



Infectious Disease Epidemiology Section
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PLAGUE

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Yersinia pestis is a nonmotile, gram-negative bacillus that belongs to the Enterobacteriaceae family.

Epidemiology

Y. pestis is maintained in complex enzootic and epizootic transmission cycles involving susceptible wild rodents and their fleas. Risk for plagues in humans is greatest when epizootics cause high mortality in commensal rat population, thereby forcing infected rat fleas *Xenopsylla cheopis* to seek alternative hosts, including humans.

Fleas: The most common mode of transmission of *Y. pestis* to humans is by the bite of infectious fleas. Some fleas are usually host specific others are more promiscuous. *Xenopsylla cheopis*, the oriental rat flea, the principal vector of urban plague is not very selective for its host. After the host death, fleas bail out in search for a new host. The bacilli multiply in the flea digestive tract and blockage occurs. A blocked flea makes repeated attempts to feed, blood is sucked into the esophagus, get mixed with the blocked contents than is regurgitated into the wound thus enhancing the transmission. At temperature $\geq 28^{\circ}\text{C}$, *X.cheopis* is able to lyse their intestinal blockage. Consequently, cleared fleas feed without regurgitation and are no longer very efficient vectors.

Rodents: More than 200 species are naturally infected with *Y. pestis* . Only a few pose significant risks to the human population.

Rattus rattus (the domestic black rat, house rat, roof rat) is the most dangerous. It is distributed throughout the world, living in close association with humans: nesting in attics, wall spaces. It breeds very well. It is an excellent host for *X.cheopis* and develops a fulminating fatal plague. In epizootics with the black rat and *X.cheopis*, both serve as amplifiers for *Y. pestis* . An epizootic may be identified by the unusual amount of dead rats found in an area (rat fall). IN some occasions, the rat population has become more resistant to plague and transmission of *Y. pestis* among the rodent population is not accompanied by large mortality.

Rattus norvegicus, the sewer rat is generally a burrowing rodent, living in cellar drains, drains, crawl spaces under houses, in the foundations. It lives around the houses but not directly in the houses. It provides an effective link between wild rodents and the domestic black rat.

Wild rodents: In the US the main wild rodents are ground squirrels (*Spermophilus*), prairie dogs (*Cynomys*) and chipmunks (*Tamias*). Prairie dogs are often sentinel animals, as they are extremely sensitive to *Yersinia pestis*. Outbreaks in rodent populations should be considered serious.

Prairie dogs and other rodents most often pass plague to cats. Lymph nodes on the cat may rupture in the hand of the owner, veterinarian, or a child. Bacteria on the hand can easily be transmitted to the face or enter the body through other cutaneous abrasions. Bubonic plague may become systemic, invading the

lungs and can be passed by droplets. Cat-associated human plague often results in the pneumonic form of plague in humans.

Other modes of transmission: direct contact with infectious body fluids or tissues while handling an infected animal whether hunted, captured or found dead; direct contact with an infected pet; ingestion of raw or undercooked meat from an infected animal (marmots or prairie dogs, goat and camel); The portal of entry may be a mucous membrane, conjunctiva or damaged skin.

Droplet transmission: Inhaling infectious respiratory droplets or other infectious materials (e.g., laboratory-generated aerosols containing *Y. pestis*) can cause infection. The contact has to be fairly close (2m) because *Y. pestis* is not a good airborne traveler. Bacilli contained in large 10-12 μm diameter become lodged in the oropharynx and cause pharyngeal plague and secondary septicemic plague. Smaller particles (1 μm or less) cause bronchopneumonia or lobar pneumonia.

Airborne transmission: *Y. pestis* does not survive well in the environment: at temperatures above 40 °C and when desiccated it dies rapidly. *Y. pestis* does not really get truly airborne and disseminate via ventilation system.

In the USA about 20% of plague cases have plague pneumonia. A few are primary plague pneumonias acquired from sick pet cats or a pet dog; most cases involved pneumonic involvement secondary to bubonic or septicemic plague. When a plague patient develops secondary plague pneumonia, person to person transmission becomes possible but rarely occurs. No person to person transmission of plague occurred in the USA since 1924. Louisiana has never reported a case of plague.

