Virginia Department of Health
Plague: Guidance for Health Care 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 gram-negative, rod-shaped bacteria. The disease is maintained in nature by wild rodents 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 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.

Plague occurs worldwide and human infections are more common in areas with persistent wild rodent infections, including sub-Saharan Africa, northeastern Brazil, the Andean region near the border of Ecuador and Peru, central, southwestern and southeastern Asia, and extreme southeastern Europe near the Caspian Sea. Globally, approximately 1,700 cases are reported each year.

In the United States, an average of 7 cases (range 1–17) are reported each year. 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: 1–6 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: 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 strongly recommended. 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 plague cases 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.
	Blood**	>1 mL	
	Aspirate, tissue or biopsy specimen	≥1 mL for aspirate	
	Ulcer swabs	>2 swabs	
	Animal necropsy specimens (lymph node, lung, liver or spleen)		
Yersinia pestis serology	Acute and convalescent	>2 mL each	An acute serum specimen should be taken as early in the illness as possible. A convalescent sample

Estimated turnaround time: 14 business days upon specimen receipt	serum (performed at CDC only)		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	Respiratory specimen (nasopharyngeal (NP) swab, BAL, tracheal aspirate, sputum)	1 swab	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.
	Clinical isolate	Isolate slant or plate	Store and ship at room temperature.
	Environmental sample		Place in a sealed container and ship at room temperature.

* 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 Clinical Microbiology/ Virology 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.

** Collect whole blood in liquid blood culture bottles according to clinical laboratory guidelines. Store and ship specimens with cold packs to keep the specimen at 4°C.

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://wwwn.cdc.gov/nndss/conditions/plague/. Note that a case definition is 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, or until two days after fever subsides. Oral therapy may be substituted once the patient improves. The antibiotic regimen guidelines from CDC are listed in Table 2; 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. Postexposure Prophylaxis

Postexposure prophylaxis (PEP) with oral antibiotics is indicated in people with known exposure to plague, such as close contact with a pneumonic plague patient or direct contact with infected body fluids or tissues. Close contact is defined as anyone who has been within 6 feet of a patient with plague while they were coughing up blood. PEP should be given for seven days after the last exposure and regimens recommended by CDC are listed in Table 3.

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 quarantine for 7 days.

Table 2. Recommended antibiotic treatment for plague*

	Antibiotic	Dose	Route	Notes
Adults	Streptomycin	1 g twice daily	IM	Not widely available in the US
	Gentamicin	5 mg/kg once daily, or 2 mg/kg loading dose followed by 1.7 mg/kg every 8 hours	IM or IV	Not FDA approved but considered an effective alternative to streptomycin.[1] Due to poor abscess penetration, consider alternative or dual therapy for patients with bubonic disease.
	Levofloxacin	500 mg once daily	IV or PO	Bactericidal. FDA approved based on animal studies but limited clinical experience treating human plague. A higher dose (750 mg) may be used if clinically indicated.
	Ciprofloxacin	400 mg every 8-12 hours	IV	Bactericidal. FDA approved based on animal studies but limited clinical experience treating human plague.
	Doxycycline	100 mg twice daily or 200 mg once daily	IV or PO	Bacteriostatic, but effective in a randomized trial when compared to gentamicin.[2]
	Moxifloxacin	400 mg once daily	IV or PO	
	Chloramphenicol	25 mg/kg every 6 hours	IV	Not widely available in the United States.
Children[3]	Streptomycin	15 mg/kg twice daily (maximum 2 g/day)	IM	Not widely available in the United States.
	Gentamicin	2.5 mg/kg/dose every 8 hours	IM or IV	Not FDA approved but considered an effective alternative to streptomycin.[1] Due to poor abscess penetration, consider alternative or dual therapy for patients with bubonic disease.
	Levofloxacin	8 mg/kg/dose every 12 hours (max 250 mg per dose)	IV or PO	Bactericidal. This dosing regimen is based on the levofloxacin package insert and is recommended for pediatric patients <50 kg and ≥6 months of age. FDA approved based on animal studies but limited clinical experience treating human plague.
	Ciprofloxacin	15 mg/kg/dose every 12 hours (maximum 400 mg/dose)	IV	Bactericidal. FDA approved based on animal studies but limited clinical experience treating human plague.
		20 mg/kg/dose every 12 hours (maximum 500 mg/dose)	PO	

	Doxycycline	Weight < 45 kg: 2.2 mg/kg twice daily (maximum 100 mg/dose) Weight ≥ 45 kg: same as adult dose	IV or PO	Bacteriostatic, but FDA approved and effective in a randomized trial when compared to gentamicin.[2] No tooth staining after multiple short courses.[4]
	Chloramphenicol (for children > 2 years)	25 mg/kg every 6 hours (maximum daily dose, 4 g)	IV	Not widely available in the United States.
Pregnant women[3]	Gentamicin	Same as adult dose	IM or IV	See notes above
	Doxycycline	Same as adult dose	IV	See notes above
	Ciprofloxacin	Same as adult dose	IV	See notes above

*Adapted from CDC's Plague Resources for Clinicians at https://www.cdc.gov/plague/healthcare/clinicians.html. These regimens are guidelines only and might need to be adjusted depending on a patient's age, medical history, underlying health conditions, or allergies.

[1]Boulanger LL, Ettestad P, Fogarty JD, Dennis DT, Romig D, Mertz G. Gentamicin and tetracyclines for the treatment of human plague: Review of 75 cases in New Mexico, 1985–1999. Clin Infect Dis. 2004 38(5):663-669.

[2]Mwengee W, Butler T, Mgema S, Mhina G, Almasi Y, Bradley C, Formanik JB, Rochester CG. Treatment of plague with gentamicin or doxycycline in a randomized clinical trial in Tanzania. Clin Infect Dis. 2006 42(5):614-21.

[3]All recommended antibiotics for plague have relative contraindications for use in children and pregnant women; however, use is justified in life-threatening situations.

[4]Todd SR, Dahlgren FS, Traeger MS, Beltrán-Aguilar ED, Marianos DW, Hamilton C, McQuiston JH, Regan JJ. No visible dental staining in children treated with doxycycline for suspected Rocky Mountain spotted fever. J Pediatr. 2015 May;166(5):1246-51.

Table 3. Recommended antibiotic regimens for post-exposure prophylaxis for plague*

	Antibiotic	**Dose**	**Route**
Adults	Doxycycline	100 mg twice daily	PO
	Ciprofloxacin	500 mg twice daily	PO
Children	Doxycycline (for children ≥ 8 years)	Weight < 45 kg: 2.2 mg/kg twice daily (maximum daily dose, 200 mg) Weight ≥ 45 kg: same as adult dose	PO
	Ciprofloxacin	20 mg/kg twice daily (maximum daily dose, 1 g)	PO
Pregnant women	Doxycycline[1]	100 mg twice daily	PO
	Ciprofloxacin[1]	500 mg twice daily	PO

* Adapted from CDC's Plague Resources for Clinicians (https://www.cdc.gov/plague/healthcare/clinicians.html) and 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 May 3;283(17):2281-90.

[1]Doxycycline and ciprofloxacin are pregnancy categories D and C, respectively. PEP should be given only when the benefits outweigh the risks.

6. Vaccination

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

7. 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.

8. 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.

9. 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.

10. Public Health Measures

- Suspected or confirmed plague cases 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 quarantine 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).

11. References and Resources

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