

Anthrax as a Biological Weapon, 2002

Updated Recommendations for Management

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Objective To review and update consensus-based recommendations for medical and public health professionals following a *Bacillus anthracis* attack against a civilian population.

Participants The working group included 23 experts from academic medical centers, research organizations, and governmental, military, public health, and emergency management institutions and agencies.

Evidence MEDLINE databases were searched from January 1966 to January 2002, using the Medical Subject Headings *anthrax*, *Bacillus anthracis*, *biological weapon*, *biological terrorism*, *biological warfare*, and *biowarfare*. Reference review identified work published before 1966. Participants identified unpublished sources.

Consensus Process The first draft synthesized the gathered information. Written comments were incorporated into subsequent drafts. The final statement incorporated all relevant evidence from the search along with consensus recommendations.

Conclusions Specific recommendations include diagnosis of anthrax infection, indications for vaccination, therapy, postexposure prophylaxis, decontamination of the environment, and suggested research. This revised consensus statement presents new information based on the analysis of the anthrax attacks of 2001, including developments in the investigation of the anthrax attacks of 2001; important symptoms, signs, and laboratory studies; new diagnostic clues that may help future recognition of this disease; current anthrax vaccine information; updated antibiotic therapeutic considerations; and judgments about environmental surveillance and decontamination.

JAMA. 2002;287:2236-2252

www.jama.com

OF THE BIOLOGICAL AGENTS that may be used as weapons, the Working Group on Civilian Biodefense identified a limited number of organisms that, in worst case scenarios, could cause disease and deaths in sufficient numbers to gravely impact a city or region. *Bacillus anthracis*, the bacterium that causes anthrax, is one of the most serious of these.

Several countries are believed to have offensive biological weapons programs, and some independent terrorist groups have suggested their intent to use biological weapons. Because the possibility of a terrorist attack using bioweapons is especially difficult to predict, detect, or prevent, it is among the most feared terrorism scenarios.¹ In September 2001, *B anthracis* spores were sent

to several locations via the US Postal Service. Twenty-two confirmed or suspect cases of anthrax infection resulted. Eleven of these were inhalational cases, of whom 5 died; 11 were cutaneous cases (7 confirmed, 4 suspected).² In this article, these attacks are termed *the anthrax attacks of 2001*. The consequences of these attacks substantiated many findings and recommendations in the Working Group on Civilian Biodefense's previous consensus statement published in 1999³; however, the new information from these attacks warrant updating the previous statement.

Before the anthrax attacks in 2001, modern experience with inhalational anthrax was limited to an epidemic in Sverdlovsk, Russia, in 1979 following an unintentional release of *B anthracis* spores from a Soviet bioweapons fac-

tory and to 18 occupational exposure cases in the United States during the 20th century. Information about the potential impact of a large, covert attack using *B anthracis* or the possible effi-

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cacy of postattack vaccination or therapeutic measures remains limited. Policies and strategies continue to rely partially on interpretation and extrapolation from an incomplete and evolving knowledge base.

CONSENSUS METHODS

The working group comprised 23 representatives from academic medical centers; research organizations; and government, military, public health, and emergency management institutions and agencies. For the original consensus statement,³ we searched MEDLINE databases from January 1966 to April 1998 using Medical Subject Headings of *anthrax*, *Bacillus anthracis*, *biological weapon*, *biological terrorism*, *biological warfare*, and *biowarfare*. Reference review identified work published before 1966. Working group members identified unpublished sources.

The first consensus statement, published in 1999,³ followed a synthesis of the information and revision of 3 drafts. We reviewed anthrax literature again in January 2002, with special attention to articles following the anthrax attacks of 2001. Members commented on a revised document; proposed revisions were incorporated with the working group's support for the final consensus document.

The assessment and recommendations provided herein represent our best professional judgment based on current data and expertise. The conclusions and recommendations need to be regularly reassessed as new information develops.

HISTORY OF CURRENT THREAT

For centuries, *B anthracis* has caused disease in animals and serious illness in humans.⁴ Research on anthrax as a biological weapon began more than 80 years ago.⁵ Most national offensive bioweapons programs were terminated following widespread ratification or signing of the Biological Weapons Convention (BWC) in the early 1970s⁶; the US offensive bioweapons program was terminated after President Nixon's 1969 and 1970 executive

orders. However, some nations continued offensive bioweapons development programs despite ratification of the BWC. In 1995, Iraq acknowledged producing and weaponizing *B anthracis* to the United Nations Special Commission.⁷ The former Soviet Union is also known to have had a large *B anthracis* production program as part of its offensive bioweapons program.⁸ A recent analysis reports that there is clear evidence of or widespread assertions from nongovernmental sources alleging the existence of offensive biological weapons programs in at least 13 countries.⁶

The anthrax attacks of 2001 have heightened concern about the feasibility of large-scale aerosol bioweapons attacks by terrorist groups. It has been feared that independent, well-funded groups could obtain a manufactured weapons product or acquire the expertise and resources to produce the materials for an attack. However, some analysts have questioned whether "weapons grade" material such as that used in the 2001 attacks (ie, powders of *B anthracis* with characteristics such as high spore concentration, uniform particle size, low electrostatic charge, treated to reduce clumping) could be produced by those not supported by the resources of a nation-state. The US Department of Defense recently reported that 3 defense employees with some technical skills but without expert knowledge of bioweapons manufactured a simulant of *B anthracis* in less than a month for \$1 million.⁹ It is reported that Aum Shinrikyo, the cult responsible for the 1995 release of sarin nerve gas in a Tokyo subway station,¹⁰ dispersed aerosols of anthrax and botulism throughout Tokyo at least 8 times.¹¹ Forensic analysis of the *B anthracis* strain used in these attacks revealed that this isolate most closely matched the Sterne 34F2 strain, which is used for animal vaccination programs and is not a significant risk to humans.¹² It is probable that the cult attacks produced no illnesses for this and other technical reasons. Al Qaeda also has sought to acquire bioweapons in its terrorist planning efforts although the ex-

tent to which they have been successful is not reported.¹³

In the anthrax attacks of 2001, *B anthracis* spores were sent in at least 5 letters to Florida, New York City, and Washington, DC. Twenty-two confirmed or suspected cases resulted. All of the identified letters were mailed from Trenton, NJ. The *B anthracis* spores in all the letters were identified as the Ames strain. The specific source (provenance) of *B anthracis* cultures used to create the spore-containing powder remains unknown at time of this publication.

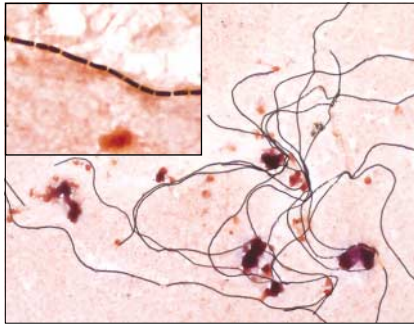
It is now recognized that the original Ames strain of *B anthracis* did not come from a laboratory in Ames, Iowa, rather from a laboratory in College Station, Tex. Several distinct Ames strains have been recognized by investigating scientists, which are being compared with the Ames strain used in the attack. At least 1 of these comparison Ames strains was recovered from a goat that died in Texas in 1997.¹⁴

Sen Daschle's letter reportedly had 2 g of *B anthracis* containing powder; the quantity in the other envelopes has not been disclosed. The powder has been reported to contain between 100 billion to 1 trillion spores per gram¹⁵ although no official analysis of the concentration of spores or the chemical composition of the powder has been published.

The anthrax attacks of 2001 used 1 of many possible methods of attack. The use of aerosol-delivery technologies inside buildings or over large outdoor areas is another method of attack that has been studied. In 1970, the World Health Organization¹⁶ and in 1993 the Office of Technology Assessment¹⁷ analyzed the potential scope of larger attacks. The 1979 Sverdlovsk accident provides data on the only known aerosol release of *B anthracis* spores resulting in an epidemic.¹⁸

An aerosol release of *B anthracis* would be odorless and invisible and would have the potential to travel many kilometers before dissipating.^{16,19} Aerosol technologies for large-scale dissemination have been developed and tested

Figure 1. Gram Stain of Blood in Culture Media



Gram-positive bacilli in long chains (original magnification $\times 20$). Enlargement shows typical "jointed bamboo-rod" appearance of *Bacillus anthracis* (original magnification $\times 100$). Reprinted from Borio et al.³⁶

by Iraq⁷ and the former Soviet Union⁸ Few details of those tests are available. The US military also conducted such trials over the Pacific Ocean in the 1960s. A US study near Johnston Atoll in the South Pacific reported a plane "sprayed a 32-mile long line of agent that traveled for more than 60 miles before it lost its infectiousness."²⁰

In 1970, the World Health Organization estimated that 50 kg of *B anthracis* released over an urban population of 5 million would sicken 250 000 and kill 100 000.¹⁶ A US Congressional Office of Technology assessment analysis from 1993 estimated that between 130 000 and 3 million deaths would follow the release of 100 kg of *B anthracis*, a lethality matching that of a hydrogen bomb.¹⁷

EPIDEMIOLOGY OF ANTHRAX

Naturally occurring anthrax in humans is a disease acquired from contact with anthrax-infected animals or anthrax-contaminated animal products. The disease most commonly occurs in herbivores, which are infected after ingesting spores from the soil. Large anthrax epizootics in herbivores have been reported.²¹ A published report states that anthrax killed 1 million sheep in Iran in 1945²²; this number is supported by an unpublished Iranian governmental document.²³ Animal vaccination programs

have reduced drastically the animal mortality from the disease.²⁴ However, *B anthracis* spores remain prevalent in soil samples throughout the world and cause anthrax cases among herbivores annually.^{22,25,26}

Anthrax infection occurs in humans by 3 major routes: inhalational, cutaneous, and gastrointestinal. Naturally occurring inhalational anthrax is now rare. Eighteen cases of inhalational anthrax were reported in the United States from 1900 to 1976; none were identified or reported thereafter. Most of these cases occurred in special-risk groups, including goat hair mill or wool or tannery workers; 2 of them were laboratory associated.²⁷

Cutaneous anthrax is the most common naturally occurring form, with an estimated 2000 cases reported annually worldwide.²⁶ The disease typically follows exposure to anthrax-infected animals. In the United States, 224 cases of cutaneous anthrax were reported between 1944 and 1994.²⁸ One case was reported in 2000.²⁹ The largest reported epidemic occurred in Zimbabwe between 1979 and 1985, when more than 10 000 human cases of anthrax were reported, nearly all of them cutaneous.³⁰

Although gastrointestinal anthrax is uncommon, outbreaks are continually reported in Africa and Asia^{26,31,32} following ingestion of insufficiently cooked contaminated meat. Two distinct syndromes are oral-pharyngeal and abdominal.^{31,33,34} Little information is available about the risks of direct contamination of food or water with *B anthracis* spores. Experimental efforts to infect primates by direct gastrointestinal instillation of *B anthracis* spores have not been successful.³⁵ Gastrointestinal infection could occur only after consumption of large numbers of vegetative cells, such as what might be found in raw or undercooked meat from an infected herbivore, but experimental data is lacking.

