

**Outline**

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By law, health care providers must report suspected or confirmed Plague to the local health department immediately (within 1 hr).

Even a single case of Plague is considered an outbreak and is a public health emergency.

To report: call SFDPH communicable disease control (24/7 Tel: 415-554-2830).

Upon receipt, SFDPH will initiate the public health response and can facilitate lab testing.

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## AGENT

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*Yersinia pestis* is one of the three pathogenic *Yersinia* species within the family *Enterobacteriaceae*. *Y. pestis* is a pleomorphic, nonmotile, nonsporulating, intracellular, gram-negative bacillus that has a characteristic bipolar appearance on Wright, Giemsa, and Wayson's stains. There are three virulent strains: *antiqua*, *medievalis*, and *orientalis*. A fourth strain, *microtus*, is nonvirulent.

The *Y. pestis* genome encodes for several virulence factors that enable the pathogen to survive and multiply within its hosts. Several proteins (F1, V, W, and Yops) inhibit phagocytosis, while the V antigen also facilitates survival within macrophages. Lipopolysaccharide endotoxin causes the classic features of endotoxic shock.

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## EPIDEMIOLOGY

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### **Plague as a Biological Weapon**

In the late 20<sup>th</sup> century, biological weapons programs in the United States and the Soviet Union developed techniques for aerosolizing *Y. pestis* in order to enhance its dissemination.

**Pneumonic plague** is thought to be the most likely clinical presentation in the event of a bioterrorist attack. Intentional release of aerosolized plague could result in an outbreak of pneumonic plague with a high case-fatality rate and the potential for widespread person-to-person transmission.

Aerosolized plague used as a bioweapon would be expected to have the following features:

- Previously healthy patients with severe, rapidly progressive pneumonia
- Many similar cases would occur, generally 2-4 days after release

- Acute multilobar pneumonia accompanied by hemoptysis, associated GI symptoms, and a fulminant clinical course would be very suspicious for pneumonic plague
- Buboes characteristic of bubonic plague would not be present
- No risk factors for plague exposure or recent travel to a plague-endemic region
- Lack of a recent, prior, local plague epizootic with rodent deaths

### **Naturally Occurring Plague**

**Reservoirs.** A number of animal species are the natural reservoirs for *Y. pestis*. Most are wild rodents, including rats, squirrels, mice, gerbils, guinea pigs, prairie dogs, and marmots. Humans are not part of the natural life cycle of *Y. pestis*. Disease occurrence in humans is dependent on the frequency of infection in local rodent populations and the degree of contact between rodents and humans. Naturally occurring outbreaks in humans usually are preceded by epizootics – i.e. large-scale deaths in susceptible animal hosts. Mammalian species other than rodents (e.g. cats, dogs, rabbits, deer) are also incidental hosts for *Y. pestis*, and can occasionally serve as sources of human exposure, either through direct contact or via flea vectors.

**Vectors.** The organisms most commonly are transmitted between animal reservoirs and to humans via bites of infected fleas, but may also occur via direct contact with infected animal carcasses. Pneumonic plague may be transmitted via inhalation of respiratory droplets from infected animals or persons.

Three bubonic plague pandemics have been recorded throughout history. The most recent began in 1894 in China and caused an estimated 12 million deaths. In California, small outbreaks of pneumonic plague with person-to-person spread occurred twice in the 20<sup>th</sup> century due to infected urban rat populations: 1919, Oakland (13 cases) and 1924, Los Angeles (39 cases).

Plague exists in wild rodent populations all over the Western United States and human cases continue to occur in persons exposed to them. Naturally occurring plague generally occurs during the summer months. From 1994 to 2003, 8 cases of plague were reported in California, and none of these occurred in San Francisco. Approximately 1,800 worldwide cases of plague are reported to the WHO annually, from all continents except Europe and Australia.

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## CLINICAL FEATURES

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The classic forms of plague are bubonic plague, septicemic plague, and pneumonic plague; these are presented in detail below. Other syndromes caused by *Y. pestis* infection include:

- **Plague meningitis.** Meningitis may occur as a complication of bacteremia and may be the presenting clinical syndrome for some cases.
- **Plague pharyngitis.** Plague pharyngitis is similar to severe pharyngitis or acute tonsillitis of other causes, with inflamed cervical nodes or a cervical bubo usually present.
- **Pestis minor.** Pestis minor is a milder form of bubonic plague in which the nodes drain and patients recover without therapy. Subclinical infections can occur, as well.

