

Plague is a zoonotic disease that affects humans and other mammals. Plague is known for having killed millions of people in Europe during the Middle Ages. Plague exists in many areas of South America, Africa, Eastern Europe and Asia. In the United States, plague occurs primarily in ground squirrels, prairie dogs, and other rodents in the western part of the country. Sporadic human cases occur, usually after exposure to wild rodents and/or their fleas. In recent decades, an average of seven human plague cases have been reported each year in the US.¹ Domestic cats have been a common source of exposure to human cases of primary pneumonic plague since 1977.^{2, 3}

A. Agent:

Yersinia pestis is a gram negative bacillus bacterium.^{2, 3}

B. Clinical Description:⁴

The three most common types of plague are bubonic, pneumonic, and septicemic. Initial symptoms are nonspecific and include: fever, chills, malaise, myalgia, nausea, sore throat, headaches, and weakness. Untreated bubonic plague has a case fatality rate of 50–60%; untreated pneumonic and septicemic plague are always fatal.

Bubonic plague - An acute lymphadenitis in the lymph nodes that drain from the flea bite site. Nodes become swollen, tender and may produce pus. Dissemination of the infection may result in septicemia and/or pneumonic plague presentations.

Pneumonic plague - Inhalation of respiratory droplets or artificially generated aerosols (i.e., bioterrorism) causing pneumonia with pleural effusion. **It is the only form of plague that is transmissible person-to-person and it is highly contagious possibly leading to localized outbreaks.**

Septicemic plague - Dissemination of the infection into the bloodstream.

- Differential Diagnosis:
Tularemia

C. Reservoirs:

Wild rodents and their fleas can carry *Y. pestis*. Lagomorphs (i.e., rabbits and hares), wild carnivores and domestic cats may also be a source of infection.^{2, 5}

D. Mode of Transmission:

Bubonic and septicemic plague is transmitted through the bite of an infected flea or by handling tissue of an infected animal. Pneumonic plague **is the only form of plague that is transmissible person-to-person; it is** transmitted by direct contact with respiratory droplets or sputum of an infected person and/or animal or through intentional release of *Y. pestis* in an act of bioterrorism.^{2, 5}

E. Incubation Period:

Ranges from 1–7 days for bubonic plague; average 1–4 days for pneumonic.²

F. Period of Communicability:

Pneumonic plague cases are infectious throughout their symptomatic illness and for 48 hours following initiation of appropriate antibiotic therapy. Person-to-person transmission of plague has occurred after patients with unrecognized pneumonic plague came into close (<6 feet) contact with family members, medical providers, or others.⁸ Any discharge from bubonic plague lesions should be considered infectious.^{2, 3}

G. Susceptibility and Resistance:

Natural infection provides temporary immunity. Immunization provides immunity that is believed to be of short benefit (i.e., approximately 6 months).²

H. Treatment:

A variety of antimicrobial classes are effective for plague. Antibiotics should be given within the first 24 hours of symptom onset. FDA-approved antimicrobials for treatment and prophylaxis of plague include streptomycin, ciprofloxacin, levofloxacin, moxifloxacin, and doxycycline. Although gentamicin, chloramphenicol, and trimethoprim-sulfamethoxazole are not FDA approved for plague, they are considered to be effective on the basis of clinical experience and animal data.^{2, 3, 6, 7, 8} Several same-class alternatives to first-line fluoroquinolones, aminoglycosides, and tetracyclines can be used to expand the repertoire of treatment and prophylaxis options to meet surge capacity, if needed.

Treatment and prophylaxis of the different clinical forms of plague (pneumonic, bubonic, septicemic, pharyngeal, and meningal) may differ and should be taken into consideration.⁸ For example, doxycycline is the preferred first-line treatment for bubonic and pharyngeal plague, while is an alternative treatment for septicemic and pneumonic plague. For patients with severe septicemic or pneumonic disease, clinicians should institute dual therapy with two distinct antimicrobial classes, with narrowing of therapy to a single antimicrobial after clinical improvement.

Clinicians should also use their judgment and CDC's guidelines to decide whether to initiate parenteral or oral antimicrobials to treat patients with plague, depending on the severity of disease and whether the patient can tolerate oral medications.⁸ Patients initially treated intravenously can be transitioned to the oral route, if deemed appropriate by the health care team, when clinical improvement is apparent.