Inhalational anthrax is expected to account for most serious morbidity and most mortality following the use of *B anthracis* as an aerosolized biological weapon. Given the absence of natu-

rally occurring cases of inhalational anthrax in the United States since 1976, the occurrence of a single case is now cause for alarm.

MICROBIOLOGY

B anthracis derives from the Greek word for coal, *anthrakis*, because of the black skin lesions it causes. *B anthracis* is an aerobic, gram-positive, spore-forming, nonmotile *Bacillus* species. The non-flagellated vegetative cell is large (1-8 μm long, 1-1.5 μm wide). Spore size is approximately 1 μm . Spores grow readily on all ordinary laboratory media at 37°C, with a "jointed bamboo-rod" cellular appearance (FIGURE 1) and a unique "curled-hair" colonial appearance. Experienced microbiologists should be able to identify this cellular and colonial morphology; however, few practicing microbiologists outside the veterinary community have seen *B anthracis* colonies beyond what they may have seen in published material.³⁷ *B anthracis* spores germinate when they enter an environment rich in amino acids, nucleosides, and glucose, such as that found in the blood or tissues of an animal or human host. The rapidly multiplying vegetative *B anthracis* bacilli, on the contrary, will only form spores after local nutrients are exhausted, such as when anthrax-infected body fluids are exposed to ambient air.²² Vegetative bacteria have poor survival outside of an animal or human host; colony counts decline to being undetectable within 24 hours following inoculation into water.²² This contrasts with the environmentally hardy properties of the *B anthracis* spore, which can survive for decades in ambient conditions.³⁷

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Inhalational Anthrax

Inhalational anthrax follows deposition into alveolar spaces of spore-bearing particles in the 1- to 5- μm range.^{38,39} Macrophages then ingest the spores, some of which are lysed and destroyed. Surviving spores are transported via lymphatics to mediastinal lymph nodes, where germination oc-

curs after a period of spore dormancy of variable and possibly extended duration.^{35,40,41} The trigger(s) responsible for the transformation of *B anthracis* spores to vegetative cells is not fully understood.⁴² In Sverdlovsk, cases occurred from 2 to 43 days after exposure.¹⁸ In experimental infection of monkeys, fatal disease occurred up to 58 days⁴⁰ and 98 days⁴³ after exposure. Viable spores were demonstrated in the mediastinal lymph nodes of 1 monkey 100 days after exposure.⁴⁴

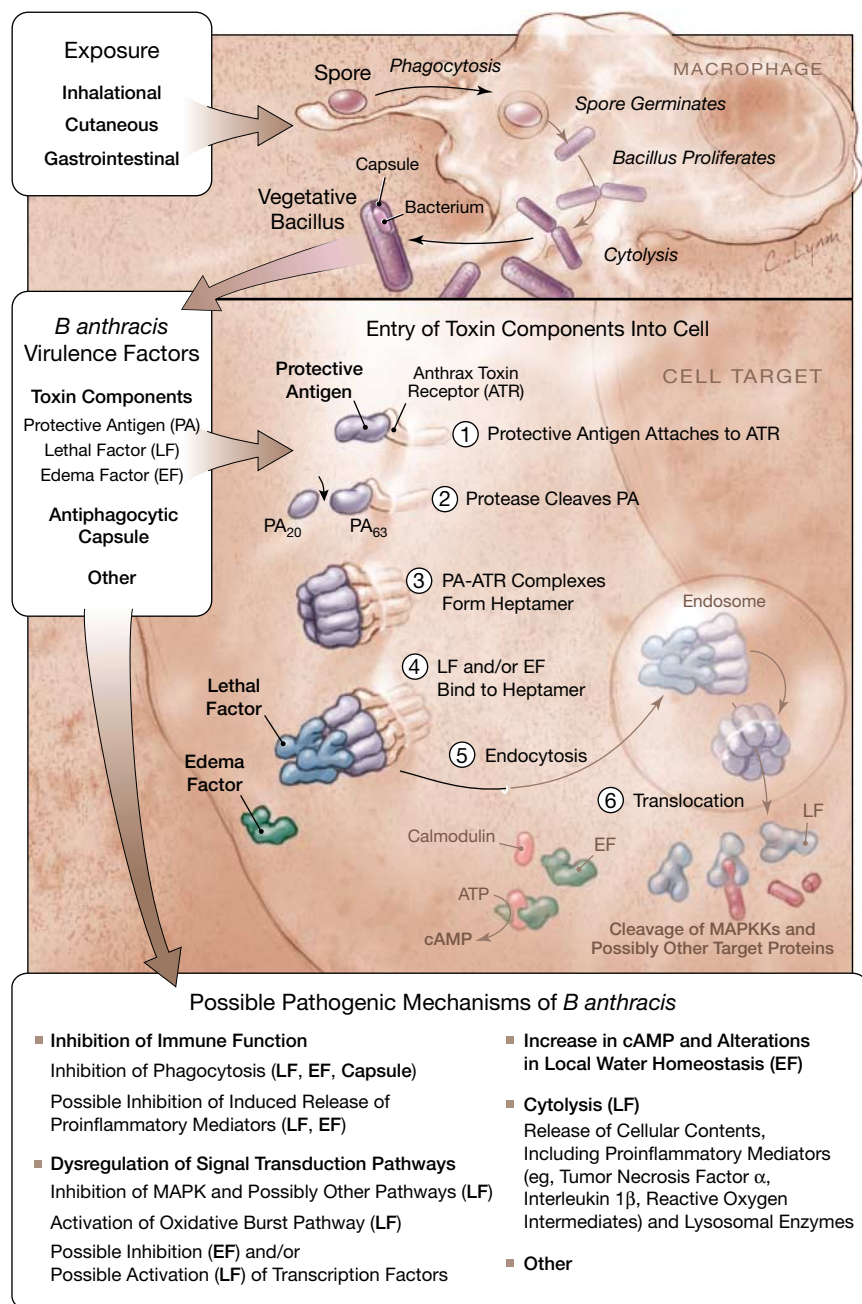
Once germination occurs, clinical symptoms follow rapidly. Replicating *B anthracis* bacilli release toxins that lead to hemorrhage, edema, and necrosis.^{32,45} In experimental animals, once toxin production has reached a critical threshold, death occurs even if sterility of the bloodstream is achieved with antibiotics.²⁷ Extrapolations from animal data suggest that the human LD₅₀ (ie, dose sufficient to kill 50% of persons exposed to it) is 2500 to 55000 inhaled *B anthracis* spores.⁴⁶ The LD₁₀ was as low as 100 spores in 1 series of monkeys.⁴³ Recently published extrapolations from primate data suggest that as few as 1 to 3 spores may be sufficient to cause infection.⁴⁷ The dose of spores that caused infection in any of the 11 patients with inhalational anthrax in 2001 could not be estimated although the 2 cases of fatal inhalational anthrax in New York City and Connecticut provoked speculation that the fatal dose, at least in some individuals, may be quite low.

A number of factors contribute to the pathogenesis of *B anthracis*, which makes 3 toxins—*protective antigen*, *lethal factor*, and *edema factor*—that combine to form 2 toxins: lethal toxin and edema toxin (FIGURE 2). The protective antigen allows the binding of lethal and edema factors to the affected cell membrane and facilitates their subsequent transport across the cell membrane. Edema toxin impairs neutrophil function in vivo and affects water homeostasis leading to edema, and lethal toxin causes release of tumor necrosis factor α and interleukin 1 β , factors that are believed to be linked to the

sudden death in severe anthrax infection.⁴⁸ The molecular target of lethal and edema factors within the affected cell is not yet elucidated.⁴⁹ In addition to

these virulence factors, *B anthracis* has a capsule that prevents phagocytosis. Full virulence requires the presence of both an antiphagocytic capsule and the

Figure 2. Pathogenesis of *Bacillus anthracis*



The major known virulence factors of *B anthracis* include the exotoxins edema toxin (PA and EF) and lethal toxin (PA and LF) and the antiphagocytic capsule. Although many exact molecular mechanisms involved in the pathogenicity of the anthrax toxins are uncertain, they appear to inhibit immune function, interrupt intracellular signaling pathways, and lyse cell targets causing massive release of proinflammatory mediators. ATP indicates adenosine triphosphate; cAMP, cyclic adenosine monophosphate; MAPKK, mitogen-activated protein kinase kinase; and MAPK, mitogen-activated protein kinase.

