Abstract: Plague as a Biological Weapon: Medical and Public Health Management

Abstracted from: Inglesby TV, Dennis DT, Henderson DA, et al. JAMA, May 3, 2000; vol. 283, no. 17: 2281-2290.

A working group of 25 representatives from major academic medical centers and research, government, military, public health, and emergency management institutions and agencies developed consensus-based recommendations for measures to be taken by medical and public health professionals following the use of plague as a biological weapon against a civilian population. Their consensus recommendations covered the following seven areas:

1. Pathogenesis and clinical manifestation
2. Diagnosis
3. Vaccination
4. Therapy
5. Postexposure prophylaxis
6. Infection control and environmental decontamination
7. Additional research needs

Background

- Plague is caused by *Yersinia pestis*. Naturally occurring human plague most commonly occurs when plague-infected fleas bite humans, who then develop bubonic plague. A small minority will develop sepsis with no bubo, a form of plague termed primary septicemic plague.
- Neither bubonic nor septicemic plague spreads directly from person to person.
- A small minority of persons with either bubonic or septicemic plague, however, will develop secondary pneumonic plague, and they can then spread the plague bacterium by respiratory droplet. Persons who inhale these droplets can develop so-called primary pneumonic plague. The last cast of human-to-human transmission of plague in the United States occurred in Los Angeles in 1924.
- Plague remains an enzootic infection of rats, ground squirrels, prairie dogs, and other rodents on every populated continent except Australia.
- Worldwide, an average of 1,700 cases have been reported annually for the past 50 years.
- In the United States, 390 cases of plague were reported from 1947 to 1996: 84% were bubonic; 13%, septicemic; and 2%, pneumonic. Case-fatality rates were 14%, 22%, and 57%, respectively. The majority of U.S. cases were in New Mexico, Arizona, Colorado, and California.
- The epidemiology of plague following its use as a biological weapon would differ substantially from that of naturally occurring infection. Intentional dissemination of plague would most likely occur via an aerosol of *Y. pestis*, resulting in a pneumonic plague outbreak. The size of the outbreak would depend on several factors, including the quantity of biological agent used, characteristics of the strain, environmental conditions, and methods of aerosolization.
- In 1970, World Health Organization (WHO) reported that, in a worst-case scenario, if 50 kg of *Y. pestis* were released over a city of 5 million, pneumonic plague could occur in as many as 150,000 persons, 36,000 of whom would be expected to die.
- Fatality rates would depend on various factors, including time between onset of symptoms and initiation of antibiotics, access to advanced supportive care, and the dose

of inhaled bacilli. The fatality rate of patients with pneumonic plague when treatment is delayed more than 24 hours after symptom onset is extremely high.

- Indications that plague had been artificially disseminated would be the occurrence of cases in locations not known to have enzootic infection, among individuals with no known risk factors (e.g., animal contact), and the absence of prior rodent deaths (historically, rats die in large numbers prior to human outbreaks, precipitating the movement of the infesting flea population from the rats to humans).

1. Pathogenesis and clinical manifestation of plague

- The bacteria migrate through cutaneous lymphatics to regional lymph nodes where they are phagocytosed but resist destruction. They rapidly multiply, causing destruction and necrosis of lymph node architecture with subsequent bacteremia, septicemia, and endotoxemia that can lead quickly to shock, disseminated intravascular coagulation, and coma.
- Following a deliberate attack, aerosolized inhaled *Y. pestis* bacilli would cause primary pneumonic plague, with the time from exposure to the development of first symptoms being 1-6 days and, most often, 2-4 days.
- The sudden appearance of a large number of previously healthy patients with fever, cough, shortness of breath, chest pain, and a fulminant course leading to death should immediately suggest the possibility of pneumonic plague or inhalational anthrax. The presence of hemoptysis in this setting would strongly suggest plague.
- The first sign of illness would be expected to be fever with cough and dyspnea, sometimes with the production of bloody, watery, or (less commonly) purulent sputum. Prominent gastrointestinal symptoms, including nausea, vomiting, abdominal pain, and diarrhea also might be present.
- Ensuing clinical findings of primary pneumonic plague are similar to those of any severe, rapidly progressing pneumonia, including bronchopneumonia: chest pain, dyspnea, cough, and hemoptysis. Unlike naturally occurring secondary pneumonic plague, there would be an absence of buboes—except, rarely, cervical buboes.

