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Plague as a Biological Weapon

Medical and Public Health Management

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THIS IS THE THIRD ARTICLE IN A series entitled *Medical and Public Health Management Following the Use of a Biological Weapon: Consensus Statements of the Working Group on Civilian Biodefense*.^{1,2} The working group has identified a limited number of agents that, if used as weapons, could cause disease and death in sufficient numbers to cripple a city or region. These agents also comprise the top of the list of "Critical Biological Agents" recently developed by the Centers for Disease Control and Prevention (CDC).³ *Yersinia pestis*, the causative agent of plague, is one of the most serious of these. Given

Objective The Working Group on Civilian Biodefense has 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.

Participants The working group included 25 representatives from major academic medical centers and research, government, military, public health, and emergency management institutions and agencies.

Evidence MEDLINE databases were searched from January 1966 to June 1998 for the Medical Subject Headings *plague*, *Yersinia pestis*, *biological weapon*, *biological terrorism*, *biological warfare*, and *biowarfare*. Review of the bibliographies of the references identified by this search led to subsequent identification of relevant references published prior to 1966. In addition, participants identified other unpublished references and sources. Additional MEDLINE searches were conducted through January 2000.

Consensus Process The first draft of the consensus statement was a synthesis of information obtained in the formal evidence-gathering process. The working group was convened to review drafts of the document in October 1998 and May 1999. The final statement incorporates all relevant evidence obtained by the literature search in conjunction with final consensus recommendations supported by all working group members.

Conclusions An aerosolized plague weapon could cause fever, cough, chest pain, and hemoptysis with signs consistent with severe pneumonia 1 to 6 days after exposure. Rapid evolution of disease would occur in the 2 to 4 days after symptom onset and would lead to septic shock with high mortality without early treatment. Early treatment and prophylaxis with streptomycin or gentamicin or the tetracycline or fluoroquinolone classes of antimicrobials would be advised.

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the availability of *Y pestis* around the world, capacity for its mass production and aerosol dissemination, difficulty in preventing such activities, high fatality rate of pneumonic plague, and potential for secondary spread of cases during an epidemic, the potential use of plague as a biological weapon is of great concern.

CONSENSUS METHODS

The working group comprised 25 representatives from major academic medical centers and research, government, military, public health, and emergency management institutions and agencies.

MEDLINE databases were searched from January 1966 to June 1998 using the Medical Subject Headings (MeSH) *plague*, *Yersinia pestis*, *biological weapon*,

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this search led to subsequent identification of relevant references published prior to 1966. In addition, participants identified other unpublished references and sources in their fields of expertise. Additional MEDLINE searches were conducted through January 2000 during the review and revisions of the statement.

The first draft of the consensus statement was a synthesis of information obtained in the initial formal evidence-gathering process. Members of the working group were asked to make formal written comments on this first draft of the document in September 1998. The document was revised incorporating changes suggested by members of the working group, which was convened to review the second draft of the document on October 30, 1998. Following this meeting and a second meeting of the working group on May 24, 1999, a third draft of the document was completed, reviewed, and revised. Working group members had a final opportunity to review the document and suggest revisions. The final document incorporates all relevant evidence obtained by the literature search in conjunction with consensus recommendations supported by all working group members.

The assessment and recommendations provided herein represent the best professional judgment of the working group based on data and expertise currently available. The conclusions and recommendations need to be regularly reassessed as new information becomes available.

HISTORY AND POTENTIAL AS A BIOTERRORIST AGENT

In AD 541, the first recorded plague pandemic began in Egypt and swept across Europe with attributable population losses of between 50% and 60% in North Africa, Europe, and central and southern Asia.⁴ The second plague pandemic, also known as the *black death* or *great pestilence*, began in 1346 and eventually killed 20 to 30 million people in Europe, one third of the European population.⁵ Plague spread slowly and inexorably from village to village by infected

rats and humans or more quickly from country to country by ships. The pandemic lasted more than 130 years and had major political, cultural, and religious ramifications. The third pandemic began in China in 1855, spread to all inhabited continents, and ultimately killed more than 12 million people in India and China alone.⁴ Small outbreaks of plague continue to occur throughout the world.^{4,5}

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.⁶ 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.⁷ 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.⁷

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.⁸ More than 10 institutes and thousands of scientists were reported to have worked with plague in the former Soviet Union.⁸ In contrast, few scientists in the United States study this disease.⁹

There is little published information indicating actions of autonomous groups or individuals seeking to develop plague as a weapon. However, in 1995 in Ohio,

a microbiologist with suspect motives was arrested after fraudulently acquiring *Y pestis* by mail.¹⁰ New antiterrorism legislation was introduced in reaction.

