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Recent reports of anthrax exposure and disease have prompted a serious assessment of clinical strategies related to bioterrorism. Few natural or intentional threats generate more concern among emergency management planners, physicians, and toxicologists in this country than the use of biological agents as an act of war or terrorism against citizens of the United States. Although a vast array of first responders, including elements of the military, police, and fire departments, emergency medicine services, and hazardous materials units have been preparing to respond to such emergencies, relatively few physicians have been involved in comprehensive efforts to defend against possible acts of bioterrorism.

Especially in a covert attack, however, primary care physicians, emergency medicine specialists, and departments of pharmacy—which would be responsible for maintaining adequate inventories of antidotes, vaccines, and antimicrobials required for such a contingency—would play a front-line role in the detection, evaluation, and response to this threat. Formal educational curricula informing clinicians about the likely agents of bioterrorism are essential to ensure that cases are identified, reported, treated, and monitored as rapidly and efficiently as possible.

As physicians are well aware, the current bioterrorist threat remains a fluid, uncertain situation. In light of rapid changes in both our understanding and approach to bioterrorist activities, and as new patterns of infection are recognized, the treatment options, epidemiology, and approaches to management and prophylaxis of these conditions are being closely monitored by medical, military, and governmental agencies.

This has important implications for clinical practice. Because diagnostic and management strategies are under constant review and evaluation, clinicians are advised to consult and monitor the most recent recommendations, reports, and advisories issued by such expert bodies as the Centers for Disease Control and Prevention and the Food and Drug Administration, as well as such publications as the Morbidity and Mortality Weekly Report *(MMWR) and* Biological Warfare Defense General Information Sheet. *Regional poison control centers also are excellent sources of current information regarding bioterrorist threats, and also may be accessed for up-to-date information.*

With these concerns in mind, this issue will review recent clinical and pharmacological developments in the field of bioterrorism. Special emphasis is devoted to antimicrobial preparedness, recent developments concerning anthrax management, and current programs under development for responding to bioterrorist activities.

— The Editor

Bioterrorism Update—Current Guidelines and Recommendations for Prevention and Treatment of Biological Threats: Part I

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Initial Assessment and Treatment

In the event of a covert biological agent attack, ED physician awareness would most likely occur when increased numbers of patients present with clinical symptoms of a suspicious nature. Because many of these diseases present with nonspecific clinical features, early recognition and timely intervention may be difficult, and therefore heightened awareness is essential.

Suspicion. Before the medical personnel approach a potential biological casualty, they need to ensure that they are appropriately protected. The rescuer will do little good if he or she becomes infected and is a subsequent casualty. HEPA-filter masks will provide adequate protection against inhalational biological warfare (BW) threats. Gowns and gloves complete the ensemble.

The initial assessment of the patient with a potential bioweapon infection often is hasty and may cloud the issue. In the early phases, many of these illnesses mimic common endemic problems. If the clinician is not asking how this patient may be different from other patients with similar illnesses, the patient may not be identified and the window for effective therapy may be missed. (*See Table 1, Epidemiological Clues of Biological Warfare.)*

Stabilization and Decontamination. Airway, breathing, and circulation problems should be addressed before any specific management is contemplated. Physical examination should concentrate on pulmonary, cardiac, and neuromuscular systems. Unusual dermatologic and vascular findings should be documented and photographed.

The incubation period of biological agents makes it unlikely that decontamination will be warranted. If the exposure is quite recent and known, then decontamination with soap and water or 0.1% bleach may be appropriate.

Diagnosis. Questions about food and water sources, vector exposure, immunization history, travel history, occupation, and illnesses in other family members may offer clues to the clinician and should be recorded in meticulous detail.

The amount of expertise available to the emergency clinician will vary with the medical practice. At tertiary care centers, a full range of laboratory capabilities should help with a prompt diagnosis. At primary care centers, specimens should be obtained and forwarded through public health channels or reference laboratories.

Nasal swabs, blood cultures, serum, sputum cultures, blood and urine for toxin analysis, and throat swabs should be considered. If the patient has diarrhea, stool specimens should be obtained. Nasal swabs may be used for both culture and polymerase chain reaction (PCR) analysis for common inhalation

Table 1. Epidemiological Clues of Biologic Warfare

- *Any* single case of an uncommon agent (smallpox, some viral hemorrhagic fevers, anthrax)
- The presence of an unusually large number of patients with similar disease or symptoms
- Many cases of unexplained diseases or deaths
- Dead or dying animals
- More severe disease than is usual for a specific pathogen
- Failure to respond to standard therapy for a specific pathogen
- Disease that is unusual for the geographic area or season
- Disease transmitted by a vector that usually is not present
- Unusual route of exposure for a disease (inhalation anthrax or plague)
- Multiple simultaneous or serial epidemics of different diseases
- A disease that is unusual for an age group or population
- Similar genetic pattern of diseases from distinct sources at different times or locations
- Discrete attack rates among those in a particular building or at a specific event
- Outbreak of disease in non-contiguous areas (not spread by travelers)
- Intelligence of a potential attack

Adapted from: USAMRIID Medical management of biologic casualties handbook. USAMRIID 2001;Fort Detrick, MD.

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Table 2. Samples to Obtain from Representative Patients

- Nasal swabs for culture and PCR (take several, if possible)
- Blood cultures (take several, if possible)
- Sputum cultures
- Blood and urine for toxin analysis
- Throat cultures and swabs
- Serum for analysis
- Stool samples — particularly if any diarrhea
- Lung washings/suction if any respiratory difficulty
- CBC, clotting studies, chemistries — more important for patient management than for epidemiology
- Clothing for environmental analysis

Table 3. Ten-Step Approach for Management of Biologic Casualties

1. SUSPECT A PROBLEM

If you don't look for it, you won't find it . . . but it still might find you.

2. PROTECT YOURSELF

Before you approach a potential biological casualty, you need to protect yourself. Gown, gloves, and HEPA-filter mask are essential.

3. ASSESS YOUR PATIENT

The ABCs are addressed before specific management.

4. DETERMINE IF DECONTAMINATION IS NEEDED

Decontamination is possible only for "fresh" exposures.

5. ESTABLISH THE DIAGNOSIS (IF POSSIBLE)

Secondary survey of the patient and in-depth lab examinations.

6. BEGIN EMPIRIC TREATMENT

Treat what you can. Empiric doxycycline and/or fluoroquinolones.

- Respiratory
  - —Inhaled anthrax
  - —Pneumonic plague
  - —Pneumonic tularemia
- Neurologic
  - —Botulism

7. PROTECT OTHERS — INFECTION CONTROL

- Smallpox — all airborne precautions and contact precautions
- Pneumonic plague — droplet precautions
- Viral hemorrhagic fever — contact precautions

8. ALERT THE AUTHORITIES

9. ASSIST IN EPIDEMIOLOGY

Ask questions about potential exposures, immunization history, travel history, occupation, food/water sources, vector exposures, activities over the preceding 3-5 days, potential spray devices; list all of these for each patient. In some of these diseases, you may be the only person able to interview the patient; by the time CDC officials get there, the patient may be intubated and unable to communicate.

10. SPREAD THE WORD

Ensure that you are proficient and that others are aware of the threat.

agents. The clinical laboratory should be notified that these specimens may represent BW agents so that utmost precautions can be taken and the use of optimum culture media can be planned. (*See Table 2, Samples to Obtain from Representative Patients.)*

While awaiting the results of the laboratory diagnosis, the clinician must formulate a clinical diagnosis. Anthrax, plague, tularemia, Q fever, psittacosis, and Staphylococcal enterotoxin B (SEB) disease all may present as pneumonia. Botulism and the encephalitis strains may present with neurological findings. Unfortunately, many of these diseases have early presentations of a simple febrile illness.

Treatment. Empiric therapy of pneumonia should be considered. Patients with smallpox or other viral illness will not suffer significant harm from empiric antibiotics. Patients with plague, anthrax, or tularemia may well be saved by appropriate, effective therapy. Fluoroquinolones or doxycycline may be considered for first-line empiric therapy, since these drugs are effective against most strains for anthrax, plague, and tularemia. Final treatment, including protection for the involved health-care workers, must be predicated on an accurate diagnosis.

Notification. Hospital administration, public health officials, and law enforcement must be notified about the possibility of a biowarfare incident. It is far better to call and activate systems early so that adequate medical supplies are available. *(See Table 3.)*

Possible Live Bacterial Agents

This list covers only a few diseases that have been researched. Much information was obtained from The United States Army Field Manual 8-9 (Handbook on the medical aspects of NBC defensive operations [FM 8-9], Part II- Biological United States Government Printing Office:1996; also available on the internet at http://www.nbc-med.org).

Anthrax. Anthrax is caused by *Bacillus anthracis. Bacillus anthracis* is of profound historical significance. Descriptions of anthrax date to 3500 years ago.[1] It was the first bacteria recognized as pathogenic, the discovery of its life cycle by Koch led to the unimicrobial theory of infection, and from it Pasteur developed the first attenuated vaccine.[2] Anthrax forms spores in moist, alkaline soil with high organic content. These spores are long-lasting and resistant. Outbreaks of natural anthrax tend to occur after heavy rainfall that is followed by drought.

Anthrax is primarily a disease of herbivores which are exposed to the spores while grazing. Under usual (non-wartime) conditions, humans become infected by contact with infected animals or contaminated animal byproducts. Anthrax also is known as “wool-sorter’s disease.” Anthrax is found in the United States and Canada, but livestock vaccination programs have made outbreaks rare. Anthrax is endemic in West Africa, Spain, Turkey, Greece, Albania, Romania, and Central Asia.

