more than a century of research. Annu Rev Entomol. 2005;50:505-28.

Galimand M, Carniel E, Courvalin P. Resistance of *Yersinia pestis* to antimicrobial agents. Antimicrob Agents Chemother. 2006;50(10):3233-6.

Girard G. Considerations sur une souche de *Pasteurella pestis*, isolee a partir d'un cheval au Congo Belge. Son etroit apparentement a la souche EV (Girard et Robic). Bull Soc Pathol Exot. 1957;50:346-50.

Godfred-Cato S, Cooley KM, Fleck-Derderian S, Becksted HA, Russell Z, Meaney-Delman D, Mead PS, Nelson CA. Treatment of human plague: a systematic review of published aggregate data on antimicrobial efficacy, 1939-2019. Clin Infect Dis. 2020;70(70 Suppl 1):S11-9.

Gordon DH, Isaacson M, Taylor P. Plague antibody in large African mammals. Infect Immun. 1979;26(2):767-9.

Gould LH, Pape J, Ettestad P, Griffith KS, Mead PS. Dog-associated risk factors for human plague. Zoonoses Public Health. 2008;55(8-10):448-54.

Harbeck M, Seifert L, Hänsch S, Wagner DM, Birdsell D et al. *Yersinia pestis* DNA from skeletal remains from the 6(th) century AD reveals insights into Justinianic Plague.PLoS Pathog. 2013;9(5):e1003349.

Hinckley AF, Biggerstaff BJ, Griffith KS, Mead PS. Transmission dynamics of primary pneumonic plague in the USA. Epidemiol Infect. 2012;140(3):554-60.

Hoogland JL, Biggins DE, Blackford N, Eads DA, Long D, Rodriguez MR, Ross LM, Tobey S, White EM. Plague in a colony of Gunnison's prairie dogs (*Cynomys gunnisoni*) despite three years of infusions of burrows with 0.05% deltamethrin to kill fleas. J Wildl Dis. 2018;54(2):347-51.

Houhamdi L, Lepidi H, Drancourt M, Raoult D. Experimental model to evaluate the human body louse as a vector of plague.J Infect Dis. 2006;194(11):1589-96.

Jones SD, Atshabar B, Schmid BV, Zuk M, Amramina A, Stenseth NC. Living with plague: Lessons from the Soviet Union's antiplague system. Proc Natl Acad Sci U S A. 2019;116(19):9155-63.

Jullien S, de Silva NL, Garner P. Plague transmission from corpses and carcasses. Emerg Infect Dis. 2021;27(8):2033-41.

Kehrmann J, Popp W, Delgermaa B, Otgonbayar D, Gantumur T, Buer J, Tsogbadrakh N. Two fatal cases of plague after consumption of raw marmot organs. Emerg Microbes Infect. 2020;9(1):1878-80.

Kool JL.Risk of person-to-person transmission of pneumonic plague. Clin Infect Dis. 2005;40(8):1166-72.

Kortepeter M, Christopher G, Cieslak T, Culpepper R, Darling Ret al., editors. Medical management of biological casualties handbook [online]. 4th ed. United States Department of Defense; 2001. Plague.Available at: http://www.dhhr.wv.gov/oeps/disease/Documents/USAMRIID_BlueBook.pdf.* Accessed 19 Nov 2002.

Leslie T, Whitehouse CA, Yingst S, Baldwin C, Kakar F et al. Outbreak of gastroenteritis caused by *Yersinia pestis* in Afghanistan. Epidemiol Infect. 2011;139(5):728-35.

Macy DW. Plague. In: Greene CE, editor. Infectious diseases of the dog and cat. Philadelphia: W.B. Saunders; 1998. p. 295-300.

Macy DW. Plague. In: Kirk RW, Bonagura JD. Current veterinary therapy X. Small animal practice. Philadelphia: WB Saunders; 1989. p. 1088-91.

Marshall JD Jr, Harrison DN, Murr JA, Cavanaugh DC. The role of domestic animals in the epidemiology of plague. 3. Experimental infection of swine. J Infect Dis. 1972;125(5):556-9.

Matchett MR, Stanley TR, Mccollister MF, Eads DA, Boulerice JT, Biggins DE. Oral sylvatic plague vaccine does not adequately protect prairie dogs (*Cynomys* spp.) for endangered black-footed ferret (*Mustela nigripes*) conservation. Vector Borne Zoonotic Dis. 2021;21(12):921-40.

Miarinjara A, Bland DM, Belthoff JR, Hinnebusch BJ. Poor vector competence of the human flea, *Pulex irritans*, to transmit *Yersinia pestis*. Parasit Vectors. 2021;14(1):317.

