

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

Table of Contents

1. Epidemiology	1
2. Clinical Manifestations.....	2
3. Specimen Collection and Laboratory Testing	2
4. Diagnosis.....	4
5. Treatment	4
6. Postexposure Prophylaxis.....	5
7. Vaccination	5
8. Infection Control.....	5
9. Decontamination	6
10. Postmortem Practices.....	6
11. Public Health Measures	6
12. References and Resources.....	7

1. Epidemiology

Plague is a rare but serious illness caused by *Yersinia pestis*, a gram-negative, bipolar-staining, non-motile, pleomorphic bacillus. Humans most commonly acquire the infection through the bites of infected fleas, but can also become infected through direct contact with contaminated tissue or inhalation of respiratory droplets. Plague in humans can present as different clinical forms, depending on the exposure, but the 3 most common forms are bubonic, pneumonic, and septicemic.

Human plague most commonly occurs when plague-infected fleas bite humans who then develop bubonic plague. Although most persons infected by this route develop bubonic plague, a small portion of untreated, infected persons might develop sepsis with no bubo, which is called septicemic plague. Neither bubonic nor septicemic plague spreads directly from person to person. A small percentage of patients with bubonic or septicemic plague might develop secondary pneumonic plague and can then spread the disease by respiratory droplets. Persons contracting plague by inhalation of respiratory droplets develop primary pneumonic 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, the western half of the United States (e.g., New Mexico, Arizona, Colorado, and California), 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, approximately 5–15 cases are reported each year. 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, 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 may be suspected. Early indications that plague may 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.

Yersinia pestis is designated as a Category A bioterrorism agent (i.e., easily disseminated or transmitted with a higher rate of mortality than Category B agents) and a select agent, which means that it could be developed as a bioterrorism agent and that possession, use or transfer of these organisms requires registration with CDC or USDA. If plague is suspected or confirmed, the local health department must be notified immediately so that a public health investigation can be initiated.

2. Clinical Manifestations

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. Patients may develop secondary septicemic plague or secondary pneumonic plague.

Primary Pneumonic Plague

- **Incubation Period:** 1–6 days
- **Signs and symptoms:** Patients exhibit acute and often fulminant onset of high fever, malaise, headache, myalgia, lethargy, and productive cough of copious watery mucoid sputum that may 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, may be prominent with pneumonic plague.

Septicemic Plague

- **Incubation Period:** Approximately 1–7 days
- **Signs and symptoms:** Patients exhibit acute onset of fever, chills, prostration, abdominal pain, nausea, and vomiting. Pupura and disseminated intravascular coagulation (DIC) are common. May progress rapidly to septic shock, meningitis, and coma. Patients may develop secondary pneumonic plague.

3. Specimen Collection and Laboratory Testing

Protocols for sentinel laboratories are no longer posted on the CDC website. The American Society for Microbiology (ASM) has agreed to take the lead in the development and dissemination of sentinel laboratory information. The ASM guidelines for specimen collection and laboratory testing for plague are available at <http://www.asm.org/images/PSAB/Ypestis.pdf> and are summarized in Table 1. Of note, the CDC's Infectious Diseases Laboratories still provides basic information on specimen requirements

and other supplemental information at <http://www.cdc.gov/laboratory/specimen-submission/list.html#Y>.

Laboratory personnel must be alerted if plague is suspected so that appropriate precautions can be taken. All work on clinical specimens or isolates suspicious of *Yersinia pestis* should be performed in a biological safety cabinet using biosafety level 2 (BSL-2) precautions. BSL-3 is recommended for activities with high potential for droplet or aerosol production, and for activities involving large-scale production or high concentrations of infectious materials. Because of the highly infectious nature of this organism, consultation with the state public health laboratory, Division of Consolidated Laboratory Services (DCLS), is strongly recommended. The DCLS Emergency Services Officer can be reached 24 hours a day/7 days a week at (804) 335-4617.

Specimens, ideally collected before initiating antibiotic treatment, should be sent to DCLS for initial testing and additional testing might also be conducted at CDC. Sample collection instructions for testing at DCLS are shown in Table 1.

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

Laboratory Test	Samples	Amount	Instructions
<i>Yersinia pestis</i> culture and identification (culture, direct fluorescent antibody, bacteriophage lysis)	Lower respiratory tract specimens (e.g., sputum, tracheal aspirate, bronchoalveolar lavage 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)		
<i>Yersinia pestis</i> serology	Acute and convalescent serum (performed at CDC only)	>2 mL each	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.

* Source: American Society for Microbiology (ASM). Sentinel level clinical laboratory guidelines for suspected agents of bioterrorism and emerging infectious diseases: *Yersinia pestis*. February 2014.

<http://www.asm.org/images/PSAB/Ypestis.pdf> (accessed December 9, 2014). If plague is suspected, notify the local health department immediately to discuss the case and laboratory testing (see www.vdh.virginia.gov/LHD/index.htm). Specimens should be sent to Division of Consolidated Laboratory Services (DCLS) after LHD has been consulted and testing has been approved by LHD/DCLS. The DCLS Emergency Duty Officer can be reached 24/7 at (804) 335-4617.