2. Diagnosis

- *Y. pestis* is a nonmotile, gram-negative bacillus, sometimes coccobacillus, that shows bipolar (also termed "safety pin") staining with Wrights, Giemsa, or Wayson stain. Direct fluorescent antibody testing may be positive. It is a lactose nonfermenter, urease and indole negative, and a member of the Enterobacteriaceae family.
- Newer, rapid diagnostic tests for plague—such as antigen detection, IgM enzyme immunoassay, immunostaining, and polymerase chain reaction (PCR)—are available only at some state health departments, CDC, and military laboratories. The routinely used passive hemagglutination antibody detection assay is mostly of retrospective value, because several days to weeks usually pass after disease onset before antibodies develop.
- Cultures of sputum, blood, or lymph node aspirate should demonstrate growth 24-48 hours after inoculation. *Y. pestis* grows optimally at 28°C on blood agar or MacConkey agar, but colonies are initially much smaller than other bacteria that may contaminate the specimen and may be overlooked.
- The laboratory should be notified that plague is suspected. The laboratory should split the culture, incubating one at 28°C for rapid growth and the second at 37°C for identification of the diagnostic capsular (F_1) antigen. Using this approach, up to 72 hours may be required to make the identification. Antimicrobial susceptibility testing should be performed at a reference laboratory.

- Pathological examination would reveal areas of profound lobular exudation and bacillary aggregation. Chest radiographs are variable, but bilateral infiltrates or consolidation are common.
- Laboratory studies may reveal leukocytosis with toxic granulations, coagulation abnormalities, aminotransferase elevations, azotemia, and other evidence of multiorgan failure.

3. Vaccination

- No vaccine of proven efficacy against primary pneumonic plague exists. The U.S.-licensed, formaldehyde-killed whole bacilli vaccine was discontinued by its manufacturers in 1999; this killed vaccine did not prevent or ameliorate the development of primary pneumonic plague.

4. Therapy for those exposed

- Recommendations for use of antimicrobials following a deliberate release of plague are made on the basis of limited knowledge: a few published trials on treating human plague and a limited number of animal studies. A further complication is the possibility that a large number of people will need treatment.
- In a contained casualty setting, where a modest number of people require treatment, the workgroup recommends parenteral antibiotic therapy. Preferred parenteral forms of the antimicrobials streptomycin or gentamicin are recommended.
- In a mass casualty setting, intravenous or intramuscular therapy may not be possible, so oral therapy, preferably with doxycycline (or tetracycline) or ciprofloxacin, should be administered.
- Patients with pneumonic plague will require substantial advanced medical supportive care. Complications of gram-negative sepsis would be expected, including adult respiratory distress syndrome, disseminated intravascular coagulation, shock, and multiorgan failure.

Working Group Recommendation for Treatment of Patients With Pneumonic Plague in the Contained and Mass Casualty Settings and for Postexposure Prophylaxis*

Patient Category	Recommended Therapy
Contained Casualty Setting	
Adults	**Preferred choices:** Streptomycin, 1g IM twice daily Gentamicin, 5 mg/kg IM or IV once daily or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV three times daily† **Alternative choices:** Doxycycline, 100 mg IV twice daily or 200 mg IV once daily Ciprofloxacin, 400 mg IV twice daily‡ Chloramphenicol, 25 mg/kg IV 4 times daily§

Children[‖]	**Preferred choices:** Streptomycin, 15 mg/kg IM twice daily (maximum daily dose 2 g) Gentamicin, 2.5 mg/kg IM or IV 3 times daily[†] **Alternative choices:** Doxycycline, If >= 45 kg, give adult dosage If < 45 kg, give 2.2 mg/kg IV twice daily (maximum 200 mg/dl) Ciprofloxacin, 15 mg/kg IV twice daily[‡] Chloramphenicol, 25 mg/kg IV 4 times daily[§]
Pregnant Women[¶]	**Preferred choice:** Gentamicin, 5 mg/kg IM or IV once daily or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV three times daily[†] **Alternative choices:** Doxycycline, 100 mg IV twice daily or 200 mg IV once daily Ciprofloxacin, 400 mg IV twice daily[‡]
Mass Casualty Setting and Postexposure Prophylaxis[#]	
Adults	**Preferred choices:** Doxycycline, 100 mg orally twice daily** Ciprofloxacin, 500 mg orally twice daily[‡] **Alternative choices:** Chloramphenicol, 25 mg/kg orally 4 times daily[§,††]
Children[‖]	**Preferred choices:** Doxycycline,** If >=45kg give adult dosage If <45 kg then give 2.2 mg/kg orally twice daily Ciprofloxacin, 20 mg/kg orally twice daily **Alternative choices:** Chloramphenicol, 25 mg/kg orally 4 times daily[§,††]
Pregnant Women[¶]	**Preferred choices:** Doxycycline, 100 mg orally twice daily and Ciprofloxacin, 500 mg orally twice daily **Alternative choices:** Chloramphenicol, 25 mg/kg orally 4 times daily[§,††]

* These are consensus recommendations of the Working Group on Civilian Biodefense and are not necessarily approved by the U.S. Food and Drug Administration. See "Therapy" section for explanations. One antimicrobial agent should be selected.