EPIDEMIOLOGY

Naturally Occurring Plague

Human plague most commonly occurs when plague-infected fleas bite humans who then develop bubonic plague. As a prelude to human epidemics, rats frequently die in large numbers, precipitating the movement of the flea population from its natural rat reservoir to humans. Although most persons infected by this route 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 percentage of patients with bubonic or septicemic plague develop secondary pneumonic plague and can then spread the disease by respiratory droplet. Persons contracting the disease by this route develop primary pneumonic plague.¹¹

Plague remains an enzootic infection of rats, ground squirrels, prairie dogs, and other rodents on every populated continent except Australia.⁴ Worldwide, on average in the last 50 years, 1700 cases have been reported annually.⁴ In the United States, 390 cases of plague were reported from 1947 to 1996, 84% of which were bubonic, 13% septicemic, and 2% pneumonic. Concomitant case fatality rates were 14%, 22%, and 57%, respectively.¹² Most US cases were in New Mexico, Arizona, Colorado, and California. Of the 15 cases following exposure to domestic cats with plague, 4 were primary pneumonic plague.¹³ In the United States, the last case of human-to-human transmission of plague occurred in Los Angeles in 1924.^{14,15}

Although pneumonic plague has rarely been the dominant manifestation of the disease, large outbreaks of pneumonic plague have occurred.¹⁶ 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.^{16,17} As

would be anticipated in the preantibiotic era, nearly 100% of these cases were reported to be fatal.^{16,17} 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.^{14,15} In northern India, there was an epidemic of pneumonic plague with 1400 deaths reported at about the same time.¹⁵ 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.¹⁸

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.¹⁹ 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.¹⁶ 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.

MICROBIOLOGY AND VIRULENCE FACTORS

Y pestis is a nonmotile, gram-negative bacillus, sometimes coccobacillus, that shows bipolar (also termed *safety pin*) staining with Wright, Giemsa, or Way-

son stain (FIGURE 1).²⁰ *Y pestis* is a lactose nonfermenter, urease and indole negative, and a member of the Enterobacteriaceae family.²¹ It 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* has a number of virulence factors that enable it to survive in humans by facilitating use of host nutrients, causing damage to host cells, and subverting phagocytosis and other host defense mechanisms.^{4,11,21,22}

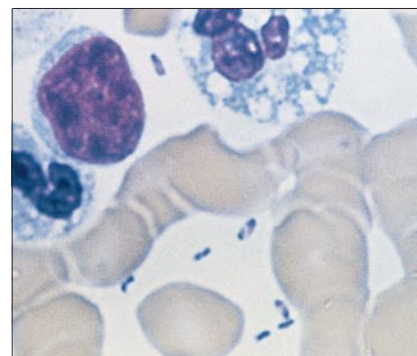
PATHOGENESIS AND CLINICAL MANIFESTATIONS

Naturally Occurring Plague

In most cases of naturally occurring plague, the bite by a plague-infected flea leads to the inoculation of up to thousands of organisms into a patient's skin. 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.²¹

Patients typically develop symptoms of bubonic plague 2 to 8 days after being bitten by an infected flea. There is sudden onset of fever, chills, and weakness and the development of an acutely swollen tender lymph node, or bubo, up to 1 day later.²³ The bubo most typically develops in the groin, axilla, or cervical region (FIGURE 2, A) and is often so painful that it prevents patients from moving the affected area of the body. Buboes are 1 to 10 cm in diameter, and the overlying skin is erythematous.²¹ They are extremely tender, nonfluctuant, and warm and are often associated with considerable surrounding edema, but seldom lymphangitis. Rarely, buboes become fluctuant and suppurate. In addition, pustules or skin ulcerations may occur at the site of the flea bite in a minority of patients. A small minority of patients infected by fleas develop *Y pes-*

Figure 1. Peripheral Blood Smear From Patient With Septicemic Plague



Smear shows characteristic bipolar staining of *Yersinia pestis* bacilli (Wright-Giemsa stain; magnification, $\times 1000$). Figure from Centers for Disease Control and Prevention, Division of Vector-Borne Infectious Diseases, Fort Collins, Colo.