** Collect whole blood in bottles according to clinical laboratory guidelines. Store and ship specimens with cold packs to keep the specimen at 4°C (<http://emergency.cdc.gov/urdo/pdf/SpecCollectionGuidelines.pdf>, accessed December 9, 2014).

4. Diagnosis

Confirmation of plague relies on the isolation of *Y. pestis* from a clinical specimen, or 4-fold or greater change in serum antibody titer to *Y. pestis* F1 antigen. The current CDC case definition for plague is available at <http://www.cdc.gov/nndss/script/casedefDefault.aspx>. 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 should not be used by healthcare providers to determine how to meet an individual patient's health needs.

5. Treatment

As soon as plague is suspected, appropriate therapy should be initiated. The drugs of choice are streptomycin or gentamicin, but tetracyclines, fluoroquinolones and chloramphenicol are also effective. The regimens listed in Table 2 are guidelines only and may need to be adjusted depending on a patient's age, medical history, underlying health conditions, or allergies. Please note that recently Levaquin (levofloxacin) has been approved by FDA for treatment and prophylaxis of plague (<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm302220.htm>).

Table 2. Recommended antibiotic treatment for plague*

	Preferred agents	Dose	Route of administration
Adults	Streptomycin ¹	1 g twice daily	IM
	Gentamicin ¹	5 mg/kg once daily, or 2 mg/kg loading dose followed by 1.7 mg/kg every 8 hours	IM or IV
	Alternative agents	Dose	Route of administration
	Doxycycline	100 mg twice daily or 200 mg once daily	IV
	Ciprofloxacin	400 mg twice daily	IV
	Chloramphenicol ²	25 mg/kg every 6 hours	IV
	Children	Preferred agents	Dose
Streptomycin ¹		15 mg/kg twice daily (maximum daily dose, 2 g)	IM
Gentamicin ¹		2.5 mg/kg every 8 hours	IM or IV
Alternative agents		Dose	Route of administration
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	IV
Ciprofloxacin		15 mg/kg twice daily (maximum daily dose, 1 g)	IV
Chloramphenicol ² (for children > 2 years)		25 mg/kg every 6 hrs (maximum daily dose, 4 g)	IV
Pregnant	Preferred agent	Dose	Route of

women			administration
	Gentamicin ^{1,3}	Same as adult dose	IM or IV
	Alternative agents	Dose	Route of administration
	Doxycycline ⁴	Same as adult dose	IV
	Ciprofloxacin ⁴	Same as adult dose	IV

*Sources: 1) 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. 2) Koirala J. Plague: disease, management, and recognition of act of terrorism. External Web Site Icon Infect Dis Clin North Am. 2006 Jun;20(2):273-87, viii. (See CDC website at <http://www.cdc.gov/plague/healthcare/clinicians.html#treatment>).

¹Aminoglycoside dose should be adjusted in patients with impaired renal function.

²Chloramphenicol serum concentration should be 5-20 µg/mL to avoid bone marrow suppression.

³Gentamicin is pregnancy category C but has been used safely and effectively for treatment of plague in pregnant women.

⁴Doxycycline and ciprofloxacin are pregnancy categories D and C, respectively. These agents should be administered only if gentamicin is not available.

6. Postexposure Prophylaxis

Postexposure prophylaxis (PEP) is indicated in persons with known exposure to plague, such as close contact with a pneumonic plague patient or direct contact with infected body fluids or tissues. The recommended antibiotic regimens for PEP are listed in Table 3.

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

	Preferred agents	Dose	Route of administration
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: 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. (See CDC website at <http://www.cdc.gov/plague/healthcare/clinicians.html#treatment>).

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

7. Vaccination

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

8. Infection Control

Use standard precautions for all types of plague. For pneumonic plague, the patient should be isolated until the patient has received at least 48 hours of effective antibiotics and has improved clinically; droplet precautions (e.g., gown, gloves, eye protection, and disposable surgical masks) should also be instituted. If large numbers of patients make isolation impractical, pneumonic plague patients may be cohorted. Patients should wear surgical masks while they are being transported. 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. Laboratories should observe biosafety level 2 conditions. Activities with a high potential for aerosol or droplet production (e.g., centrifuging, grinding, vigorous shaking, animal studies) require biosafety level 3 conditions.

9. Decontamination

Y. pestis is very 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 would only 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 (see <http://www.vdh.virginia.gov/medExam/ContactUs.htm>). 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. Autopsy 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 plague cases should be reported immediately to the local health department.
- Laboratory specimens should be sent to the state public health laboratory (DCLS) for confirmation and other studies after consultation and approval. The DCLS Emergency Services Officer can be reached 24 hours a day/7 days a week at (804) 335-4617.
- Designated public health authority should begin an epidemiologic investigation. The activities include:
 - Collect detailed information from the patient about the source of the exposure, in particular history of animal contact and flea bites or contact with another ill person.
 - Identify and treat close contacts with an appropriate antibiotic.

- Put 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.
- Investigate contacts of the case-patient for compatible illness to identify a potential common exposure.
- Implement control measures to prevent disease and additional exposures.
- If appropriate, flea and rodent control should be a part of the investigation and follow-up.
- VDH will work with the CDC, Federal Bureau of Investigation (FBI) and other state or federal agencies as necessary.

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