Special populations, including pregnant or lactating women, neonates, the elderly, immunocompromised, and obese patients, have [unique considerations](#) that should be addressed when recommending antimicrobial treatment and prophylaxis for plague. These populations exhibit physiologic differences that might influence their susceptibility to plague and severity of disease as well as their metabolism of and response to certain antimicrobial regimens.⁸

I. Clinical Case Definition:⁹

An illness characterized by acute onset of fever as reported by the patient or healthcare provider with or without one or more of the following specific clinical manifestations:

- Regional lymphadenitis (bubonic plague)
- Septicemia (septicemic plague)
- Pneumonia (pneumonic plague)
- Pharyngitis with cervical lymphadenitis (pharyngeal plague)
- Plague meningitis is an uncommon clinical manifestation, reported to occur among 0.2%–7% of patients with naturally occurring plague (meningeal plague)

J. Laboratory Criteria for Diagnosis:⁹

Confirmatory Testing

- **Isolation of *Yersinia pestis* from a clinical specimen** with culture identification validated by a secondary assay (e.g., bacteriophage lysis assay, direct fluorescent antibody assay) as performed by a CDC or Laboratory Response Network (LRN) laboratory*; OR
- Fourfold or greater change in paired serum **antibody titer** to *Yersinia pestis* F1 antigen.

*CDC and ASPHL positive cultures are routinely confirmed with a secondary assay. Clinical laboratories using automated blood culture systems may not use secondary assays and so their results may not be confirmatory.

Presumptive Testing

- Elevated serum antibody titer(s) to *Yersinia pestis* fraction 1 (F1) antigen (without documented fourfold or greater change) in a patient with no history of plague vaccination; OR
- Detection of *Yersinia pestis* specific DNA or antigens, including F1 antigen, in a clinical specimen by direct fluorescent antibody assay (DFA), immunohistochemical assay (IHC), or PCR.

Note: Other laboratory tests, including rapid bedside tests, are in use in some low resourced international settings but are not recommended as laboratory evidence of plague infection in the United States.

Epidemiologic Linkage

- Person that is epidemiologically linked to a person or animals with confirmatory laboratory evidence within the prior two weeks;
- Close contact with a confirmed pneumonic plague case, including but not limited to presence within two meters of a person with active cough due to pneumonic plague; OR

- A person that lives in, or has traveled within two weeks of illness onset to a geographically localized area with confirmed plague epizootic activity in fleas or animals as determined by the
- relevant local authorities.

Case Classification: Refer to the [ADHS Case Definition Manual](#) ⁹

K. Classification of Import Status:⁹

A case is considered imported if the person became infected outside of the United States. This should be considered when there is opportunity for exposure and epidemiological evidence more suggestive of infection elsewhere. A case may also be imported from one state into another, or one local jurisdiction into another. All opportunities for exposure and epidemiological evidence should be documented for assessment of import status.

L. Laboratory Testing:

- Clinical samples that may be submitted to ASPHL for identification of *Yersinia pestis* include whole blood in EDTA and sputum
- Acceptable autopsy specimens are: abscess material, biopsy of lymph node, lung, liver, spleen and bone marrow scrapings
- Acceptable animal samples: aspirates, necropsy specimens, abscess material, biopsy of lymph node, lung, liver, spleen, bone marrow scrapings.
- Consider collecting an additional specimen to send concurrently to Translational Genomics Research Institute (TGen) for genetic analysis (note: sending specimens from ASPHL after identification of a select agent is very difficult)
- Serological testing is available at CDC for difficult or unusual cases. Specimens sent to CDC must have prior authorization from the ADHS VBZD team (vbzd@azdhs.gov).

TEST	SPECIMEN TYPE	TRANSPORT	AVAILABILITY
PCR	Clinical: Isolate (liquid or plated), blood, serum, bronchial wash, transtracheal aspirate, sputum, nasopharyngeal swab	If being tested for PCR ONLY then ship on dry ice and store at -70°C.	ASPHL
	Environmental: Powder, environmental swab		
Culture	Clinical: Bronchial wash, transtracheal aspirate, sputum, blood, tissue	If being tested for BOTH culture and PCR then ship on wet ice at 2-8°C.	ASPHL
	Environmental: Water, soil (mud), air, plants (green/wood), food/drink, paper, powder, environmental swabs, containers, vectors (mosquito, fleas, ticks)		
DFA	Serum, lymphoid aspirate, tissue smear, tissue biopsy, blood in blood culture bottle, bronchial/tracheal wash, isolate, bone	Transport on wet ice or a cool pack.	CDC

M. Assessing Laboratory Results:

Cultures are identified by observing typical colonial morphology. Typical colonies are presumptively identified by use of a Real-Time PCR. A positive PCR test is considered presumptive positive for plague. Cultures are held for 5-7 days before reporting as negative. All presumptive positive results are reported to the submitting agency and to the ADHS VBZD Team. Cultures suspected of containing Plague are tested and confirmed using conventional biochemicals. A positive isolate of *Y. pestis* will be forwarded to CDC for additional confirmation.