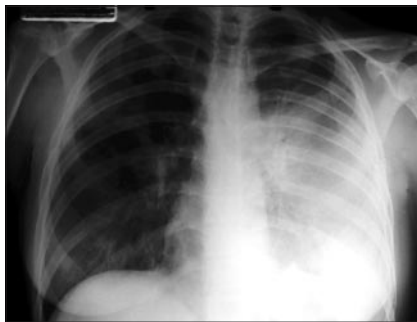
tis septicemia without a discernable bubo, the form of disease termed *primary septicemic plague*.²³ Septicemia can also arise secondary to bubonic plague.²¹ Septicemic plague may lead to disseminated intravascular coagulation, necrosis of small vessels, and purpuric skin lesions (Figure 2, B). Gangrene of acral regions such as the digits and nose may also occur in advanced disease, a process believed responsible for the name *black death* in the second plague pandemic (Figure 2, C).²¹ However, the finding of gangrene would not be expected to be helpful in diagnosing the disease in the early stages of illness when early antibiotic treatment could be lifesaving.

Secondary pneumonic plague develops in a minority of patients with bubonic or primary septicemic plague—approximately 12% of total cases in the United States over the last 50 years.⁴ This process, termed *secondary pneumonic plague*, develops via hematogenous spread of plague bacilli to the lungs. Patients commonly have symptoms of severe bronchopneumonia, chest pain, dyspnea, cough, and hemoptysis.^{16,21}

Primary pneumonic plague resulting from the inhalation of plague bacilli occurs rarely in the United States.¹² Reports of 2 recent cases of primary pneumonic plague, contracted after handling cats with pneumonic plague, reveal that both patients had pneumonic symptoms as well as prominent gastro-

Figure 2. Patients With Naturally Occurring Plague

A, Cervical bubo in patient with bubonic plague; B, petechial and ecchymotic bleeding into the skin in patient with septicemic plague; and C, gangrene of the digits during the recovery phase of illness of patient shown in B. In plague following the use of a biological weapon, presence of cervical bubo is rare; purpuric skin lesions and necrotic digits occur only in advanced disease and would not be helpful in diagnosing the disease in the early stages of illness when antibiotic treatment can be life-saving. Figures from Centers for Disease Control and Prevention, Division of Vector-Borne Infectious Diseases, Fort Collins, Colo.

Figure 3. Chest Radiograph of Patient With Primary Pneumonic Plague

Radiograph shows extensive lobar consolidation in left lower and left middle lung fields. Figure from Centers for Disease Control and Prevention, Division of Vector-Borne Infectious Diseases, Fort Collins, Colo.

intestinal symptoms including nausea, vomiting, abdominal pain, and diarrhea. Diagnosis and treatment were delayed more than 24 hours after symptom onset in both patients, both of whom died.^{24,25}

Less common plague syndromes include plague meningitis and plague pharyngitis. Plague meningitis follows the hematogenous seeding of bacilli into the meninges and is associated with fever and meningismus. Plague pharyngitis follows inhalation or ingestion of plague bacilli and is associated with cervical lymphadenopathy.²¹

Plague Following Use of a Biological Weapon

The pathogenesis and clinical manifestations of plague following a biologi-

cal attack would be notably different than naturally occurring plague. Inhaled aerosolized *Y pestis* bacilli would cause primary pneumonic plague. The time from exposure to aerosolized plague bacilli until development of first symptoms in humans and nonhuman primates has been found to be 1 to 6 days and most often, 2 to 4 days.^{12,16,19,26} 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.^{16,19,27} Prominent gastrointestinal symptoms, including nausea, vomiting, abdominal pain, and diarrhea, might be present.^{24,25}

The ensuing clinical findings of primary pneumonic plague are similar to those of any severe rapidly progressive pneumonia and are quite similar to those of secondary pneumonic plague. Clinicopathological features may help distinguish primary from secondary pneumonic plague.¹¹ In contrast to secondary pneumonic plague, features of primary pneumonic plague would include absence of buboes (except, rarely, cervical buboes) and, on pathologic examination, pulmonary disease with areas of profound lobular exudation and bacillary aggregation.¹¹ Chest radiographic findings are variable but bilateral infiltrates or consolidation are common (FIGURE 3).²²

Laboratory studies may reveal leukocytosis with toxic granulations, co-

agulation abnormalities, aminotransferase elevations, azotemia, and other evidence of multiorgan failure. All are nonspecific findings associated with sepsis and systemic inflammatory response syndrome.^{11,21}

The time from respiratory exposure to death in humans is reported to have been between 2 to 6 days in epidemics during the preantibiotic era, with a mean of 2 to 4 days in most epidemics.¹⁶