Table 1. Initial Symptoms, Physical Findings, and Test Results in Patients With Inhalational Anthrax Following US Anthrax Attacks in October and November 2001*

Symptoms (N = 10)	
Fever and chills	10
Sweats, often drenching	7
Fatigue, malaise, lethargy	10
Cough, minimal	9
or nonproductive	
Nausea or vomiting	9
Dyspnea	8
Chest discomfort or	7
pleuritic pain	
Myalgias	6
Headache	5
Confusion	4
Abdominal pain	3
Sore throat	2
Rhinorrhea	1
Physical Findings	
Fever >37.8°C	7
Tachycardia, heart rate	8
>100/min	
Hypotension, <110 mm Hg	1
Laboratory Results	
White blood cell count, median	9800 × 10 ³ /μL
Differential neutrophilia, >70%	7
Neutrophil band forms, >5%	4†
Elevated transaminases,	9
SGOT or SPGT >40 U/L‡	
Hypoxemia, alveolar-arterial	6
oxygen gradient >30 mm Hg	
on room air oxygen	
saturation <94%	
Metabolic acidosis	2
Elevated creatinine,	1
>1.5 mg/dL (132.6 μmol/L)	
Chest X-ray Film Findings	
Any abnormality	10
Mediastinal widening	7
Infiltrates or consolidation	7
Pleural effusion	8
Chest Computed Tomographic Findings§	
Any abnormality	8
Mediastinal lymphadenopathy,	7
widening	
Pleural effusion	8
Infiltrates or consolidation	6

*This table was adapted with permission from Jernigan, et al.⁶¹

†Five persons had laboratory results measuring neutrophil band forms.

‡SGOT indicates serum glutamic oxalacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

§Eight persons had computed tomographic scan results.

3 toxin components.³⁷ An additional factor contributing to *B anthracis* pathogenesis is the high concentration of bacteria occurring in affected hosts.⁴⁹

Inhalational anthrax reflects the nature of acquisition of the disease. The term *anthrax pneumonia* is misleading because typical bronchopneumonia does not occur. Postmortem pathological studies of patients from Sverdlovsk

showed that all patients had hemorrhagic thoracic lymphadenitis, hemorrhagic mediastinitis, and pleural effusions. About half had hemorrhagic meningitis. None of these autopsies showed evidence of a bronchoalveolar pneumonic process although 11 of 42 patient autopsies had evidence of a focal, hemorrhagic, necrotizing pneumonic lesion analogous to the Ghon complex associated with tuberculosis.⁵⁰ These findings are consistent with other human case series and experimentally induced inhalational anthrax in animals.^{40,51,52} A recent reanalysis of pathology specimens from 41 of the Sverdlovsk patients was notable primarily for the presence of necrotizing hemorrhagic mediastinitis; pleural effusions averaging 1700 mL in quantity; meningitis in 50%; arteritis and arterial rupture in many; and the lack of prominent pneumonitis. *B anthracis* was recovered in concentrations of up to 100 million colony-forming units per milliliter in blood and spinal fluid.⁵³

In animal models, physiological sequelae of severe anthrax infection have included hypocalcemia, profound hypoglycemia, hyperkalemia, depression and paralysis of respiratory center, hypotension, anoxia, respiratory alkalosis, and terminal acidosis,^{54,55} suggesting that besides the rapid administration of antibiotics, survival might improve with vigilant correction of electrolyte disturbances and acid-based imbalance, glucose infusion, and early mechanical ventilation and vasopressor administration.

Historical Data. Early diagnosis of inhalational anthrax is difficult and requires a high index of suspicion. Prior to the 2001 attacks, clinical information was limited to a series of 18 cases reported in the 20th century and the limited data from Sverdlovsk. The clinical presentation of inhalational anthrax had been described as a 2-stage illness. Patients reportedly first developed a spectrum of nonspecific symptoms, including fever, dyspnea, cough, headache, vomiting, chills, weakness, abdominal pain, and chest pain.^{18,27} Signs of illness and laboratory studies

were nonspecific. This stage of illness lasted from hours to a few days. In some patients, a brief period of apparent recovery followed. Other patients progressed directly to the second, fulminant stage of illness.^{4,27,56}

This second stage was reported to have developed abruptly, with sudden fever, dyspnea, diaphoresis, and shock. Massive lymphadenopathy and expansion of the mediastinum led to stridor in some cases.^{57,58} A chest radiograph most often showed a widened mediastinum consistent with lymphadenopathy.⁵⁷ Up to half of patients developed hemorrhagic meningitis with concomitant meningismus, delirium, and obtundation. In this second stage, cyanosis and hypotension progressed rapidly; death sometimes occurred within hours.^{4,27,56}

In the 20th-century series of US cases, the mortality rate of occupationally acquired inhalational anthrax was 89%, but the majority of these cases occurred before the development of critical care units and, in most cases, before the advent of antibiotics.²⁷ At Sverdlovsk, it had been reported that 68 of the 79 patients with inhalational anthrax died.¹⁸ However a separate report from a hospital physician recorded 358 ill with 45 dead; another recorded 48 deaths among 110 patients.⁵⁹ A recent analysis of available Sverdlovsk data suggests there may have been as many as 250 cases with 100 deaths.⁶⁰ Sverdlovsk patients who had onset of disease 30 or more days after release of organisms had a higher reported survival rate than those with earlier disease onset. Antibiotics, antianthrax globulin, corticosteroids, mechanical ventilation, and vaccine were used to treat some residents in the affected area after the accident, but how many were given vaccine and antibiotics is unknown, nor is it known which patients received these interventions or when. It is also uncertain if the *B anthracis* strain (or strains) to which patients was exposed were susceptible to the antibiotics used during the outbreak. However, a community-wide intervention about the 15th day after exposure did appear to diminish the projected attack rate.⁶⁰ In fatal cases, the

interval between onset of symptoms and death averaged 3 days. This is similar to the disease course and case fatality rate in untreated experimental monkeys, which have developed rapidly fatal disease even after a latency as long as 58 days.⁴⁰

2001 Attacks Data. The anthrax attacks of 2001 resulted in 11 cases of inhalational anthrax, 5 of whom died. Symptoms, signs, and important laboratory data from these patients are listed in TABLE 1. Several clinical findings from the first 10 patients with inhalational anthrax deserve emphasis.^{36,61-66} Malaise and fever were presenting symptoms in all 10 cases. Cough, nausea, and vomiting were also prominent. Drenching sweats, dyspnea, chest pain, and headache were also seen in a majority of patients. Fever and tachycardia were seen in the majority of patients at presentation, as were hypoxemia and elevations in transaminases.

Importantly, all 10 patients had abnormal chest x-ray film results: 7 had mediastinal widening; 7 had infiltrates; and 8 had pleural effusions. Chest computed tomographic (CT) scans showed abnormal results in all 8 patients who had this test: 7 had mediastinal widening; 6, infiltrates; 8, pleural effusions.

Data are insufficient to identify factors associated with survival although early recognition and initiation of treatment and use of more than 1 antibiotic have been suggested as possible factors.⁶¹ For the 6 patients for whom such information is known, the median period from presumed time of exposure to the onset of symptoms was 4 days (range, 4-6 days). Patients sought care a median of 3.5 days after symptom onset. All 4 patients exhibiting signs of fulminant illness prior to antibiotic administration died.⁶¹ Of note, the incubation period of the 2 fatal cases from New York City and Connecticut is not known.

Cutaneous Anthrax

Historically, cutaneous anthrax has been known to occur following the deposition of the organism into skin;

previous cuts or abrasions made one especially susceptible to infection.^{30,67} Areas of exposed skin, such as arms, hands, face, and neck, were the most frequently affected. In Sverdlovsk, cutaneous cases occurred only as late as 12 days after the original aerosol release; no reports of cutaneous cases appeared after prolonged latency.¹⁸

After the spore germinates in skin tissues, toxin production results in local edema. An initially pruritic macule or papule enlarges into a round ulcer by the second day. Subsequently, 1- to 3-mm vesicles may appear that discharge clear or serosanguinous fluid containing numerous organisms on Gram stain. As shown in FIGURE 3, development of a painless, depressed, black eschar follows, often associated with extensive local edema. The anthrax eschar dries, loosens, and falls off in the next 1 to 2 weeks. Lymphangitis and painful lymphadenopathy can occur with associated systemic symptoms. Differential diagnosis of eschars includes tularemia, scrub typhus, rickettsial spotted fevers, rat bite fever, and ecthyma gangrenosum.⁶⁸ Non-infectious causes of eschars include arachnid bites⁶³ and vasculitides. Although antibiotic therapy does not appear to change the course of eschar formation and healing, it does decrease the likelihood of systemic disease. Without antibiotic therapy, the mortality rate has been reported to be as high as 20%; with appropriate antibiotic treatment, death due to cutaneous anthrax has been reported to be rare.⁴

Following the anthrax attacks of 2001, there have been 11 confirmed or probable cases of cutaneous anthrax. One case report of cutaneous anthrax resulting from these attacks has been published (Figure 3).⁶³ This child had no reported evidence of prior visible cuts, abrasions, or lesions at the site of the cutaneous lesion that developed. The mean incubation period for cutaneous anthrax cases diagnosed in 2001 was 5 days, with a range of 1 to 10 days, based on estimated dates of exposure to *B anthracis*-contaminated letters. Cutaneous lesions occurred on the forearm, neck, chest, and fingers.⁶⁹

Figure 3. Lesion of Cutaneous Anthrax Associated With Microangiopathic Hemolytic Anemia and Coagulopathy in a 7-Month-Old Infant



By hospital day 12, a 2-cm black eschar was present in the center of the cutaneous lesion. Reprinted from Freedman et al.⁶³

The only published case report of cutaneous anthrax from the attacks of 2001 is notable for the difficulty in recognition of the disease in a previously healthy 7-month-old, the rapid progression to severe systemic illness despite hospitalization, and clinical manifestations that included microangiopathic hemolytic anemia with renal involvement, coagulopathy, and hyponatremia.⁶³ Fortunately, this child recovered, and none of the cutaneous cases of anthrax diagnosed after the 2001 attacks were fatal.