N. Outbreak Definition:

There are no formal outbreak definitions; however, the investigator may consider the possibility of an outbreak when there is an unusual clustering of cases in time and/or space. Notify ADHS VBZD team immediately.

Investigation Guidelines

O. Time Frame of Reporting: ¹¹

Healthcare providers should submit a report through an electronic reporting system authorized by the Department or by telephone within 24 hours after a case or suspect case is diagnosed, treated, or detected or an occurrence is detected.

Laboratories should submit a report immediately after receiving one specimen for detection of the agent. Report the receipt of subsequent specimens within five working days after receipt. Submit a report within 24 hours after obtaining a positive test result. Laboratories should also submit an isolate of the organism for each positive culture, if available, or a specimen for each positive test result to the Arizona State Laboratory within one working day.

P. Investigation and Reporting Formats:

Please refer to the Department-provided formats for submitting Epidemiologic Investigation Reports [[Excel](#)] for guidance on the required investigation fields and forms for the relevant morbidity. All the investigation forms can be found on the [ADHS Forms for Reporting and Investigation](#).

Q. Investigation Steps:

▪ Confirm Diagnosis

- i. Before contacting the patient or family, determine what information has been released about the patient's diagnosis and identify if the needed epidemiologic data can be found in the medical record alone.
- ii. Obtain information that supports clinical findings in the case definition and information on the onset date of the symptoms.
 - a. **Identify if it could be a pneumonic plague case** (this is the only form of plague that is transmissible person to person, **see Contact Management and Isolation Restriction sections**)
- iii. Obtain information on any laboratory tests performed and results.
- iv. For hospitalization, obtain medical records, including admission notes, progress notes, lab report(s), and discharge summary.
- v. Inform program manager of suspect case.

▪ **Conduct Case Investigation**

Epidemiological investigation reports should be submitted in MEDSIS by filling out the full DSO and Travel Table and follow these steps:

- i. To help identify the source of the infection, the investigator should focus within the 1–7 days before onset on the following potential source(s) of infection.
 - Recent travel history in an endemic plague area – Include detailed information on method of travel and itinerary for cases with primary pneumonic plague during the 1–4 days prior to symptom onset.
 - Handling the carcasses of wild animals, especially burrowing rodents, rabbits or hares, coyotes, or other carnivores.
 - Handling of a sick cat or history of flea bites from an endemic area.
 - Contact with individuals with confirmed, presumptive or suspect plague.
 - Occupation and location of workplace; primarily indoors, outdoors or both.
- ii. Examine the possibility of a bioterrorism event based on information available. Report suspicions to proper authorities (be sure to alert the program manager who can then inform the appropriate preparedness staff, bureau chief, and Federal Bureau of Investigation [FBI] partners).
- iii. Public health interventions may be needed to limit contact to a potential source of infection.
- iv. Report all cases to ADHS VBZD Team.

IMPORTANT: With no known endemic exposure through residence, occupation, or recent travel, refer to Managing Special Situations.

▪ **Conduct Contact Investigation^{2,8}**

- Consider the following contacts:
 - Bubonic case contact: Persons exposed to the fleas, blood or wound exudate, of a case or animal that has or is suspected of having bubonic plague.
 - **Pneumonic case contact: Persons within 2 meters (6 to 7 feet) of an infectious, coughing pneumonic plague patient or their respiratory secretions in the past 7 days.**
 - In epidemic conditions in which fleas are known to be involved, household members and sexual partners should be considered contacts and evaluated for treatment and/or disinfection needs.
- Establish and maintain a detailed line list of all cases and contacts with accurate identifying and locating information.
- Refer contacts for proper prophylaxis therapy (if necessary) and place under medical surveillance for fever and cough for 7 days after exposure. Pre-exposure prophylaxis for first responders and health care providers who care for patients with pneumonic plague is not considered necessary as long as standard and droplet precautions can be maintained.⁸
- First-line pre- and postexposure prophylaxis for adults potentially exposed to *Yersinia pestis* include ciprofloxacin, levofloxacin, moxifloxacin, and doxycycline. Pre-exposure prophylaxis can be discontinued 48 hours after the last perceived exposure. Recommended duration for postexposure prophylaxis is 7 days.⁸