## Pneumonic Plague

*Y. pestis* can enter the lungs either through direct inhalation of respiratory droplets from infected humans or animals (primary pneumonic plague) or through hematogenous spread as a complication of bubonic or septicemic plague (secondary pneumonic plague).

<b>PRIMARY PNEUMONIC PLAGUE: CLINICAL FEATURES</b>	
<b>Incubation Period</b>	1-4 days (up to 6 days)
<b>Signs &amp; Symptoms</b>	Acute, often fulminant onset of: <ul style="list-style-type: none"> <li>• Fever, malaise, headache, myalgias</li> <li>• Associated GI symptoms including nausea, vomiting, diarrhea, and abdominal pain</li> <li>• Dyspnea, cyanosis, chest pain, and (in children) tachypnea</li> <li>• Productive cough, commonly with hemoptysis</li> </ul>
<b>Laboratory Findings</b>	<ul style="list-style-type: none"> <li>• CXR findings include alveolar infiltrates progressing to lobar consolidation, pleural effusion</li> <li>• Rarely, mediastinal widening on CXR due to adenopathy</li> <li>• Gram-negative bipolar bacilli usually visible on sputum gram stain</li> </ul>

## Bubonic Plague

*Y. pestis* survives in the flea midgut after a blood meal from an infected host. The organism is transmitted to a new host when the flea regurgitates into the bloodstream during its next feeding. *Y. pestis* migrates to regional lymph nodes where it causes hemorrhagic lymphadenitis, creating the swollen, painful buboes that are characteristic of bubonic plague. The organisms often enter the bloodstream, causing hemorrhagic lesions in other lymph nodes and organs.

<b>BUBONIC PLAGUE: CLINICAL FEATURES</b>	
<b>Incubation Period</b>	1-8 days
<b>Signs &amp; Symptoms</b>	<ul style="list-style-type: none"> <li>• Sudden onset of fever, chills, headache, lethargy</li> <li>• Painful swollen lymph node – a “bubo” - occurs in groin, axilla, and/or cervical region, proximal to the inoculation site</li> <li>• Buboes may suppurate and rupture</li> <li>• Skin lesions may occur at site of flea bite (i.e., papules, vesicles, pustules) but are present in &lt;10% of cases</li> <li>• Nausea, vomiting, and/or diarrhea are common</li> </ul> May progress to secondary pneumonic plague or secondary septicemic plague
<b>Laboratory Findings</b>	<ul style="list-style-type: none"> <li>• Elevated WBC with left shift</li> <li>• Gram-positive bipolar bacilli usually visible on smear of bubo aspirate</li> <li>• Additional findings correlate with progression to sepsis, pneumonia, and/or meningitis</li> </ul>

## Septicemic Plague

In primary septicemic plague there is systemic sepsis caused by *Y. pestis*, but without noticeable, preceding lymph node or pulmonary involvement. Up to 25% of naturally-occurring plague cases may present with primary septicemic plague. Secondary septicemic plague occurs commonly with either bubonic or pneumonic plague.

Septicemic plague causes a gram-negative sepsis syndrome with multiorgan involvement, DIC, and shock. In the late stages of infection, high-density bacteremia often occurs, with identifiable organisms on peripheral blood smear. Meningitis can occur and is characterized by a thick, purulent exudates in CSF.

<b>PRIMARY SEPTICEMIC PLAGUE: CLINICAL FEATURES</b>	
<b>Incubation Period</b>	1-4 days
<b>Signs &amp; Symptoms</b>	<ul style="list-style-type: none"><li>• Fever, chills, headache, malaise, and GI disturbances</li><li>• Purpuric skin lesions and gangrene of the distal digits (acral necrosis) are common</li><li>• May progress to meningitis and/or pneumonia</li><li>• Often progresses rapidly to septic shock, DIC, multi-organ failure, and death</li></ul>
<b>Laboratory Findings</b>	<ul style="list-style-type: none"><li>• Consistent with severe bacterial infection and sepsis</li><li>• Organisms may be identifiable on peripheral blood smear</li></ul>

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## DIFFERENTIAL DIAGNOSIS

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Diagnosis of plague during the initial stages requires a high index of suspicion because of the nonspecific, flu-like picture early in the disease. Early diagnosis is desirable as prompt administration of antibiotics can be critical to survival.

### Differential: Pneumonic Plague

The differential diagnosis of pneumonic plague includes any severe pneumonia, and should be considered in any case of severe gram-negative pneumonia.

