Medical Education Systems Inc.

Use of Anthrax Vaccine in the USA

Medical Education Systems, Inc

TOLL FREE: 877-295-4719
LOCAL: 619-295-0284
FAX: 619-295-0252
EMAIL: info@mededsys.com
WEBSITE: www.mededsys.com
P.O Box 83939 San Diego, CA 92138-3939.

Use of Anthrax Vaccine in the United States

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Recommendations and Reports

Learning Objectives

- Identify the five main changes in the 2000 recommendations regarding anthrax vaccine
- Identify which animals are most commonly infected with anthrax
- Identify the pathogenesis of anthrax
- Identify the primary steps to the control and prevention of anthrax

Summary

These recommendations from the Advisory Committee on Immunization Practices (ACIP) update the previous recommendations for anthrax vaccine adsorbed (AVA) (CDC. Use of anthrax vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2000;49:1--20; CDC. Use of anthrax vaccine in response to terrorism: supplemental recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2002;51:1024--6) and reflect the status of anthrax vaccine supplies in the United States. This statement 1) provides updated information on anthrax epidemiology; 2) summarizes the evidence regarding the effectiveness and efficacy, immunogenicity, and safety of AVA; 3) provides recommendations for pre-event and preexposure use of AVA; and 4) provides recommendations for postexposure use of AVA. In certain instances, recommendations that did not change were clarified. No new licensed anthrax vaccines are presented.

Substantial changes to these recommendations include the following: 1) reducing the number of doses required to complete the pre-event and preexposure primary series from 6 doses to 5 doses, 2) recommending intramuscular rather than subcutaneous AVA administration for preexposure use, 3) recommending AVA as a component of postexposure prophylaxis in pregnant women exposed to aerosolized Bacillus anthracis *spores, 4) providing guidance regarding preexposure vaccination of emergency and other responder organizations under the direction of an occupational health program, and 5) recommending 60 days of antimicrobial prophylaxis in conjunction with 3 doses of AVA for optimal protection of previously unvaccinated persons after exposure to aerosolized* B. anthracis *spores.*

Introduction

Anthrax is a zoonotic disease caused by the spore-forming bacterium *Bacillus anthracis* (*1,2*). The disease most commonly occurs in wild and domestic mammals (e.g., cattle, sheep, goats, camels, antelope, and other herbivores) (*3*). Anthrax occurs in humans when they are exposed to infected animals or tissue from infected animals or when they are directly exposed to *B. anthracis* spores (*4--6*). Depending on the route of exposure, anthrax can occur in three forms: cutaneous, gastrointestinal, or inhalation.

Today, *B. anthracis* is considered one of the most serious biowarfare or bioterrorism agents because of the ability of the spores to persist in the environment, the ability of the aerosolized spores to readily cause infection via respiratory (inhalation) exposure, and the high mortality of resulting inhalation anthrax (*7--9*). CDC has classified anthrax as a category A biological warfare agent (*10*), meaning it has great potential to adversely affect public health. The lethality of aerosolized *B. anthracis* spores was demonstrated in 1979 when an unintentional release of *B. anthracis* spores from a military microbiology facility in the former Soviet Union resulted in 64 deaths (*11*). The cases of anthrax that occurred after *B. anthracis* spores were distributed through the U.S. mail in 2001 further underscored the potential dangers of this organism as a bioterrorism threat (*12--15*).

Vaccines against anthrax were first developed as early as 1880 and used in livestock (*16*). An acellular product for human use was developed in 1954 and used in the first U.S. efficacy study of human anthrax vaccine (*17*). This product was later modified, resulting in anthrax vaccine adsorbed (AVA) (*18*), the vaccine currently approved for use in the United States. AVA prepared using *B. anthracis* V770-NP1-R was first licensed in the United States in 1972 as a 6-dose, subcutaneously (SC) administered priming series with annual boosters for persons in occupations placing them at risk for exposure. AVA also is available as a component of a postexposure prophylaxis (PEP) regimen under an Investigational New Drug (IND) protocol (*19*) and may be made available under an Emergency Use Authorization (EUA) (*20--22*).

Methods

In 2000 and 2002, CDC provided recommendations from the Advisory Committee on Immunization Practices (ACIP) for the use of anthrax vaccine for prevention and as a component of PEP (*23*,*24*). Because of 1) new safety and immunogenicity data for AVA, 2) a pending licensure change for AVA, 3) the need to incorporate anthrax vaccine recommendations into one document, and 4) new epidemiology data, the ACIP Anthrax Vaccine Work Group convened for

the first time for an in-person meeting in October 2007. The work group consisted of 35 members representing the Department of Defense (DoD), the American College of Occupational and Environmental Medicine, the InterAgency Board for Equipment Standardization and Interoperability, the Office of the Biomedical Advanced Research and Development Authority, the National Institutes of Health (NIH), the American Veterinary Medical Association, the American Academy of Pediatrics, the American College of Obstetrics and Gynecology, the National Association of County and City Health Officials, and the Food and Drug Administration (FDA). The work group subsequently held 12 conference calls over 11 months to review and discuss both published and unpublished scientific data related to AVA. Relevant literature was identified through consultations with expert partners and other researchers. These data included safety evaluations, immunogenicity studies, efficacy analyses, vaccine supply information, and contemporary experience with the use of AVA both as a preexposure vaccine and as a component of PEP. Work group members developed recommendation options during their calls. When scientific evidence was lacking, recommendations incorporated expert opinions of the work group members.

In December 2008, FDA approved a dose reduction and route change for AVA administration (*25*) following submission of a biologics license application (BLA) (*26*) supplement that was originally submitted in June 2005 by Emergent BioSolutions (Rockville, Maryland). This approval was based on data from the CDC-sponsored Anthrax Vaccine Research Program (AVRP) phase 4 clinical trial (referred to as the AVRP clinical trial in this report).

During the ACIP meeting in February 2008, presentations were made on anthrax epidemiology and transmission, published AVA safety and efficacy data, and unpublished data from the AVRP clinical trial. In June 2008, draft recommendations were presented to ACIP. During the October 2008 meeting, revised recommendations, with the exception of the dose reduction and route change, were presented to ACIP for a vote. In February 2009, ACIP recommended a new, 5-dose pre-event and preexposure priming series administered intramuscularly (IM) (*27*).

Background

B. anthracis is a facultatively anaerobic, gram-positive, encapsulated, spore-forming, nonmotile rod. The infectious form of *B. anthracis* that is predominantly found in the environment is the spore, which is approximately 1 μm × 2 μm; anthrax is contracted from these spores, which are highly resistant to heat, cold, drought, UV light, and gamma radiation. *B. anthracis* has three major virulence factors: an antiphagocytic capsule and two exotoxins, referred to as lethal toxin and edema toxin. These toxins are responsible for the primary clinical manifestations of hemorrhage, edema, necrosis, and death.

Disease is categorized according to the route of human exposure to *B. anthracis* spores: cutaneous, gastrointestinal, or inhalation.

The precise infectious dose of *B. anthracis* in humans by the various routes is not known; inhalation anthrax can develop in susceptible hosts after exposure to a relatively small number of

spores (*28,29*). Based on data from studies of nonhuman primates, the lethal dose has been estimated to range from 2,500 to 760,000 spores (*11,30*). The majority of human anthrax cases worldwide are naturally occurring (i.e., not a result of bioterrorism). The case-fatality rate for anthrax ranges from <1% (for cutaneous anthrax treated with appropriate antimicrobial agents) to 86%--89% (during the 1979 outbreak in the former Soviet Union and in the United States during the 20th century, respectively) (*6,11,31,32*).