Gastrointestinal Anthrax

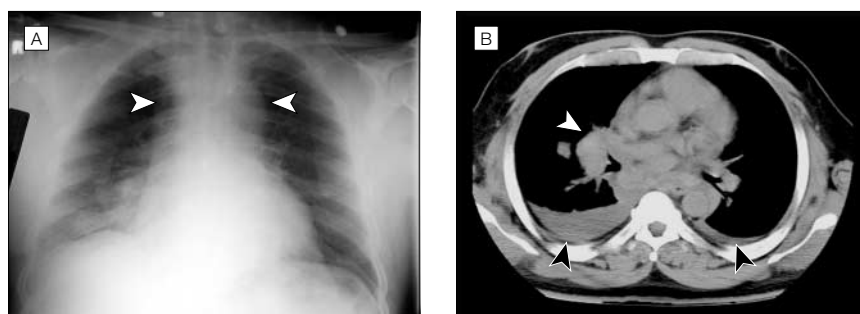
Some think gastrointestinal anthrax occurs after deposition and germination of spores in the upper or lower gastrointestinal tract. However, considering the rapid transit time in the gastrointestinal tract, it seems more likely that many such cases must result from the ingestion of large numbers of vegetative bacilli from poorly cooked infected meat rather than from spores. In any event, the oral-pharyngeal form of disease results in an oral or esophageal ulcer and leads to the development of regional lymphadenopathy, edema, and sepsis.^{31,33} Disease in the lower gastrointestinal tract manifests as primary intestinal lesions occurring predominantly in the terminal ileum or cecum,⁵⁰ presenting initially with nausea, vomiting, and malaise and progressing rapidly to bloody diarrhea, acute abdomen, or sep-

Table 2. Diagnosis of Inhalational Anthrax Infection*

Category	Findings
Epidemiology	Sudden appearance of several cases of severe acute febrile illness with fulminant course and death or Acute febrile illness in persons identified as being at risk following a specific attack (eg, those in the 2001 attacks: postal workers, members of the news media, and politicians and their staff)
Diagnostic tests	Chest radiograph: widened mediastinum, infiltrates, pleural effusion Chest computed tomographic scan: hyperdense hilar and mediastinal nodes, mediastinal edema, infiltrates, pleural effusion Thoracentesis: hemorrhagic pleural effusions
Microbiology	Peripheral blood smear: gram-positive bacilli on blood smear Blood culture growth of large gram-positive bacilli with preliminary identification of <i>Bacillus</i> species†
Pathology	Hemorrhagic mediastinitis, hemorrhagic thoracic lymphadenitis, hemorrhagic meningitis; DFA stain of infected tissues

*See Table 1 for list of febrile illness symptoms and signs.

†Most rapid assays are available only at laboratories participating in the Laboratory Response Network.

Figure 4. Chest Radiograph and Computed Tomography (CT) Image

A, Portable chest radiograph of 56-year-old man with inhalational anthrax depicts a widened mediastinum (white arrowheads), bilateral hilar fullness, a right pleural effusion, and bilateral perihilar air-space disease. B, Noncontrast spiral CT scan depicts an enlarged and hyperdense right hilar lymph node (white arrowhead), bilateral pleural effusions (black arrowheads), and edema of the mediastinal fat. Reprinted from Mayer et al.⁶⁶

sis. Massive ascites has occurred in some cases of gastrointestinal anthrax.³⁴ Advanced infection may appear similar to the sepsis syndrome occurring in either inhalational or cutaneous anthrax.⁴ Some authors suggest that aggressive medical intervention as would be recommended for inhalational anthrax may reduce mortality. Given the difficulty of early diagnosis of gastrointestinal anthrax, however, mortality may be high.⁴ Postmortem examinations in Sverdlovsk showed gastrointestinal submucosal lesions in 39 of 42 patients,⁵⁰ but all of these patients were also found to have definitive pathologic evidence of an inhalational source of infection. There were no gastrointestinal cases of anthrax diagnosed in either the Sverdlovsk series or following the anthrax attacks of 2001.

DIAGNOSIS

TABLE 2 lists the epidemiology, diagnostic tests, microbiology, and pathology for a diagnosis of inhalational anthrax infection. Given the rarity of anthrax infection, the first clinical or laboratory suspicion of an anthrax illness must lead to early initiation of antibiotic treatment pending confirmed diagnosis and should provoke immediate notification of the local or state public health department, local hospital epidemiologist, and local or state public health laboratory. In the United States, a Laboratory Response Network (LRN) has been established through a collaboration of the Association of Public Health Laboratories and the CDC (details are available at: <http://www.bt.cdc.gov/LabIssues/index.asp>). Currently 81 clinical laborato-

ries in the LRN can diagnose bioweapons pathogens. Several preliminary diagnostic tests for *B anthracis* can be performed in hospital laboratories using routine procedures. *B anthracis* is a gram-positive, nonhemolytic, encapsulated, penicillin-sensitive, spore-forming bacillus. Confirmatory tests such as immuno-histochemical staining, gamma phage, and polymerase chain reaction assays must still be performed by special reference laboratories in the LRN.

The determination of individual patient exposure to *B anthracis* on the basis of environmental testing is complex due to the uncertain specificity and sensitivity of rapid field tests and the difficulty of assessing individual risks of exposure. A patient (or patients) seeking medical treatment for symptoms of inhalational anthrax will likely be the first evidence of a clandestine release of *B anthracis* as a biological weapon. The appearance of even a single previously healthy patient who becomes acutely ill with nonspecific febrile illness and symptoms and signs consistent with those listed in Table 1 and whose condition rapidly deteriorates should receive prompt consideration for a diagnosis of anthrax infection. The recognition of cutaneous cases of anthrax may also be the first evidence of an anthrax attack.⁷⁰

The likely presence of abnormal findings on either chest x-ray film or chest CT scan is diagnostically important. Although anthrax does not cause a classic bronchopneumonia pathologically, it can cause widened mediastinum, massive pleural effusions, air bronchograms, necrotizing pneumonic lesions, and/or consolidation, as has been noted above.^{36,55,56,61,64-66} The result can be hypoxemia and chest imaging abnormalities that may or may not be clinically distinguishable from pneumonia. In the anthrax attacks of 2001, each of the first 10 patients had abnormal chest x-ray film results and each of 8 patients for whom CT scans were obtained had abnormal results. These included widened mediastinum on chest radiograph and effusions on chest CT scan (FIGURE 4). Such findings in a previ-

ously healthy patient with evidence of overwhelming febrile illness or sepsis would be highly suggestive of advanced inhalational anthrax.

The bacterial burden may be so great in advanced inhalational anthrax infection that bacilli are visible on Gram stain of peripheral blood, as was seen following the 2001 attacks. The most useful microbiologic test is the standard blood culture, which should show growth in 6 to 24 hours. Each of the 8 patients who had blood cultures obtained prior to initiation of antibiotics had positive blood cultures.⁶¹ However, blood cultures appear to be sterilized after even 1 or 2 doses of antibiotics, underscoring the importance of obtaining cultures prior to initiation of antibiotic therapy (J. Gerberding, oral communication, March 7, 2002). If the laboratory has been alerted to the possibility of anthrax, biochemical testing and review of colonial morphology could provide a preliminary diagnosis 12 to 24 hours after inoculation of the cultures. Definitive diagnosis could be promptly confirmed by an LRN laboratory. However, if the clinical laboratory has not been alerted to the possibility of anthrax, *B anthracis* may not be correctly identified. Routine procedures customarily identify a *Bacillus* species in a blood culture approximately 24 hours after growth, but some laboratories do not further identify *Bacillus* species unless specifically requested. This is because the isolation of *Bacillus* species most often represents growth of the common contaminant *Bacillus cereus*.⁷¹ Given the possibility of future anthrax attacks, it is recommended that routine clinical laboratory procedures be modified, so *B anthracis* is specifically excluded after identification of a *Bacillus* species bacteremia unless there are compelling reasons not to do so. If it cannot be excluded then the isolate should be transferred to an LRN laboratory.

Sputum culture and Gram stain are unlikely to be diagnostic of inhalational anthrax, given the frequent lack of a pneumonic process.³⁷ Gram stain of sputum was reported positive in only 1 case

of inhalational anthrax in the 2001 series. If cutaneous anthrax is suspected, a Gram stain and culture of vesicular fluid should be obtained. If the Gram stain is negative or the patient is taking antibiotics already, punch biopsy should be performed, and specimens sent to a laboratory with the ability to perform immunohistochemical staining or polymerase chain reaction assays.^{69,70} Blood cultures should be obtained and antibiotics should be initiated pending confirmation of the diagnosis of inhalational or cutaneous anthrax.

Nasal swabs were obtained in some persons believed to be at risk of inhalational anthrax following the anthrax attacks of 2001. Although a study has shown the presence of *B anthracis* spores in nares of some monkeys following experimental exposure to *B anthracis* spores for some time after exposure,⁷² the predictive value of the nasal swab test for diagnosing inhalational anthrax in humans is unknown and untested. It is not known how quickly antibiotics make spore recovery on nasal swab tests impossible. One patient who died from inhalational anthrax had a negative nasal swab.³⁶ Thus, the CDC advised in the fall of 2001 that the nasal swab should not be used as a clinical diagnostic test. If obtained for an epidemiological purpose, nasal swab results should not be used to rule out infection in a patient. Persons who have positive nasal swab results for *B anthracis* should receive a course of post-exposure antibiotic prophylaxis since a positive swab would indicate that the individual had been exposed to aerosolized *B anthracis*.

Antibodies to the protective antigen (PA) of *B anthracis*, termed anti-PA IgG, have been shown to confer immunity in animal models following anthrax vaccination.^{73,74} Anti-PA IgG serologies have been obtained from several of those involved in the 2001 anthrax attacks, but the results of these assays are not yet published. Given the lack of data in humans and the expected period required to develop an anti-PA IgG response, this test should not be used as a diagnostic test for anthrax infection in the acutely

ill patient but may be useful for epidemiologic purposes.