**Key features that may help to distinguish plague pneumonia are:**

- **Bubo(es), if present (secondary pneumonic plague)**
- **No response to typical antibiotic therapy for community-acquired pneumonia**

Other conditions to consider:

- Community-acquired pneumonia (e.g. bacterial, *Mycoplasma*, *Legionella*, *Chlamydia*)
- Viral pneumonia (e.g. influenza, RSV, CMV, hantavirus)
- Q fever
- Inhalational anthrax

- Tularemia
- Ricin

### **Differential: Bubonic Plague**

**Key feature that may help to distinguish bubonic plague:**

- **Presence of painful adenitis (buboes) progressing to systemic disease.**

Other conditions to consider:

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|---|--------------------------------|
| • Cat scratch disease                         | • Lymphogranuloma venereum     |
| • Ulceroglandular tularemia                   | • Chancroid                    |
| • Staphylococcal or streptococcal adenitis    | • Primary genital herpes       |
| • Mycobacterial infection, including scrofula | • Strangulated inguinal hernia |

### **Differential: Septicemic Plague**

A key feature that may help to distinguish septicemic plague from other sepsis syndromes is the presence of painful adenitis (buboes). However, primary septicemic plagues may occur in the absence of buboes.

**Key feature that may help to distinguish septicemic plague:**

- **Presence of painful adenitis (buboes) progressing to systemic disease.** (However, primary septicemic plague may occur in the absence of buboes.)

Other conditions to consider:

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|------------------------|----------------|
| • Gram-negative sepsis | • Malaria      |
| • Meningococemia       | • Appendicitis |
| • Rickettsiosis        |                |

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## **LABORATORY DIAGNOSIS**

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There are no widely available, rapid diagnostic tests for plague. Initial identification of the organism relies on microscopic evaluation of blood, sputum, CSF, fluid aspirated from a bubo, or skin lesion scrapings (if a skin lesion is present).

Order a gram stain, culture, and Giemsa, Wright's, or Wayson stain of the material. Store and transport blood at room temperature. Transport other samples at room temperature, but store under refrigeration if transport time will be > 2 hours. If plague is highly suspected, order an additional blood culture for incubation at

**If you are testing or considering testing for Plague, you should:**

- **IMMEDIATELY notify SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830). SFDPH can authorize and facilitate testing, and will initiate the public health response as needed.**
- **Inform your lab that Plague is under suspicion. Some commercial bacterial test systems cannot reliably identify *Y. pestis*.**

room temperature which is optimal for *Y. pestis* growth. If a bubo is present, an aspirate may be obtained by inserting a 20-gauge needle on a 10-mL syringe, injecting 1-2 mL of sterile saline into the bubo, and withdrawing the fluid.

On gram stain, *Y. pestis* organisms appear as single cells or short chains of plump, gram-negative rods. With Giemsa, Wright's or Wayson stains, *Y. pestis* appears as a bipolar "closed safety pin" whereas this bipolar morphology may or may not be evident on Gram stain. Bipolar staining is not exclusive to *Y. pestis* however it is still considered to be suggestive of the diagnosis.

*Y. pestis* is slow-growing in culture. Cultures of blood, bubo aspirate, sputum, CSF, or skin lesion scrapings may not demonstrate growth until 48 hours after inoculation. Also, many commercial bacterial identification systems do not include *Y. pestis* in the identification databank or may misidentify *Y. pestis* as another enteric pathogen (*Y. pseudotuberculosis*, *Shigella*, *H<sub>2</sub>S-negative Salmonella*, or *Acinetobacter*). Consultation with SFDPH is advised if plague is suspected, in order to obtain bacteriological confirmation at an approved public health laboratory.

Direct fluorescent antibody (DFA) testing for *Y. pestis* capsular (F1) antigen may be helpful for presumptive plague identification in patient samples. Several serologic tests are available at CDC reference labs, including passive hemagglutination and ELISA tests. A single titer of more than 1:10 is presumptively positive for plague if the patient has not been vaccinated previously. With paired sera 4-6 weeks apart, a fourfold increase in titer is considered confirmatory.

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## TREATMENT AND PROPHYLAXIS

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**These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events ([www.sfdph.org/cdcp](http://www.sfdph.org/cdcp)).**

### Treatment of Plague

Supportive care and timely administration of antibiotics are the keys to successful management of plague. Plague pneumonia is almost always fatal if antibiotics are not begun within 12-24 hours of symptoms. Many patients would be expected to require intensive care with respiratory support owing to complications of gram-negative sepsis. In a contained casualty setting where the medical care delivery system can effectively manage the number of patients, IV antibiotics should be administered to all patients for 10 days (**Table 1**). Oral antibiotics can be substituted once the patient's condition improves. In a mass casualty setting where the medical care delivery system is not able to meet the demands for patient care, use of oral antibiotics may be necessary (**Table 2**).