DIAGNOSIS

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.²⁸

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.¹ The presence of hemoptysis in this setting would strongly suggest plague (TABLE 1).²²

There are no widely available rapid diagnostic tests for plague.²⁸ Tests that would be used to confirm a suspected diagnosis—antigen detection, IgM enzyme immunoassay, immunostaining, and polymerase chain reaction—are available only at some state health departments, the CDC, and military laboratories.²¹ 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.^{4,21,29} A Wright, Giemsa, or Wayson stain will often show bipolar staining (Figure 1), 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 (Table 1).²²

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 semi-automated bacterial identification systems. Some of these systems may misidentify *Y pestis*.^{12,30} In laboratories without automated bacterial identification, as many as 6 days may be required for

Table 1. Diagnosis of Pneumonic Plague Infection Following Use of a Biological Weapon

Epidemiology and symptoms	Sudden appearance of many persons with fever, cough, shortness of breath, hemoptysis, and chest pain
	Gastrointestinal symptoms common (eg, nausea, vomiting, abdominal pain, and diarrhea)
	Patients have fulminant course and high mortality
Clinical signs	Tachypnea, dyspnea, and cyanosis
	Pneumonic consolidation on chest examination
	Sepsis, shock, and organ failure
	Infrequent presence of cervical bubo (Purpuric skin lesions and necrotic digits only in advanced disease)
Laboratory studies	Sputum, blood, or lymph node aspirate
	Gram-negative bacilli with bipolar (safety pin) staining on Wright, Giemsa, or Wayson stain
	Rapid diagnostic tests available only at some health departments, the Centers for Disease Control and Prevention, and military laboratories
Pathology	Pulmonary infiltrates or consolidation on chest radiograph
	Lobular exudation, bacillary aggregation, and areas of necrosis in pulmonary parenchyma

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.²⁰

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.

VACCINATION

The US-licensed formaldehyde-killed whole bacilli vaccine was discontinued by its manufacturers in 1999 and is no longer available. Plans for future licensure and production are unclear. This killed vaccine demonstrated efficacy in preventing or ameliorating bubonic disease, but it does not prevent or amelio-

rate the development of primary pneumonic plague.^{19,31} It was used in special circumstances for individuals deemed to be at high risk of developing plague, such as military personnel working in plague endemic areas, microbiologists working with *Y pestis* in the laboratory, or researchers working with plague-infected rats or fleas. Research is ongoing in the pursuit of a vaccine that protects against primary pneumonic plague.^{22,32}

THERAPY

Recommendations for the use of antibiotics following a plague biological weapon exposure are conditioned by the lack of published trials in treating plague in humans, limited number of studies in animals, and possible requirement to treat large numbers of persons. A number of possible therapeutic regimens for treating plague have yet to be adequately studied or submitted for approval to the Food and Drug Administration (FDA). For these reasons, the working group offers consensus recommendations based on the best available evidence. The recommendations do not necessarily represent uses currently approved by the FDA or an official position on the part of any of the federal agencies whose scientists participated in these discussions. Recommendations will need to be revised as further relevant information becomes available.

In the United States during the last 50 years, 4 of the 7 reported primary pneumonic plague patients died.¹² Fatality rates depend on various factors including time to 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.^{14,24,25,33}

Historically, the preferred treatment for plague infection has been streptomycin, an FDA-approved treatment for plague.^{21,34,35} Administered early during the disease, streptomycin has reduced overall plague mortality to the 5% to 14% range.^{12,21,34} 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 successfully³⁶⁻³⁹ and is recommended as an acceptable alternative by experts.^{23,40} In 1 case series, 8 patients with plague were treated with gentamicin with morbidity or mortality equivalent to that of patients treated with streptomycin (Lucy Boulanger, MD, Indian Health Services, Crown Point, NM, written communication, July 20, 1999). In vitro studies and an in vivo study in mice show equal or improved activity of gentamicin against many strains of *Y pestis* when compared with streptomycin.^{41,42} In addition, gentamicin is widely available, inexpensive, and can be given once daily.³⁵