Environmental factors: Bubonic plague epidemics and rat enzootics occur at temperatures ranging from 10-26 °C with a relatively high humidity. On the other hand, wild rodent plague enzootics are more common in semi-arid regions. Sporadic cases of human plague transmitted from wildlife, are more common during the warmer months when there is increased flea and rat activity. Pneumonic plague epidemics occur usually in the winter when humidity and overcrowding are higher.

Because of bioterrorism possibility, pneumonic plague is a disease of concern. Pneumonic plague outbreaks are of special interest. Although pneumonic plague has rarely been the dominant manifestation of the disease, large outbreaks of pneumonic plague have occurred. In an outbreak in Manchuria in 1910-1911, as many as 60,000 persons developed pneumonic plague; a second large Manchurian pneumonic plague outbreak occurred in 1920-1921. As would be anticipated in the preantibiotic era, nearly 100% of these cases were reported to be fatal. Reports from the Manchurian outbreaks suggested that indoor contacts of affected patients were at higher risk than outdoor contacts and that cold temperature, increased humidity, and crowding contributed to increased spread. In northern India, there was an epidemic of pneumonic plague with 1400 deaths reported at about the same time. While epidemics of pneumonic plague of this scale have not occurred since, smaller epidemics of pneumonic plague have occurred recently. In 1997 in Madagascar, 1 patient with bubonic plague and secondary pneumonic infection transmitted pneumonic plague to 18 persons, 8 of whom died.

Plague in the USA: Although plague has enzootic foci among wild rodent populations in North America from the Pacific coast eastward to Texas, Oklahoma, Kansas, and the Dakotas, human cases have been concentrated in two principal regions:

- 1) a southwestern area that includes New Mexico, northeastern Arizona, southern Colorado, and southern Utah
- 2) a Pacific Coast region located in California, Oregon, and western Nevada.

In the United States, 341 cases of plague in humans were reported to CDC during 1970-1995 (average: 13 cases per year). Of these cases, 80% occurred in the southwestern states of New Mexico, Arizona, and Colorado. Another 9% of cases were reported from California. Nine other western states reported limited

numbers of cases. Modes of transmission were determined for 284 of these case-patients and included flea bite (n=222; 78%); direct contact with infected animals (n=56; 20%); and inhalation of infectious respiratory droplets or other airborne materials from infected animals (n=7; 2%). Five of the seven persons who were infected by inhalation were exposed to infected domestic cats, and a sixth person (a veterinarian) also may have had such an exposure.

In the United States, most cases of plague in humans occur in the summer months, when risk for exposure to infected fleas is greatest. The majority of these cases, especially those in the Southwest, are acquired in or near the patient's residence. Risks for acquiring the disease are associated with conditions that provide food and shelter for plague-susceptible rodents near human dwellings. Less often, plague is acquired while working or while participating in recreational activities the latter having occurred most often among patients from California.

Population at risk:

- Veterinarians and their assistants engaged in small-animal practices in plague enzootic areas have a definite risk of exposure to plague infection from their free-roaming patients.
- In endemic/epidemic regions, low socio-economic areas with poor housing, housing located near docks, warehouses and granaries are at higher risk. In US port cities, areas near the port facilities would be considered at high risk.
- In the western USA areas with houses built in the enzootic regions which have preserved as much as possible the natural habitat, usually more expensive housing, are at higher risk.

The incubation period usually is 2 to 6 days for bubonic plague and 1 to 3 days for primary pneumonic plague.

Clinical Description

The three principal clinical presentations of plague are bubonic, septicemic, and pneumonic plague.

Bubonic plague, characterized by development of an acute regional lymphadenopathy, or bubo, is the most common clinical form of disease, accounting for 80%-90% of cases in the United States. Buboes typically involve lymph nodes that drain the site of initial infection and are most often located in the inguinal, axillary, or cervical regions. The incubation period for bubonic plague usually ranges from and rarely exceeds 2 to 6 days. The case-fatality rate for infected persons who are not treated is 50%-60%.

Septicemic plague, which occurs when *Y. pestis* invades and continues to multiply in the bloodstream, can occur secondarily to bubonic plague or can develop without detectable lymphadenopathy (i.e., primary septicemic plague). In the United States during 1947-1977, approximately 10% of plague patients presented with septicemic plague; approximately 50% of these persons died as a result of disease. Complications of this form of plague include septic shock, consumptive coagulopathy, meningitis, and coma.