There are three forms of anthrax: cutaneous, inhalation, and gastrointestinal. Almost all naturally occurring cases of anthrax are cutaneous or gastrointestinal. In the United States, only three cases were reported between 1984 and 1993.[3] The case fatality rate of cutaneous anthrax is 20% without antibiotic treatment and less than 1% with antibiotics. The case-fatality rate of intestinal anthrax is estimated to be about 25-60%. In the United States, a case-fatality rate of 89% (16 of 18 cases) has been reported for inhalation anthrax.

Anthrax is likely to be disseminated as an aerosol of the very persistent spores. The incubation time is from 1-6 days, but

anthrax may have a prolonged incubation period of up to two months. The longer incubation periods are seen most frequently when partial treatment has been given. The spores can be quite stable, even in the alveolus.

The infectious dose of anthrax by any route is not precisely known. Based on data from the studies of primates, the estimated infectious dose that will cause infectious anthrax is 8000-50,000 spores.[4,5] Between two and 45 days after inhalation exposure, the individual becomes acutely ill with a rapidly developing disease that normally results in about 80% mortality. The duration of the disease is between two and five days.

Presentation. Anthrax spores germinate at the primary site of the infection. The bacillus causes local edema and necrosis. When the bacilli are ingested by macrophages, they are carried to lymph nodes and cause regional hemorrhagic lymphadenitis. Anthrax is not destroyed by the macrophages because it produces an antiphagocytic capsule. Hematogenous spread can cause septicemia, toxemia, and hemorrhagic meningitis. Uncontrolled intravascular multiplication with fatal toxemia often occurs. Animal studies suggest that after the bacterial count reaches 10 million/mL, antibiotic therapy is futile.[6]

Subsequent production of exotoxin is responsible for extensive local edema and tissue necrosis. The bacillus secretes three toxins: edema factor, lethal factor, and protective antigen. The edema factor increases intracellular cyclic adenosine monophosphate and causes massive edema. The lethal factor causes the release of tumor necrosis factor and interleukin-1, resulting in shock. Protective antigen acts as a membrane channel and transports the other two factors into the cellular cytoplasm.

More than 95% of naturally occurring anthrax is cutaneous. The primary lesion is usually a painless pruritic papule on the head, neck, or extremities. It appears about 3-4 days after exposure. Over the next day or so, this papule undergoes central necrosis and dries into a black eschar. The eschar sloughs in 2-3 weeks. Localized disease becomes systemic and fatal in about 5-25% of untreated cases. Excision of eschar may cause this systemic dissemination.

Gastrointestinal anthrax is very rare and results from the ingestion of contaminated meat. Death results from peritonitis or anthrax toxemia.

The inhalation form of anthrax is particularly uncommon and particularly lethal. In its early presentation, inhalation anthrax could be confused with a plethora of viral or bacterial respiratory illnesses. The patient progresses over 2-3 days and then suddenly develops respiratory distress, shock, and death within 24-36 hours. Dyspnea, strident cough, and chills are common during this inexorable downhill course. Widening of the mediastinum and marked pleural effusions on chest radiograph are common. Evidence of infiltrates on the chest x-ray is uncommon. Other suggestive findings include chest wall edema, hemorrhagic pleural effusions, and hemorrhagic meningitis.

Diagnosis. Diagnosis can be made by culture of blood, pleural fluid, or cerebrospinal fluid. The blood culture most often is positive. In fatal cases, impressions of mediastinal lymph nodes or spleen will be positive. Anthrax toxin may be detected in blood by immunoassay.

Some previous cases were diagnosed on autopsy by a pathologist who noted a peculiar "cardinal's cap" meningeal inflammation that is typical in anthrax.[7] All victims had hemorrhagic mediastinitis.

Pulmonary anthrax is a very rare form of anthrax. Multiple cases seen in one city should be prima facie evidence that BW is being waged. This usually fatal diseases starts with fever, malaise, myalgia, and cough. The non-specific symptoms progress to chest discomfort, cyanosis, stridor, diaphoresis, rales, and death. The disease is difficult to diagnose within the treatable stage. Chest x-ray may show a widened mediastinum. Untreated, the disease progresses to toxemia with hypotension and hemorrhage.

Therapy. Initial therapy should focus on supportive therapy for the airway and correction of fluid volume deficits as appropriate. Penicillin is considered the drug of choice for treatment of naturally occurring anthrax. However, penicillin-resistant strains do exist in nature, and one could expect that anthrax used for a biologic weapon would be penicillin-resistant. Tetracycline and erythromycin have been used for patients who are allergic to penicillin. Induction of resistance to these antibiotics is an easy genetic manipulation exercise, and warfare strains should be presumed to be resistant to these antibiotics until proven otherwise. Chloramphenicol, gentamicin, and ciprofloxacin would be appropriate choices for initial therapy. The United States military and the American Medical Association (AMA) working group recommend ciprofloxacin or doxycycline for initial therapy.[8,9] This therapy is not supported by the Food and Drug Administration (FDA) for those younger than age 18 or for pregnant females, but given the alternatives is probably appropriate.[10] Therapy should be continued for at least 60 days if the antibiotic-treated patient survives anthrax infection, because of the possibility of delayed germination of spores.

Prophylaxis. Two types of anthrax vaccine for human use are available in the United States and United Kingdom.[11] Both are based on the partially purified protective antigen of the *B. anthracis* adsorbed to an aluminum adjuvant.[12] The usual immunization series is six 0.5 mL doses over a span of 18 months. The military feels that a primary series of three 0.5 mL doses (at 0, two, and four weeks) will be protective against both cutaneous and inhalation anthrax for about six months after the primary series. These immunizations were given to many coalition troops during the Gulf War in anticipation of Saddam Hussein's employment of this agent. Since 1997, the Department of Defense required anthrax immunization for all active duty service personnel.

Although "minor" reactions to the vaccine are common (6% of immunized population), major reactions are uncommon. Obviously, the vaccine is contraindicated for those who are known to be sensitive to it and those who already have had clinical anthrax. *(See Table 4, Recommendations for Post-Exposure Prophylaxis.)*

A live anthrax vaccine is used in Russia to immunize both livestock and human beings. It is a spore vaccine with both STI-1 and strain 3 mixtures. The Russians feel that this vaccine is superior for stimulating cell-mediated immunity.[13] There would be considerable resistance to use of the Russian vaccine in Western countries because of concerns over purity and residual virulence of a live vaccine.

Table 4. Interim Recommendations for Postexposure Prophylaxis for Prevention of Inhalational Anthrax After Intentional Exposure to *Bacillus anthracis*

CATEGORY	INITIAL THERAPY	DURATION
Adults (including pregnant women and immunocompromised persons)	Ciprofloxacin 500 mg po BID or Doxycycline 100 mg po BID	60 days
Children	Ciprofloxacin 10-15 mg/kg po Q12 hrs* or Doxycycline: > 8 yrs and > 45 kg: 100 mg po BID; > 8 yrs and ≤ 45 kg: 2.2 mg/kg po BID ≤ 8 yrs: 2.2 mg/kg po BID	60 days

*Ciprofloxacin dose should not exceed 1 gram per day in children

Source: Oct. 19, 2001. *MMWR Morb Mortal Wkly Rep.*

There is no available evidence that these vaccines will adequately protect against an aerosol challenge.[14] New vaccines with a highly purified protective antigen or designer attenuated strains have been used in laboratories, but are not commercially available.[15,16]

Antibiotic prophylaxis with ciprofloxacin (500 mg PO bid), or doxycycline (100 mg PO bid) also is recommended by the U.S. military for imminent attack by a biological weapon. Note that these are the same agents recommended for plague and tularemia. Although penicillin is the drug of choice for natural anthrax, terrorists may use anthrax that deliberately has been made resistant to penicillins. Other available fluoroquinolones probably would be as effective as ciprofloxacin, but have not be adequately tested. Should the attack be confirmed as anthrax, then antibiotics should be continued for at least 60 days for all who are exposed.

Children should receive prophylaxis with oral ciprofloxacin (20-30 mg/kg per day divided every 12 hours) or oral doxycycline (5 mg/kg divided every 12 hours).[17,18] Although these antibiotics are "contraindicated" in children, some think that the minimal damage to teeth or growth plates would be far easier on the child than infection with anthrax.

Those exposed also should be started on anti-anthrax vaccine with the standard schedule (if it is available) if they have not been previously immunized. Those who have received fewer than three doses of vaccine prior to exposure should receive a single "booster" injection. If vaccine is not available, then antibiotics should be continued until the patient can be observed safely and closely when the antibiotics are discontinued. (Inhaled spores are not destroyed by antibiotics and may persist beyond the recommended course of antibiotics.)

Animal carcasses should be burned, not buried, to prevent long-term environmental contamination. Human remains should be cremated if possible.

Brucellosis. Brucellosis is a zoonotic disease caused by a small, non-motile coccobacilli. The natural reservoir is domestic herbivores such as goats, sheep, cattle, and pigs. There are four species that are pathogenic in humans: *Brucella melitensis*, *B. abortus* (cattle), *B. suis* (pigs), and *B. canis* (dogs). Humans become infected when they ingest raw infected meat or milk or inhale contaminated aerosols, or through skin contact. Human infection also is called undulant fever. Human-to-human transmission is rare, if it occurs at all. Infections in laboratory workers suggest that brucellosis is quite infective via the aerosol route. It is estimated that as few as 100 bacteria are sufficient to cause the disease in humans.

Brucella species have been long considered as BW agents because of the stability, persistence, and ease of infection without human-to-human transfer. Brucellosis can be spread by aerosol spray or by contamination of food supply. It persists for a long period in wet ground or food.

Presentation. The incubation period is about 8-14 days, but may be considerably longer. Clinical disease is a nonspecific febrile illness with headache, fatigue, myalgia, anorexia, chills, sweats, and cough. The fever often rises to 105°F. Cough and pleuritic chest pain occurs in up to 20% of cases.