Mize EL, Britten HB. Detections of *Yersinia pestis* east of the known distribution of active plague in the United States. Vector Borne Zoonotic Dis. 2016;16(2):88-95.

Neerinckx S, Bertherat E, Leirs H. Human plague occurrences in Africa: an overview from 1877 to 2008.10. Trans R Soc Trop Med Hyg. 2010;104(2):97-103.

Nichols MC, Ettestad PJ, Vinhatton ES, Melman SD, Onischuk L, Pierce EA, Aragon AS. *Yersinia pestis* infection in dogs: 62 cases (2003-2011). J Am Vet Med Assoc. 2014;244(10):1176-80.

Nyirenda SS, Hang'ombe BM,,Kilonzo BS, Kabeta MN, Cornellius M, Sinkala Y. Molecular, serological and epidemiological observations after a suspected outbreak of plague in Nyimba, eastern Zambia. Trop Doct. 2017;47(1):38-43.

Nyirenda SS, Hang'ombe BM, Kilonzo B, Kangwa HL, Mulenga E, Moonga L. Potential roles of pigs, small ruminants, rodents, and their flea vectors in plague epidemiology in Sinda District, Eastern Zambia J Med Entomol. 2017;54(3):719-25.

Orloski KA, Lathrop SL. Plague: a veterinary perspective. J Am Vet Med Assoc. 2003;222(4):444-8.

Park YH, Remmers EF, Lee W, Ombrello AK, Chung LK, et al. Ancient familial Mediterranean fever mutations in human pyrin and resistance to *Yersinia pestis*. Nat Immunol. 2020;21(8):857-67.

Pennisi MG, Egberink H, Hartmann K, Lloret A, Addie D, et al. *Yersinia pestis* infection in cats: ABCD guidelines on prevention and management. J Feline Med Surg. 2013;15(7):582-4.

Piarroux R, Abedi AA, Shako JC, Kebela B, Karhemere S et al. Plague epidemics and lice, Democratic Republic of the Congo Emerg Infect Dis. 2013;19(3):505-6.

Porter RS, Kaplan JL, editors. The Merck Manual [online]. . Whitehouse Station, NJ: Merck and Co.; 2009. Plague and other *Yersinia* infections. Available at: http://www.merckmanuals.com/professional/infectious_diseases/gram-negative_bacilli/plague_and_other_yersinia_infections.html#v1007213. Accessed Sept 2013.

Prentice MB, Rahalison L. Plague. Lancet. 2007;369(9568):1196-207.

Public Health Agency of Canada. Material Safety Data Sheet – Yersinia pestis. Office of Laboratory Security; 2001 Mar. Available at: https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment/yersinia-pestis-material-safety-data-sheets-msds.html. Accessed 16 September 2013.

Rahelinirina S, Rajerison M, Telfer S, Savin C, Carniel E, Duplantier JM. The Asian house shrew *Suncus murinus* as a reservoir and source of human outbreaks of plague in Madagascar. PLoS Negl Trop Dis. 2017;11(11):e0006072.

Randremanana R, Andrianaivoarimanana V, Nikolay B, Ramasindrazana B, Paireau J, et al. Epidemiological characteristics of an urban plague epidemic in Madagascar, August-November, 2017: an outbreak report. Lancet Infect Dis. 2019;19(5):537-45.

Randriantseheno LN, Rahantamalala A, Randrianierenana AL, Rajerison M, Andrianaivoarimanana V. Development and evaluation of loop-mediated isothermal amplification for detection of *Yersinia pestis* in plague biological samples. PLoS One. 2020;15(8):e0237655.

Ratsitorahina M, Rabarijaona L, Chanteau S, Boisier P. Seroepidemiology of human plague in the Madagascar highlands. Trop Med Int Health. 2000;5(2):94-8.

Renapurkar DM. *Suncus murinus*. Observations on ecology, distribution, status to plague in Bombay. J Hyg Epidemiol Microbiol Immunol. 1989;33(1):45-9.

Rocke TE, Pussini N, Smith SR, Williamson J, Powell B, Osorio JE. Consumption of baits containing raccoon pox-based plague vaccines protects black-tailed prairie dogs (*Cynomys ludovicianus*). Vector Borne Zoonotic Dis. 2010;10(1):53-8.

Rocke TE, Williamson J, Cobble KR, Busch JD, Antolin MF, Wagner DM. Resistance to plague among black-tailed prairie dog populations. Vector Borne Zoonotic Dis. 2012;12(2):111-6.