Pneumonic plague is the least common but most dangerous and fatal form of the disease. It can develop as a secondary complication of septicemic plague or result from inhalation of infectious respiratory droplets expelled from a human or animal that has plague pneumonia. Signs of pneumonic plague include severe pneumonia accompanied by high fever, dyspnea, and often hemoptysis. The incubation period for primary pneumonic plague is 1-3 days. Patients who do not receive adequate treatment within 18 hours after onset of respiratory symptoms are unlikely to survive.

Laboratory Tests

Y. pestis can be identified in the lymph node aspirate (from buboes), blood (all clinical forms), sputum or tracheal wash (pneumonic cases) and CSF.

- The Gram stain shows the plump gram negative bacilli with a bipolar closed safety pin morphology.
- Direct fluorescent assay (FA) shows the bacilli.
- Cultures are essential to bring confirmation. The Cary-Blair transportation medium can be used if the specimens needs to be transported. Inoculation is made on sheep blood agar, brain heart infusion broth or Mc Conkey or deoxycolate agar. *Y. pestis* grows optimally at 28°C on blood agar or MacConkey agar, typically requiring 48 hours for observable growth, but colonies are initially much smaller than other Enterobacteriaceae and may be overlooked. *Y. pestis* is a nonmotile, gram-negative bacillus, sometimes coccobacillus, that shows bipolar (also termed safety pin) staining with Wright, Giemsa, or Wayson stain.
- Polymerase chain reaction for rapid diagnosis of *Y. pestis* is available at the OPH laboratory.

Serologic tests are not very useful

- Passive hemagglutination (PHA). Titers remained elevated (64) for months and low titers may persist for life.
- Hemagglutination inhibition testing Two samples taken at 8 weeks interval and showing an increase in titer are necessary to prove recent infection
- ELISA IgM to detect anti-F1 antibodies: not very sensitive, some false negative

The microbiology laboratory should be informed when plague organisms are suspected in submitted specimens to minimize risks of transmission to laboratory personnel.

Surveillance

Plague is a reportable condition as are other diseases of major public health concern because of the severity of disease and potential for epidemic spread. Report by telephone immediately upon recognition that a case, a suspected case, or a positive laboratory result is known;

Case Definition

Clinical description

The disease is characterized by fever, chills, headache, malaise, prostration, and leukocytosis that manifests in one or more of the following principal clinical forms:

- Regional lymphadenitis (bubonic plague)
- Septicemia without an evident bubo (septicemic plague)
- Plague pneumonia, resulting from hematogenous spread in bubonic or septicemic cases (secondary pneumonic plague) or inhalation of infectious droplets (primary pneumonic plague)
- Pharyngitis and cervical lymphadenitis resulting from exposure to larger infectious droplets or ingestion of infected tissues (pharyngeal plague)

Laboratory criteria for diagnosis

Presumptive

- Elevated serum antibody titer(s) to *Yersinia pestis* fraction 1 (F1) antigen (without documented fourfold or greater change) in a patient with no history of plague vaccination or
- Detection of F1 antigen in a clinical specimen by fluorescent assay

Confirmatory

- Isolation of *Y. pestis* from a clinical specimen or
- Detection by PCR
- Fourfold or greater change in serum antibody titer to *Y. pestis* F1 antigen

Case classification

- Suspect: a clinically compatible case without presumptive or confirmatory laboratory results

- Probable: a clinically compatible case with presumptive laboratory results
- Confirmed: a clinically compatible case with confirmatory laboratory results

Immunization

An inactivated whole-cell *Y. pestis* vaccine is recommended only for persons whose occupation regularly places them at high risk for exposure to *Y. pestis* or plague-infected rodents (eg, some field biologists and laboratory workers). Primary immunization consists of 3 intramuscular doses; the second and third doses are given 1 to 3 months and 5 to 6 months, respectively, after the first dose. Booster doses can be given 3 times at 6-month intervals when vaccine recipients have continuing high risk of exposure and a serum passive hemagglutination *Y. pestis* antibody titer of less than 1:128. Additional booster doses can be administered at 1- to 2-year intervals. Since safety and immunogenicity have been evaluated only in persons 18 years of age and older, recommendations for immunization of children have not been established.