Postmortem findings are especially important following an unexplained death. Thoracic hemorrhagic necrotizing lymphadenitis and hemorrhagic necrotizing mediastinitis in a previously healthy adult are essentially pathognomonic of inhalational anthrax.^{50,58} Hemorrhagic meningitis should also raise strong suspicion of anthrax infection.^{32,50,58,75} However, given the rarity of anthrax, a pathologist might not identify these findings as caused by anthrax unless previously alerted to this possibility.

If only a few patients present contemporaneously, the clinical similarity of early inhalational anthrax infection to other acute febrile respiratory infections may delay initial diagnosis although probably not for long. The severity of the illness and its rapid progression, coupled with unusual radiological findings, possible identification of *B anthracis* in blood or cerebrospinal fluid, and the unique pathologic findings should serve as an early alarm. The index case of inhalational anthrax in the 2001 attacks was identified because of an alert clinician who suspected the disease on the basis of large gram-positive bacilli in cerebrospinal fluid in a patient with a compatible clinical illness, and as a result of the subsequent analysis by laboratory staff who had recently undergone bioterrorism preparedness training.⁶⁵

VACCINATION

The US anthrax vaccine, named anthrax vaccine adsorbed (AVA), is an inactivated cell-free product, licensed in 1970, and produced by Bioport Corp, Lansing, Mich. The vaccine is licensed to be given in a 6-dose series. In 1997, it was mandated that all US military active- and reserve-duty personnel receive it.⁷⁶ The vaccine is made from the cell-free filtrate of a nonencapsulated attenuated strain of *B anthracis*.⁷⁷ The principal antigen responsible for inducing immunity is the PA.^{26,32} In the rabbit model, the quantity of antibody to PA has been corre-

lated with the level of protection against experimental anthrax infection.⁷⁸

Preexposure vaccination with AVA has been shown to be efficacious against experimental challenge in a number of animal studies.⁷⁸⁻⁸⁰ A similar vaccine was shown in a placebo-controlled human trial to be efficacious against cutaneous anthrax.⁸¹ The efficacy of postexposure vaccination with AVA has been studied in monkeys.⁴⁰ Among 60 monkeys exposed to 8 LD₅₀ of *B anthracis* spores at baseline, 9 of 10 control animals died, and 8 of 10 animals treated with vaccine alone died. None of 29 animals died while receiving doxycycline, ciprofloxacin, or penicillin for 30 days; 5 developed anthrax once treatment ceased. The remaining 24 all died when rechallenged. The 9 receiving doxycycline for 30 days plus vaccine at baseline and day 14 after exposure did not die from anthrax infection even after being rechallenged.⁴⁰

The safety of the anthrax vaccine has been the subject of much study. A recent report reviewed the results of surveillance for adverse events in the Department of Defense program of 1998-2000.⁸² At the time of that report, 425976 service members had received 1 620793 doses of AVA. There were higher rates of local reactions to the vaccine in women than men, but "no patterns of unexpected local or systemic adverse events" were identified.⁸² A recent review of safety of AVA anthrax vaccination in employees of the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) over the past 25 years reported that 1583 persons had received 10722 doses of AVA.⁸³ One percent of these inoculations (101/10722) were associated with 1 or more systemic events (defined as headache, malaise, myalgia, fever, nausea, vomiting, dizziness, chills, diarrhea, hives, anorexia, arthralgias, diaphoresis, blurred vision, generalized itching, or sore throat). The most frequently reported systemic adverse event was headache (0.4% of doses). Local or injection site reactions were reported in 3.6%. No long-term sequelae were reported in this series.

The Institute of Medicine (IOM) recently published a report on the safety and efficacy of AVA,⁸⁴ which concluded that AVA is effective against inhalational anthrax and concluded that if given with appropriate antibiotic therapy, it may help prevent the development of disease after exposure. The IOM committee also concluded that AVA was acceptably safe. Committee recommendations for new research include studies to describe the relationship between immunity and quantitative antibody levels; further studies to test the efficacy of AVA in combination with antibiotics in preventing inhalational anthrax infection; studies of alternative routes and schedules of administration of AVA; and continued monitoring of reported adverse events following vaccination. The committee did not evaluate the production process used by the manufacturer.

A recently published report⁸⁵ analyzed a cohort of 4092 women at 2 military bases from January 1999 to March 2000. The study compared pregnancy rates and adverse birth outcomes between groups of women who had been vaccinated with women who had not been vaccinated and the study found that anthrax vaccination with AVA had no effect on pregnancy or adverse birth outcomes.

A human live attenuated vaccine has been produced and used in countries of the former Soviet Union.⁸⁶ In the Western world, live attenuated vaccines have been considered unsuitable for use in humans because of safety concerns.⁸⁶

Current vaccine supplies are limited, and the US production capacity remains modest. Bioport is the single US manufacturing facility for the licensed anthrax vaccine. Production has only recently resumed after a halt required the company to alter production methods so that it conformed to the US Food and Drug Administration (FDA) Good Manufacturing Practice standard. Bioport has a contract to produce 4.6 million doses of vaccine for the US Department of Defense that cannot be met until at least 2003 (D.

A. Henderson, oral communication, February 2002).

The use of AVA was not initiated immediately in persons believed to have been exposed to *B anthracis* during the 2001 anthrax attacks for a variety of reasons, including the unavailability of vaccine supplies. Subsequently, near the end of the 60-day period of antibiotic prophylaxis, persons deemed by investigating public health authorities to have been at high risk for exposure were offered postexposure AVA series (3 inoculations at 2-week intervals, given on days 1, 14, and 28) as an adjunct to prolonged postexposure antibiotic prophylaxis. This group of affected persons was also offered the alternatives of continuing a prolonged course of antibiotics or of receiving close medical follow-up without vaccination or additional antibiotics.⁸⁷ This vaccine is licensed for use in the preexposure setting, but because it had not been licensed for use in the postexposure context, it was given under investigational new drug procedures.

The working group continues to conclude that vaccination of exposed persons following a biological attack in conjunction with antibiotic administration for 60 days following exposure provide optimal protection to those exposed. However, until ample reserve stockpiles of vaccine are available, reliance must be placed on antibiotic administration. To date, there have been no reported cases of anthrax infection among those exposed in the 2001 anthrax attacks who took prophylactic antibiotics, even in those persons not complying with the complete 60-day course of therapy.

Preexposure vaccination of some persons deemed to be in high-risk groups should be considered when substantial supplies of vaccine become available. A fast-track program to develop recombinant anthrax vaccine is now under way. This may lead to more plentiful vaccine stocks as well as a product that requires fewer inoculations.⁸⁸ Studies to evaluate intramuscular vs subcutaneous routes of administration and less frequent dosing of AVA are also under way. (J. Hughes, oral communication, February 2002.)

THERAPY

Recommendations for antibiotic and vaccine use in the setting of an aerosolized *B anthracis* attack are conditioned by a very small series of cases in humans, a limited number of studies in experimental animals, and the possible necessity of treating large numbers of casualties. A number of possible therapeutic strategies have yet to be explored experimentally or to be submitted for approval to the 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 and will need to be revised as further relevant information becomes available.

Given the rapid course of symptomatic inhalational anthrax, early antibiotic administration is essential. A delay of antibiotic treatment for patients with anthrax infection may substantially lessen chances for survival.^{89,90} Given the difficulty in achieving rapid microbiologic diagnosis of anthrax, all persons in high-risk groups who develop fever or evidence of systemic disease should start receiving therapy for possible anthrax infection as soon as possible while awaiting the results of laboratory studies.

There are no controlled clinical studies for the treatment of inhalational anthrax in humans. Thus, antibiotic regimens commonly recommended for empirical treatment of sepsis have not been studied. In fact, natural strains of *B anthracis* are resistant to many of the antibiotics used in empirical regimens for sepsis treatment, such as those regimens based on the extended-spectrum cephalosporins.^{91,92} Most naturally occurring *B anthracis* strains are sensitive to penicillin, which historically has been the preferred anthrax therapy. Doxycycline is the preferred option among the tetracycline class because of its proven efficacy in monkey studies⁵⁶ and its ease of administration. Other members of this class of antibiotics are suitable alternatives. Although treatment of anthrax in-

fection with ciprofloxacin has not been studied in humans, animal models suggest excellent efficacy.^{40,56,93} In vitro data suggest that other fluoroquinolone antibiotics would have equivalent efficacy although no animal data using a primate model of inhalational anthrax are available.⁹² Penicillin, doxycycline, and ciprofloxacin are approved by the FDA for the treatment of inhalational anthrax infection,^{56,89,90,94} and other antibiotics are under study. Other drugs that are usually active in vitro include clindamycin, rifampin, imipenem, aminoglycosides, chloramphenicol, vancomycin, cefazolin, tetracycline, linezolid, and the macrolides.

Reports have been published of a *B anthracis* strain that was engineered to resist the tetracycline and penicillin classes of antibiotics.⁹⁵ Balancing considerations of treatment efficacy with concerns regarding resistance, the working group in 1999 recommended that ciprofloxacin or other fluoroquinolone therapy be initiated in adults with presumed inhalational anthrax infection.³ It was advised that antibiotic resistance to penicillin- and tetracycline-class antibiotics should be assumed following a terrorist attack until laboratory testing demonstrated otherwise. Once the antibiotic susceptibility of the *B anthracis* strain of the index case had been determined, the most widely available, efficacious, and least toxic antibiotic was recommended for patients requiring treatment and persons requiring postexposure prophylaxis. Since the 1999 consensus statement publication, a study⁹⁶ demonstrated the development of in vitro resistance of an isolate of the Sterne strain of *B anthracis* to ofloxacin (a fluoroquinolone closely related to ciprofloxacin) following subculturing and multiple cell passage.

