VDH VIRGINIA DEPARTMENT OF HEALTH

Virginia Department of Health
Plague: Guidance for Healthcare Providers
Key Medical and Public Health Interventions
after Identification of a Suspected Case

Contents

1. Epidemiology

Plague is a rare but serious illness caused by *Yersinia pestis*, which are small gram-negative, rod-shaped bacteria with a safety pin appearance. The disease is maintained in nature by wild rodents (e.g., ground squirrels, prairie dogs, chipmunks, wood rats, deer mice and voles) and rabbits and hares that serve as the reservoir and the flea vector. Wild carnivores that consume infected animals or domestic animals that interact with infected wildlife or fleas can also become infected. Humans most commonly acquire the infection through the bite of infected fleas, but they can also become infected through direct contact with contaminated tissue, body fluids, or inhalation of respiratory droplets from animals or humans with pneumonic plague.

There are three main clinical forms of plague: bubonic, septicemic, and pneumonic plague. Bubonic plague, characterized by enlarged, painful lymph nodes (buboes), is the most common form. It usually results from being bitten by infected fleas. Septicemic plague, which can occur as the first symptom of plague or develop secondarily from untreated bubonic plague, typically results from being bitten by infected fleas or handling an infected animal. Pneumonic plague, which is the most serious form and the only form in which the bacteria can spread from person to person, can develop after inhaling contaminated respiratory droplets from infected animals or people or from untreated bubonic or septicemic plague. The infectious dose is very low, requiring less than 100 colony-forming units to be inhaled.

Rare forms of plague include pharyngeal, meningitic, cutaneous, ocular, and gastrointestinal.

Plague occurs worldwide and human infections are more common in areas with persistent wild rodent infections. Plague occurs in:

- The Americas - northeastern Brazil, the Andean region near the border of Ecuador and Peru, and the western half of the United States

- East-central and southern Africa, and African countries bordering the Mediterranean Sea - including Botswana, the Democratic Republic of Congo (DRC), Kenya, Madagascar, Malawi, Mozambique, the United Republic of Tanzania, Uganda, Zambia, Zimbabwe, and Algeria
- Central, southwestern, and southeastern Asia - plague is endemic in China, India, Lao People's Democratic Republic, Mongolia, Myanmar, Viet Nam, and Indonesia
- Extreme southeastern Europe near the Caspian Sea

Outbreaks occasionally appear in areas that have been free of the disease for many decades. Since the beginning of the 1990s, there has been an increase in the annual incidence of human cases of plague; moreover, the disease has reappeared in countries where it had not been reported for decades. Currently, the distribution of plague coincides with the geographical distribution of its natural foci.

Globally, approximately 1,700 cases are reported each year. From 2004–2009, 99.7% of cases were reported from 8 African countries. DRC has the most active foci of plague worldwide, averaging more than 1,000 suspected cases a year since 2004; following the eruption of several severe outbreaks of pneumonic plague in DRC, the diagnosis is now systematically evoked when a deadly outbreak with hemorrhagic signs is reported in Central Africa.

In the United States, an average of 7 cases (range 1–17) are reported each year. Over 80% of these are bubonic plague. These cases typically occur in one of two regions: 1) Northern New Mexico, northern Arizona, and southern Colorado and 2) California, southern Oregon, and far western Nevada. Plague does not occur naturally in Virginia and no cases of plague have been reported in Virginia since the nineteenth century.

Risk factors for plague include traveling to plague-endemic areas and camping, hunting, or hiking in areas where plague-infected animals reside. Veterinarians or pet owners who handle infected domestic cats (which are particularly susceptible to plague), hunters who handle infected wild animals, and laboratorians who handle plague cultures might be at increased risk if personal protective equipment is not used or appropriate procedures are not followed. If travel history does not implicate a possible source of exposure, bioterrorism might be suspected. Early indications that plague might have been used as a biological weapon include the occurrence of cases in locations not known to have enzootic infection, the occurrence of cases in persons without known risk factors, the absence of prior rodent deaths, or sudden outbreak of illness in patients presenting with severe pneumonia and sepsis.