Immunized persons should take the same preventive measures as unimmunized persons.

Treatment

Historically, the preferred treatment for plague infection has been streptomycin, an FDA-approved treatment for plague. Administered early during the disease, streptomycin has reduced overall plague mortality to the 5% to 14% range. However, streptomycin is infrequently used in the United States and only modest supplies are available.³⁵ Gentamicin is not FDA approved for the treatment of plague but has been used successfully and is recommended as an acceptable alternative by experts. In one case series, 8 patients with plague were treated with gentamicin with morbidity or mortality equivalent to that of patients treated with streptomycin.

Tetracycline and doxycycline also have been used in the treatment and prophylaxis of plague; both are FDA approved for these purposes. There are no controlled clinical trials comparing either tetracycline or doxycycline to aminoglycosides in the treatment of plague, but anecdotal case series and a number of medical authorities support use of this class of antimicrobials for prophylaxis and for therapy in the event that streptomycin or gentamicin cannot be administered.

The fluoroquinolone family of antimicrobials has demonstrated efficacy in animal studies. Ciprofloxacin has been demonstrated to be at least as efficacious as aminoglycosides and tetracyclines in studies of mice with experimentally induced pneumonic plague. In vitro studies also suggest equivalent or greater activity of ciprofloxacin, levofloxacin, and ofloxacin against *Y. pestis* when compared with aminoglycosides or tetracyclines. However, there have been no trials of fluoroquinolones in human plague, and they are not FDA approved for this indication.

The 1970 WHO analysis reported that sulfadiazine reduced mortality for bubonic plague but was ineffective against pneumonic plague and was less effective than tetracycline overall. In a study comparing trimethoprim-sulfamethoxazole with streptomycin, patients treated with trimethoprim-sulfamethoxazole had a longer median duration of fever and a higher incidence of complications. Authorities have generally considered trimethoprim-sulfamethoxazole a second-tier choice. Some have recommended sulfonamides only in the setting of pediatric prophylaxis. No sulfonamides have been FDA approved for the treatment of plague.

Antimicrobials that have been shown to have poor or only modest efficacy in animal studies have included rifampin, aztreonam, ceftazidime, cefotetan, and cefazolin; these antibiotics should not be used.

Children: The treatment of choice for plague in children has been streptomycin or gentamicin. If aminoglycosides are not available or cannot be used, recommendations for alternative antimicrobial treatment with efficacy against plague are conditioned by balancing risks associated with treatment against those posed by pneumonic plague. Children aged 8 years and older can be treated with tetracycline antibiotics safely. However, in children younger than 8 years, tetracycline antibiotics may cause discolored teeth, and rare instances of retarded skeletal growth have been reported in infants. Chloramphenicol is considered safe in children except for children younger than 2 years who are at risk of "gray baby syndrome". Some concern exists that fluoroquinolones use in children may cause arthropathy, although fluoroquinolones have been used to treat serious infections in children. No comparative studies assessing efficacy or safety of alternative treatment strategies for plague in children has or can be performed.

In a mass casualty setting or for postexposure prophylaxis, we recommend that doxycycline be used. Alternatives are listed for both settings. The working group assessment is that the potential benefits of these antimicrobials in the treating of pneumonic plague infection substantially outweigh the risks.

Pregnant Women: It has been recommended that aminoglycosides be avoided in pregnancy unless severe illness warrants, but there is no more efficacious treatment for pneumonic plague. Pregnant women in the contained casualty setting should receive gentamicin. Since streptomycin has been associated with rare reports of irreversible deafness in children following fetal exposure, this medication should be avoided if possible. The tetracycline class of antibiotics has been associated with fetal toxicity including retarded skeletal growth, although a large case-control study of doxycycline use in pregnancy showed no significant increase in teratogenic risk to the fetus. Liver toxicity has been reported in pregnant women following large doses of intravenous tetracycline (no longer sold in the United States), but it has also been reported following oral administration of tetracycline to nonpregnant individuals. Balancing the risks of pneumonic plague infection with those associated with doxycycline use in pregnancy, the recommendation is that doxycycline be used to treat pregnant women with pneumonic plague if gentamicin is not available.