Naturally Occurring Anthrax

Throughout much of the 20th century, anthrax in humans was grouped into two categories: agricultural or industrial (*6,33*). *B. anthracis* spores can remain viable and infective in soil for decades, during which time they serve as a potential source of infection for grazing livestock that might become infected when they ingest or inhale the spores. *B. anthracis* spores in soil generally do not pose a direct infection risk for humans, who are typically infected by *B. anthracis* spores through contact with contaminated animal products or an infected animal (*28*). Agricultural cases of anthrax occur among persons who have direct contact with infected sick or dying animals or who handle infected carcasses or tissues. Persons at risk for acquiring anthrax through agricultural exposure might include ranchers, veterinarians, slaughterhouse or abattoir workers, and butchers.

Industrial cases of anthrax result from the cutaneous inoculation or inhalation of particles containing *B. anthracis* spores generated during the cleaning and industrial processing of contaminated hides, hair, or wool from infected animals. Workers in wool and mohair processing facilities were historically at risk for contracting both inhalation and cutaneous anthrax, which made the disease a substantial health hazard in the wool industry in the 19th century and throughout the first half of the 20th century (*4,34*). Industrial processing of animal hair or hides accounted for 153 (65%) of 236 anthrax cases reported to CDC during 1955--1999 (*35*); commercial products made from animal hair or hides accounted for an additional five (2%) cases. Of these 158 cases, the majority (94%) were cutaneous anthrax; 10 (6%) cases were inhalation anthrax.

Naturally occurring anthrax cases also have occurred outside of agricultural and industrial settings as a result of contact with products from anthrax-infected animals.

Such products include anthrax-contaminated bristle shaving brushes, animal skins, animal hair or yarn, and bone meal (*31,36--41*). During 2006--2008, three inhalation cases (in the United Kingdom, United States, and Scotland) and two cutaneous cases (in the United States) were associated with drums made from imported contaminated hides (*36,39,42--44*).

Estimating the worldwide incidence of naturally occurring human anthrax is difficult because reporting of anthrax cases is unreliable in many settings (*28*). However, anthrax is most

commonly observed in agricultural regions with inadequate control programs for anthrax in livestock. Anthrax outbreaks affecting domestic animals in these regions lead to direct or indirect human infection. Enzootic and endemic regions include South America, Central America, southern and eastern Europe, Asia, Africa, the Caribbean, and the Middle East (*28*). The largest recent epidemic of human anthrax occurred in Zimbabwe during 1978--1980 and involved 9,445 cases, including 141 (1.5%) deaths (*5*). The incidence of anthrax in animals in the United States has decreased since the middle of the 20th century, from 25 states reporting animal outbreaks in 1951 to eight states reporting outbreaks for the 10-year period from 1997 to 2006 (*45,46*) Outbreaks among both domestic animals and wildlife continue to be reported from the Great Plains states from Texas to North Dakota and in western states, including California, Montana, Nevada, and New Mexico (*45*). Cases that occur sporadically in both domestic livestock and free-ranging wildlife might not be recognized.

Anthrax is a nationally notifiable disease (information available at http://www.cdc.gov/ncphi/disss/nndss/nndsshis.htm). In the 21st century, naturally occurring cases of anthrax in the United States have occurred sporadically, with two or fewer cases reported each year. Of the 242 naturally occurring human anthrax cases reported to CDC during 1955--2007, 232 (96%) were cutaneous, 10 (4%) were inhalation, and none were gastrointestinal (CDC, unpublished data, 2010). The only reported case of gastrointestinal anthrax in the United States occurred in 1941 (*47*) and resulted from an industrial exposure, not from contaminated food. Although gastrointestinal exposure to anthrax has been documented in the United States, no confirmed cases of anthrax resulted from the exposures (*48*). In 2010, CDC received a report of a woman with severe gastrointestinal symptoms after exposure to *B. anthracis* spores (CDC, unpublished data, 2010).

Bioterrorism-Related Anthrax

In 2001, 22 confirmed or suspected human cases of anthrax occurred in the eastern United States (referred to as the bioterrorism events of 2001 in this report) when *B. anthracis* spores were sent through the mail in powder-containing envelopes to news media companies and U.S. congressional leaders (*14,15,49*). Eleven of the 22 cases were inhalation anthrax, and 11 were cutaneous; 20 of the cases occurred in mail handlers or persons exposed to buildings where contaminated mail was processed or received (*15*). Five persons with inhalation anthrax died. The source of exposure was unknown in two of the fatal cases (*50,51*); however, cross-contaminated mail was considered a possible source.

B. anthracis has been a focus of offensive and defensive biological warfare research programs worldwide (*10*). Anthrax was used against livestock and draft animals as a bioweapon by Germany during World War I; during World War II, Japan conducted weapon field trials with anthrax in Manchuria. Numerous countries, including the United States, the United Kingdom, the former Soviet Union, and Iraq, conducted anthrax weapons research at various times during World War II, the Cold War, and the decades that followed (*52,53*).

In 1979, at least 96 persons were infected and 64 persons died during an anthrax outbreak in the Soviet city of Sverdlosk after anthrax was unintentionally released from a military microbiologic facility believed to be a biowarfare facility (*11*). In 1993, a religious cult, Aum Shinrikyo, unsuccessfully attempted to use *B. anthracis* as a weapon near Tokyo, Japan (*54*).

In 2008, the Department of Homeland Security issued a statement indicating that anthrax poses a threat sufficient to affect U.S. national security (*55*). WHO experts have estimated that 50 kg of *B. anthracis* spores released upwind of a population center of 500,000 persons could result in 95,000 deaths and 125,000 hospitalizations (*56*), and a release of 100 kg of spores upwind of the Washington, DC, metropolitan area would result in an estimated 130,000 to 3 million deaths (*57*). An intentionally dispersed strain of *B. anthracis* might have different characteristics from a naturally occurring strain. Intentionally dispersed strains might demonstrate antimicrobial resistance or increased dispersion capabilities. Primary aerosolization (dispersion of particles in air resulting from the initial release) and secondary aerosolization (resulting from agitation of the settled particles from the primary release) are important considerations in bioterrorist acts (*58--64*). The magnitude of risk for inhalation anthrax from secondary aerosolization of *B. anthracis* spores is uncertain.

The bioterrorism events of 2001 prompted extensive biodefense research, as well as the creation and implementation of bioterrorism preparedness plans. Since 2001, in addition to increasing the number of public health mechanisms by which drugs and vaccines are distributed and dispensed or administered (i.e., EUA), emergency response and preparedness measures have focused on improving the effectiveness and timeliness of distributing and dispensing antimicrobials and vaccine for PEP.

Efforts also have been made to improve the availability and timely distribution and administration of AVA in postevent settings. Because AVA is not licensed for postexposure use, the vaccine may be made available under an IND protocol or possibly under an EUA in an emergency (*19--22*).

Pathogenesis and Disease

B. anthracis enters the host in the form of spores (*65*) at the epidermis (cutaneous anthrax), the gastrointestinal epithelium (gastrointestinal anthrax), or the lung mucosa (inhalation anthrax). It is unknown whether *B. anthracis* has an active invasive process, and the symptoms and incubation period vary depending on the route of exposure to the spores. In general, symptoms of any form of anthrax usually begin within 7 days of exposure (*1*).