Therapy should continue for 10 days. Oral therapy should be substituted when the patient's condition improves. IM indicates intramuscularly; IV indicates intravenously.
†Aminoglycosides must be adjusted according to renal function. Evidence suggests that gentamicin, 5 mg/kg IM or IV once daily, would be efficacious in children, although this is not yet widely accepted clinical practice. Neonates up to 1 week of age and premature infants should receive gentamicin, 2.5 mg/kg IV twice a day.
‡ Other fluoroquinolones can be substituted at doses appropriate for age. Ciprofloxacin dosage should not exceed 1 g/d in children.
§ Concentration should be maintained between 5 and 20 µg/mL. Concentrations greater than 25 µl/mL can cause reversible bone marrow suppression.
|| Refer to "Management of Special Groups" for details. In children, ciprofloxacin dose should not exceed 1g/d, and chloramphenicol should not exceed 4g/d. Children younger then 2 years should not receive chloramphenicol.
¶ Refer to "Management of Special Groups" for details and discussion of breastfeeding women; in neonates, gentamicin-loading dose of 4 mg/kg should be given initially.
# Duration of treatment of plague in mass casualty setting is 10 days. Duration of postexposure prophylaxis to prevent plague infection is 7 days.
** Tetracycline could be substituted for doxycycline.
†† Children younger than 2 years should not receive chloramphenicol. Oral formulation available only outside the U.S.

5. Postexposure prophylaxis

- Once plague is confirmed or strongly suspected in a particular area, anyone in that area with fever (of 38.5°C or higher) or cough should immediately be treated with antimicrobials for presumptive pneumonic plague. Delaying therapy until tests confirm plague will greatly decrease the person's chance of survival.
- Doxycycline is the first-choice antibiotic for postexposure prophylaxis; other recommended antibiotics are included in the Table.
- Asymptomatic persons who have had household, hospital, or other close contact (2 meters or less) with persons with untreated pneumonic plague should receive postexposure prophylaxis for 7 days and be monitored for fever and cough. Tetracycline, doxycycline, sulfonamides, and chloramphenicol have been recommended for these individuals. On the basis of mice studies, fluoroquinolones might also be protective.
- Persons refusing prophylaxis should be closely monitored for the development of fever or cough for the first 7 days after exposure and should be treated immediately if either occurs.
- Clinical deterioration of patients despite early presumptive therapy could indicate antimicrobial resistance and should be promptly evaluated.
- Special measures should be taken for treatment or prophylaxis of those unaware of the outbreak or those requiring special assistance, such as persons who are homeless or who have cognitive disorders.

6. Infection control and decontamination of the environment

- National infection control guidelines recommend the use of disposable surgical masks to prevent transmission via respiratory droplets.
- Other respiratory droplet precautions (gown, gloves, and eye protection) also should be used by persons caring for pneumonic plague cases.
- Patients with pneumonic plague should be isolated until they have had at least 48 hours of antibiotic therapy and shown clinical improvement.
- 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 (centrifuging, grinding, vigorous shaking, animal studies) require biosafety level 3 conditions.
- Bodies of patients who have died should be handled with routine strict precautions. Aerosol-generating procedures (bone-sawing associated with surgery or post-mortem examinations) should be avoided.
- There is no evidence to suggest that environmental decontamination following an aerosol release is warranted. *Y. pestis* is very sensitive to sunlight and heating and does not survive long outside its host. According to the WHO analysis, a plague aerosol would be viable for 1 hour after release, long before the first cases would alert health personnel to a clandestine attack.

7. Additional research needs

- Additional knowledge about the organism, its genetics, and its pathogenesis will improve the ability to respond to a bioterrorist attack.
- Improved rapid diagnostic and standard laboratory microbiology techniques are necessary.
- Improved understanding of prophylactic and therapeutic regimens is needed.