Of the oral antibiotics historically used to treat plague, only trimethoprim-sulfamethoxazole has a category C pregnancy classification; however, many experts do not recommend trimethoprim-sulfamethoxazole for treatment of pneumonic plague. Therefore, the working group recommends that pregnant women receive oral doxycycline for mass casualty treatment or postexposure prophylaxis. If the patient is unable to take doxycycline or the medication is unavailable, ciprofloxacin or other fluoroquinolones would be recommended in the mass casualty setting.

The recommendation for treatment of breastfeeding women is to provide the mother and infant with the same antibiotic based on what is most safe and effective for the infant: gentamicin in the contained casualty setting and doxycycline in the mass casualty setting. Fluoroquinolones would be the recommended alternative.

Immunosuppressed Persons: The antibiotic treatment or postexposure prophylaxis for pneumonic plague among those who are immunosuppressed has not been studied in human or animal models of pneumonic plague infection. Therefore, the consensus recommendation is to administer antibiotics according to the guidelines developed for immunocompetent adults and children.

Prophylaxis

Antimicrobial	Age	Dosage
Tetracycline	Adults	2 g/day in two or four equal doses at 12- or 6-hour intervals for 7 days, po
	Children	25-50 mg/kg/day in 2 or 4 equal doses at 12 or 6 hours interval for 7 days po
Doxycycline	Adults	100-200 mg/day in two equal doses at 12 hrs interval for 7 days, po
	Children	2-4 mg/kg/day in two equal doses at 12-hour intervals for 7 days, po
TMP SXT	Adults	1.6-3.2 g/day sulfamethoxazole component in two equal doses at 12-hour intervals for 7 days, po
	Children	40 mg/kg/day, sulfamethoxazole component in two equal doses at 12-hour intervals for 7 days, po

Information is for single exposures. Prolonged use of antimicrobial prophylaxis should be supervised by a physician in consultation with public health officials.
Use of tetracycline during pregnancy should be avoided.

Prevention of transmission

Residents of Areas in Which Plague Is Endemic

In the western United States, most persons with plague become infected when rodent plague epizootics occur near their residences. Recommended means of reducing the risk for acquiring plague in and around homes include a) eliminating sources of food and shelter for rodents near homes, b) modifying homes to prevent rodent access, c) treating domestic dogs and cats weekly with appropriate insecticides, d) avoiding direct contact with sick or dead rodents, and e) handling severely ill cats with extreme caution (these animals should be examined by a veterinarian).

Persons Who Participate in Outdoor Activities

Hikers, campers, and other persons who participate in outdoor recreational activities in areas where plague is endemic should a) avoid handling sick or dead animals, b) avoid rodent nests and burrows, c) use insect repellents containing N, N-diethyl-mtoluamide (DEET) on skin and repellents or appropriate insecticidal sprays on clothing, and d) treat accompanying pets with appropriate insecticides. Hunters should always wear gloves when handling dead animals.

Medical Personnel and Persons Having Close Contact with Infected Persons

Persons suspected of having pneumonic plague should be maintained under respiratory droplet precautions for 48 hours after antibiotic treatment begins. Persons who have confirmed cases of pneumonic plague should be kept under droplet precautions until sputum cultures are negative. Patients in whom pneumonic plague has been excluded warrant standard precautions only. Prophylactic antibiotics should be administered to persons who have had close exposure (i.e., within 6.5 feet or 2 meters) to persons suspected of having pneumonic plague. Persons who have not had such exposure are unlikely to become infected but should be monitored closely.

Laboratory Workers

Routine bacteriologic work involving plague can be performed in biosafety level 2 laboratories. Standard precautions (e.g., the use of a biological safety cabinet to contain aerosols that are generated unintentionally) are sufficient to prevent clinical laboratory workers from being infected with *Y. pestis*. Few laboratory-associated cases have been reported; these cases have involved unusual exposures in clinical diagnostic laboratories or in laboratories that conduct research involving live *Y. pestis*.

Persons Who Work with Potentially Infected Animals

These workers should be informed on how to minimize their exposure to the tissues and fleas of potentially infective animals. Precautionary measures include a) avoiding areas where high mortality in com-

mensal rat populations has been observed, b) wearing gloves when handling animals, c) applying insect repellents containing DEET to clothes and skin, and d) treating clothes with appropriate insecticides.