Most naturally occurring *B. anthracis* bacteria are sensitive to a wide range of antimicrobial agents. Before initiating antimicrobial treatment, appropriate specimens should be obtained for isolation of the organism by culture. In practice, *B. anthracis* is readily identifiable using a range of standard microbiological tests, including Gram stain, cell and colony morphology, sensitivity of the gamma phage of McCloy, and production of the γ-linked poly-d-glutamic acid (γDGA) capsule in blood or under culture in 20% carbon dioxide.

Most cutaneous and gastrointestinal infections occur at the site of preexisting lesions (*66*). Inhalation anthrax occurs after inhalation of aerosolized particles containing viable *B. anthracis* spores and their deposition at the alveolar epithelial surface (*6,66*). Inhalation anthrax is not pneumonia; in this form of disease, the mediastinal lymph nodes are usually the nidus of bacterial proliferation. Spores also can germinate at the pulmonary epithelial surface, and lung tissue might be infected as a consequence of fulminant systemic bacterial proliferation from other portals of entry (*67*). Regardless of the route of exposure, vegetative *B. anthracis* can spread through the blood stream, causing systemic disease (i.e., systemic anthrax) that results in hypotensive shock and sudden death (*65*). Systemic anthrax is typically fatal unless diagnosed and treated promptly (*11*). Anthrax meningitis can occur secondary to any of the three forms of anthrax. Although meningitis can occur without any other clinical signs and symptoms of anthrax, the condition is most often associated with inhalation anthrax.

The pathogenicity and proliferation of *B. anthracis* in the host are primarily a result of the combined actions of the γDGA capsule and the two protein exotoxins, edema toxin (a complex composed of protective antigen [PA] and edema factor) and lethal toxin (a complex of PA and lethal factor) (*68*). Production of the capsule and toxins parallels the germination and outgrowth of *B. anthracis* spores (*69*). The capsule is considered to be antiphagocytotic, and the exotoxins disarm the innate and acquired immune responses (*70--72*). Edema toxin increases host intracellular cyclic adenosine monophospate (cAMP) levels, resulting in cytokine modulation, upregulation of the anthrax toxin receptor, and disruption of interstitial fluid balance (*73,74*). Lethal toxin inactivates members of the mitogen-activated protein kinase kinase (MAPKK) family, causing an imbalance in the production or release of a range of cytokines (*75,76*). In cases of cutaneous anthrax and those in which the nidus of infection remains localized, the combined effects of the toxins are tissue edema and local tissue necrosis. In cases of systemic anthrax secondary to any form of initial disease, the toxins cause hemorrhagic tissue and organ necrosis, hypoxic insult, and edema. In cases of inhalation anthrax, the edema is most prominent in the pleura, whereas in gastrointestinal anthrax, the fluid accumulation is most prominent as ascites (*77,78*).

Cutaneous Anthrax

More than 95% of all naturally occurring *B. anthracis* infections worldwide are cutaneous. This form of anthrax is associated with handling infected animals or contaminated items such as meat, wool, hides, leather, or hair products from infected animals (*79*). Cutaneous anthrax has characteristic signs and symptoms and is recognizable if the physician is familiar with the disease.

The majority of cutaneous anthrax lesions develop in exposed areas such as the face, neck, arms, and hands. The lesion begins as a small, often pruritic papule that quickly enlarges and develops a central vesicle or bulla, which ruptures or erodes, leaving an underlying necrotic ulcer. A characteristic firmly adherent, black eschar develops over the surface of the ulcer. The lesion is usually painless. Satellite vesicles and ulcers might also form (*80*). Edematous swelling of the surrounding tissues occurs, often with regional lymphadenopathy and lymphangitis. Systemic signs and symptoms, including fever, malaise, and headache, might accompany the cutaneous

lesion (*1*). Historically, case-fatality rates for cutaneous anthrax have been as high as 20% without appropriate treatment but <1% with appropriate antimicrobial therapy (*6*).

Because the progression of the disease is mediated by toxins, the lesions progress through the various stages once they have appeared, even with antimicrobial therapy. Discharge from cutaneous lesions might be infectious; however, the risk for person-to-person transmission of cutaneous anthrax is very low (*81*).

Differential diagnoses for a blackened eschar or other lesion include staphylococcal or streptococcal cellulitis or lymphadenitis, eczema, and herpes simplex or varicella zoster. In addition, depending on the epidemiologic history or route of exposure, parapoxvirus infection (orf virus and pseudocowpox virus) should be considered, because they are the most common parapoxviruses in U.S. food animals such as cattle, sheep, and goats. The differential diagnoses also include brown recluse spider bite, rickettsial pox, ecthyma gangrenosum, ulceroglandular tularemia, plague, typhus, glanders, erysipelas, cat-scratch disease, rat-bite fever, aspergillosis, mucormycosis, vaccinia, cutaneous leishmaniasis, cutaneous tuberculosis, and leprosy (*80,82*).

The incubation period for cutaneous disease is reported to be 5--7 days (range: 1--12 days) (*83*). However, during the 1979 Sverdlovsk outbreak, cutaneous cases reportedly developed up to 13 days after the aerosol release of spores (*11*), and an outbreak in Algeria was reported with a median incubation period of 19 days (*84*).

Gastrointestinal Anthrax

Gastrointestinal anthrax typically occurs after eating raw or undercooked contaminated meat, although spores consumed through any route, including spores that are inhaled and subsequently swallowed, can result in gastrointestinal anthrax. In the United States, no cases of gastrointestinal anthrax have been reported since 1941 (*47*). Although gastrointestinal anthrax could occur as a result of bioterrorist activity, no bioterrorism-associated cases have been reported. Gastrointestinal anthrax can occur in two forms: 1) intestinal or abdominal or 2) oropharyngeal. Data from human cases and outbreaks are limited, although clinical disease likely ranges from asymptomatic to fatal (*85*). The primary site of infection is the gastrointestinal epithelium. Infection might be associated with preexisting lesions in the alimentary tract, which might play a role in the development of oropharyngeal lesions. However, studies in mice demonstrated infection in the Peyer patches of the small intestine after intragastric deposition of spores (*67*).

The intestinal form develops when spores infect the gastrointestinal tract epithelium after consumption of undercooked, contaminated meat.

Signs and symptoms range from subclinical gastrointestinal disturbances to clinical illness with nausea and vomiting, fever, anorexia, and abdominal pain and tenderness and can progress to hematemesis and bloody diarrhea. Abdominal distension with voluminous, hemorrhagic ascites might be present (*85,86*). The disease might progress to septicemia and toxemia, cyanosis, shock, and death (*86--88*). Extensive edema of infected intestinal segments and mesentery can develop, and lesions might become necrotic and ulcerated. Infection of the mesenteric lymph nodes accompanied by lymphadenopathy might develop (*86*). An eschar might develop on the wall of

the terminal ileum or cecum (*86,89*), and the upper gastrointestinal tract is occasionally affected (*85,90--92*).

The oropharyngeal form occurs after infection of the oropharyngeal epithelium and is characterized by lesions at the base of the tongue or tonsils, with sore throat, dysphagia, fever, and regional lymphadenopathy. Edematous lesions develop, which progress to necrotic ulcers covered with a pseudomembrane. Edema and swelling develop in the oropharynx and neck, accompanied by cervical lymphadenopathy, pharyngitis, and fever (*85,88*).