Following the anthrax attacks of 2001, the CDC⁹⁷ offered guidelines advocating use of 2 or 3 antibiotics in combination in persons with inhalational anthrax based on susceptibility testing with epidemic strains. Limited early information following the attacks suggested that persons with inhalational anthrax treated

intravenously with 2 or more antibiotics active against *B anthracis* had a greater chance of survival.⁶¹ Given the limited number of persons who developed inhalational anthrax, the paucity of comparative data, and other uncertainties, it remains unclear whether the use of 2 or more antibiotics confers a survival advantage, but combination therapy is a reasonable therapeutic approach in the face of life-threatening illness. Another factor supporting the initiation of combination antibiotic therapy for treatment of inhalational anthrax is the possibility that an engineered strain of *B anthracis* resistant to 1 or more antibiotics might be used in a future attack. Some infectious disease experts have also advocated the use of clindamycin, citing the theoretical benefit of diminishing bacterial toxin production, a strategy used in some toxin-mediated streptococcal infections.⁹⁸ There are no data as yet that bear specifically on this question. Central nervous system penetration is another consideration; doxycycline or fluoroquinolone may not reach therapeutic levels in the cerebrospinal fluid. Thus, in the aftermath of the anthrax attacks, some infectious disease authorities recommended preferential use of ciprofloxacin over doxycycline, plus augmentation with chloramphenicol, rifampin, or penicillin when meningitis is established or suspected.

The *B anthracis* isolate recovered from patients with inhalational anthrax was susceptible to all of the antibiotics expected in a naturally occurring strain.⁹⁷ This isolate showed an inducible β -lactamase in addition to a constitutive cephalosporinase. The importance of the inducible β -lactamase is unknown; these strains are highly susceptible to penicillin in vitro, with minimum inhibiting concentrations less than .06 $\mu\text{g}/\text{mL}$. A theoretical concern is that this sensitivity could be overcome with a large bacterial burden. For this reason, the CDC advised that patients with inhalational anthrax should not be treated with penicillin or amoxicillin as monotherapy and that ciprofloxacin or doxycycline be considered the standards based on in vitro activ-

Table 3. Recommended Therapy for Inhalational Anthrax Infection in the Contained Casualty Setting^{a,b}

Category	Initial IV Therapy ^{c,d}	Duration
Adults	Ciprofloxacin, 400 mg every 12 h or Doxycycline, 100 mg every 12 h ^f and 1 or 2 Additional antimicrobials ^d	IV treatment initially ^e before switching to oral antimicrobial therapy when clinically appropriate: Ciprofloxacin 500 mg twice daily or Doxycycline 100 mg twice daily Continue oral and IV treatment for 60 d ⁱ
Children	Ciprofloxacin, 10-15 mg/kg every 12 h ^{g,h} or Doxycycline ^{f,l} for those aged >8 y and weight >45 kg: 100 mg every 12 h; >8 y and weight ≤45 kg: 2.2 mg/kg every 12 h; ≤8 y: 2.2 mg/kg every 12 h and 1 or 2 Additional antimicrobials ^d	IV treatment initially ^e before switching to oral antimicrobial therapy when clinically appropriate: Ciprofloxacin 10-15 mg/kg every 12 h ^h or Doxycycline ^f for those aged >8 y and weight >45 kg: 100 mg twice daily >8 y and weight ≤45 kg: 2.2 mg/kg twice daily ≤8 y: 2.2 mg/kg 2 daily Continue oral and IV treatment for 60 d ⁱ
Pregnant women ^k	Same for nonpregnant adults	IV treatment initially before switching to oral antimicrobial therapy when clinically appropriate ^b ; oral therapy regimens are the same for nonpregnant adults
Immunocompromised persons	Same for nonimmunocompromised adults and children	

^aThis table is adapted with permission from *Morbidity and Mortality Weekly Report*.⁹⁷ For gastrointestinal and oropharyngeal anthrax, use regimens recommended for inhalational anthrax.

^bCiprofloxacin or doxycycline should be considered an essential part of first-line therapy for inhalational anthrax.

^cSteroids may be considered as an adjunct therapy for patients with severe edema and for meningitis based on experience with bacterial meningitis of other etiologies.

^dOther agents with in vitro activity include rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin. Because of concerns of constitutive and inducible β-lactamases in *Bacillus anthracis*, penicillin and ampicillin should not be used alone. Consultation with an infectious disease specialist is advised.

^eInitial therapy may be altered based on clinical course of the patient; 1 or 2 antimicrobial agents may be adequate as the patient improves.

^fIf meningitis is suspected, doxycycline may be less optimal because of poor central nervous system penetration.

^gIf intravenous (IV) ciprofloxacin is not available, oral ciprofloxacin may be acceptable because it is rapidly and well absorbed from the gastrointestinal tract with no substantial loss by first-pass metabolism. Maximum serum concentrations are attained 1 to 2 hours after oral dosing but may not be achieved if vomiting or ileus is present.

^hIn children, ciprofloxacin dosage should not exceed 1 g/d.

ⁱThe American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections (ie, Rocky Mountain spotted fever).

^jBecause of the potential persistence of spores after an aerosol exposure, antimicrobial therapy should be continued for 60 days.

^kAlthough tetracyclines are not recommended during pregnancy, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones of fetus are dose related; therefore, doxycycline might be used for a short time (7-14 days) before 6 months of gestation. The high death rate from the infection outweighs the risk posed by the antimicrobial agent.

ity, efficacy in the monkey model, and FDA approval.

In the contained casualty setting (a situation in which a modest number of patients require therapy), the working group supports these new CDC antibiotic recommendations⁹⁷ (TABLE 3) and advises the use of intravenous antibiotic administration. These recommendations will need to be revised as new data become available.

If the number of persons requiring therapy following a bioterrorist attack with anthrax is sufficiently high (ie, a mass casualty setting), the working group recognizes that combination drug therapy and intravenous therapy may no longer be possible for reasons of logistics and/or exhaustion of equipment and antibiotic supplies. In such circumstances, oral therapy may be the only feasible option (TABLE 4). The threshold number of cases at which combination and parenteral therapy become impossible depends on a variety of factors, including local and regional health care resources.

In experimental animals, antibiotic therapy during anthrax infection has prevented development of an immune response.^{40,95} This suggests that even if the antibiotic-treated patient survives anthrax infection, the risk of recurring disease may persist for a prolonged period because of the possibility of delayed germination of spores. Therefore, we recommend that antibiotic therapy be continued for at least 60 days postexposure, with oral therapy replacing intravenous therapy when the patient is clinically stable enough to take oral medication.

Cutaneous anthrax historically has been treated with oral penicillin. For reasons articulated above, the working group recommends that oral fluoroquinolone or doxycycline in the adult dosage schedules described in TABLE 5 be used to treat cutaneous anthrax until antibiotic susceptibility is proven. Amoxicillin is a suitable alternative if there are contraindications to fluoroquinolones or doxycycline such as pregnancy, lactating mother, age younger than 18 years,

or antibiotic intolerance. For cutaneous lesions associated with extensive edema or for cutaneous lesions of the head and neck, clinical management should be conservative as per inhalational anthrax treatment guidelines in Table 3. Although previous guidelines have suggested treating cutaneous anthrax for 7 to 10 days,^{32,71} the working group recommends treatment for 60 days postexposure in the setting of bioterrorism, given the presumed concomitant inhalational exposure to the primary aerosol. Treatment of cutaneous anthrax generally prevents progression to systemic disease although it does not prevent the formation and evolution of the eschar. Topical therapy is not useful.⁴

In addition to penicillin, the fluoroquinolones and the tetracycline class of antibiotics, other antibiotics effective in vitro include chloramphenicol, clindamycin, extended-spectrum penicillins, macrolides, aminoglycosides, vancomycin, cefazolin, and other first-generation cephalosporins.^{91,99} The efficacy of these antibiotics has not yet been tested

Table 4. Recommended Therapy for Inhalational Anthrax Infection in the Mass Casualty Setting or for Postexposure Prophylaxis*

Category	Initial Oral Therapy†	Alternative Therapy if Strain Is Proved Susceptible	Duration After Exposure, d
Adults	Ciprofloxacin, 500 mg orally every 12 h	Doxycycline, 100 mg orally every 12 h‡ Amoxicillin, 500 mg orally every 8 h§	60
Children	Ciprofloxacin, 20-30 mg/kg per d orally taken in 2 daily doses, not to exceed 1 g/d	Weight ≥20 kg: amoxicillin, 500 mg orally every 8 h§ Weight <20 kg: amoxicillin, 40 mg/kg taken orally in 3 doses every 8 h§	60
Pregnant women¶	Ciprofloxacin, 500 mg orally every 12 h	Amoxicillin, 500 mg orally every 8 h§	60
Immunosuppressed persons	Same as for nonimmunosuppressed adults and children		

*Some of these recommendations are based on animal studies or in vitro studies and are not approved by the US Food and Drug Administration.

†In vitro studies suggest ofloxacin (400 mg orally every 12 hours, or levofloxacin, 500 mg orally every 24 hours) could be substituted for ciprofloxacin.

‡In vitro studies suggest that 500 mg of tetracycline orally every 6 hours could be substituted for doxycycline. In addition, 400 mg of gatifloxacin or monifloxacin, both fluoroquinolones with mechanisms of action consistent with ciprofloxacin, taken orally daily could be substituted.

§According to the Centers for Disease Control and Prevention recommendations, amoxicillin is suitable for postexposure prophylaxis only after 10 to 14 days of fluoroquinolones or doxycycline treatment and then only if there are contraindications to these 2 classes of medications (eg, pregnancy, lactating mother, age <18 years, or intolerance of other antibiotics).

||Doxycycline could also be used if antibiotic susceptibility testing, exhaustion of drug supplies, adverse reactions preclude use of ciprofloxacin. For children heavier than 45 kg, adult dosage should be used. For children lighter than 45 kg, 2.5 mg/kg of doxycycline orally every 12 hours should be used.