Persons Who Work in Veterinary Clinics

Persons working in veterinary practices in areas where plague is enzootic should be educated on the risks of handling cats infected with *Y pestis*. Such persons should wear gloves and eye protection and take appropriate respiratory precautions when examining cats that have fever and obvious acute lymphadenopathy, oral lesions, or pneumonia.

Persons Living, Working, or Traveling in Other Countries

In most countries of Africa, Asia, and South America in which plague is enzootic, the risk for acquiring plague is greatest in semiarid grassland or mountainous areas. The likelihood of plague spreading from wild-rodent foci into village or urban centers is greatest when a) environmental conditions precipitate an increase in or movement of rodent populations, thus leading to increased population densities of plague-susceptible rodents and their fleas or b) natural disasters or other events interrupt routine sanitary practices. Whenever possible, persons living in regions where plague is enzootic should avoid rodent-infested locations, especially if unusually high numbers of dead rodents have been reported. Persons who must work in such areas should avoid handling sick and dead rodents and use repellents and appropriate insecticides to reduce their risk for being bitten by fleas. Travelers to plague-endemic areas generally are at low risk for infection with *Y pestis*. Persons who travel to these areas should avoid rat-infested sites with recently reported cases of plague among humans, especially those sites at which dead rats have been observed. To reduce the likelihood of being bitten by fleas, travelers can apply insect repellents to skin and repellents and insecticides to clothing and outer bedding. Short-term prophylactic use of antibiotics should be considered only for circumstances of exceptionally high risk of exposure to plague.

Hospital precaution and isolation:

Previous public health guidelines have advised strict isolation for all close contacts of patients with pneumonic plague who refuse prophylaxis. In the modern setting, however, pneumonic plague has not spread widely or rapidly in a community, and therefore isolation of close contacts refusing antibiotic prophylaxis is not recommended by the working group. Instead, persons refusing prophylaxis should be carefully watched for the development of fever or cough during the first 7 days after exposure and treated immediately should either occur.

Modern experience with person-to-person spread of pneumonic plague is limited; few data are available to make specific recommendations regarding appropriate infection control measures. The available evidence indicates that person-to-person transmission of pneumonic plague occurs via respiratory droplets; transmission by droplet nuclei has not been demonstrated. In large pneumonic plague epidemics earlier this century, pneumonic plague transmission was prevented in close contacts by wearing masks. Commensurate with this, existing national infection control guidelines recommend the use of disposable surgical masks to prevent the transmission of pneumonic plague.

Given the available evidence, the working group recommends that, in addition to beginning antibiotic prophylaxis, persons living or working in close contact with patients with confirmed or suspect pneumonic plague that have had less than 48 hours of antimicrobial treatment should follow respiratory droplet precautions and wear a surgical mask. Further, the working group recommends avoidance of unnecessary close contact with patients with pneumonic plague until at least 48 hours of antibiotic therapy and clinical improvement has taken place. Other standard respiratory droplet precautions (gown, gloves, and eye protection) should be used as well.

The patient should remain isolated during the first 48 hours of antibiotic therapy and until clinical improvement occurs. If large numbers of patients make individual isolation impossible, patients with pneumonic plague may be cohorted while undergoing antibiotic therapy. Patients being transported

should also wear surgical masks. Hospital rooms of patients with pneumonic plague should receive terminal cleaning in a manner consistent with standard precautions, and clothing or linens contaminated with body fluids of patients infected with plague should be disinfected as per hospital protocol.

Microbiology laboratory personnel should be alerted when *Y. pestis* is suspected. Four laboratory-acquired cases of plague have been reported in the United States. Simple clinical materials and cultures should be processed in biosafety level 2 conditions. Only during activities involving high potential for aerosol or droplet production (eg, centrifuging, grinding, vigorous shaking, and animal studies) are biosafety level 3 conditions necessary.

Bodies of patients who have died following infection with plague should be handled with routine strict precautions. Contact with the remains should be limited to trained personnel, and the safety precautions for transporting corpses for burial should be the same as those when transporting ill patients. Aerosol-generating procedures, such as bone-sawing associated with surgery or postmortem examinations, would be associated with special risks of transmission and are not recommended. If such aerosol-generating procedures are necessary, then high-efficiency particulate air filtered masks and negative-pressure rooms should be used as would be customary in cases in which contagious biological aerosols, such as *Mycobacterium tuberculosis*, are deemed a possible risk.