The differential diagnoses of hemorrhagic gastroenteritis or oropharyngeal lesions suspected to be gastrointestinal anthrax should include the following (*28*): food poisoning, acute appendicitis, ruptured viscus, diverticulitis, dysentery, parapharyngeal abscess, malignancy, hemorrhagic gastroenteritis from other infectious causes, necrotizing clostridial enteritis, streptococcal pharyngitis, Vincent angina, Ludwig angina, and diseases causing acute cervical lymphadenitis, acute gastritis, or acute abdomen. Organisms may be isolated from vomitus or feces, from swabs of oropharyngeal lesions, or from blood or ascites fluid (*79,88*). The incubation period for gastrointestinal disease is estimated to be 1--6 days; the case-fatality ratio is unknown but is estimated to range from 25% to 60% (*1,88*).

Inhalation Anthrax

Inhalation anthrax is a systemic infection caused by inhalation of *B. anthracis* spores. The mediastinal lymph nodes are most often the nidus of bacterial proliferation. Inhalation anthrax has historically accounted for 5% of all anthrax cases in the United States (*31*). This form of the disease results from the inhalation of aerosolized *B. anthracis* spore-containing particles that are ≤5 microns (*66*). Spore-containing aerosols can be generated through industrial processing or work with spore-contaminated animal products such as wool, hair, or hides; by laboratory procedures such as vortexing of cultures; or as a result of the intentional release of aerosolized spores. Inhaled spores lodge in the alveolar recesses and can become dormant, remaining dormant for weeks to months They are subsequently taken up by alveolar macrophages and then germinate (*93--95*), leading to substantial variability in the incubation period.

Early studies of inhalation anthrax demonstrated that inhaled spores are phagocytosed by macrophages in the lungs and transported to the pulmonary-associated lymph nodes, where germination and vegetative growth occur, followed by bacteremia and dissemination to the rest of the body (*94--96*).

Once taken up by alveolar macrophages, some spores are transported to the pulmonary-associated lymph nodes, where they continue to germinate, multiply, and release toxins (*69,97--100*), resulting in hemorrhagic necrosis of the thoracic lymph nodes that drain the lungs, or a hemorrhagic mediastinitis. Animal models also have demonstrated rapid phagocytosis of *B. anthracis* spores by interstitial dendritic cells, followed by dendritic cell migration to the thoracic lymph nodes (*100*). Exposure to aerosolized spores also has resulted in infection of nasal-

associated lymphoid tissues in <24 hours, followed by subsequent spread to mandibular lymph nodes (*67*). Necrotizing pneumonitis occasionally develops (*12,101,102*).

Initial signs and symptoms of inhalation anthrax are nonspecific and might include sore throat, mild fever, and muscle aches; these symptoms might initially be mistaken for an upper respiratory infection (*79,103*).

Approximately 2--3 days later, infected patients generally become progressively ill as respiratory symptoms develop, including severe dyspnea and hypoxemia, and the disease progresses with development of hypotension, diaphoresis, worsening dyspnea, shock, cyanosis, and stridor (*104*). Chest radiography often reveals the characteristic widened mediastinum (*12,79*).

Antimicrobial agents are effective against germinating and vegetative *B. anthracis*, but dormant spores are refractory to antimicrobials. Studies in nonhuman primates receiving antimicrobials suggest that inhaled *B. anthracis* spores can persist for up to 100 days in a dormant state at the alveolar surface epithelium (*95*). Inhalation anthrax has developed up to 58 days after experimental aerosol exposure in primates that received postexposure antimicrobial prophylaxis for the first 30 days after aerosol exposure (*93*). Reported incubation periods for inhalation anthrax in humans range from 1 to 43 days (*11,31*).

Disease development can be prevented as long as the administered antimicrobial agent is maintained at levels sufficient to kill germinating *B. anthracis* organisms while dormant spores are cleared from the host. Cessation of antimicrobial treatment before clearance of the spores might allow residual spores to germinate and cause infection; therefore, the onset of inhalation anthrax might appear to be delayed (*11,93,95,102,105,106*). This late germination has not been observed in persons who have had a cutaneous or gastrointestinal exposure.

Studies in animals suggest that incubation periods might decrease when the inoculum quantity increases (*95,107,108*). Similarly, in one reported human case, in a patient aged 51 years who was a previously healthy office worker in a textile mill (*31*), epidemiologic and exposure data suggested that the incubation period was as short as 1 day. The textile mill processed imported goat hair and previously had reported workers with cutaneous anthrax; however, no inhalation cases had been reported. The affected office worker had rarely entered the mill but developed inhalation anthrax in 1961, 1 day after visiting a dusty carding room in the mill. Subsequent investigation determined that both the goat hair being processed and the mill itself were widely contaminated with *B. anthracis.* In the 1979 Sverdlosk outbreak of inhalation anthrax, cases were reported 2--43 days after the initial release (*11*). Although the exact date of exposure in the Sverdlosk outbreak was not confirmed, the modal incubation period was reported as 9--10 days (*11,65*), which is slightly longer than the estimated incubation periods of 2--6 days in the few reported outbreaks of inhalation anthrax (*11,106*).

The Sverdlosk data are limited regarding use of antimicrobials and vaccine; the number of people who received an intervention and the effectiveness of the intervention are unknown. Therefore, estimations of the incubation period during this outbreak are difficult to calculate (*109*). During the U.S. bioterrorism events of 2001, the median incubation period for six of the first 10 cases was 4 days (range: 4--6 days) (*12*). A review of all the 2001 inhalation cases

indicates that the estimated incubation period was 4.5 days (*15*), a period consistent with previous reports (*1*).

Case-fatality ratios of 86% and 89% were reported after the 1979 Sverdlosk outbreak in the former Soviet Union and in the United States during in the 20th century, respectively (*11,31,32*). During the bioterrorism events of 2001, the case-fatality ratio for patients with inhalation anthrax treated in intensive care units was 45% (five of 11 cases) (*15*).

Bacteremic Dissemination and Meningitis

After infection at the primary cutaneous, gastrointestinal, or inhalation site, lymphatic and hematogenous proliferation of anthrax bacilli can result in dissemination to other organs and organ systems (i.e., systemic anthrax). Massive septicemia with 10^7 to 10^8 bacteria per milliliter of blood and toxemia can develop, systemic effects including high fever and shock develop quickly, and death usually follows rapidly (*65*). Laboratory animal and nonhuman primate model studies demonstrate hematogenous spread to abdominal organs and the central nervous system (*107,110--112*) with systemic inflammation, increased vascular permeability, and disseminated intravascular coagulation (*113*). Autopsy findings among decedents of the 1979 Sverdlosk outbreak and the bioterrorism events of 2001 included hepatic congestion, congestive necrosis of the spleen, and submucosal gastrointestinal lesions (*101,114*).