Gastrointestinal symptoms are common in adults, but less frequent in children. Ileitis, colitis, and granulomatous or mononuclear infiltrative hepatitis may occur in up to 60% of cases. These patients may have both hepatomegaly and splenomegaly.

The disease may progress and include arthritis, lymphadenopathy, arthralgias, osteomyelitis, epididymitis, orchitis, and endocarditis. Infections may spread to both bone and joints. This may include vertebral osteomyelitis, intravertebral disk space infection, paravertebral abscess, and sacroiliac infections in a minority of cases. Some patients may develop meningitis or encephalitis.

Disability is pronounced, but lethality is about 5% or less in usual cases. The disease may be followed by recovery and relapse. The duration of the disease usually is a few weeks, but brucellosis may last for years.

Diagnosis. Diagnosis of this disease is by blood culture, bone marrow culture, or serology. There are no other laboratory findings that contribute to a diagnosis of brucellosis.

Pulmonary symptoms may not correlate with radiographic findings. The chest x-ray is often normal, but may show lung abscesses, miliary nodules, pneumonia, enlarged hilar lymph nodes, or pleural effusion.

Therapy. The U.S. military recommends doxycycline (100 mg bid) plus rifampin (900 mg/day) for six weeks. Alternative therapy proposed has been doxycycline (100 mg bid) for six weeks and streptomycin (1 gm/day) for three weeks. TMP-SMX has been given for four to six weeks, but is thought to be less effective. Relapse and treatment failure is common.

Prophylaxis. There is no information available about chemoprophylaxis for this disease. Human vaccines are not available

routinely in the United States, but have been developed by other countries. A variant of *Brucella abortus*, S19-BA, has been used in the former USSR to protect occupationally exposed groups. Efficacy is limited and annual re-vaccination is needed. A similar vaccine is available in China. Neither of these two vaccines would meet Western requirements for safety and effectiveness.[19]

Cholera. Cholera is a well known diarrheal disease caused by *Vibrio cholera*, acquired in humans through ingestion of contaminated water. The organism causes a profound secretory "rice water" diarrhea by elaborating an enterotoxin.

Although cholera can be spread by aerosols, a more likely terrorist or military employment would be contamination of food or water supplies. There is negligible direct human to human transmissibility. The bacterium does not have long persistence in food or pure water and is not persistent when applied by aerosols.

Presentation. Cholera can cause profuse watery diarrhea that causes hypovolemia and hypotension. Without treatment, cholera can rapidly kill adults and children alike from severe dehydration and resultant shock. The incubation period is 1-5 days, and the course of the illness is about one week. The patient may have vomiting early in the illness. There is little abdominal pain associated with the disease.

Diagnosis. Gram staining of the stool sample will show few or no red or white cells. Renal failure may complicate severe dehydration. Electrolyte abnormalities are common with the profound fluid loss; generally hypokalemia predominates.

E. coli, rotavirus, and toxic ingestions such as staphylococcal food poisoning, *Bacillus cereus*, or even clostridia species all can cause similar watery diarrhea. Bacteriologic diagnosis of cholera diarrhea has been well studied for decades. Vibrio species can be seen and identified readily with darkfield or phase contrast microscopes. Culture will prove the diagnosis but is not necessary for treatment.

Therapy. Treatment of cholera primarily is supportive. Although most emergency physicians in the United States are used to treating significant hypovolemia with intravenous fluid replacement, it is unlikely to be readily available if an epidemic of cholera is caused by terrorist or enemy action. The World Health Organization (WHO) oral rehydration formula is appropriate, but generally not stocked in sufficient quantities in most cities. Certainly Pedialyte and such sport drinks as Gatorade will provide interim oral hydration. If a cholera epidemic is treated, then intravenous fluids should be reserved for those patients who are vomiting and can't tolerate oral rehydration, those patients who have more than seven liters per day of stool, and those patients who have such hypovolemia that they have shock.

Tetracycline and doxycycline have both been found to shorten the course of the diarrhea. Other effective drugs include ampicillin (250 mg every 6 hours for 5 days) and TMP-SMX (one tablet every 12 hours). Appropriate scale should be used for pediatric doses.

Prophylaxis. The currently available vaccine is a killed suspension of *V. cholera*. It provides incomplete protection and lasts for no longer than six months. It requires two injections with a booster dose every six months. Improved vaccines are being tested but are not yet available.

Plague (*Yersinia pestis*). Plague is a zoonotic disease caused by *Yersinia pestis.* It is naturally found on rodents and prairie dogs and their fleas. Under normal conditions, three syndromes are recognized: inhalational (pneumonic), septicemic, and bubonic. The usual first infection is the bubonic form.

Because of its high mortality (about 200 million deaths throughout history), *Y. pestis* has attracted attention as a possible BW agent. During World War II, Unit 731 of the Japanese Army released plague infected fleas from aircraft over Chinese cities. The U.S. Army worked with *Y. pestis* as a potential biowarfare agent in the 1950s and 1960s. In 1994, defectors revealed that the Russians had conducted research on *Y. pestis*, the plague bacterium, to make it more virulent and stable in the environment.

The plague can retain viability in water for 2-30 days, moist areas for up to two years, and in near-freezing temperatures for several months to a year. Person-to-person transmissibility is high and the bacterium is highly infective. The persistence is low, but the transmissibility is so high that this is immaterial.

Plague could be spread by either infected vectors such as fleas or by an aerosol spray. At least 30 types of fleas and more than 200 species of mammals serve as reservoirs for this disease. Only Australia and Antarctica have no enzootic foci of plague.

Presentation. There are three forms of plague in man: bubonic, pneumonic, and septicemic. In bubonic plague, the incubation period is 1-10 days. The onset is acute, with malaise, fever (often quite high), and purulent lymphadenitis. The lymphadenitis is most often inguinal, but cervical and axillary nodes also are involved. As the disease progresses, the nodes become tender, fluctuant, and finally necrotic. One-fourth of patients will have various types of skin lesions. Pustules, vesicles, eschars, and papules all are found in the lymphatic drainage of the bubo.

The bubonic form may progress to the septicemic form with seeding of the central nervous system (CNS) and lungs. Secondary septicemia is common, with more than 80% of blood cultures positive in patients with bubonic form. Only about 25% of bubonic plague patients will progress to clinical septicemia. Plague meningitis occurs in about 6% of cases.

Those patients with septicemia will have symptoms similar to other patients with gram-negative septicemia, including chills, high fever, hypotension, vomiting, and diarrhea. Plague septicemia also can cause thrombosis in the acral vessels. This causes necrosis and gangrene of fingers and toes. Black necrotic extremities and more proximal purpura may be seen.

If the organisms are seeded to the lungs, then the pneumonic form follows and the patient becomes contagious through coughing and droplet spread. The course of the disease is 2-3 days, and the disease is quite lethal.

In primary pneumonic plague, the incubation period is 2-3 days. The onset is acute and fulminant, with malaise, fever, chills, cough with bloody sputum, and toxemia. The pneumonia progresses rapidly to respiratory failure with dyspnea, stridor, and cyanosis.

In untreated patients, the mortality is more than 50% for the bubonic and septicemic form. In the pneumonic form, the mortality approaches 100%. The terminal events are circulatory collapse, hemorrhage, and peripheral thrombosis in septicemic plague. In

pneumonic plague, the terminal event often is respiratory failure and circulatory collapse. Multi-organ failure is common.

Diagnosis. A presumptive diagnosis can be made by finding the typical safety pin bipolar staining organisms in Giemsa stained specimens. Appropriate specimens are lymph node aspirate, sputum, or cerebrospinal fluid (CSF). Immunofluorescent staining is available and helpful if readily accessible. *Y. pestis* can be readily cultured from any of these sources.

Nonspecific laboratory findings include leukocytosis with left shift. Increased fibrin split products are common and indicative of a low-grade disseminated intravascular coagulation (DIC), blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin may be elevated with multi-organ failure.

Therapy. The mortality of bubonic plague can be reduced to less than 5% with prompt therapy. The mortality of pneumonic plague is still greater than 50%, even with therapy. Survival is unlikely when treatment is delayed beyond 18 hours of infection.

The usual supportive therapy is indicated. Streptomycin, tetracycline, doxycycline, ciprofloxacin, and chloramphenicol are useful if given within the first 24 hours after symptoms of pneumonic plague begin. Supportive therapy of complications is essential.

Incision and drainage of buboes is not recommended. Aspiration is safer and provides both diagnosis and symptomatic relief.

Prophylaxis. The possibility of rapid death combined with both a vector (flea) transmission and direct person-to-person transmission make plague an ominous biowarfare threat.

Plague vaccine is available, but probably does not protect against an aerosol exposure and subsequent pneumonic plague. The plague vaccine is a whole-cell, formalin-killed product. The usual dose is 0.5 mL given at weeks zero, one, and two. Current whole-cell plague vaccines stimulate immunity against the bubonic form but probably are not effective for the pneumonic form.[20,21] Plague vaccines providing protection against aerosol exposure are not yet available, but are under development.[22]

This disease is readily contagious and strict isolation of the patients is essential. Both droplet and aerosol transmission is described in pneumonic plague.[23] Patients with pneumonic plague should be isolated to protect against droplet transmission.[24] This isolation includes the use of surgical masks when standing within one meter of the patient and no special ventilation precautions. The more stringent standard-of-care using well-ventilated rooms with negative pressure ventilation and class N95 respirators is advocated by some.[25]

Both ciprofloxacin and doxycycline are acceptable for prophylaxis for contact or possible exposure to plague aerosol. Note that these are the same agents recommended for anthrax and tularemia. Tetracycline and chloramphenicol are acceptable alternatives. If symptoms start, treatment antibiotics should be started.

Psittacosis. Psittacosis, also called parrot fever, is a bacterial disease caused by *Chlamydia psittaci.* It is transmitted from birds to man by inhalation of dried avian feces and would be easily aerosolized for use as a BW agent.