If plague is suspected or confirmed, the local health department must be notified immediately so that a public health investigation can be initiated. *Yersinia pestis* is designated as a Category A bioterrorism agent (i.e., one that is easily disseminated or transmitted with a higher rate of mortality than Category B bioterrorism agents) and a select agent, which means that possession, use or transfer of these bacteria requires registration with the Centers for Disease Control and Prevention (CDC) through the Federal Select Agent Program.

2. Clinical Manifestations

Although several different clinical forms of plague exist, the three main forms are described below. Acute fever, chills, headache, and malaise can be present with these three forms.

Bubonic Plague

- Incubation period: 2–8 days

- Signs and symptoms: Patients develop sudden onset of fever, headache, weakness, chills and swollen, extremely painful lymph nodes (buboes). Buboes generally develop in the nodes that drain the site of the initial infection (typically in the groin, axilla, or cervical region). Nausea, vomiting, and diarrhea are common. The lymphadenopathy of primary bubonic plague usually presents unilaterally. If untreated, patients can develop secondary septicemic plague or secondary pneumonic plague. This form usually results from the bite of an infected flea.

Pneumonic Plague

- Incubation period: 1–3 days
- Signs and symptoms: Patients develop high fever, malaise, headache, myalgia, lethargy, and productive cough of copious watery mucoid sputum that might be bloody, and chest pain. Pneumonia rapidly progresses to dyspnea, stridor, and cyanosis. Patients develop respiratory failure, shock, and ecchymosis (i.e., blood flows into subcutaneous tissue, marked by a purple discoloration of the skin). Gastrointestinal symptoms, such as nausea, vomiting, diarrhea, and abdominal pain, might be prominent with pneumonic plague. This form of plague usually results from inhaling respiratory droplets, but it can develop from untreated bubonic or septicemic plague.

Septicemic Plague

- Incubation period: Poorly defined, but may be approximately 1–7 days
- Signs and symptoms: Patients develop fever, chills, prostration, abdominal pain, nausea, and vomiting. Purpura and disseminated intravascular coagulation (DIC) are common. The disease progresses rapidly to septic shock, meningitis, and coma. Patients with septicemic plague might develop secondary pneumonic plague. Septicemic plague usually results from the bite of an infected flea or from handling an infected animal.

3. Laboratory Testing and Diagnosis

Notification when Plague is Suspected

If plague is suspected, the healthcare provider should notify the local health department immediately per Virginia's disease reporting regulations. The local health department will discuss options for public health testing. If VDH approves public health testing, specimens may be sent to Division of Consolidated Laboratory Services (DCLS) for testing. The health department will facilitate notification and shipment to DCLS. Specimens potentially containing *Y. pestis* should never be shipped to DCLS without prior approval.

Laboratory Biosafety

Laboratory personnel **must** be alerted if plague is suspected so that they can take appropriate precautions during processing. When plague is suspected, laboratory work should be performed within a Class II Biological Safety Cabinet (BSC) and using biosafety level 3 (BSL-3) precautions, especially when performing activities with a high potential for droplet or aerosol production. BSL-3 precautions include wearing personal protective equipment (PPE) (e.g., gown, gloves, and face/eye protection) and respiratory protection. Because of the highly infectious nature of this organism, consultation with DCLS is strongly recommended. The DCLS Emergency Officer can be reached 24 hours a day/7 days a week at 804-335-4617.

Sample Collection

Sample collection instructions for testing at DCLS (and potentially at CDC) are shown in Table 1. Because of the highly infectious nature of this organism, consultation with DCLS about specimen

collection and handling is required. The DCLS Emergency Officer can be reached 24 hours a day/7 days a week at 804-335-4617.