¶See "Management of Pregnant Population" for details.

in humans or animal studies. The working group recommends the use of these antibiotics only to augment fluoroquinolones or tetracyclines or if the preferred drugs are contraindicated, not available, or inactive in vitro in susceptibility testing. *B anthracis* strains exhibit natural resistance to sulfamethoxazole, trimethoprim, cefuroxime, cefotaxime sodium, aztreonam, and ceftazidime.^{91,92,99} Therefore, these antibiotics should not be used.

Pleural effusions were present in all of the first 10 patients with inhalational anthrax in 2001. Seven needed drainage of their pleural effusions, 3 required chest tubes.⁶⁹ Future patients with inhalational anthrax should be expected to have pleural effusions that will likely require drainage.

Postexposure Prophylaxis

Guidelines for which populations would require postexposure prophylaxis to prevent inhalational anthrax following the release of a *B anthracis* aerosol as a biological weapon will need to be developed by public health officials depending on epidemiological circumstances. These decisions would require estimates of the timing, location, and conditions of the exposure.¹⁰⁰ Ongoing case monitoring would be needed to define the high-risk groups, to direct follow-up, and to guide the addition or deletion of groups requiring postexposure prophylaxis.

There are no FDA-approved postexposure antibiotic regimens following ex-

Table 5. Recommended Therapy for Cutaneous Anthrax Infection Associated With a Bioterrorism Attack*

Category	Initial Oral Therapy†	Duration, d‡
Adults	Ciprofloxacin, 500 mg twice daily† or Doxycycline, 100 mg twice daily†	60
Children§	Ciprofloxacin, 10-15 mg/kg every 12 h (not to exceed 1 g/d)† or Doxycycline for those aged§ >8 y and weight >45 kg: 100 mg every 12 h >8 y and weight ≤45 kg: 2.2 mg/kg every 12 h ≤8 y: 2.2 mg/kg every 12 h	60
Pregnant women	Ciprofloxacin, 500 mg twice daily or Doxycycline, 100 mg twice daily	60
Immunocompromised persons	Same for nonimmunocompromised adults and children	

*This table is adapted with permission from the *Morbidity and Mortality Weekly Report*.⁹⁹ Cutaneous anthrax with signs of systemic involvement, extensive edema, or lesions on the head or neck require intravenous therapy, and a multidrug approach is recommended (Table 3).

†Ciprofloxacin or doxycycline should be considered first-line therapy. Amoxicillin can be substituted if a patient cannot take a fluoroquinolone or tetracycline class drug. Adults are recommended to take 500 mg of amoxicillin orally 3 times a day. For children, 80 mg/kg of amoxicillin to be divided into 3 doses in 8-hour increments is an option for completion of therapy after clinical improvement. Oral amoxicillin dose is based on the need to achieve appropriate minimum inhibitory concentration levels.

‡Previous guidelines have suggested treating cutaneous anthrax for 7 to 10 days, but 60 days is recommended for bioterrorism attacks, given the likelihood of exposure to aerosolized *Bacillus anthracis*.

§The American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections (eg, Rocky Mountain spotted fever).

||Although tetracyclines or ciprofloxacin is not recommended during pregnancy, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones of a fetus are dose related; therefore, doxycycline might be used for a short time (7-14 days) before 6 months of gestation.

posure to a *B anthracis* aerosol. Therefore, for postexposure prophylaxis, we recommend the same antibiotic regimen as that recommended for treatment of mass casualties; prophylaxis should be continued for at least 60 days postexposure (Table 4). Preliminary analysis of US postal workers who were advised to take 60 days of antibiotic prophylaxis for exposure to *B anthracis* spores following the anthrax attacks of 2001 showed that 2% sought medical attention because of concern of possible

severe allergic reactions related to the medications, but no persons required hospitalization because of an adverse drug reaction.¹⁰¹ Many persons did not begin or complete their recommended antibiotic course for a variety of reasons, including gastrointestinal tract intolerance, underscoring the need for careful medical follow-up during the period of prophylaxis.¹⁰¹ In addition, given the uncertainties regarding how many weeks or months spores may remain latent in the period following discontinu-

ation of postexposure prophylaxis, persons should be instructed to report immediately flulike symptoms or febrile illness to their physicians who should then evaluate the need to initiate treatment for possible inhalational anthrax. As noted above, postexposure vaccination is recommended as an adjunct to postexposure antibiotic prophylaxis if vaccine is available.

Management of Special Groups

Consensus recommendations for special groups as set forth herein reflect the clinical and evidence-based judgments of the working group and at this time do not necessarily correspond with FDA-approved use, indications, or labeling.

Children. It has been recommended that ciprofloxacin and other fluoroquinolones should not be used in children younger than 16 to 18 years because of a link to permanent arthropathy in adolescent animals and transient arthropathy in a small number of children.⁹⁴ However, balancing these risks against the risks of anthrax infections caused by an engineered antibiotic-resistant strain, the working group recommends that ciprofloxacin be used as a component of combination therapy for children with inhalational anthrax. For postexposure prophylaxis or following a mass casualty attack, monotherapy with fluoroquinolones is recommended by the working group⁹⁷ (Table 4).

The American Academy of Pediatrics has recommended that doxycycline not be used in children younger than 9 years because the drug has resulted in retarded skeletal growth in infants and discolored teeth in infants and children.⁹⁴ However, the serious risk of infection following an anthrax attack supports the consensus recommendation that doxycycline, instead of ciprofloxacin, be used in children if antibiotic susceptibility testing, exhaustion of drug supplies, or adverse reactions preclude use of ciprofloxacin.

According to CDC recommendations, amoxicillin was suitable for treatment or postexposure prophylaxis of possible anthrax infection following the anthrax attacks of 2001 only after 14

to 21 days of fluoroquinolone or doxycycline administration because of the concern about the presence of a β -lactamase.¹⁰² In a contained casualty setting, the working group recommends that children with inhalational anthrax receive intravenous antibiotics (Table 3). In a mass casualty setting and as postexposure prophylaxis, the working group recommends that children receive oral antibiotics (Table 4).

The US anthrax vaccine is licensed for use only in persons aged 18 to 65 years because studies to date have been conducted exclusively in this group.⁷⁷ No data exist for children, but based on experience with other inactivated vaccines, it is likely that the vaccine would be safe and effective.

Pregnant Women. Fluoroquinolones are not generally recommended during pregnancy because of their known association with arthropathy in adolescent animals and small numbers of children. Animal studies have discovered no evidence of teratogenicity related to ciprofloxacin, but no controlled studies of ciprofloxacin in pregnant women have been conducted. Balancing these possible risks against the concerns of anthrax due to engineered antibiotic-resistant strains, the working group recommends that pregnant women receive ciprofloxacin as part of combination therapy for treatment of inhalational anthrax (Table 3). We also recommend that pregnant women receive fluoroquinolones in the usual adult dosages for postexposure prophylaxis or monotherapy treatment in the mass casualty setting (Table 4). The tetracycline class of antibiotics has been associated with both toxic effects in the liver in pregnant women and fetal toxic effects, including retarded skeletal growth.⁹⁴

Balancing the risks of anthrax infection with those associated with doxycycline use in pregnancy, the working group recommends that doxycycline can be used as an alternative to ciprofloxacin as part of combination therapy in pregnant women for treatment of inhalational anthrax. For postexposure prophylaxis or in mass casualty settings, doxycycline can also be used as

an alternate to ciprofloxacin in pregnant women. If doxycycline is used in pregnant women, periodic liver function testing should be performed. No adequate controlled trials of penicillin or amoxicillin administration during pregnancy exist. However, the CDC recommends penicillin for the treatment of syphilis during pregnancy and amoxicillin as a treatment alternative for chlamydial infections during pregnancy.⁹⁴ According to CDC recommendations, amoxicillin is suitable postexposure prophylaxis or treatment of inhalational anthrax in pregnancy only after 14 to 21 days of fluoroquinolone or doxycycline administration.¹⁰²

Ciprofloxacin (and other fluoroquinolones), penicillin, and doxycycline (and other tetracyclines) are each excreted in breast milk. Therefore, a breastfeeding woman should be treated or given prophylaxis with the same antibiotic as her infant based on what is most safe and effective for the infant.

Immunosuppressed Persons. The antibiotic treatment or postexposure prophylaxis for anthrax among those who are immunosuppressed has not been studied in human or animal models of anthrax infection. Therefore, the working group consensus recommends administering antibiotics in the same regimens recommended for immunocompetent adults and children.

INFECTION CONTROL

There are no data to suggest that patient-to-patient transmission of anthrax occurs and no person-to-person transmission occurred following the anthrax attacks of 2001.^{18,67} Standard barrier isolation precautions are recommended for hospitalized patients with all forms of anthrax infection, but the use of high-efficiency particulate air filter masks or other measures for airborne protection are not indicated.¹⁰³ There is no need to immunize or provide prophylaxis to patient contacts (eg, household contacts, friends, coworkers) unless a determination is made that they, like the patient, were exposed to the aerosol or surface contamination at the time of the attack.

In addition to immediate notification of the hospital epidemiologist and state health department, the local hospital microbiology laboratories should be notified at the first indication of anthrax so that safe specimen processing under biosafety level 2 conditions can be undertaken as is customary in most hospital laboratories.⁵⁶ A number of disinfectants used for standard hospital infection control, such as hypochlorite, are effective in cleaning environmental surfaces contaminated with infected bodily fluids.^{22,103}

Proper burial or cremation of humans and animals who have died because of anthrax infection is important in preventing further transmission of the disease. Serious consideration should be given to cremation. Embalming of bodies could be associated with special risks.¹⁰³ If autopsies are performed, all related instruments and materials should be autoclaved or incinerated.¹⁰³ The CDC can provide advice on postmortem procedures in anthrax cases.