Anthrax meningitis has been reported with all three clinical forms of anthrax and likely results from hematogenous spread across the blood-brain barrier, generally presenting as hemorrhagic meningitis. Anthrax meningitis is characterized by a fulminant, rapidly progressive clinical course; even with aggressive therapy, cases are usually fatal (*115,116*). The likelihood of the development of clinical or subclinical meningitis in patients with severe systemic *B. anthracis* infections is high. In rare cases, anthrax meningitis has been reported without any other associated primary (i.e., cutaneous, gastrointestinal, or inhalation) manifestation of anthrax (*115,116*). A review of 82 cases of inhalation anthrax that occurred during 1900--2005 included 70 fatal cases. Among the 70 patients who died, 11 of 61 patients for whom data were available had signs of meningeal involvement, compared with none of 12 patients who survived; 44 of the 70 patients who died developed meningoencephalitis during the course of their disease, compared with none of the 12 patients who survived. Development of meningoencephalitis during the course of disease was found to be significantly associated with death ($p = 0.003$) (*104*). Studies in nonhuman primates have demonstrated meningeal involvement in 33%--77% of experimental inhalation anthrax cases (*93,108,110,112*).

Control and Prevention

Human anthrax is best controlled through prevention, including preexposure vaccination for persons at high risk for encountering aerosolized *B. anthracis* spores, reduction of animal illness by vaccination of livestock at risk for anthrax, and environmental controls to decrease exposure

to contaminated animal products, such as imported hair and skins. After a person is exposed to aerosolized *B. anthracis* spores, a combination of antimicrobials and vaccine provides the best available protection.

Reduction of Risk for Exposure

The incidence of naturally occurring human anthrax in the United States is greatly reduced through vaccinating and preventing infection in livestock, improving industrial hygiene, and decreasing the use of contaminated raw imported materials. Effective animal disease control programs have reduced the incidence of animal anthrax, and therefore human anthrax, worldwide.

Since the initiation of annual vaccination of livestock in endemic regions in 1957, naturally occurring human cases in the United States have decreased from 38 cases in 1956 to fewer than two cases annually during 1980--2008. Anthrax in livestock can be controlled through vaccination programs, rapid detection and reporting of cases, and proper disposal of dead animals with suspected or confirmed anthrax, preferably by incineration (*28,45*). In countries where anthrax is common and vaccination coverage among livestock is low, humans should avoid contact with livestock and products from animals that have not been inspected and found to be healthy before and after slaughter (*1,3*). In addition, consumption of meat from animals that experienced sudden, unexplained death or meat of uncertain origin should be avoided (*1,5*). Restrictions on the importation of hides and wools from countries in which anthrax is enzootic can reduce the number of U.S. cases.*

Methods for sterilizing or inactivating spores on contaminated materials include steam sterilization or ethylene oxide gas sterilization, boiling or using dry heat, or treating with formaldehyde, glutaraldehyde, or hypochlorite for specified periods of time and exposure concentrations; air drying does not destroy *B. anthracis* spores (*28,117--119*). Industrial exposure and infection have been controlled through improvements in industry hygiene standards, mechanization of animal processing, and strict importation guidelines. Although these improvements have reduced the risk among employees working with animals and animal products, the risk has not been completely eliminated (*120,121*). Precautions to minimize exposure when working with potentially contaminated animal hides have been published (*36*,*43*) and should be followed.

Vaccination

Vaccine Development

The first effective anthrax vaccines using live, attenuated cultures of *B. anthracis* were demonstrated in 1880 by William S. Greenfield and in 1881 by Louis Pasteur (*16,122*). Pasteur's

vaccine required a primary inoculation of *B. anthracis* that had been incubated at 42°--43°C for 15--20 days (type I vaccine) followed by a second inoculation (type II vaccine) of less attenuated *B. anthracis* that had been incubated at 42°--43°C for 10--12 days. This duplex vaccine was used widely until approximately 1935, when the procedure was modified to exclude the type I vaccine and reduce the virulence of the type II vaccine by the addition of 1%--10% saponin. Although effective, the virulence of heat-attenuated vaccines varied. In 1939, Max Sterne developed a live, attenuated spore vaccine from an avirulent, noncapsulated variant of *B. anthracis* (*123,124*). The Sterne-type vaccines replaced the Pasteur heat-attenuated formulations as the veterinary vaccines of choice. The veterinary vaccine that is currently used in the United States is based on the *B. anthracis* Sterne $34F_2$ strain and is produced using a deep culture technique at approximately 10^5 doses per liter. Receipt of a single dose provides the animal with effective immunity for at least 1 year; revaccination is recommended to ensure protection for >1 year (*105*).

The feasibility of using acellular vaccines against *B. anthracis* was first suggested by investigators who discovered that injections of sterilized edema fluid from anthrax lesions provided protection in laboratory animals (*125,126*). This discovery led to the exploration of the use of artificially cultivated *B. anthracis* filtrates as vaccines (*127--131*) and thereby to the human anthrax vaccines currently licensed and used in the United States and Europe.

The first such U.S. product was developed in 1954 as a cell-free filtrate from an aerobic culture of the Vollum strain of *B. anthracis*, precipitated with aluminum potassium sulfate (alum), and evaluated for potency (*132,133*). This vaccine provided protection in monkeys, caused minimal reactivity and short-term adverse events in humans, and was used in the original efficacy study of human vaccination against anthrax in the United States (*17*). In the 1960s, the vaccine manufacturing process in the United States was modified, leading to changes in the *B. anthracis* strain used (from the Vollum strain to V770--NP1--R) and a switch to a microaerophilic culture method. These alterations optimized the production of a stable and immunogenic formulation of vaccine antigen and increased the production scale. Subsequently, the Michigan Department of Public Health (MDPH), under a contract with DoD, pursued premarket approval of the vaccine (*128,134,135*).

The formulation for which MDPH sought premarket approval became AVA; the vaccine was licensed by NIH in 1970 and reapproved for licensure by FDA in 1985 (*136*). The safety and immunogenicity of the three generations of anthrax vaccine have been evaluated, and the resulting data support the FDA licensure of AVA (*135*). AVA is now marketed as BioThrax (Emergent BioSolutions, Lansing, Michigan) and is licensed for use in persons aged 18--65 years who are at high risk for exposure. AVA is not licensed for use in children (i.e., persons aged <18 years) or pregnant women (*137*).

AVA

AVA is the only licensed human anthrax vaccine in the United States. AVA was originally licensed for SC administration as a series of 6 priming doses (0, 2, and 4 weeks and 6, 12, and 18 months) followed by annual booster doses. AVA is a sterile, milky-white suspension prepared

from cell-free filtrates of microaerophilic cultures of a toxigenic, nonencapsulated strain of *B. anthracis* V770-NP1-R. The production cultures are grown in a chemically defined protein-free medium consisting of a mixture of amino acids, vitamins, inorganic salts, and sugars. Each 0.5-mL dose contains proteins from the sterile filtrate culture fluid (released during the growth period), including the protein PA (83 kDa), and contains no dead or live bacteria. The final product is formulated to contain 1.2 mg/mL aluminum, added as aluminum hydroxide in 0.85% sodium chloride, and 25 μg/mL benzethonium chloride and 100 μg/mL formaldehyde, added as preservatives (*137*).

Route of Administration and Immunogenicity

Numerous studies have demonstrated the immunogenicity of AVA in humans and animals. However, a serologic correlate of protection has not been fully defined. Several studies have demonstrated seroconversion (fourfold rise in anti-PA immunoglobulin G [IgG] titers) rates of 85%--100% among adults receiving 2 and 3 doses of SC or IM AVA (*138--141*), indicating a strong, long-lasting immune response to the vaccine. Additional data have demonstrated statistically significant increases in anti-PA IgG levels among those with a prolonged interval between the first and second doses of AVA when compared with persons receiving AVA as originally licensed (*142*).