Presentation. The incubation period is about 1-2 weeks. Symptoms include fever, nausea, vomiting, headache, and muscular pains. Later in the course, the patient may have delirium and disorientation. The course of the disease may last 3-4 weeks, with about 10% fatality rate. Psittacosis may be spread from human to human.

Therapy. As with all chlamydia, tetracycline and erythromycin would be expected to be effective therapy.

Tularemia. Tularemia, or "rabbit fever," is caused by *Francisella tularensis,* a small, nonmotile, aerobic, gram-negative bacillus.[26] It is a facultative, intracellular organism that multiplies within macrophages. There are two strains of tularemia based on virulence testing. The more virulent type A form is prevalent in the United States.

Tularemia can infect humans through the skin, mucous membranes, gastrointestinal tract, and lungs. Humans can contract this disease naturally by handling an infected animal or by the bite of ticks, mosquitoes, or deerflies. The natural disease has a mortality rate of 5-10%. Tularemia occurs throughout the United States and Europe. It is endemic in the United States and has been reported in every state except Hawaii. In Europe, it has been reported in Northern Europe, particularly the Scandinavian countries and those of the former Soviet Union.

Tularemia has long been considered as a potential BW weapon. It was one of the agents used by Unit 731 of the Japanese army. Tularemia was investigated and then stockpiled by the United States during the 1950s and 1960s for use as a bioweapon. During the cold war, drug-resistant tularemia was developed by the Soviet Union.

Although tularemia does not form spores, it is quite hardy. Tularemia can remain viable for weeks in water, decaying animal carcasses, and soil. It shows prolonged resistant for months to temperatures of freezing and below. As few as 50 organisms can cause disease in humans if inhaled. Many more are required for infection through the oral route. This organism can be produced in either a wet or dry preparation and used similar to other bacteria discussed in this publication. Tularemia can be spread in many ways.

Natural tularemia can be spread by arthropods, direct contact, ingestion of contaminated food, soil, or water, handling infectious tissues of animals, or inhalation of infective aerosols. Tularemia is perhaps one of the most contagious diseases known. Laboratory workers are particularly vulnerable.[27,28] Inspection of an open culture plate in a laboratory can cause infection.

Presentation. Like plague, tularemia has an glandular form, a pneumonic form, and a septicemic form. It also has an ulceroglandular, an oculoglandular, and an oropharyngeal form not seen with plague.

Ulceroglandular tularemia is the most common natural form of tularemia. It occurs through inoculation of the skin or mucous membranes with blood or tissue fluids from an infected animal or human. The indurated, non-healing, punched-out ulcer lasts about 1-3 weeks. The patient may have fever, chills, headache and malaise. Lymphadenitis is common, and the lymph nodes may be fluctuant and drain spontaneously. The skin lesion usually is located on the fingers of the hand where contact occurred.

Glandular is the second most common form. The most commonly infected nodes are the inguinal and femoral lymph nodes in adults and the cervical nodes in children. No skin ulcer is noted.

Oculoglandular tularemia occurs when the inoculum is in the eye or periorbital skin. Patients have painful, purulent conjunctivitis. Preauricular and cervical adenopathy may be found.

Oropharyngeal and gastrointestinal forms occur when tularemia bacilli are ingested. It also may infect the oropharynx in about 25% of cases. The pharynx may be erythematous, or the patient may have ecchymoses, ulcers, or exudates.

The septicemic form can occur in 5-15% of natural cases. The clinical features include fever, prostration, and weight loss. The disease (also called typhoidal tularemia) has a mortality of 30-60%.

The pneumonic form may occur when contaminated dusts are inhaled or by a deliberate aerosol. The onset will be 3-5 days after the exposure to dust or aerosol. Progression of tularemia from ulceroglandular disease to pneumonic form occurs in 10-30% of patients. Up to 80% of septicemic cases progress to pulmonary involvement. The resulting pneumonia is atypical and may be fulminant. Fever, headache, malaise, substernal discomfort, and cough are prominent. The cough is often nonproductive.

Diagnosis. As noted, the diagnosis of pneumonic tularemia will be difficult clinically, with several types of atypical pneumonia as differential diagnosis.

The laboratory is unhelpful early in this disease. White blood cell counts may be elevated. Lymphocytosis may be seen late in the disease. Blood cultures usually are not helpful.

Bacterial agglutination or ELISA serologic testing will give the most diagnostic information. Culture of tularemia is the definitive means of confirming the diagnosis. Pharyngeal washings, sputum specimens, and even fasting gastric aspirates are useful for culture.

A chest x-ray may or may not show pneumonia. About 50% of patients will have pneumonia on chest x-ray. Patients with pneumonia also may have a pleural effusion.

Therapy. Recommended treatment is streptomycin or gentamicin for 10-14 days. Tetracycline and chloramphenicol also are useful, but the military reports that there has been a significant relapse rate with both tetracycline and chloramphenicol. They recommend that these agents be given for a minimum of 14 days. A fully streptomycin-resistant strain of tularemia is known. Ciprofloxacin is recommended by military and infectious disease experts for therapy and prophylaxis of both children and adults.

Prophylaxis. Human to human spread is unusual, and isolation is not required. Laboratory workers are at high risk of contagion, however. Laboratories should be alerted that tularemia is suspected. These specimens are best handled in a level 3 laboratory, although with extreme care, a level 2 laboratory may be able to manage the samples safely.

A live vaccine strain is available to United States military personnel. This vaccine is delivered intradermally and provides protection to an aerosol challenge by the third week post-immunization. Protection is dependent on the inhaled dose of tularemia, and inhalation of massive quantities of bacteria may overwhelm the protective effects of the vaccine.[29] Protection fell after 14 months, suggesting that a booster dose is appropriate.

This vaccine is not available for civilian use. Post exposure prophylaxis with ciprofloxacin, doxycycline, or tetracycline is recommended when aerosol exposure is known. This should be started within 24 hours of the exposure and continued for two weeks. Note that these are the same agents recommended for plague and anthrax.

Possible Viral Agents

Q Fever. *Presentation.* Q fever is a rickettsial zoonotic disease caused by *Coxiella burnetii.* The usual animals affected are sheep, cattle, and goats. Human disease usually is caused by inhalation of particles contaminated with *Coxiella*.

Coxiella is resistant to heat and desiccation and is highly infectious by the aerosol route. A single inhaled organism can cause clinical illness. A BW attack would produce disease similar to the natural illness.

Q fever is a self-limiting febrile illness of two days to two weeks. The incubation period is about 10-20 days. The patient usually is ill, but uneventful recovery is the rule. Q fever pneumonia is a frequent complication and may be noted only on radiographs in most cases. Some patients will have nonproductive cough and pleuritic chest pain.

About one-third of patients will have acute hepatitis. This can present with both fever and abnormal liver function tests in the absence of pulmonary signs.

Other complications are not common and may include chronic hepatitis, endocarditis, meningitis, encephalitis, and osteomyelitis.

Diagnosis. Q fever's presentation as a febrile illness with an atypical pneumonia is similar to a host of other atypical pneumonias, including mycoplasma, legionnaire's disease, chlamydia pneumonia, psittacosis, or Hantavirus. More rapidly progressive Q fever cases may resemble tularemia or plague.

The diagnosis can be confirmed serologically, and other laboratory findings are unlikely to be helpful. It is difficult to isolate rickettsia, and Q fever is no exception. ELISA testing is available at reference laboratories.

Most patients with Q fever will have slightly elevated liver enzymes. A leukocytosis may be present. Sputum examination often is not helpful.

It is difficult to isolate rickettsia and Q fever is no exception. ELISA testing is available at reference laboratories.

The chest x-ray is abnormal in half of the patients. Chest x-ray abnormalities include patchy infiltrates typical of a viral or mycoplasma pneumonia. Hilar adenopathy may be noted.

Therapy. As with other rickettsial diseases such as Rocky Mountain spotted fever, the treatment of choice is tetracycline, doxycycline, or erythromycin. Although not tested, azithromycin and Biaxin would be expected to be effective. Ciprofloxacin and other quinolones have been shown to be active and should be used in the patient unable to take the other recommended medications.

Prophylaxis. A formalin inactivated whole-cell vaccine is available as an investigational drug in the United States and has been used for those who are at risk of occupational infection with Q fever.[30] A Q fever vaccine is licensed in Australia. One dose will provide immunity for an aerosol challenge within three weeks. Protection lasts for at least five years.

Skin testing is required to prevent a severe local reaction in previously immune individuals. A live attenuated strain (M44) has been used in the former USSR.[31]

Q fever is a significant hazard to laboratory personnel who work with the organism.

Prophylaxis is not uniformly effective. Tetracycline or doxycycline has been recommended.

Smallpox. Smallpox is an orthopox virus that affects primates, particularly man. Smallpox was described more than 2000 years ago. It apparently originated in India or western Asia and then spread to China. About 700 AD, smallpox spread to Japan, Europe, and North Africa.[32] European colonization in the Americas and Africa was associated with extensive epidemics of smallpox among native populations in these continents in the 1500s and 1600s.

There are two types of smallpox; variola major, with a mortality of 20-30% in unvaccinated individuals; and variola minor, with a mortality of about 1%. Infection with variola minor protects against subsequent infection with variola major. The intranasal or intradermal introduction of dried smallpox variola minor scabs was used to prevent smallpox nearly 1000 years ago. Subsequently, Jenner substituted intradermal cowpox, a milder Orthopox virus infection, to prevent smallpox in 1798. Vaccinia, a related Orthopox of uncertain origin, has replaced cowpox for vaccination.

The virus can be transmitted by face-to-face contact, secretions, and aerosols. It is a durable virus and can exist for long periods outside the host. It is remotely possible that it still is living outside of the repository labs. Fortunately, aerosol vaccinia (and probably variola virus) is deactivated within 24 hours by ultraviolet light and heat. By the time casualties present to the emergency department with clinical symptoms, they would not need to be decontaminated.