Table 1. Sample collection for suspected cases of plague and testing at DCLS*

Laboratory Test and Turnaround Time	Samples	Amount	Instructions
Yersinia pestis culture and identification (culture, direct fluorescent antibody, bacteriophage lysis) Estimated turnaround time: 3-5 business days for culture confirmation (at DCLS) upon specimen receipt	Lower respiratory tract specimens (e.g., sputum, tracheal aspirate, broncheoalveolar lavage [BAL] fluid, pleural fluid)	>1 mL	Store specimens containing suspected live bacteria at 2°–8°C to maintain viability. If processing is delayed, tissue samples should be directly frozen at -70°C. Anticoagulants such as heparin, citrate and EDTA are acceptable because they do not inhibit the viability of bacteria. Respiratory specimens, lymph node aspirates, blood, tissue/biopsy/autopsy/necropsy specimens should all be transported at 4°C. Swabs must be in a Cary-Blair or Amies medium, not frozen.
	Aspirate, tissue, or biopsy specimen	≥1 mL for aspirate	
	Ulcer swabs	>2 swabs	
	Animal necropsy specimens (lymph node, lung, liver, or spleen)	N/A	
	Acute and convalescent serum (performed at CDC only)	>2 mL each	
Yersinia pestis serology Estimated turnaround time: 14 business days upon specimen receipt	Respiratory specimen (nasopharyngeal [NP] swab, BAL, tracheal aspirate, sputum)	1 swab	An acute serum specimen should be taken as early in the illness as possible. A convalescent sample should be collected 4–6 weeks or more after disease onset. Sera may be stored at 2°–8°C for up to 14 days. If testing is delayed for a longer period, serum samples should be frozen.
Yersinia pestis PCR Estimated turnaround time: 1 business day upon specimen receipt	Clinical isolate	Isolate slant or plate	Place respiratory sample or NP swab in a sterile container (do not use transport media). Store specimens at 4°C and ship on cold packs as soon as possible.
	Environmental sample	N/A	Store and ship at room temperature in a sealed container.

*Adapted from American Society for Microbiology (ASM)'s Sentinel level clinical laboratory guidelines for suspected agents of bioterrorism and emerging infectious diseases: *Yersinia pestis* (2016). If plague is suspected, notify the local health department immediately to discuss the case and laboratory testing. If VDH approves public health testing, specimens may be sent to Division of Consolidated Laboratory Services (DCLS) with the DCLS Request Form; include the name of the test on the form (e.g., *Yersinia pestis* serology). For questions about collecting specimens, contact the DCLS Emergency Officer available 24/7 at 804-335-4617.

Diagnosis
Confirmation of plague relies on the isolation and identification of *Y. pestis* in a clinical specimen (e.g., lymph node aspirate, blood, sputum) or detecting a 4-fold or greater change in serum antibody titer to *Y. pestis* F1 antigen. A presumptive diagnosis can be made based on an elevated antibody titer to *Y. pestis* F1 antigen (without a 4-fold or greater change in acute and convalescent specimens), detection of F1 antigen by fluorescent assay, or microscopic visualization of bipolar-staining, ovoid, gram-negative organisms with a "safety pin" appearance. For situations in which live organisms cannot be cultured (e.g., postmortem situations), samples of lymphoid, spleen, lung, and liver tissue or bone marrow samples can be tested by direct fluorescent antibody (DFA) or PCR.

Case Definitions used by Public Health
The current CDC case definition for plague is available at https://ndc.services.cdc.gov/conditions/plague/. Note that a case definition is a set of uniform criteria used to define a disease for public health surveillance. Case definitions enable public health to classify and count cases consistently across reporting jurisdictions and they should not be used by healthcare providers to determine how to meet an individual patient's health needs.

4. Treatment

Because untreated plague can be rapidly fatal, early diagnosis and treatment are critical. As soon as plague is suspected, appropriate (intravenous) antibiotic therapy should be initiated. Gentamicin and fluoroquinolones are typically first-line treatments. The duration of treatment is 10 to 14 days; treatment duration can be extended for patients with ongoing fever or other concerning signs or symptoms. Oral therapy may be substituted once the patient improves. The antibiotic regimen guidelines from CDC are in the 2021 MMWR titled, "Antimicrobial Treatment and Prophylaxis of Plague: Recommendations for Naturally Acquired Infections and Bioterrorism Response." Treatment tables from this reference are as follows:

- TABLE 1. Treatment of adults and children with pneumonic or septicemic plague
- TABLE 2. Treatment of adults and children with bubonic or pharyngeal plague
- TABLE 3. Treatment of patients of all ages and pregnant women with plague meningitis
- TABLE 5. Treatment of pregnant women with pneumonic, septicemic, bubonic, or pharyngeal plague
- TABLE 7. Treatment of neonates aged ≤28 days with pneumonic or septicemic plague
- TABLE 8. Treatment of neonates aged ≤28 days with bubonic or pharyngeal plague

These are only guidelines and treatment might need to be adjusted depending on a patient's age, medical history, underlying health conditions, or allergies.