In December 2008, FDA approved a BLA supplement submitted by Emergent BioSolutions for use of AVA in a pre-event or preexposure setting. The current licensed schedule consists of 5 0.5-ml IM injections (at 0 and 4 weeks and 6, 12, and 18 months) and 0.5-ml booster injections at 1-year intervals after the 18-month dose. Although ACIP now recommends 5 doses of AVA administered IM for pre-event or preexposure prophylaxis, persons with medical contraindications to IM administration (e.g., persons with coagulation disorders) may continue to receive the vaccine by SC administration (*25*). However, when administering AVA as a component of PEP, the vaccine should only be administered with 3 doses by the SC route under an IND or EUA.

A randomized study of 173 participants compared the first 3 AVA doses of the originally licensed schedule (SC injections at 0, 2, and 4 weeks) with alternate regimens (SC or IM injections at 0 and 4 weeks and SC or IM injections at 0 and 2 weeks). The antibody concentrations for the group that followed the originally licensed schedule were comparable to those from the groups receiving injections at 0--4 weeks. In addition, the groups that received AVA 4 weeks apart had peak anti-PA IgG concentrations that were approximately threefold higher than those for the groups that received AVA 2 weeks apart (*143*). This study suggested that increasing the interval between the first AVA doses might lead to an immune response comparable to that of the originally licensed schedule, with fewer doses required to achieve that response. However, the results of the study could not be used to support a change in the use of the vaccine because of the small sample size.

In 2000, the U.S. Congress funded the CDC-sponsored AVRP clinical trial, a large, phase 4, double-blind, randomized, placebo-controlled study to assess the immune response to a reduced-dose schedule and a change in the route of administration from SC to IM (*140*). The AVRP clinical trial enrolled 1,564 civilian participants in five U.S. sites during May 2002--March 2004.

Fifty-one percent of the participants were women, and 49% were men; ages ranged from 18--61 years and were evenly distributed among study groups. Approximately 75% of participants were white, 15% were black, and 10% were categorized as other. Participants were randomly assigned one of the following six vaccination schedules, with vaccinations administered over 42 months: 1) the originally licensed schedule of 8 SC doses (4 doses for the reported interim analysis); 2) 8 IM doses (4 IM doses for the reported interim analysis); 3--5) 7, 5, or 4 IM doses (3 IM doses through month 6, with the three groups combined into one group for purposes of the interim analysis); and 6) placebo (*140*). As of February 2009, when ACIP voted on the revised recommendations, data were available for review through dose 4.

In 2005, CDC submitted data to FDA from the interim analysis of the first 1,005 enrolled participants who, at the time of the analysis, had received 4 doses of AVA by the SC route or the IM route or 3 doses by the IM route. Emergent BioSolutions subsequently filed a supplemental BLA. The primary outcome measures of this analysis were noninferiority of the anti-PA IgG geometric mean concentration (GMC), the geometric mean titer (GMT), and the proportion of responders with a fourfold increase in titer at week 8 (4 weeks after the week 4 dose) and month 7 (4 weeks after the month 6 dose) (*140*). At week 8, antibody responses were significantly higher in women than men in the 4-IM and 3-IM groups but not in the 4-SC group. By month 7, no significant differences between men and women had been detected in any of the groups analyzed. Antibody levels also were significantly higher in whites compared with blacks at week 8 ($p<0.05$), but by month 7, they were equivalent.

Serological noninferiority analyses of antibody responses (anti-PA IgG GMC) demonstrated the noninferiority of both the 3-IM regimen and the 4-IM regimen to the originally licensed schedule at month 7 (Figure).

CDC is analyzing animal data and designing bridging studies to correlate nonhuman primate immune responses to AVA with survival from inhalation anthrax. Bridging of these data to human immune responses to AVA will provide additional information regarding immune correlates of protection against anthrax in nonhuman primates and serological markers of protection in vaccinated humans.

Efficacy

Evidence for the efficacy of AVA comes from several studies in animals (including in nonhuman primates) and from a controlled vaccine trial in humans (*17*), observational data in humans (*135,136*), and immunogenicity data for humans and other mammals (*129,130,139,141,144*). A recent review provided support for the efficacy of AVA for persons aged 18--65 years (*145*)*;* no data are available regarding the efficacy of anthrax vaccine for persons aged <18 years and >65 years.

The protective efficacy of the alum-precipitated vaccine (the original form of the PA filtrate vaccine) and AVA (adsorbed to aluminum hydroxide) has been demonstrated in several animal models using different routes of administration (*127--129,132,144,146--151*). The Rhesus macaque (*Macaca mulatta*) is considered a suitable model of inhalation anthrax in humans

(*108,152*), and AVA has been shown to be protective against an aerosol challenge in macaques using *B. anthracis* strains of high virulence (*132,149,153--155*).

Initial evidence for efficacy in humans came from the Brachman study, a placebo-controlled, single-blind, clinical trial among workers in four northeastern U.S. mills that processed raw, imported goat hair (*17*). The study was conducted during 1955--1959 using the alum-precipitated vaccine, the precursor to the currently licensed AVA. A total of 1,249 workers were included: 379 received the full series of anthrax vaccine, 414 received placebo, 116 received an incomplete series of injections (with either vaccine or placebo), and 340 received no treatment (observational group). Before vaccination, the yearly average number of human cutaneous and inhalation anthrax cases among employees in these mills was 1.2 cases per 100 employees. During the study, 26 anthrax cases (five inhalation and 21 cutaneous) were reported from the four mills. All five inhalation cases (four of which were fatal) occurred in participants who had not received vaccine; two had received placebo, and three had been in the observational group. Twenty of the 21 cutaneous cases occurred among participants who had not been fully vaccinated. Fifteen of the 21 had received placebo injections, three had received no injections (observational group), and three had received some doses of anthrax vaccine. Among the three cases that occurred in vaccinated persons, one occurred just before administration of the scheduled third dose, one occurred 13 months after completion of the scheduled 6 doses (but before any booster doses were received), and one occurred just before receipt of the first booster dose. The efficacy analysis in this study included all cases of anthrax, regardless of the route of exposure or manifestation of the disease, providing a combined efficacy of 92.5% based on person-time of occupational exposure (*17*).

During 1962--1974, CDC collected surveillance data, independently of the Brachman clinical study, on cases of anthrax in mill workers or persons living near mills in the United States (*135,136*). Vaccinated persons received either AVA or the earlier formulation used in the original 1950s clinical trial (*17*). No cases of inhalation anthrax were identified in any of the workers. Twenty-seven cases of cutaneous anthrax were identified by CDC, 24 of which were in unvaccinated persons. In vaccinated persons, one case occurred after receiving 1 dose of anthrax vaccine, and two cases occurred after receiving 2 doses of anthrax vaccine. No documented cases of anthrax were reported for persons who had received at least 3 of the recommended 6 doses of anthrax vaccine. A civilian advisory panel reviewed the CDC surveillance data and determined the vaccine to be effective (*136*).

In March 2002, a committee appointed by the Institute of Medicine (IOM) released a comprehensive review of the most current safety and efficacy data available for AVA (*152*). The committee found human efficacy data to be limited to the Brachman study (*17*) and the CDC surveillance data (*135,136*) but concluded that the combination of human data and animal data demonstrated that AVA effectively protects humans from anthrax, including inhalation anthrax (*152*).