The last "wild" case of smallpox was detected in Somalia in October 1977, and the last reported human case occurred in a laboratory in 1978.[33] As a direct consequence, no one is being immunized against smallpox anymore, and the population immunity has fallen dramatically. Currently, vaccinia vaccination is used only for laboratory workers exposed to vaccinia or recombinant poxvirus vectors.

Smallpox was used as a biologic weapon in the United States during the French and Indian War. In modern times, however, smallpox was considered an unlikely agent of biowarfare because there was a high level of population immunity to the virus, there is an effective vaccine, and the use of the vaccine can rapidly control outbreaks.[34]

Theoretically, the virus now exists in only two laboratories in the world in the United States and in Russia. Were smallpox virus released as an act of terrorism, the results could be catastrophic. A large proportion of the adult population and all of the pediatric population have no immunity. There is little available vaccine and no effective treatment. The expected case fatality rate is probably about 25%, and many more would be critically ill.

Presentation. The majority of smallpox cases present with a typical rash that is most dense on the face and extremities. The lesions appear during a one- to two-day period and evolve at the same rate. (In chickenpox [varicella], new lesions appear in crops and lesions of different ages are present in adjacent areas of the skin. Chickenpox lesions are more numerous in the trunk than in the extremities.)

Smallpox has a long incubation period of about 10-17 days. The illness has a prodrome of 2-3 days with malaise, fever, headache, and backache. Over the next 7-10 days, all of the characteristic lesions erupt, progress from macules to papules to vesicles to pustules, and then crust and scarify. The disease is fatal in about 35% of cases.[35]

Some patients will develop disseminated intravascular coagulopathy (hemorrhagic smallpox). Hemorrhagic smallpox is uniformly fatal. The illness has a somewhat shortened incubation period and is accompanied by high fever and head, back, and abdominal pain. Shortly after the pain starts, the patient develops a dusky erythema, followed by petechiae and flank hemorrhages into the skin and mucous membranes. Death occurs by the fifth or sixth day after the rash.[36] Pregnant women are particularly susceptible to this variant of smallpox. Hemorrhagic cases of smallpox were frequently misdiagnosed as meningococcemia.

Another variant of smallpox is malignant smallpox, a "flat-type" smallpox associated with severe toxemia and high mortality. In the malignant form, the abrupt onset and shortened incubation period are similar to the hemorrhagic variant. In malignant smallpox, the skin lesions develop slowly and do not progress to the pustular stage, hence the description as "flat." The skin develops the appearance of a fine-grained, reddish-colored crepe rubber. Hemorrhage is sometimes noted within the skin. These flat lesions disappear without scabs in survivors. Some patients will have desquamation of large areas of affected skin. Diagnosis of this variant of smallpox may be quite difficult until viral studies are available. These patients were frequently misdiagnosed because the appearance was atypical.

The most common sequelae of smallpox are scarring, particularly facial. Rarely, smallpox may cause blindness due to ocular involvement (keratitis). Other complications include smallpox pneumonia and arthritis (may have permanent joint deformities).

The seasonal occurrence of smallpox is similar to chickenpox and measles. Its incidence is highest during the winter and early spring. Large outbreaks in natural smallpox were rare during the summer. Transmission of smallpox is slowed because the disease usually is not infective until the patient has been confined to bed with high fever and rash appears. Unfortunately, this means that in-hospital infectivity is quite high. (In Germany, a smallpox patient with a cough, isolated in a single room, infected persons on three floors of a hospital.)[37] This infectivity would be increased when diagnosis is delayed, as in malignant or hemorrhagic smallpox.

In natural smallpox, the disease is infective from the appearance of the rash through the first 7-10 days of the rash. An aerosol release of variola virus would disseminate widely, since the virus is stable in aerosol and the infectious dose is quite small. During epidemics in the 1960s and 1970s in Europe, as many as 10-20 second-generation cases were infected from a single case.[38] The illness associated with variola minor generally is less severe and fewer systemic symptoms are seen.[39] The rash often is sparse. This presentation also may be seen in those who have residual immunity from prior vaccination. In the partially

immune patient, the rash is atypical and scant. The evolution of the lesions may be more rapid.

Monkeypox is a milder form that has been reported in the Democratic Republic of the Congo (formerly Zaire). The clinical picture is indistinguishable from smallpox. The case fatality rate of verified monkeypox in patients who were not vaccinated against smallpox was 11% (15% for children younger than age 5).[40] As with smallpox, the disease is significantly milder in vaccinated persons. A major differential point of monkeypox is the presence of large cervical and inguinal lymph nodes. These are uncommon in both smallpox and chickenpox.

Vaccinia produces a localized pustular lesion at the site of inoculation, with localized lymph node involvement. When administered to immunocompromised patients, vaccinia may become progressive. Generalized vaccinia occurs 6-9 days after inoculation. The patient also accidentally may spread vaccinia to other body sites (e.g., ocular vaccinia). Postinfectious encephalitis following inoculation with vaccinia is possible. The most important clue about disseminated vaccina is a vaccination or exposure to a recently vaccinated individual.

Diagnosis. Like many viral diseases, the diagnosis is best made by clinical impression. Smallpox has an incubation period of 10-14 days followed by the abrupt onset of fever, headache, malaise, and backache. Three to four days after the onset of symptoms, a characteristic rash appears on the oropharynx, face, forearms, and hand. The rash evolves from macules to papules to vesicles and finally to pustules. After 8-9 days, the pustules will rupture and crust over. The rash has profuse involvement of the face, forearms, and lower legs. The trunk and abdomen usually are spared.

Routine labs are not helpful, although leukopenia is frequent. Clotting factors may be depressed and thrombocytopenia may be found. Diagnosis may be made with immunofluorescence, electron microscopy, or culture. Orthopox viruses are large, brick-shaped viruses with a single double-stranded DNA molecule. A recently developed polymerase chain reaction (PCR)-based assay of the hemagglutinin gene allows classification of all of the species of the Orthopox virus family.[41]

Therapy. Therapy is entirely supportive. Three compounds (cidofovir, its cyclic derivative, and ribavirin) have significant antiviral activity against variola.[42] These medications have not been used in treatment and may or may not be effective.

Vaccination administered within four days of first exposure has been shown to offer some protection against acquiring the infection and significant protection against a fatal outcome. An emergency vaccination program should include all health workers at clinics or hospitals that may receive such patients and all disaster workers such as EMS, hospital staff, police, public health staff, and mortuary staff. These personnel should be vaccinated as soon as the first case is diagnosed, irrespective of prior vaccination status. Vaccination should be considered for any other persons who would be responsible for patient care during a suspected outbreak of smallpox and for the investigation and control of suspected outbreaks of smallpox.

Prophylaxis. Prophylaxis against smallpox has been available since the time of Jenner and is well documented.[43] Since smallpox is presumed to have been eradicated worldwide, there is no recommendation or requirement for routine vaccination.

Adequate stocks of smallpox vaccine are probably not available for exposure of large portions of the population. The WHO retains about 500,000 doses of vaccinia and 60-70 million doses are retained elsewhere. Not all of these doses may be properly stored or monitored for potency. The United States may have adequate stocks to vaccinate up to 10 million persons.[44] These aging stocks of smallpox vaccine may not be sufficiently potent, although properly sealed and stored vaccine has an almost indefinite shelf life. Genetically-engineered vaccinia strains are being investigated and the production of vaccine in cell culture is under study.[45,46] Large-scale manufacture is years away. *(See Table 5, Vaccines for Biological Warfare.)*

Those who have been vaccinated at some time in the past will usually have an accelerated immune response. Those who have been previously vaccinated may be somewhat safer in situations with close patient contact.

Isolation of all contacts of exposed patients would be quite difficult. If the weaponized smallpox is like the natural variety, patients are not infective until the onset of the rash. A practical strategy argues that all contacts should have their temperatures taken daily, preferably in the evening. A fever of 101°F (38°C) or higher should be cause for isolation of the contact until clinical or laboratory diagnosis of the disease or other cause of the fever. All close contacts should be promptly vaccinated. Experience during the smallpox global eradication program showed that patients who had no rash did not transmit infection, so "isolation on fever" is a logical step. The malignant (flat) form of the rash and the hemorrhagic form of the rash are just as infective as the classic rash.

The person-to-person infectivity, high mortality, and stability of the virus make variola a potential BW threat. Other animal poxviruses could be easily genetically engineered to be virulent in humans.

A human cell culture-derived vaccinia is being developed at Fort Detrick.

Smallpox vaccine is not without complications, since vaccinia can be lethal to immunosuppressed patients. Indeed, among 5.5 million vaccinations done during the 1961-1962 outbreaks of smallpox in the United Kingdom, vaccination caused at least 18 deaths.[47] With transplantation, more aggressive cancer chemotherapy, use of high dose steroids, and HIV infections, the number of immunosuppressed individuals has grown markedly since 1952. Each of these patients is at mortal risk from the prophylaxis of smallpox.

Objects in contact with a contaminated patient need to be cleansed with live steam or sodium hypochlorite solution (or other standard disinfectants). The virus may remain viable for extended periods of time in clothing or linens. Bed linens and dressing material should be autoclaved before laundry or disposal.