Tetracycline and doxycycline also have been used in the treatment and prophylaxis of plague; both are FDA approved for these purposes. In vitro studies have shown that *Y pestis* susceptibility to tetracycline⁴³ and doxycycline^{41,44} is equivalent to that of the aminoglycosides. In another investigation, 13% of *Y pestis* strains in Madagascar were found to have some in vitro resistance to tetracycline.⁴⁵ Experimental murine models of *Y pestis* infection have yielded data that are difficult to extrapolate to humans. Some mouse studies have shown doxycycline to be a highly efficacious treatment of infection^{44,46} or prophylaxis⁴⁷ against na-

turally occurring plague strains. Experimental murine infection with F₁-deficient variants of *Y pestis* have shown decreased efficacy of doxycycline,^{47,48} but only 1 human case of F₁-deficient plague infection has been reported.⁴⁹ Russell and colleagues⁵⁰ reported poor efficacy of doxycycline against plague-infected mice, but the dosing schedules used in this experiment would have failed to maintain drug levels above the minimum inhibitory concentration due to the short half-life of doxycycline in mice. In another study, doxycycline failed to prevent death in mice intraperitoneally infected with 29 to 290 000 times the median lethal inocula of *Y pestis*.⁵¹

There are no controlled clinical trials comparing either tetracycline or doxycycline to aminoglycoside 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.^{23,27,38-40,52-54} Based on evidence from in vitro studies, animal studies, and uncontrolled human data, the working group recommends that the tetracycline class of antibiotics be used to treat pneumonic plague if aminoglycoside therapy cannot be administered. This might be the case in a mass casualty scenario when parenteral therapy was either unavailable or impractical. Doxycycline would be considered pharmacologically superior to other antibiotics in the tetracycline class for this indication, because it is well absorbed without food interactions, is well distributed with good tissue penetration, and has a long half-life.³⁵

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.^{44,50,51} In vitro studies also suggest equivalent or greater activity of ciprofloxacin, levofloxacin, and ofloxacin against *Y pestis* when compared with aminoglycosides or tetracyclines.^{41,55} However, there have been no

trials of fluoroquinolones in human plague, and they are not FDA approved for this indication.

Chloramphenicol has been used to treat plague infection and has been recommended for treatment of plague meningitis because of its ability to cross the blood-brain barrier.^{21,34} However, human clinical trials demonstrating the superiority of chloramphenicol in the therapy of classic plague infection or plague meningitis have not been performed. It has been associated with dose dependent hematologic abnormalities and with rare idiosyncratic fatal aplastic anemia.³⁵

A number of different sulfonamides have been used successfully in the treatment of human plague infection: sulfathiazole,⁵⁶ sulfadiazine, sulfamerazine, and trimethoprim-sulfamethoxazole.^{57,58} 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.⁵⁹ 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.⁵⁸ Authorities have generally considered trimethoprim-sulfamethoxazole a second-tier choice.^{21,23,34} Some have recommended sulfonamides only in the setting of pediatric prophylaxis.²² 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.⁴²

Antibiotic resistance patterns must also be considered in making treatment recommendations. Naturally occurring antibiotic resistance to the tetracycline class of drugs has occurred rarely.⁴ Recently, a plasmid-mediated multidrug-resistant strain was isolated in Madagascar.⁶⁰ A report published by Russian scientists cited quinolone-resistant *Y pestis*.⁶¹ There have been assertions that Russian scientists have en-

gineered multidrug-resistant strains of *Y pestis*,⁸ although there is as yet no scientific publication confirming this.

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 (TABLE 2). 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 (Table 2).

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.²³

Once it was known or strongly suspected that pneumonic plague cases were 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.³⁹ Clinical deterioration of patients despite early initiation of empiric therapy could signal antimicrobial resistance and should be promptly evaluated.

Table 2. Working Group Recommendations 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, 1 g 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 3 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/d)
	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 3 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 choice Chloramphenicol, 25 mg/kg orally 4 times daily§**
Children¶¶	Preferred choice Doxycycline, †† If ≥45 kg, 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†† 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 Food and Drug Administration. See "Therapy" section for explanations. One antimicrobial agent should be selected. Therapy should be continued for 10 days. Oral therapy should be substituted when patient's condition improves. IM indicates intramuscularly; IV, 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 in clinical practice. Neonates up to 1 week of age and premature infants should receive gentamicin, 2.5 mg/kg IV twice daily.

‡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 µg/mL can cause reversible bone marrow suppression.^{35,62}

¶Refer to "Management of Special Groups" for details. In children, ciprofloxacin dose should not exceed 1 g/d, chloramphenicol should not exceed 4 g/d. Children younger than 2 years should not receive chloramphenicol.

¶¶Refer to "Management of Special Groups" for details and for discussion of breastfeeding women. In neonates, gentamicin loading dose of 4 mg/kg should be given initially.⁶³

#Duration of treatment of plague in mass casualty setting is 10 days. Duration of postexposure prophylaxis to prevent plague infection is 7 days.