▪ Isolation and Restrictions²

- i. Cases with **pneumonic plague** should **be on strict respiratory isolation until they have been on appropriate antimicrobial therapy for at least 48 hours.**
 - Strict isolation includes: reverse air exchange, gown, gloves and mask. If the original hospital does not have these resources, arrangements to transfer the case to a facility with adequate resources should be made.
- ii. Household contacts and close contacts of pneumonic plague cases that refuse chemoprophylaxis must be quarantined with close supervision for 7 days.
- iii. Cases with bubonic drainage should be managed with standard universal precautions up to 48 hours after the start of appropriate antibiotic treatment.
- iv. There are no restrictions for contacts of bubonic plague cases.

▪ Case Management²

Pneumonic cases: Follow up to verify that the case has completed treatment and is no longer symptomatic.

▪ Contact Management^{2, 8}

- i. Contacts, pneumonic plague: All contacts developing a temperature of >101°F or a new cough within 6 days of exposure are treated as a suspect case and instructed to seek medical treatment to promptly begin parenteral antibiotic treatment.
- ii. Provide chemoprophylaxis to all asymptomatic contacts.⁸
 - First-line pre- and postexposure prophylaxis for adults potentially exposed to *Yersinia pestis* include ciprofloxacin, levofloxacin, moxifloxacin, and doxycycline. Pre-exposure prophylaxis can be discontinued 48 hours after the last perceived exposure. Recommended duration for postexposure prophylaxis is 7 days.
 - If the contact refuses prophylaxis or is unable to take antibiotics because of contraindications, they must be maintained under quarantine for 7 days and placed on fever watch.
 - Follow-up should focus on determining if the contact has completed chemoprophylaxis and is asymptomatic for 7 days after last exposure.
- iii. Based upon evaluation, contacts of bubonic cases may need treatment; if no treatment is necessary, they should be placed under active surveillance for 7 days after last known contact date.

▪ Environmental and Non-pharmaceutical Control Measures^{2, 3}

- i. Disinfect articles contaminated with blood, sputum or purulent discharges from confirmed, probable and suspected cases.
- ii. Use an effective insecticide to eliminate all fleas from the patient, clothing, and living quarters, as well as from any domestic animals.
- iii. Discourage rodents from developing residence in or close to human dwellings and reduce rodent populations.
- iv. If rodent destruction is necessary, implement only after satisfactory flea control measures have been accomplished.
- v. Apply insect repellents to skin and clothing.
- vi. Handle dead animals with gloves.
- vii. Use appropriate biosafety precautions in laboratories dealing with plague specimens. Alert laboratory personnel when plague is suspected.

▪ Education

The public in enzootic areas or travelers to such areas should be educated on the modes of human and domestic animal exposure. As opportunities allow, the following general messages should be distributed:

- Importance of rat proofing buildings and appropriately storing and disposing of food, garbage, and refuse.
- Avoid flea bites by use of insecticide.
- For rural plague areas, warnings should be issued not to camp near rodent burrow and to avoid handling rodents.
- Dogs and cats in enzootic areas or transported to such areas should be treated with appropriate insecticides.
- Wear gloves when handling animal carcasses.

R. Outbreak Guidelines

N/A

Special Situations

S. Special Situations:

Bioterrorism Potential:⁸

- *Yersinia pestis* is a category A biological agent. Category A biological agents are known to have the following properties:
 - Can be easily disseminated or transmitted from person to person.
 - Result in high mortality rates and have the potential for major public health impact.
 - Might cause public panic and social disruption.
 - Require special action for public health preparedness.
- *Y. pestis* is a potential bioterrorism weapon. Because of the rarity of naturally occurring primary pneumonic plague, a single case should cause one to consider the possibility of bioterrorism or other criminal intentional act.
 - However, it should be noted that plague is endemic in parts of AZ, especially around the 4-corners area of the SW US and cases of pneumonic plague have been reported (most often due to exposure to felines – mountain lions, cats, etc).
- The first indication of terrorist attack causing plague infections would most likely be a sudden outbreak of illness presenting as severe pneumonia and sepsis. Sudden appearance of many persons with fever, cough, shortness of breath, hemoptysis, and chest pain with gastrointestinal symptoms common (e.g., nausea, vomiting, abdominal pain, and diarrhea) and patients have fulminant course and high mortality.
- If you suspect that you are dealing with a bioterrorism situation, notify your program manager or supervisor immediately.

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