Venezuelan Equine Encephalitis. Venezuelan equine encephalitis (VEE), Western equine encephalitis (WEE), and Eastern equine encephalitis (EEE) are similar viruses. These viruses are quite difficult to distinguish clinically and share similar aspects of epidemiology and transmission. Natural infections are transmitted by the bites of a wide variety of mosquitoes. There is no evi-

Table 5. Vaccines for Biological Weapons

DISEASE	VACCINE	AVAILABILITY[†]
Anthrax *Bacillus anthracis*	Three versions: Two killed, one live Appear equally effective in prevention (about 90%) Untested (in the United States) in humans for inhalation anthrax Full treatment is six shots plus an annual booster. When combined with administration of antibiotics, probably is effective in prevention of inhalation anthrax.	Only to military personnel and others whose jobs put them at high risk; approved only for healthy adults age 18-65 years.
Argentine hemorrhagic fever	Experimental, live vaccine in IND status. Protects against both Argentine and Bolivian hemorrhagic fevers.	New drug protocols.
Botulism *Clostridia* species	The CDC provides a pentavalent antitoxin which gives protection from toxin types A, B, C, D, and E. Military heptavalent antitoxin is believed effective against all types of botulism toxin but still is in experimental status. CDC vaccine has been administered to several thousand volunteers and to occupationally at-risk workers (fully licensed). Induces protective levels of antitoxin. A monovalent antitoxin for type A alone is available from the California Health Department for treatment of infant botulism. Pentavalent vaccine in IND status for prophylaxis use only.	Antitoxin not used for prophylaxis. Toxoid has been recommended only for those at high risk for toxin aerosols. Standard treatment is supportive care. Post-exposure prophylaxis has been demonstrated in animals. Horse serum
Hantaan hemorrhagic fever	Experimental vaccinia-vectored Hantaan vaccine	Available only to laboratory workers at USAMRIID
Plague *Yersinia pestis*	Does not prevent pneumonic plague. Somewhat effective against bubonic plague version. Pneumonic plague treated with antibiotics.	Recommended only for people who work with the plague pathogen *Yersinia pestis,* or veterinarians who work with animals in plague areas.
Rift Valley fever	Both inactivated and live-attenuated Rift Valley fever vaccines currently are under investigation.	New drug protocols.
Smallpox *Variola major*	Given prior to exposure, inoculation provides almost 100% protection against the disease. It is mostly effective up to four days after exposure. People who were previously vaccinated will have more protection and faster onset of protection when revaccinated. Some antivirals also may be effective.	Extremely limited. The United States has up to 10 million doses; 40 million more on order. Contraindicated for immunosuppressed individuals. Not recommended since 1980.
Staphylococcal enterotoxin B	Experimental vaccine in development (not at IND status yet)	Animal work appears promising.
Tularemia *F. tularensis*	Provides partial protection against infection by inhalation or direct contact. Antibiotics are the treatment of choice for all cases of tularemia.	Only given to those who work routinely with tularemia bacteria. Not yet approved by the FDA.
Venezuelan equine encephalitis	Two IND human vaccines: TC-83, a live-attenuated cell, vaccine, produced by the Salk Institute, which has been license for horses and used as an IND for humans working in labs with VEE; and C-84, which has been tested but not licensed for use in humans. C-84 is used to boost non-responders to TC-83.	Available as IND only.
Yellow fever	The only licensed vaccine for any of the hemorrhagic fevers is yellow fever vaccine.	Available, required for travel to Africa and South America.

[†] *Most of these vaccines were developed before bioterrorism emerged as a threat. Only smallpox vaccine was produced in bulk. Few of these vaccines are widely available at this time.*

dence of human-to-human or horse-to-human direct transmission.

The infective dose in humans is thought to be as little as 100 organisms. This means that neither the population density of mosquitoes or the concentration of virus particles in an aerosol need to be great for significant spread of VEE.

VEE was tested as a BW agent during the 1950s and 1960s. Natural aerosol transmission is not known to occur. VEE is not particularly stable when spread by aerosol and does not persist for any length of time. The high infectivity of the virus is a principle reason that VEE was considered a potentially effective warfare agent.

These viruses could be produced by relatively unsophisticated and inexpensive systems in large amounts. An aerosol of VEE would be highly contagious. It also could be spread by infected mosquitoes. The VEE complex is stable during transport and storage.

In 1969-1971, a highly pathogenic strain of VEE moved from South America to the United States. In Mexico, more than 17,000 people were infected, but there were no fatalities. More than 10,000 horses died in Texas alone. Vaccination of more than 3.2 million animals and control of mosquito populations along the Gulf Coast and the Rio Grande valley finally controlled the epidemic.

Presentation. VEE is a febrile incapacitating illness. Most infections are relatively mild. Only a small percentage of patients will develop encephalitis. EEE and WEE are predominantly encephalitis infections.

The onset is sudden after an incubation period of 1-6 days. The acute phase runs about 24-72 hours and is characterized by chills, spiking fevers (often high), rigors, headache, malaise, photophobia, and myalgias. Some patients may have nausea, vomiting, cough, sore throat, and diarrhea. The patient may have conjunctivitis, pharyngeal erythema, and muscle tenderness. The disease may last for 1-2 weeks.

About 4% of children and 1% or less of adults will develop signs of encephalitis. Of these, 10% of adults and up to 35% of children may die. Experimental aerosol challenges in animals suggest that CNS involvement in deliberate infections may be higher.

Diagnosis. Diagnosis of VEE, WEE, and EEE infections can be made by serologic techniques or by IgM ELISA after about five days of illness.

An outbreak of VEE may be difficult to differentiate from influenza on clinical grounds. An increased number of neurologic cases or coexisting disease in horses may be the first clue to a deliberate infection.

Therapy. There is no effective therapy for VEE and related illnesses. Treatment is entirely supportive with volume replacement and symptomatic care. Patients with encephalitis may require anticonvulsants.

Isolation is not required, since this disease is not transmitted human to human. The patient should be treated in a screened room, since the disease is transmissible by a wide variety of mosquitoes.

The virus is quite sensitive to all known disinfectants.

Prophylaxis. Since the mosquito vectors for VEE are widely dispersed in the United States, a bioterrorism event with VEE, in the appropriate locale and during the proper season, could pose a continuing threat.

There are two IND human vaccines. The first (TC-83) is a live-attenuated cell vaccine produced by the Salk Institute. It has been licensed for horses and used as an IND for humans working in labs with VEE. The second (C-84) has been tested but not licensed in humans. This vaccine is used to boost non-responders to TC-83.

There is no pre-exposure or post-exposure prophylaxis available. Interferons have been studied and are effective in animals.

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Physician CME Questions

73. Which of the following is a form of anthrax?
    A. Cutaneous
    B. Inhalation
    C. Gastrointestinal
    D. All of the above

74. Which of the following might be seen in a patient with inhalation anthrax?
    A. Dyspnea
    B. Strident cough
    C. Chills
    D. Respiratory distress
    E. All of the above

75. Anthrax can be diagnosed by which of the following cultures?
    A. Blood
    B. Pleural fluid
    C. Cerebrospinal fluid
    D. All of the above

76. A patient with brucellosis may present with which of the following?
    A. Nonspecific febrile illness with headache
    B. Myalgia
    C. Chills
    D. Anorexia
    E. All of the above

77. Brucellosis can be diagnosed by:
    A. blood culture.
    B. bone marrow culture.
    C. serology.
    D. All of the above

78. Humans can contract tularemia through:
    A. handling an infected animal.
    B. the bite of a tick.
    C. the bite of a mosquitoe.
    D. the bite of a deerfly.
    E. All of the above

79. Patients with Q fever pneumonia may have which of the following?
    A. Nonproductive cough
    B. Pleuritic chest pain

C. Normal chest x-ray
D. Both A and B are correct

80. Diagnosis of small pox is best made by which of the following?
A. Serology
B. Clinical impression
C. Blood culture
D. Bone marrow culture

Emergency Medicine Reports CME Objectives

To help physicians:

- quickly recognize or increase index of suspicion for specific conditions;
- understand the epidemiology, etiology, pathophysiology, and clinical features of the entity discussed;
- be educated about how to correctly perform necessary diagnostic tests;
- take a meaningful patient history that will reveal the most important details about the particular medical problem discussed;
- apply state-of-the-art therapeutic techniques (including the implications of pharmaceutical therapy discussed) to patients with the particular medical problems discussed;
- understand the differential diagnosis of the entity discussed; understand both likely and rare complications that may occur;
- and provide patients with any necessary discharge instructions.

In Future Issues:

Bioterrorism: Part II

Firsthand Report from Ground Zero: An Audio Conference on Disaster Planning

The unimaginable has happened in New York City. At Saint Vincents Hospital, less than three miles from the site of the World Trade Center attack, their disaster plan was put to the test as dedicated professionals rose to the unique challenge of responding to the attack. American Health Consultants, publisher of *Emergency Medicine Reports,* invites you to learn from the firsthand experience of the professionals at Saint Vincents how to take a new look at your disaster plans so that you will be ready if the unimaginable happens in your community:

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BIOTERRORISM WATCH

Preparing for and responding to biological, chemical and natural disasters

Clinicians must be voice of reason, reassurance now that bioterrorism battle has been joined

The threat is real, but we are far from defenseless

A new era of bioterrorism has begun with the intentional anthrax scares that have left several people dead and many more exposed as this issue went to press.

But amid the shrill coverage of the widening anthrax investigations, the scramble for gas masks and the expected hoarding of Cipro, there must be a voice of calm and reason. That voice must be your own.

Infection control professionals, hospital epidemiologists, and other key clinicians involved in health care bioterrorism readiness and response must set the tone for a panicky public and an uneasy health care work force, emphasizes veteran epidemiologist **William Schaffner**, MD, chairman of preventive medicine at Vanderbilt University School of Medicine in Nashville.

"We have to re-instill a sense of confidence for people who work in the health care system," he says. "Start with the doctors. They are the ones who are going to be more panicked than the nurses."

Restoring calm to health care community

The current situation is reminiscent of the early stages of the HIV epidemic, when there was much anxiety about the communicability of the disease and whether even casual contact would spell a death sentence for health care workers.

In that chilling time of alarmist reactions and burning mattresses, Schaffner recalls that ICPs, epidemiologists, and other clinicians, stepped into the fray to provide calming confidence and accurate risk data.