**Children younger than 2 years should not receive chloramphenicol. Oral formulation available only outside the United States.

††Tetracycline could be substituted for doxycycline.

Management of Special Groups

Consensus recommendations for special groups as set forth in the following reflect the clinical and evidence-based judgments of the working group and do not necessarily correspond to FDA approved use, indications, or labeling.

Children. The treatment of choice for plague in children has been streptomycin or gentamicin.^{21,40} 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.^{35,40} 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.³⁵ Chloramphenicol is considered safe in children except for children younger than 2 years who are at risk of "gray baby syndrome."^{35,40} Some concern exists that fluoroquinolone use in children may cause arthropathy,³⁵ although fluoroquinolones have been used to treat serious infections in children.⁶⁴ No comparative studies assessing efficacy or safety of alternative treatment strategies for plague in children has or can be performed.

Given these considerations, the working group recommends that children in the contained casualty setting receive streptomycin or gentamicin. In a mass casualty setting or for postexposure prophylaxis, we recommend that doxycycline be used. Alternatives are listed for both settings (Table 2). 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,^{35,65} but there is no more efficacious treatment for pneumonic plague. Therefore, the working group recommends that pregnant women in

the contained casualty setting receive gentamicin (Table 2). Since streptomycin has been associated with rare reports of irreversible deafness in children following fetal exposure, this medication should be avoided if possible.³⁵ The tetracycline class of antibiotics has been associated with fetal toxicity including retarded skeletal growth,³⁵ although a large case-control study of doxycycline use in pregnancy showed no significant increase in teratogenic risk to the fetus.⁶⁶ 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.³⁵ Balancing the risks of pneumonic plague infection with those associated with doxycycline use in pregnancy, the working group recommends 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 classification⁶⁵; 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 (Table 2).

The working group 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 (Table 2).

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.

POSTEXPOSURE PROPHYLAXIS RECOMMENDATIONS

The working group recommends 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 (Table 2). For infants in this setting, tachypnea would also be an additional indication for immediate treatment.²⁹ 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 days²⁹ and watch for fever and cough. Close contact is defined as contact with a patient at less than 2 meters.^{16,31} Tetracycline, doxycycline, sulfonamides, and chloramphenicol have each been used or recommended as postexposure prophylaxis in this setting.^{16,22,29,31,59} Fluoroquinolones could also be used based on studies in mice.⁵¹

The working group recommends the use of doxycycline as the first choice antibiotic for postexposure prophylaxis; other recommended antibiotics are noted (Table 2). Contacts who develop fever or cough while receiving prophylaxis should seek prompt medical attention and begin antibiotic treatment as described in Table 2.

INFECTION CONTROL

Previous public health guidelines have advised strict isolation for all close contacts of patients with pneumonic plague who refuse prophylaxis.²⁹ In the modern setting, however, pneumonic plague has not spread widely or rapidly in a community,^{4,14,24} 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.¹⁴⁻¹⁷ In large pneumonic plague epidemics earlier this century, pneumonic plague transmission was prevented in close contacts by wearing masks.^{14,16,17} Commensurate with this, existing national infection control guidelines recommend the use of disposable surgical masks to prevent the transmission of pneumonic plague.^{29,67}

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.^{29,31}

The patient should remain isolated during the first 48 hours of antibiotic therapy and until clinical improvement occurs.^{29,31,59} If large numbers of pa-

tients 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.²⁹

Microbiology laboratory personnel should be alerted when *Y pestis* is suspected. Four laboratory-acquired cases of plague have been reported in the United States.⁶⁸ Simple clinical materials and cultures should be processed in biosafety level 2 conditions.^{31,69} 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.⁶⁹

Bodies of patients who have died following infection with plague should be handled with routine strict precautions.²⁹ 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.⁷⁰ 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.⁷¹

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 sporulat-

ing 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.⁷² Although some reports suggest that the bacterium may survive in the soil for some time,⁷² 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.⁷ In the setting of a clandestine release of plague bacilli, the aerosol would have dissipated long before the first case of pneumonic plague occurred.

ADDITIONAL RESEARCH

Improving the medical and public health response to an outbreak of plague following the use of a biological weapon will require additional knowledge of the organism, its genetics, and pathogenesis. In addition, improved rapid diagnostic and standard laboratory microbiology techniques are necessary. An improved understanding of prophylactic and therapeutic antibiotic regimens would be of benefit in defining optimal antibiotic strategy.

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