5. Preexposure Prophylaxis

Preexposure prophylaxis for first responders and health care providers who will care for patients with pneumonic plague is not considered necessary if standard and droplet precautions can be maintained. In cases of surgical mask shortages, patient overcrowding, poor ventilation in hospital wards, or other situations, preexposure prophylaxis might be warranted if sufficient supplies of antimicrobials are available. Prophylaxis can be discontinued 48 hours after the last perceived exposure. Preexposure prophylaxis guidelines from CDC are found in "Antimicrobial Treatment and Prophylaxis of Plague: Recommendations for Naturally Acquired Infections and Bioterrorism Response":

- TABLE 4. Pre- and postexposure prophylaxis for adults and children potentially exposed to Yersinia pestis
- TABLE 6. Pre- and postexposure prophylaxis for pregnant women potentially exposed to Yersinia pestis

6. Postexposure Prophylaxis

Postexposure prophylaxis (PEP) with oral antibiotics is indicated in people with known exposure to plague, such as close (< 6 feet), sustained contact with a patient or animal with pneumonic plague or direct contact with infected body fluids or tissues. PEP should be given for seven days after the last exposure and regimens recommended by CDC are found in "Antimicrobial Treatment and Prophylaxis of Plague: Recommendations for Naturally Acquired Infections and Bioterrorism Response":

- TABLE 4. Pre- and postexposure prophylaxis for adults and children potentially exposed to Yersinia pestis
- TABLE 6. Pre- and postexposure prophylaxis for pregnant women potentially exposed to Yersinia pestis
- TABLE 9. Postexposure prophylaxis for neonates aged ≤28 days potentially exposed to Yersinia pestis

Those who are taking PEP should be under public health surveillance for 7 days. Individuals who develop a fever or cough should seek prompt medical treatment. Contacts who refuse prophylaxis should be placed under strict quarantine with careful surveillance for 7 days.

7. Vaccination

A vaccine for plague is not commercially available in the United States.

8. Infection Control

Standard Precautions should be used for all types of plague. For patients with pneumonic signs, the patient should also be isolated and placed on Droplet Precautions until the patient has received at least 48 hours of appropriate antibiotic therapy. Droplet Precautions include putting a mask on the patient (if tolerated) when transporting the patient and healthcare workers wearing a mask upon entering the patient's room. If large numbers of patients make isolation impractical, pneumonic plague patients may be cohorted. Hospital rooms should receive terminal cleaning consistent with standard precautions. Clothing and linens contaminated with the body fluids of pneumonic plague patients should be disinfected per hospital protocol.

9. Decontamination

Y. pestis is sensitive to sunlight and heating and does not survive long outside its host. There is no evidence to suggest that environmental decontamination following an aerosol release is warranted. A plague aerosol is estimated to remain viable for approximately 1 hour after release. In laboratory settings, surfaces can be disinfected using a fresh solution of 10% bleach.

10. Postmortem Practices

If plague is suspected as a cause of death, the District Office of the Chief Medical Examiner should be notified immediately. Consultation should occur regarding whether an autopsy should be conducted, parties responsible for conducting the autopsy, and proper personal protective procedures to follow. Contact with and transport of the body should be limited to trained personnel.

Standard precautions should be used for postmortem practices. These include using a surgical scrub suit, surgical cap, impervious gown or apron with full sleeve coverage, a form of eye protection (e.g., goggles or face shield), shoe covers, and double surgical gloves with an interposed layer of cut-proof synthetic mesh. Personnel should wear N-95 respirators during autopsies. Powered air-purifying respirators (PAPRs) equipped with N-95 or high-efficiency particulate air (HEPA) filters should be considered for postmortem practices. Bodies infected with biological terrorism agents including *Y. pestis* should not be embalmed. Aerosol-generating procedures should be avoided.

11. Public Health Measures

- Suspected or confirmed cases of plague should be reported immediately to the local health department.
- Laboratory specimens should be sent to DCLS for confirmation and other studies after consultation and approval by VDH.
- VDH should conduct an epidemiologic investigation that includes the following activities:
    - Collecting detailed information from the patient about his or her exposure history (including travel, animal contact and flea bites, and contact with other ill persons) and possible sources of infection.
    - Identifying contacts of the case-patient for compatible illness to identify a potential common exposure and assess the need for PEP and further public health follow-up.
    - As appropriate, recommending appropriate PEP for close contacts. Placing household and face-to-face contacts of pneumonic plague patients under surveillance for 7 days. Individuals who develop a fever or cough should seek prompt medical treatment. Contacts who refuse prophylaxis should be placed under strict quarantine with close surveillance for 7 days.
    - Implementing control measures to prevent disease and additional exposures.
- VDH will work with CDC and other state or federal agencies as necessary for the public health investigation. If bioterrorism is suspected, VDH will work with the Federal Bureau of Investigation (FBI).