"I'm beginning to think that we may be in a similar position now," he says. "We could have a very powerful educational and reassuring effect. Everybody's anxious about this, but I think we can diminish the level of anxiety," Schaffner adds.

Infection control methods in place

Health care workers must be educated about bioterrorism agents and provided reassurance that the patient isolation precautions developed by the Centers for Disease Control and Prevention (CDC) are extremely effective, urges Schaffner.[1]

"The barrier precautions are going to work for bioterrorism. Once you get to chemical [weapons] then you get into the whole 'moon suit' issue. But for bioterrorism, we don't need that," he says.

For example, systems of barrier precautions such as gloves, gowns, and masks to isolate patients infected with all manner of infectious diseases are already in place in virtually all U.S. hospitals.

"They work," he says. "Look, we all know pulmonary tuberculosis is communicable. I'm an infectious disease doctor, have been for 30 years. I've seen a lot of patients with tuberculosis, but I have also been meticulous about my use of [face masks and respirators]. My tuberculin test continues to be negative."

This supplement was prepared by Gary Evans, editor of *Hospital Infection Control*. Telephone: (706) 742-2515. E-mail: gary.evans@ahcpub.com.

A Bioterrorism Time Line

1155 Barbarossa uses the bodies of dead soldiers to poison the wells at the battle of Tortona.

1346 Mongols catapult corpses of plague victims into the city of Kaffa to infect the defenders.

1763 British commander Sir Jeffrey Amherst ordered the transfers of blankets used by British smallpox victims to Native American tribes, ostensibly as a gesture of goodwill, with the intention of inducing illness.

1970 The United States ends its programs of developing biological agents for use in warfare. The offensive use of such weapons was forbidden by U.S. policy under executive orders of President Richard Nixon.

1972 Soviet Union signs off on Biological and Toxin Weapons Convention, but continues a high-intensity program to develop and produce biological weapons at least through the early 1990s. Hundreds of tons of weaponized anthrax spores are stockpiled, along with dozens of tons of smallpox and plague. Many of these agents are reputed to have been specifically designed to be resistant to common antibiotics.

1984 Members of the Rajneesh cult contaminated salad bars in Oregon with salmonella, resulting in the infection of 751 people. The Paris Police raided a residence suspected of being a safe house for the German Red Army Faction. During the search, they found documentation and a bathtub filled with flasks containing *Clostridium Botulinum.*

1990s Japan's Aum Shinrykyo cult plans attacks using biological agents, specifically, anthrax and botulinum toxin. While these biological attacks were not successful, cult members later implemented the release of sarin nerve gas in the Tokyo subway system.

1995 A U.S. microbiologist with right-wing ties orders bubonic plague cultures by mail. The ease with which he obtained these cultures prompts new legislation to ensure that biologic materials are destined for legitimate medical and scientific purposes.

1998 A variety of feigned exposures to anthrax spores occurred in several U.S. cities including Indianapolis, where a full-scale response by emergency services and public health occurred before the episode was found to be a hoax.

Sources

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2. Bosker G. Bioterrorism: An update for clinicians, pharmacists, and emergency management planners. *Emergency Medicine Reports* (in press) 2001. ■

And anthrax, of course, is not communicable from person to person, reminds Schaffner, who investigated a case of occupational anthrax in an animal-hide worker when he was a epidemiologist for the CDC in the late 1960s.

"The bacteria do not cause a conventional pneumonia," he says. "They replicate locally and then release toxins. Because the bacteria never replicate to very high numbers the person is not communicable. It is not so much an infection as it is an intoxication."

Inordinate fear of anthrax could cause another problem — hoarding and misuse of Ciprofloxacin and other antibiotics. That tactic eventually could contribute to emerging resistance in pathogens such as *Streptococcus pneumoniae,* Schaffner notes.

"It is one thing for a hospital and the health department to develop an inventory in the event of an emergency," he says. "I do not recommend that individuals do that. I'm quite concerned that with antibiotics in their medicine cabinets there will be a temptation to just use it now and again for inadequate reasons in inadequate doses. If there was a recipe for antibiotic resistance — that's it."

More terror than toll

While the anthrax mailing campaign now under way sends out another shock wave with every news report, the tactic will likely result in more terror than actual toll. The rapid administration of antibiotics has offset illness following exposures, the disease is not communicable from those actually infected, and everyone is now on high alert for suspicious mailings.

Indeed, if the wave of anthrax mailings continues, postal-treatment technologies may become a growth industry.

Regardless, anthrax is problematic as a bioweapon because only a certain micron size of the inhaled spore will lodge in the upper lungs where it can release its toxins, says **Allan J. Morrison Jr.**, MD, MSc, FACP, a bioterrorism expert and health care epidemiologist for the Inova Health System in Washington, DC.

"If it is too large, it won't go in," says Morrison, a former member of the U.S. Army Special Forces. "If it's too small, it goes in and moves about freely without ever lodging. This is not as easy as getting a culture, growing it in your home, and the next day having infectious microbes.

"The sizing, preparation, and ability to deliver such a weapon are extremely difficult," he adds.

The Aum Shinrykyo cult in Tokyo attempted at least eight releases of anthrax or botulism during 1990 to 1995 without getting any casualties, he recalls. **(See time line, p. 2.)** Variables such as humidity can come into play, clumping up spores even if they are perfectly sized for inhalation. Anthrax spores bound for human targets are also at the whims of ultraviolet light, rain, and wind dispersal patterns, Morrison says.

"It is a very hostile climate for microbes on planet earth." Morrison says. "The intent may be widespread, but the ability to deliver weapons grade agents is going to be restricted to a very small subgroup. And even among them, they still will require optimal climatic conditions to carry it out. There will be causalities, as in war, but the distinction here is that there has not been widespread infection."

While anthrax is the current weapon of choice, the direst scenarios usually turn to the most feared weapon in the potential arsenal of bioterrorism: smallpox.

"Invariably, I have seen smallpox described as 'highly infectious,'" Schaffner says. "It's not. That is erroneous." For example, during the global eradication efforts in the 1960s, African natives infected with smallpox were often found living with extended families in huts, he adds. "It would usually take two to three incubation periods for smallpox to move through an extended family."

"It doesn't happen all it once. This was a critical concept in the strategy to eradicate smallpox. If you could find smallpox, you could vaccinate around that case and prevent further transmission. If it had been a frighteningly [rapid] communicable disease, that strategy would never have worked," Schaffner explains.

In addition, some medical observers question the certitude of the general consensus that all those vaccinated decades ago are again susceptible to smallpox. They argue that those immunized during the eradication campaign may at least have some greater protection against fatal infection.[2]

Regardless, rather than dropping like flies, as many as 70% of those infected with smallpox actually survive and then have lifelong immunity.

While there are many other agents to discuss and prevention plans to outline in the weeks and months ahead, perhaps the greatest protective factor is the unprecedented level of awareness in the health care system. The world has changed so much since Sept. 11th that hospitals are probably more prepared for bioterrorism than they have ever been. Everywhere, lines of communication have been opened with health departments and affiliated clinics, emergency plans have been reviewed and hot-button phone numbers posted on the wall.

"We're on alert," says **Fran Slater**, RN, MBA, CIC, CPHQ administrative director of performance improvement at Methodist Hospital in Houston. "We are *all* on alert."

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Should clinicians get smallpox vaccinations?

Questions arise, stockpile expansion fast-tracked

The recent decision to accelerate production of a new smallpox vaccine is raising the complex question of whether health care workers — front-line soldiers in the war against bioterrorism — should be immunized against the disease.

As opposed to the current anthrax attacks, a biological release of smallpox would result in incoming patients with an infectious disease. Even health care workers directly exposed to anthrax could be treated with ciprofloxacin and several other antibiotics, so the anthrax vaccine is not a likely candidate for health care.

On the other hand, legitimate questions have been raised about whether health care workers will stay on the job during a smallpox outbreak unless they and their families are rapidly vaccinated. The only known stocks of smallpox virus are held by the United States and Russia, but many bioterrorism experts have warned for years that another nation or group might have secret stocks.

"I think if smallpox [vaccine] became available, we should definitely immunize all the health care workers," says **Martin Evans**, MD, hospital epidemiologist at the University of Kentucky Chandler Medical Center in Lexington. "A lot of people think [health care workers] ought to

be high on the list because they are part of the response team if there was an outbreak in the community. Not to sound self-serving, but I think we ought to immunize the medical community."

But the question currently is somewhat moot because the Centers for Disease Control and Prevention (CDC) is not wavering from its established policy of mobilizing the available vaccine only if smallpox is released. "I'm sure CDC wants to conserve its current stocks for dealing with an outbreak so it could immunize contacts," Evans says. "If [the agency has] already used [its stock] by immunizing all the health care workers in the country, then it won't be able to respond."

15 million doses stockpiled

Currently, there are some 15 million doses of the old smallpox vaccine available, according to Secretary of Health and Human Services **Tommy Thompson,** who recently announced plans to accelerate production of a new smallpox vaccine. Forty million new doses of vaccine are expected to be available by mid-to-late 2002, moving the project up considerably from its original completion date of 2004 or 2005.

The manufacturer of the new vaccine is Acambis Inc. (formerly OraVax) — based in Cambridge, UK, and Cambridge and Canton, MA. The new vaccine will be a purified derivative of the same strain of cowpox virus (vaccinia) that was used in the United States previously, because the old vaccine's efficacy was clearly demonstrated by direct exposures to those infected. While the method of immunization through scarification will be essentially the same, the new vaccine will be produced in a mammalian cell culture that contains no animal protein.