Aminoglycosides are the drug of choice. Streptomycin is FDA-approved for plague. Gentamicin is not FDA-approved for plague, but has been used effectively and is recommended as an alternative to streptomycin. Tetracyclines, fluoroquinolones, and chloramphenicol are additional alternatives, albeit with potential for adverse events in children and pregnant women. Penicillins, cephalosporins, macrolides, rifampin, and aztreonam are ineffective. Natural antibiotic resistance

to the drugs of choice is rare, but genetically-engineered resistant strains could be encountered in a bioterrorism scenario.

<b>TABLE 1. TREATMENT OF PLAGUE IN THE CONTAINED CASUALTY SETTING</b>	
<b>Patient Category</b>	<b>Therapy Recommendation*</b>
<b>Adults: Preferred Choices</b>	Streptomycin, 1 gm IM q12 hrs† <i>or</i> Gentamicin, 5 mg/kg IM or IV once daily, or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV q8 hrs‡§
<b>Adults: Alternative Choices</b>	Doxycycline, 100 mg IV q12 hrs or 200 mg IV once daily§ <i>or</i> Ciprofloxacin, 400 mg IV q12 hrs §†† <i>or</i> Chloramphenicol, 25 mg/kg IV q6 hrs (max 4 g/day)‡‡
<b>Children: Preferred Choices</b>	Streptomycin, 15 mg/kg IM q12 hrs (max 2 g/day) <i>or</i> Gentamicin 2.5 mg/kg IM or IV q8 hrs ‡
<b>Children: Alternative Choices</b>	Doxycycline: ≥45 kg, give adult dosage <45 kg, give 2.2 mg/kg IV q12 hrs (max 200 mg/day) <i>or</i> Ciprofloxacin, 15 mg/kg IV q12 hrs (max 1 g/day) †† <i>or</i> Chloramphenicol, 25 mg/kg IV q6 hrs (max 4 g/day)‡‡ §§
<p>* Treatment duration is 10 days.            † In pregnant women, gentamicin is the only preferred choice; streptomycin can cause irreversible deafness in children exposed in utero.            ‡ Aminoglycoside doses must be further adjusted for newborns, and according to renal function.            § Acceptable for pregnant women. Although fetal toxicity may occur with doxycycline use, the recommendation is for doxycycline or ciprofloxacin if gentamicin is not available or if oral antibiotics must be used.            †† Other fluoroquinolones may be substituted at dosages appropriate for age.            ‡‡ Therapeutic concentration 5 - 20 mcg/mL; concentrations &gt;25 mcg/mL can cause reversible bone marrow suppression.            §§ According to the Working Group on Civilian Biodefense, children younger than 2 years of age should not receive chloramphenicol due to risk of 'gray baby syndrome'. However, the American Academy of Pediatrics (AAP) has recommended chloramphenicol as the drug of choice for plague meningitis in children.</p>	
<i>Source: Working Group on Civilian Biodefense. Inglesby TV, JAMA 2000; 283(17):2281-2290.</i>	

### **Prophylaxis of Persons Exposed to Plague**

Exposure is defined as proximity to aerosolized *Y. pestis* or close physical contact with a confirmed case. Close physical contact is defined as proximity less than 6.5 feet (2m) to a person who is symptomatic with plague and who has received <48 hours of appropriate antimicrobial therapy.

Household and health worker contacts should be considered exposed and receive prophylaxis. In the setting of an outbreak, certain persons with early, nonspecific symptoms such as fever >38.5°C or a new cough may be recommended to begin antimicrobial therapy, and those who develop fever or cough while receiving antibiotic prophylaxis may be recommended for immediate

evaluation and treatment of plague. **In the event of an outbreak, SFDPH will provide situational guidance on prophylaxis ([www.sfdph.org/cdcp](http://www.sfdph.org/cdcp)).**