The committee also determined that the mechanism of action of AVA protects humans from various *B. anthracis* strains and that a naturally occurring or bioengineered strain probably could not overcome AVA and cause anthrax (*152*).

The duration of AVA protection in humans after the initial priming series is unknown. Persons are considered protected from anthrax for as long as they continue receiving AVA according to the licensed schedule. A 2002 study of military personnel who had received 1, 2, or 3 priming doses during the early 1990s, followed by 1 dose 18--24 months later, demonstrated that 99.3% of participants had measurable anamnestic responses (*143*). Data from animal studies suggest that the duration of protection after 2 doses might be 1--2 years and that 3 IM doses of AVA provide significant levels of protection in rhesus macaques for up to 4 years (*140,144,149,155*). Persisting, detectable PA-specific memory B cells in the blood might be useful markers for duration of immunity because of their ability to proliferate and differentiate rapidly into anti-PA antibody--secreting plasma cells. In a study of patients with clinical anthrax, peak anti-PA IgG levels after infection correlated with the number of PA-specific memory B cells in circulation up to at least 1 year after infection (*156*). Circulating PA-specific memory B cells also were detectable in AVA vaccine recipients. These data suggest that both survivors of inhalation anthrax and vaccine recipients develop long-term protective immunity to anthrax; quantitative analysis of PA-specific IgG B cell memory might be a useful predictor of the duration of protection against anthrax (*156*).

Safety

At least eight reviews (*9,135,136,145,152,157--159*) and 35 other publications include evaluations of AVA safety.

Prelicensure Adverse Event Surveillance

Local Reactions. In prelicensure evaluations, 6,985 persons received 16,435 SC doses: 9,893 initial series doses and 6,542 annual boosters (*160*).

Severe local reactions (defined as edema or induration of >120 mm) occurred after 1% of vaccinations. Moderate local reactions (defined as edema and induration of 30--120 mm) occurred after 3% of vaccinations. Mild local reactions (defined as erythema, edema, and induration of <30 mm) occurred after 20% of vaccinations. In a study of the alum-precipitated precursor to AVA, moderate local reactions were documented in 4% of vaccine recipients and mild reactions in 30% of recipients (*17*).

Systemic Reactions. In prelicensure evaluations, systemic reactions (i.e., fever, chills, body aches, or nausea) occurred in <0.06% (in four of approximately 7,000) of vaccine recipients (*160*). In the study of the alum-precipitated precursor to AVA, systemic reactions occurred in 0.2% of vaccine recipients (*17*).

Postlicensure Adverse Event Surveillance

During January 1, 1998--December 31, 2008, nearly 12.4 million doses of AVA were distributed for DoD and domestic licensed use (AT Waytes, Emergent BioSolutions, personal communication, November 5, 2009); 8.4 million of these doses were administered to approximately 2.1 million military personnel during March 1, 1998--December 31, 2008 (P Garman, Military Vaccine Agency, personal communication, November 5, 2009). Less than 1% of all AVA doses were distributed to nonmilitary sources (AT Waytes, Emergent BioSolutions, personal communication, November 5, 2009).

The Vaccine Adverse Event Reporting System (VAERS) has been used extensively to monitor adverse events that occur after vaccination with AVA. VAERS (*161--163*), a U.S. national passive surveillance system for reporting adverse events that occur after administration of U.S. licensed vaccines, plays an important role in the identification of adverse events that warrant further investigation. Although VAERS data are useful for detecting rare adverse events and assessing reporting trends, they cannot be used to assess incidence rates or causality. Reports can be submitted voluntarily by anyone, including health-care providers, patients, manufacturers, or family members; therefore, reports might vary in quality and completeness, often lack detail, and might include inaccurate information. Because VAERS is a passive surveillance system, actual rates for adverse events cannot be calculated because the number of doses administered is unknown. Underreporting is another important limitation, as is differential reporting (e.g., increased reporting rates for specific vaccines or specific adverse events), which often occurs for more serious and unexpected events, events occurring soon after vaccination, events surrounded by publicity, and reports related to litigation proceedings (*163,164*). Hypotheses generated by VAERS must be confirmed by epidemiological studies (*163*).

During January 1, 1998--December 31, 2008, VAERS received 6,015 nonduplicate reports from U.S. sources of adverse events after receipt of AVA, either alone or concurrently with other vaccines (CDC, unpublished data, 2010). Of these, 600 (9.9%) were categorized as serious events (i.e., events resulting in death, hospitalization, or permanent disability) (*165*). Approximately 74% of all reported adverse events that occurred after administration of AVA were in persons aged <40 years. Twenty-six percent occurred in women and 72% in men; sex was not specified in 2% of the reports.

The majority (75%) received AVA alone, and 25% received the vaccine concurrently with other vaccines. Eighty three percent of AVA reports were documented as being administered or funded by the military (CDC, unpublished data, 2010).

Adverse events reported to VAERS are coded using terms from the *Medical Dictionary for Regulatory Activities* (MedDRA) (*166*). Approximately 800 different MedDRA terms were reported in conjunction with AVA during 1998--2008. The 10 most common adverse events that occurred after AVA administration (either alone or concurrently with other vaccines) were arthralgia (n = 1,036, 17.2%), headache (n = 981, 16.3%), pruritis (n = 878, 14.6%), pain (824, 13.7%), injection-site erythema (n = 753, 12.5%), fever (n = 655, 10.9%), erythema (626, 10.4%), pain at the injection site (613, 10.2%), rash (606, 10.1%), and myalgia (583, 9.7%) (*172*).

As of December 31, 2008, VAERS had received 25 reports of death among AVA recipients. Causes of death included a spectrum of cardiovascular disorders, unintentional or intentional injuries, malignancies, and chronic illnesses (CDC, unpublished data, 2010). Death reports have been summarized elsewhere (*27,167,168*).

Reports to VAERS after AVA administration have been reviewed by several expert groups (*157,158,167,168*). In 2003, IOM (*169*) recommended that CDC partner with DoD to follow up on signals generated by reviews of VAERS and DoD data, using the DoD Defense Medical Surveillance System (DMSS), a relational surveillance database containing data from military recipients of AVA and other vaccines (*170*).

Short-Term Adverse Events. Data on the safety of AVA are only available for persons aged 18--65 years; no information is available on the safety of this vaccine in children or older adults (>65 years). Much of the published data comes from the routine DoD anthrax vaccination program. Several studies, including clinical trials and uncontrolled observational studies, have examined immediate or short-term adverse events (e.g., hours to days) that occurred after receipt of AVA (*171*--*177*). The majority of these events have been limited to local reactions (e.g., erythema, swelling, pain or tenderness, itching, and nodules) or mild, self-limited systemic symptoms (e.g., fever, chills, myalgia, arthralgia, and malaise). After a comprehensive review, the IOM committee (*152*) found no evidence that AVA recipients had a higher risk than the general population for life-threatening or permanently disabling adverse events immediately after receiving AVA and that rates and types of immediate or short-term reactions were comparable to those for other vaccines regularly administered to adults (*152*).

After the bioterrorism events of 2001, 1,727 persons participated in the CDC Anthrax Vaccine and Antimicrobial Availability program and received either AVA and antimicrobials or only antimicrobials (*178*). Among the enrollees, 199 participants opted to receive AVA and antimicrobials. Local and systemic adverse event profiles for AVA recipients compared with those for persons who received only antimicrobials indicated that a higher proportion of persons who received AVA reported adverse events than did persons who received only antimicrobials. The most commonly reported adverse events among vaccine recipients were discomfort at the injection site (70.9%), erythema (45.2%), induration (58.8%), and swelling (39.7%). Participants who received AVA by the SC route in the AVRP clinical trial reported warmth, tenderness, erythema, induration, and nodule development more frequently than participants who received AVA by the IM route.