12. References and Resources

American Academy of Pediatrics. “Plague” In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2021-2024 Report of the Committee on Infectious Diseases.* 32nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2021. Accessed online April 5, 2023.

American Society for Microbiology (ASM). Sentinel Level Clinical Laboratory Guidelines for Suspected Agents of Bioterrorism and Emerging Infectious Diseases: *Yersinia pestis* (revised March 2016). Accessed online April 7, 2023. https://asm.org/ASM/media/Policy-and-Advocacy/LRN/Y-pestis-fixed-figures.pdf

Bertherat E, Gage K. Plague. In: Heymann DL, ed. *Control of Communicable Diseases Manual.* 21st ed. Washington, DC: American Public Health Association; 2022. Accessed online March 9, 2023.

CDC. Emergency Preparedness and Response: Plague Information. Accessed online April 7, 2023. https://emergency.cdc.gov/agent/plague/index.asp

CDC. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings (Last update May 2022). Accessed online April 7, 2023. http://www.cdc.gov/hicpac/2007IP/2007isolationPrecautions.html

CDC. Human Plague: FAQs. Accessed online April 13, 2023. https://www.cdc.gov/plague/faq/index.html#mortality.

CDC. Human Plague: Transmission from person to person. Accessed online April 7, 2023. https://www.cdc.gov/plague/resources/Human-Plague-508.pdf

CDC. Maps and Statistics: Plague in the United States. Accessed online April 7, 2023. https://www.cdc.gov/plague/maps/index.html

CDC. Medical Examiners, Coroners, and Biologic Terrorism: A Guidebook for Surveillance and Case Management. MMWR. 2004; 53: RR-8. Accessed online April 7, 2023. http://www.cdc.gov/mmwr/pdf/rr/rr5308.pdf

CDC. Meechan P, Hatcher B, and Potts J eds. *Biosafety in Microbiological and Biomedical Laboratories*. 6th edition. June 2020. Accessed online April 2, 2023. https://www.cdc.gov/labs/BMBL.html

CDC. National Notifiable Diseases Surveillance System Case Definitions. Accessed online April 7, 2023. https://ndc.services.cdc.gov/conditions/plague/

CDC. Plague. Accessed online April 7, 2023. https://www.cdc.gov/plague/

Inglesby TV, Dennis DT, Henderson DA, et al. Plague as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *JAMA.* 2000; 283(17):2281-2290.

Koirala J. Plague: disease, management, and recognition of act of terrorism. *Infect Dis Clin North Am.* 2006; 20(2):273-287, viii.

Kool JL. Risk of person-to-person transmission of pneumonic plague. *Clin Infect Dis.* 2005;40(8):1166-1172.

Nelson CA, Meaney-Delman D, Fleck-Derderian S, Cooley KM, Yu PA, Mead PS. Antimicrobial Treatment and Prophylaxis of Plague: Recommendations for Naturally Acquired Infections and Bioterrorism. MMWR Recomm Rep 2021;70(No. RR-3):1–27. DOI: http://dx.doi.org/10.15585/mmwr.rr7003a1

Pien BC, Saah JR, Miller SE, Woods CW. Use of sentinel laboratories by clinicians to evaluate potential bioterrorism and emerging infections. *Clin Infect Dis.* 2006; 42(9):1311-1324.

Rollins SE, Rollins SM, Ryan ET. *Yersinia pestis* and the plague. *Am J Clin Pathol.* 2003;119 Suppl:S78-85.

United States Department of Labor. Occupational Safety & Health Administration. Plague – Controls Accessed online April 5, 2023. https://www.osha.gov/SLTC/plague/controls.html

World Health Organization. Global distribution of natural plague foci as of March 2016. Accessed online April 13, 2023. plague-map-2016.png (1195×625) (who.int)