Plague as a bioweapon

Advances in living conditions, public health, and antibiotic therapy make future pandemics improbable. However, plague outbreaks following use of a biological weapon are a plausible threat. In World War II, a secret branch of the Japanese army, Unit 731, is reported to have dropped plague-infected fleas over populated areas of China, thereby causing outbreaks of plague. In the ensuing years, the biological weapons programs of the United States and the Soviet Union developed techniques to aerosolize plague directly, eliminating dependence on the unpredictable flea vector. In 1970, the World Health Organization (WHO) reported that, in a worst-case scenario, if 50 kg of *Y. pestis* were released as an aerosol 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. The plague bacilli would remain viable as an aerosol for 1 hour for a distance of up to 10 km. Significant numbers of city inhabitants might attempt to flee, further spreading the disease.

While US scientists had not succeeded in making quantities of plague organisms sufficient to use as an effective weapon by the time the US offensive program was terminated in 1970, Soviet scientists were able to manufacture large quantities of the agent suitable for placing into weapons. More than 10 institutes and thousands of scientists were reported to have worked with plague in the former Soviet Union. In contrast, few scientists in the United States study this disease.

Epidemiology of Plague Following Use of a Biological Weapon

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 probably occur via an aerosol of *Y. pestis*, a mechanism that has been shown to produce disease in nonhuman primates. A pneumonic plague outbreak would result with symptoms initially resembling those of other severe respiratory illnesses. The size of the outbreak would depend on factors including the quantity of biological agent used, characteristics of the strain, environmental conditions, and methods of aerosolization. Symptoms would begin to occur 1 to 6 days following exposure, and people would die quickly following onset of symptoms. Indications that plague had been artificially disseminated would be the occurrence of cases in locations not known to have enzootic infection, in persons without known risk factors, and in the absence of prior rodent deaths.

Diagnosis of a terrorist outbreak

Given the rarity of plague infection and the possibility that early cases are a harbinger of a larger epidemic, the first clinical or laboratory suspicion of plague must lead to immediate notification of the hospital epidemiologist or infection control practitioner, health department, and the local or state health laboratory. Definitive tests can thereby be arranged rapidly through a state reference laboratory or, as necessary, the Diagnostic and Reference Laboratory of the CDC and early interventions instituted.

The early diagnosis of plague requires a high index of suspicion in naturally occurring cases and even more so following the use of a biological weapon. There are no effective environmental warning systems to detect an aerosol of plague bacilli.

The first indication of a clandestine terrorist attack with plague would most likely be a sudden outbreak of illness presenting as severe pneumonia and sepsis. If there are only small numbers of cases, the possibility of them being plague may be at first overlooked given the clinical similarity to other bacterial or viral pneumonias and that few Western physicians have ever seen a case of pneumonic plague. However, 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.

There are no widely available rapid diagnostic tests for plague. Tests that would be used to confirm a suspected diagnosis are: antigen detection, IgM enzyme immunoassay, immunostaining, and polymerase chain reaction. The routinely used passive hemagglutination antibody detection assay is typically only of retrospective value since several days to weeks usually pass after disease onset before antibodies develop.

Microbiologic studies are important in the diagnosis of pneumonic plague. A Gram stain of sputum or blood may reveal gram-negative bacilli or coccobacilli. A Wright, Giemsa, or Wayson stain will often show bipolar staining, and direct fluorescent antibody testing, if available, may be positive. In the unlikely event that a cervical bubo is present in pneumonic plague, an aspirate (obtained with a 20-gauge needle and a 10-mL syringe containing 1-2 mL of sterile saline for infusing the node) may be cultured and similarly stained.

Cultures of sputum, blood, or lymph node aspirate should demonstrate growth approximately 24 to 48 hours after inoculation. Most microbiology laboratories use either automated or semiautomated bacterial identification systems. Some of these systems may misidentify *Y. pestis*. In laboratories without automated bacterial identification, as many as 6 days may be required for identification, and there is some chance that the diagnosis may be missed entirely. Approaches for biochemical characterization of *Y. pestis* are described in detail elsewhere.