Acambis stated on its web site that it would have no other comment on the project other than to confirm it has "accelerated" its production plans. But when the project was first announced in 2000, company officials said they had the ability to scale up production well beyond the requested 40 million doses. They were even scouting for other global markets. That means the capability to produce smallpox vaccine in abundance is on the horizon, and the question of immunizing health care workers will invariably arise. *Bioterrorism Watch* was unable to get a CDC response on the question as this issue went to press, but CDC director **Jeffrey Koplan**, MD, MPH, outlined the agency's position in an Oct. 2, 2001 Health Alert posted on a CDC web site.

"Smallpox vaccination is not recommended and, as you know, the vaccine is not available to health providers or the public," Koplan said. "In the absence of a confirmed case of smallpox anywhere in the world, there is no need to be vaccinated against smallpox. There also can be severe side effects to the smallpox vaccine, which is another reason we do not recommend vaccination. In the event of an outbreak, the CDC has clear guidelines to swiftly provide vaccine to people exposed to this disease. The vaccine is securely stored for use in the case of an outbreak."

One factor in favor of the CDC's position to rapidly deploy the vaccine — rather than do widespread vaccinations — is that immunization should still be effective several days after a smallpox exposure. In the smallpox global eradication campaign, epidemiologists found they could give vaccine two to three days after an exposure and still protect against the disease. Even at four and five days out, immunization might prevent death. Still, though the new vaccine will be improved in many ways, the hazards and risk factors of introducing cowpox into the human body are expected to be roughly the same as those documented with the old vaccine.

"We are looking at probably about one death per million primary vaccinations," says **D.A. Henderson**, MD, director of the Center for Civilian Biodefense Studies at Johns Hopkins University in Baltimore. "We are looking at one in 300,000 developing post-vaccinal encephalitis — an inflammation of the brain, which occasionally is fatal and sometimes can leave people permanently impaired."

Based on those estimates, if the new stockpile of 40 million doses is eventually rolled out, approximately 40 of those immunized will die, and another 133 will develop encephalitis. In addition to those severe outcomes, the arm lesion created during inoculation can be very large and painful, serving as a reservoir to self-inoculate the eyes or even infect immune-compromised patients.

The downside is real, but as more vaccine becomes available immunization will certainly be discussed at hospitals in previously targeted areas such as New York City and Washington, DC. If they are not immunized in advance, health care workers are going to want vaccine very quickly if they are expected to take care of smallpox patients, says **Allan J. Morrison Jr.**, MD, MSc, FACP, health care epidemiologist for the Inova Health System in Washington, DC. "Forget about smallpox patients. We're talking about taking care of any patients." ■

Emergency Medicine Reports
The Practical Journal for Emergency Physicians

Bioterrorism: Part I

Epidemiological Clues of Biologic Warfare

- *Any* single case of an uncommon agent (smallpox, some viral hemorrhagic fevers, anthrax)
- The presence of an unusually large number of patients with similar disease or symptoms
- Many cases of unexplained diseases or deaths
- Dead or dying animals
- More severe disease than is usual for a specific pathogen
- Failure to respond to standard therapy for a specific pathogen
- Disease that is unusual for the geographic area or season
- Disease transmitted by a vector that usually is not present
- Unusual route of exposure for a disease (inhalation anthrax or plague)
- Multiple simultaneous or serial epidemics of different diseases
- A disease that is unusual for an age group or population
- Similar genetic pattern of diseases from distinct sources at different times or locations
- Discrete attack rates among those in a particular building or at a specific event
- Outbreak of disease in non-contiguous areas (not spread by travelers)
- Intelligence of a potential attack

Adapted from: USAMRIID Medical management of biologic casualties handbook. USAMRIID 2001;Fort Detrick, MD.

Samples to Obtain from Representative Patients

- Nasal swabs for culture and PCR (take several, if possible)
- Blood cultures (take several, if possible)
- Sputum cultures
- Blood and urine for toxin analysis
- Throat cultures and swabs
- Serum for analysis
- Stool samples — particularly if any diarrhea
- Lung washings/suction if any respiratory difficulty
- CBC, clotting studies, chemistries — more important for patient management than for epidemiology
- Clothing for environmental analysis

Ten-Step Approach for Management of Biologic Casualties

1. SUSPECT A PROBLEM

If you don't look for it, you won't find it . . . but it still might find you.

2. PROTECT YOURSELF

Before you approach a potential biological casualty, you need to protect yourself. Gown, gloves, and HEPA-filter mask are essential.

3. ASSESS YOUR PATIENT

The ABCs are addressed before specific management.

4. DETERMINE IF DECONTAMINATION IS NEEDED

Decontamination is possible only for "fresh" exposures.

5. ESTABLISH THE DIAGNOSIS (IF POSSIBLE)

Secondary survey of the patient and in-depth lab examinations.

6. BEGIN EMPIRIC TREATMENT

Treat what you can. Empiric doxycycline and/or fluoroquinolones.

- Respiratory
  - —Inhaled anthrax
  - —Pneumonic plague
  - —Pneumonic tularemia
- Neurologic
  - —Botulism

7. PROTECT OTHERS — INFECTION CONTROL

- Smallpox — all airborne precautions and contact precautions
- Pneumonic plague — droplet precautions
- Viral hemorrhagic fever — contact precautions

8. ALERT THE AUTHORITIES

9. ASSIST IN EPIDEMIOLOGY

Ask questions about potential exposures, immunization history, travel history, occupation, food/water sources, vector exposures, activities over the preceding 3-5 days, potential spray devices; list all of these for each patient. In some of these diseases, you may be the only person able to interview the patient; by the time CDC officials get there, the patient may be intubated and unable to communicate.

10. SPREAD THE WORD

Ensure that you are proficient and that others are aware of the threat.

Interim Recommendations for Postexposure Prophylaxis for Prevention of Inhalational Anthrax After Intentional Exposure to *Bacillus anthracis*

CATEGORY	INITIAL THERAPY	DURATION
Adults (including pregnant women and immunocompromised persons)	Ciprofloxacin 500 mg po BID or Doxycycline 100 mg po BID	60 days
Children	Ciprofloxacin 10-15 mg/kg po Q12 hrs* or Doxycycline: > 8 yrs and > 45 kg: 100 mg po BID; > 8 yrs and ≤ 45 kg: 2.2 mg/kg po BID ≤ 8 yrs: 2.2 mg/kg po BID	60 days

*Ciprofloxacin dose should not exceed 1 gram per day in children

Source: Oct. 19, 2001. *MMWR Morb Mortal Wkly Rep.*

Vaccines for Biological Weapons

DISEASE	VACCINE	AVAILABILITY†
Anthrax *Bacillus anthracis*	Three versions: Two killed, one live Appear equally effective in prevention (about 90%) Untested (in the United States) in humans for inhalation anthrax Full treatment is six shots plus an annual booster. When combined with administration of antibiotics, probably is effective in prevention of inhalation anthrax.	Only to military personnel and others whose jobs put them at high risk; approved only for healthy adults age 18-65 years.
Argentine hemorrhagic fever	Experimental, live vaccine in IND status. Protects against both Argentine and Bolivian hemorrhagic fevers.	New drug protocols.
Botulism *Clostridia* species	The CDC provides a pentavalent antitoxin which gives protection from toxin types A, B, C, D, and E. Military heptavalent antitoxin is believed effective against all types of botulism toxin but still is in experimental status. CDC vaccine has been administered to several thousand volunteers and to occupationally at-risk workers (fully licensed). Induces protective levels of antitoxin. A monovalent antitoxin for type A alone is available from the California Health Department for treatment of infant botulism. Pentavalent vaccine in IND status for prophylaxis use only.	Antitoxin not used for prophylaxis. Toxoid has been recommended only for those at high risk for toxin aerosols. Standard treatment is supportive care. Post-exposure prophylaxis has been demonstrated in animals. Horse serum
Hantaan hemorrhagic fever	Experimental vaccinia-vectored Hantaan vaccine	Available only to laboratory workers at USAMRIID
Plague *Yersinia pestis*	Does not prevent pneumonic plague. Somewhat effective against bubonic plague version. Pneumonic plague treated with antibiotics.	Recommended only for people who work with the plague pathogen *Yersinia pestis,* or veterinarians who work with animals in plague areas.
Rift Valley fever	Both inactivated and live-attenuated Rift Valley fever vaccines currently are under investigation.	New drug protocols.
Smallpox *Variola major*	Given prior to exposure, inoculation provides almost 100% protection against the disease. It is mostly effective up to four days after exposure. People who were previously vaccinated will have more protection and faster onset of protection when revaccinated. Some antivirals also may be effective.	Extremely limited. The United States has up to 10 million doses; 40 million more on order. Contraindicated for immunosuppressed individuals. Not recommended since 1980.
Staphylococcal enterotoxin B	Experimental vaccine in development (not at IND status yet)	Animal work appears promising.
Tularemia *F. tularensis*	Provides partial protection against infection by inhalation or direct contact. Antibiotics are the treatment of choice for all cases of tularemia.	Only given to those who work routinely with tularemia bacteria. Not yet approved by the FDA.
Venezuelan equine encephalitis	Two IND human vaccines: TC-83, a live-attenuated cell, vaccine, produced by the Salk Institute, which has been license for horses and used as an IND for humans working in labs with VEE; and C-84, which has been tested but not licensed for use in humans. C-84 is used to boost non-responders to TC-83.	Available as IND only.
Yellow fever	The only licensed vaccine for any of the hemorrhagic fevers is yellow fever vaccine.	Available, required for travel to Africa and South America.

† *Most of these vaccines were developed before bioterrorism emerged as a threat. Only smallpox vaccine was produced in bulk. Few of these vaccines are widely available at this time.*

Supplement to *Emergency Medicine Reports*, November 5, 2001: "Bioterrorism Update—Current Guidelines and Recommendations for Prevention and Treatment of Biological Threats: Part I." *Author:* **Charles Stewart, MD, FACEP,** Emergency Physician, Colorado Springs, CO.

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