Roth JD. Sylvatic plague management and prairie dogs - a meta-analysis. J Vector Ecol. 2019;44(1):1-10.

Roug A, Engebretsen K, van Wettere A, Young JK. Disease surveillance of cougars (*Puma concolor*) in Utah, USA. J Wildl Dis. 2023;59(1):197-201.

Runfola JK, House J, Miller L, Colton L, Hite D, Hawley A, Mead P, Schriefer M, Petersen J, Casaceli C, Erlandson KM, Foster C, Pabilonia KL, Mason G, Douglas JM Jr; Centers for Disease Control and Prevention (CDC). Outbreak of human pneumonic plague with dog-to-human and possible human-to-human transmission--Colorado, June-July 2014. MMWR Morb Mortal Wkly Rep. 2015;64(16):429-34.

Russell RE, Tripp DW, Rocke TE. Differential plague susceptibility in species and populations of prairie dogs. Ecol Evol. 2019;9(20):11962-71.

Salkeld DJ, Stapp P. Seroprevalence rates and transmission of plague (*Yersinia pestis*) in mammalian carnivores. Vector Borne Zoonotic Dis. 2006;6(3):231-9.

Schaffer PA, Hershkowitz CS, Dowers KL, Golchanour JL, Harris LJ, Aboellial TA, Morley PS, Brault SA, Pabilonia KL, Mason GL, House JA, Daniels JB. Delayed diagnosis of fatal pneumonic canine plague: clinical and pathologic features in two naturally infected Colorado dogs. BMC Vet Res. 2020;16(1):160.

Stenseth NC, Atshabar BB, Begon M, Belmain SR, Bertherat E et al. Plague: past, present, and future. PLoS Med. 2008;5(1):e3.

St Romain K, Tripp DW, Salkeld DJ, Antolin MF. Duration of plague (*Yersinia pestis*) outbreaks in black-tailed prairie dog (*Cynomys ludovicianus*) colonies of northern Colorado. Ecohealth. 2013;10(3):241-5.

Sun W, Roland K, Curtiss R 3rd. Developing live vaccines against plague. J Infect Dev Ctries. 2011;5(9):614-27.

Tourdjman M, Ibraheem M, Brett M, Debess E, Progulske B et al. Misidentification of *Yersinia pestis* by automated systems, resulting in delayed diagnoses of human plague infections--Oregon and New Mexico, 2010-2011.Clin Infect Dis. 2012;55(7):e58-60.

Tovar Padua L, Kamali A, Kim H, Green NM, Civen R, et al. Unique case of disseminated plague with multifocal osteomyelitis. J Pediatric Infect Dis Soc. 2017;6(3):e165-8.

United States Geological Survey (USGS). National Wildlife Health Center. Sylvatic plague immunization in black-footed ferrets and prairie dogs. USGS; 2008 Oct. Available at: http://www.nwhc.usgs.gov/disease_information/sylvatic_plague/index.jsp.* Accessed 7 Oct 2009.

Urich SK, Chalcraft L, Schriefer ME, Yockey BM, Petersen JM. Lack of antimicrobial resistance in *Yersinia pestis* isolates from 17 countries in the Americas, Africa, and Asia. Antimicrob Agents Chemother. 2012;56(1):555-8.

von Reyn CF, Barnes AM, Weber NS, Hodgin UG. Bubonic plague from exposure to a rabbit: a documented case, and a review of rabbit-associated plague cases in the United States. Am J Epidemiol. 1976;104(1):81-7.

von Reyn CF, Barnes AM, Weber NS, Quan T, Dean WJ. Bubonic plague from direct exposure to a naturally infected wild coyote. Am J Trop Med Hyg 1976; 25:626-9.

Wang H, Cui Y, Wang Z, Wang X, Guo Z et al. A dog-associated primary pneumonic plague in Qinghai Province, China. Clin Infect Dis. 2011;52(2):185-90.

Williams ES, Thorne ET, Quan TJ, Anderson SL. Experimental infection of domestic ferrets (*Mustela putorius furo*) and Siberian polecats (*Mustela eversmanni*) with *Yersinia pestis*. J Wildl Dis. 1991;27(3):441-5.

Wolfe LL, Shenk TM, Powell B, Rocke TE. Assessment of a recombinant F1-V fusion protein vaccine intended to protect Canada lynx (*Lynx canadensis*) from plague. J Wildl Dis. 2011;47(4):888-92.

Wong D, Wild MA, Walburger MA, Higgins CL, Callahan M et al. Primary pneumonic plague contracted from a mountain lion carcass. Clin Infect Dis. 2009;49(3):33-8.

* Link defunct