If a laboratory using automated or nonautomated techniques is notified that plague is suspected, it should split the culture: 1 culture incubated at 28°C for rapid growth and the second culture incubated at 37°C for identification of the diagnostic capsular (F1) antigen. Using these methods, up to 72 hours may be required following specimen procurement to make the identification (May Chu, PhD, CDC, Fort Collins, Colo, written communication, April 9, 1999). Antibiotic susceptibility testing should be performed at a reference laboratory because of the lack of standardized susceptibility testing procedures for *Y. pestis*. A process establishing criteria and training measures for laboratory diagnosis of this disease is being undertaken jointly by the Association of Public Health Laboratories and the CDC.

Recommendations for Antibiotic Therapy

The working group treatment recommendations are based on literature reports on treatment of human disease, reports of studies in animal models, reports on in vitro susceptibility testing, and antibiotic safety. Should antibiotic susceptibility testing reveal resistance, proper antibiotic substitution would need to be made.

In a contained casualty setting, a situation in which a modest number of patients require treatment, the working group recommends parenteral antibiotic therapy. Preferred parenteral forms of the antimicrobials streptomycin or gentamicin are recommended. However, in a mass casualty setting, intravenous or intramuscular therapy may not be possible for reasons of patient care logistics and/or exhaustion of equipment and antibiotic supplies, and parenteral therapy will need to be supplanted by oral therapy. In a mass casualty setting, the working group recommends oral therapy, preferably with doxycycline (or tetracycline) or ciprofloxacin.

Patients with pneumonic plague will require substantial advanced medical supportive care in addition to antimicrobial therapy. Complications of gram-negative sepsis would be expected, including adult respiratory distress syndrome, disseminated intravascular coagulation, shock, and multiorgan failure.

Once it is known or strongly suspected that pneumonic plague cases are occurring, anyone with fever or cough in the presumed area of exposure should be immediately treated with antimicrobials for presumptive pneumonic plague. Delaying therapy until confirmatory testing is performed would greatly decrease survival. Clinical deterioration of patients despite early initiation of empiric therapy could signal antimicrobial resistance and should be promptly evaluated.

Postexposure Prophylaxis Recommendations

Recommendations are that in a community experiencing a pneumonic plague epidemic, all persons developing a temperature of 38.5°C or higher or new cough should promptly begin parenteral antibiotic treatment. If the resources required to administer parenteral antibiotics are unavailable, oral antibiotics should be used according to the mass casualty recommendations. For infants in this setting, tachypnea would also be an additional indication for immediate treatment. Special measures would need to be initiated for treatment or prophylaxis of those who are either unaware of the outbreak or require special assistance, such as the homeless or mentally handicapped persons. Continuing surveillance of patients would be needed to identify individuals and communities at risk requiring postexposure prophylaxis.

Asymptomatic persons having household, hospital, or other close contact with persons with untreated pneumonic plague should receive postexposure antibiotic prophylaxis for 7 days and watch for fever and cough. Close contact is defined as contact with a patient at less than 2 meters. Tetracycline, doxycycline, sulfonamides, and chloramphenicol have each been used or recommended as postexposure prophylaxis in this setting. Fluoroquinolones could also be used based on studies in mice.

Doxycycline is the first choice antibiotic for postexposure prophylaxis; other recommended antibiotics are noted. Contacts who develop fever or cough while receiving prophylaxis should seek prompt medical attention and begin antibiotic treatment.

Environmental Decontamination

There is no evidence to suggest that residual plague bacilli pose an environmental threat to the population following the dissolution of the primary aerosol. There is no spore form in the *Y. pestis* life cycle, so it is far more susceptible to environmental conditions than sporulating bacteria such as *Bacillus anthracis*. Moreover, *Y. pestis* is very sensitive to the action of sunlight and heating and does not survive long outside the host. Although some reports suggest that the bacterium may survive in the soil for some time,

there is no evidence to suggest environmental risk to humans in this setting and thus no need for environmental decontamination of an area exposed to an aerosol of plague. In the WHO analysis, in a worst case scenario, a plague aerosol was estimated to be effective and infectious for as long as 1 hour. In the setting of a clandestine release of plague bacilli, the aerosol would have dissipated long before the first case of pneumonic plague occurred.