<b>TABLE 2. TREATMENT OF PLAGUE IN THE MASS CASUALTY SETTING OR POST-EXPOSURE PROPHYLAXIS</b>	
<b>Patient Category</b>	<b>Therapy Recommendation*</b>
<b>Adults: Preferred Choices</b>	Doxycycline, 100 mg PO BID§ <i>or</i> Ciprofloxacin, 500 mg PO BID§††
<b>Adults: Alternative Choice</b>	Chloramphenicol, 25 mg/kg PO QID (max 4 g/day)‡‡
<b>Children: Preferred Choices</b>	Doxycycline: ≥45 kg, give adult dosage <45 kg, give 2.2 mg/kg PO BID (max 200 mg/day) <i>or</i> Ciprofloxacin, 20 mg/kg PO BID (max 1 g/day) ††
<b>Children: Alternative Choice</b>	Chloramphenicol, 25 mg/kg PO QID (max 4 g/day)‡‡ §§
<p>* Treatment duration in mass casualty setting is 10 days. Duration of post-exposure prophylaxis is 7 days.            § Acceptable for pregnant women.            †† Other fluoroquinolones may be substituted at dosages appropriate for age.            ‡‡ Therapeutic concentration 5 - 20 mcg/mL; concentrations &gt;25 mcg/mL can cause reversible bone marrow suppression.            §§ According to the Working Group on Civilian Biodefense, children younger than 2 years of age should not receive chloramphenicol due to risk of 'gray baby syndrome'.</p>	
<p><i>Source: Working Group on Civilian Biodefense. Inglesby TV, JAMA 2000; 283(17):2281-2290.</i></p>	

## **Vaccine**

A formaldehyde-killed whole bacilli vaccine was discontinued by its manufacturers in 1999 and is no longer available. Plans for future production are unclear. Research is ongoing in the pursuit of a vaccine that protects against primary pneumonic plague.

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## **INFECTIOUS DISEASE CONTROL\***

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**These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events ([www.sfdph.org/cdcp](http://www.sfdph.org/cdcp)).**

Pneumonic plague is spread from person-to-person by respiratory droplet transmission (coughing, sneezing). For patients with suspected or confirmed pneumonic plague, **Droplet** and **Standard Precautions** should be observed. Droplet Precautions should be maintained until 48-72 hours of antibiotics have been administered AND the patient is showing clinical improvement.

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\* For description of Precautions, see chapter on Infection Control

For suspected or confirmed bubonic plague, **Droplet, Contact** and **Standard Precautions** should initially be observed. Contact Precautions should be maintained until 48-72 hours of appropriate antibiotics have been administered AND the patient is showing clinical improvement.

Aerosol-generating procedures should be avoided if possible. Since plague is not transmitted by airborne particles, negative air pressure isolation rooms are not indicated except for aerosol-generating procedures. Multiple patients with pneumonic plague may be cohorted as long as all patients are receiving appropriate antimicrobial therapy.

In general, environmental decontamination following an aerosol event has not been recommended, since experts have estimated that an aerosol of *Y. pestis* organisms would be infectious for only about 1 hour. A recent study demonstrated that *Y. pestis* can survive on selected environmental surfaces for at least several days; however the potential for re-aerosolization of these organisms was not addressed. Commercially available bleach or 0.5% hypochlorite solution (1:10 dilution of household bleach) is considered adequate for cleaning.

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## REFERENCES

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AAP. The Red Book: 2003 Report of the Committee on Infectious Diseases. 26th ed. Elk Grove Village, IL; American Academy of Pediatrics; 2003; p.487.

CDC. Fatal human plague—Arizona and Colorado, 1996. MMWR 1997;46(27):617-20

CIDRAP. Plague: Current, comprehensive information on pathogenesis, microbiology, epidemiology, diagnosis, and treatment. April 14, 2005. ([www.cidrap.umn.edu](http://www.cidrap.umn.edu))

Franz DR, Jahrling PB, Friedlander AM, et al. Clinical recognition and management of patients exposed to biological warfare agents. JAMA 1997;278(5):399-411

Inglesby TV et al, for the Working Group on Civilian Biodefense. Plague as a biological weapon: medical and public health management. JAMA 2000;283(17):2281-90

Inglesby TV, et al. A plague on your city: observations from TOPOFF. Biodefense Quarterly 2000(2)

LA County DHS. Terrorism Agent Information and Treatment Guidelines for Clinicians and Hospitals. June 2003. ([www.labt.org/Zebra.asp](http://www.labt.org/Zebra.asp))

McGovern TW, Friedlander AM. Plague. In: Textbook of military medicine: medical aspects of chemical and biological warfare. ([www.vnh.org/MedAspChemBioWar/](http://www.vnh.org/MedAspChemBioWar/))

Rose LJ, Donlan R, Banerjee SN, et al. Survival of *Yersinia pestis* on environmental surfaces. Appl Environ Microbiol 2003 Apr;69(4):2166-71

WHO. Plague manual 1997: epidemiology, distribution, surveillance, and control. ([www.who.int/csr/resources/publications/plague/WHO\\_CDS\\_CSR\\_EDC\\_99\\_2\\_EN/en/](http://www.who.int/csr/resources/publications/plague/WHO_CDS_CSR_EDC_99_2_EN/en/))