DECONTAMINATION

Recommendations for decontamination in the event of an intentional aerosolization of *B anthracis* spores are based on evidence concerning aerosolization techniques, predicted spore survival, environmental exposures at Sverdlovsk and among goat hair mill workers, and environmental data collected following the anthrax attacks of 2001. The greatest risk to humans exposed to an aerosol of *B anthracis* spores occurs when spores first are made airborne, the period called *primary aerosolization*. The aerobiological factors that affect how long spores remain airborne include the size of the dispersed particles and their hydrostatic properties.¹⁰⁰ Technologically sophisticated dispersal methods, such as aerosol release from military aircraft of large quantities of *B anthracis* spores manipulated for use in a weapon, are potentially capable of exposing high numbers of victims over large areas. Recent research by Canadian investigators has demonstrated that even "low-tech" delivery systems, such as the opening of envelopes containing powdered spores in

indoor environments, can rapidly deliver high concentrations of spores to persons in the vicinity.¹⁰⁴ In some circumstances, indoor airflows, activity patterns, and heating, ventilation, and air conditioning systems may transport spores to other parts of the building.

Following the period of primary aerosolization, *B anthracis* spores may settle on surfaces, possibly in high concentrations. The risk that *B anthracis* spores might pose by a process of secondary aerosolization (resuspension of spores into the air) is uncertain and is likely dependent on many variables, including the quantity of spores on a surface; the physical characteristics of the powder used in the attack; the type of surface; the nature of the human or mechanical activity that occurs in the affected area and host factors.

A variety of rapid assay kits are available to detect *B anthracis* spores on environmental surfaces. None of these kits has been independently evaluated or endorsed by the CDC, FDA, or Environmental Protection Agency, and their functional characteristics are not known.¹⁰⁵ Many false-positive results occurred following the anthrax attacks of 2001. Thus, any result using currently available rapid assay kits does not necessarily signify the presence of *B anthracis*; it is simply an indication that further testing is required by a certified microbiology laboratory. Similarly, the sensitivity and false-negative rate of disease kits are unknown.

At Sverdlovsk, no new cases of inhalational anthrax developed beyond 43 days after the presumed date of release. None were documented during the months and years afterward, despite only limited decontamination and vaccination of 47 000 of the city's 1 million inhabitants.⁵⁹ Some have questioned whether any of the cases with onset of disease beyond 7 days after release might have represented illness following *secondary aerosolization* from the ground or other surfaces. It is impossible to state with certainty that secondary aerosolizations did not occur in Sverdlovsk, but it appears unlikely. The epidemic curve reported is typical for

a common-source epidemic,^{3,60} and it is possible to account for virtually all confirmed cases having occurred within the area of the plume on the day of the accident. Moreover, if secondary aerosolization had been important, new cases would have likely continued well beyond the observed 43 days.

Although persons working with animal hair or hides are known to be at increased risk of developing inhalational or cutaneous anthrax, surprisingly few occupational exposures in the United States have resulted in disease. During the first half of the 20th century, a significant number of goat hair mill workers were heavily exposed to aerosolized spores. Mandatory vaccination became a requirement for working in goat hair mills only in the 1960s. Prior to that, many unvaccinated person-years of high-risk exposure had occurred, but only 13 cases of inhalational anthrax were reported.^{27,54} One study of environmental exposure, conducted at a Pennsylvania goat hair mill, showed that workers inhaled up to 510 *B anthracis* particles of at least 5 μm in diameter per person per 8-hour shift.⁵⁴ These concentrations of spores were constantly present in the environment during the time of this study, but no cases of inhalational anthrax occurred.

Field studies using *B anthracis*-like surrogates have been carried out by US Army scientists seeking to determine the risk of secondary aerosolization. One study concluded that there was no significant threat to personnel in areas contaminated by 1 million spores per square meter either from traffic on asphalt-paved roads or from a runway used by helicopters or jet aircraft.¹⁰⁶ A separate study showed that in areas of ground contaminated with 20 million *Bacillus subtilis* spores per square meter, a soldier exercising actively for a 3-hour period would inhale between 1000 and 15 000 spores.¹⁰⁷

Much has been written about the technical difficulty of decontaminating an environment contaminated with *B anthracis* spores. A classic case is the experience at Gruinard Island, Scotland. During World War II, British mili-

tary undertook explosives testing with *B anthracis* spores. Spores persisted and remained viable for 36 years following the conclusion of testing. Decontamination of the island occurred in stages, beginning in 1979 and ending in 1987 when the island was finally declared fully decontaminated. The total cost is unpublished, but materials required included 280 tons of formaldehyde and 2000 tons of seawater.¹⁰⁸

Following the anthrax attacks of 2001, substantial efforts were undertaken to decontaminate environmental surfaces exposed to *B anthracis* spores. Sections of the Hart Senate office building in Washington, DC, contaminated from opening a letter laden with *B anthracis*, were reopened only after months of decontamination procedures at an estimated cost of \$23 million.¹⁰⁹ Decontamination efforts at many other buildings affected by the anthrax attacks of 2001 have not yet been completed.

Prior to the anthrax attacks of 2001, there had been no recognition or scientific study showing that *B anthracis* spores of "weapons grade" quality would be capable of leaking out the edges of envelopes or through the pores of envelopes, with resulting risk to the health of those handling or processing those letters. When it became clear that the Florida case of anthrax was likely caused by a letter contaminated with *B anthracis*, assessment of postal workers who might have handled or processed that letter showed no illness.⁶⁹ When the anthrax cases were discovered, each was linked to a letter that had been opened. At first, there was no evidence of illness among persons handling or processing unopened mail. This fact influenced the judgment that persons handling or processing unopened *B anthracis* letters were not at risk. These judgments changed when illness was discovered in persons who had handled or processed unopened letters in Washington, DC. Much remains unknown about the risks to persons handling or processing unopened letters containing *B anthracis* spores. It is not well understood how the me-

chanical systems of mail processing in a specific building would affect the risk of disease acquisition in a worker handling a contaminated letter in that facility. It is still uncertain what the minimum dose of spores would be to cause infection in humans although it may theoretically be as few as 1 to 3 spores.⁴⁷ The mechanisms of disease acquisition in the 2 fatal inhalational anthrax cases in New York City and in Connecticut remain unknown although it is speculated that disease in these 2 cases followed the inhalation of small numbers of spores present in some manner in "cross-contaminated" mail.

The discovery of *B anthracis* spores in a contaminated letter in the office of Sen Daschle in the Hart office building led the Environmental Protection Agency to conduct tests in this office to assess the risk of secondary aerosolization of spores. Prior to the initiation of decontamination efforts in the Hart building, 17 blood agar gel plates were placed around the office and normal activity in the office was simulated. Sixteen of the 17 plates yielded *B anthracis*. Although this experiment did not allow conclusions about the specific risk of persons developing anthrax infection in this context, it did demonstrate that routine activity in an environment contaminated with *B anthracis* spores could cause significant spore resuspension.¹¹⁰

Given the above considerations, if an environmental surface is proved to be contaminated with *B anthracis* spores in the immediate area of a spill or close proximity to the point of release of *B anthracis* biological weapons, the working group believes that decontamination of that area would likely decrease the risk of acquiring anthrax by secondary aerosolization. However, as has been demonstrated in environmental decontamination efforts following the anthrax attacks of 2001, decontamination of buildings or parts of buildings following an anthrax attack is technically difficult. For these reasons, the working group would advise that decisions about methods for decontamination following an anthrax attack follow

full expert analysis of the contaminated environment and the anthrax weapon used in the attack and be made in consultation with experts on environmental remediation. If vaccines were available, postexposure vaccination might be a useful intervention for those working in highly contaminated areas, because it could further lower the risk of anthrax infection.

In the setting of an announced alleged *B anthracis* release, such as the series of anthrax hoaxes occurring in many areas of the United States in 1998¹¹¹ and following the anthrax attacks of 2001, any person coming in direct physical contact with a substance alleged to be containing *B anthracis* should thoroughly wash the exposed skin and articles of clothing with soap and water.¹¹² In addition, any person in direct physical contact with the alleged substance should receive postexposure antibiotic prophylaxis until the substance is proved not to be *B anthracis*. The anthrax attacks of 2001 and new research¹⁰⁴ have shown that opening letters containing substantial quantities of *B anthracis* spores in certain conditions can confer risk of disease to persons at some distance from the location of where the letter was opened. For this reason, when a letter is suspected of containing (or proved to contain) *B anthracis*, immediate consultation with local and state public health authorities and the CDC for advised medical management is warranted.

Additional Research

Development of a recombinant anthrax vaccine that would be more easily manufactured and would require fewer doses should remain a top priority. Rapid diagnostic assays that could reliably identify early anthrax infection and quickly distinguish from other flulike or febrile illnesses would become critical in the event of a large-scale attack. Simple animal models for use in comparing antibiotic prophylactic and treatment strategies are also needed. Operational research to better characterize risks posed by environmental contamination of spores,

particularly inside buildings, and research on approaches to minimize risk in indoor environments by means of air filters or methods for environmental cleaning following a release are also needed. A better understanding of the genetics and pathogenesis of anthrax, as well as mechanisms of virulence and immunity, will be of importance in the prospective evaluation of new therapeutic and diagnostic strategies. Novel therapeutic approaches with promise, such as the administration of competitors against the protective antigen complex,¹¹³ should also be tested in animals and developed where evidence supports this. Recent developments such as the publishing of the *B anthracis* genome and the discovery of the crystalline structure of the lethal and edema factor could hold great clinical hope for both the prevention and treatment of anthrax infection.¹¹⁴

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Acknowledgment: The working group wishes to thank Jeanne Guillemin, PhD, Matthew Meselson, PhD, Timothy Townsend, MD, Martin Hugh-Jones, MA, VetMB, MPH, PhD, and Philip Brachman, MD, for their review and commentary on the originally published manuscript, and Molly D'Esopo for her efforts in the preparation of the revised manuscript.

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