Although fatigue and headache were the most commonly reported systemic adverse events among clinical trial participants, they were reported by <11% of participants. Women reported significantly more injection-site and systemic adverse events than men (*140*).

Several reviews have noted that women report a higher proportion of certain adverse events after AVA than men (*152,157,167,168*); this phenomenon has been documented with other vaccines as well (*179*). A comprehensive review of VAERS AVA data in 2004 demonstrated that women were 3 times more likely than men to have or report an adverse event.

Women were not more likely to be hospitalized than men because of adverse events, although women accounted for a greater proportion of reported injection-site adverse events and moderate or extensive injection-site inflammation (*157*). A study of female AVRP clinical trial participants to assess the effect of progesterone levels on adverse events and immune response is ongoing; final data will be available in late 2010.

Long-Term (Chronic) Adverse Events. DoD has published several studies of long-term health effects among vaccinated and unvaccinated military personnel (*180--184*). Additional studies have assessed the long-term health of vaccinated researchers and fertility parameters for vaccinated males (*185,186*). None of the studies found that the risk for adverse health effects or chronic diseases (e.g., cancer or infertility) was higher after anthrax vaccination. These studies of long-term health effects support the IOM finding (*152*) that no convincing evidence exists to indicate that the risk for developing long-term adverse health effects is higher among anthrax vaccine recipients. As with all vaccines, the possibility for rare adverse reactions does exist with AVA.

The Vaccine Analytic Unit (VAU) (*170*), which was developed to implement the IOM recommendations (*169*), is a collaborative CDC and DoD project with FDA participation. Using data from DMSS, VAU can analyze vaccine safety data for all vaccines administered to active-duty and reserve service personnel. In a matched case-control study, VAU investigators found no significant associations between optic neuritis and previous receipt of AVA, smallpox, hepatitis B, or influenza vaccines (*187*). In addition, VAU found no association between concurrent receipt of multiple vaccinations and hospitalization risk among U.S. military personnel (*188*). Studies to address additional topics (e.g., Stevens Johnson syndrome/toxic epidermal necrolysis, type 1 diabetes mellitus, atrial fibrillation, and diffuse connective tissue diseases) are ongoing.

Effect of Route of Administration on Adverse Events

A small randomized study on the effects of route of administration on adverse events found that systemic adverse events were uncommon and similar for IM and SC groups. All local reactions (i.e., tenderness, erythema, warmth, induration, and subcutaneous nodules) were significantly more common after SC injection than after IM injection. Women who received IM injections 4 weeks apart reported fewer of certain local adverse events than did women who received SC injections 2 weeks apart (*143*).

The AVRP clinical trial demonstrated that the proportion of injection-site adverse events was lower in the group receiving 4 IM injections than in the group receiving 4 SC injections, especially among women, who experienced a significant decrease in the occurrence of warmth, tenderness, itching, erythema, induration, edema, and nodules. In addition, the duration of injection-site adverse events in the 4-IM group was shorter than that experienced by the 4-SC group. Persons in the 4-IM group also experienced significantly fewer moderate and severe injection-site adverse events (7.0%) than persons in the 4-SC group (10.2%, $p = 0.04$). Analog pain scale scores used to assess pain immediately after injection were significantly lower in the 4-IM group compared with the 4-SC group ($p<0.01$).

In all study groups, women were almost twice as likely as men to experience an injection-site adverse event (OR = 1.93, $p<0.01$); however, the absolute differences between women and men for warmth, itching, erythema, induration, and nodules were largest in the 4-SC group. Route of administration was not associated with the occurrence of systemic adverse events, and the differences between men and women in regards to systemic adverse events were generally consistent across all study groups (including the placebo group) (*140*).

Effect of Vaccination on Pregnancy and Breastfeeding

A paucity of data exists regarding the use of AVA during pregnancy; however, in general, the use of inactivated vaccines is considered safe during pregnancy (*189--193*). Some evidence indicates that nonspecific stimulation of the maternal immune system might decrease the risk for birth defects (*194,195*). Potential benefits gained from the use of AVA during pregnancy might outweigh the risk in certain situations. DoD policy is to exempt pregnant military women from anthrax vaccination; however, some women were inadvertently vaccinated with AVA while pregnant, as reported in a recent study that evaluated approximately 115,000 live births to military women (*196*). The study suggested that infants born to women who received anthrax vaccine in their first trimester of pregnancy had slightly higher odds of experiencing birth defects than infants born to never-vaccinated women (OR = 1.20, 95% confidence interval [CI] = 1.02--1.42) or to women vaccinated only after pregnancy (OR = 1.02, CI = 1.01--1.43). When infants born to women vaccinated during their first trimester were compared with infants born to women vaccinated outside the first trimester, no statistical association with birth defects was found (OR = 1.18, CI = 1.00--1.41). Of the 10 specific defects assessed in this study, only atrial septal defect (ASD) demonstrated a significant increase among infants born to women vaccinated during the first trimester. These findings were limited, partly because the code for ASD (per the International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]) is the same as the code for patent foramen ovale, a common finding in preterm infants. When preterm infants with ASD as the only reported birth defect were excluded from analyses, the association between ASD and vaccination in the first trimester was no longer statistically significant. In addition, late recognition of pregnancy, a moderate risk factor for many birth defects, including ASD, might explain the number of women vaccinated during their first trimester. After review of these data and discussions with the authors of this study, ACIP concluded that AVA is safe to administer during pregnancy but recommended that pregnant women defer vaccination unless exposure to anthrax poses an immediate risk for disease (*27*).

Another study of 385 women who had received at least 1 dose of AVA before becoming pregnant (*197*) found no evidence of miscarriage, infertility, or other reproductive problems among vaccinated women. In addition, the study did not support the hypothesis that AVA administration resulted in decreased pregnancy rates among those vaccinated before pregnancy.

No data have been collected on the use of AVA among breastfeeding women. Therefore, whether anti-anthrax antibodies are transferred through milk from mother to infant is unknown; however, data from similar vaccines indicate that this might occur (*198*). No biological reason suggests that breastfeeding women or breastfed children have an increased risk for adverse events after the mother receives anthrax vaccine. Administration of other inactivated vaccines during breastfeeding is not medically contraindicated (*199*).

Vaccination of Children

AVA use in children has not been studied, and the vaccine is not licensed for use in this population. A 2004 review demonstrated that children aged <18 months experienced more local erythema and induration after receipt of vaccines containing an aluminum hydroxide adjuvant than after receipt of nonadjuvanted vaccines. Erythema and induration were not reported in children aged 10--18 years, although these older children experienced local pain lasting up to 14 days after administration of vaccines with aluminum hydroxide adjuvants (*200*). The concentration of aluminum per dose of AVA is similar to that in the diptheria/tetanus/pertussis (DTaP) vaccine and is less than that in the combined DTaP/polio/hepatitis B vaccine (*201*). Because AVA contains aluminum hydroxide, local adverse events are likely to be similar to those described in adults administered AVA and in children administered other vaccines with similar aluminum hydroxide concentrations; ACIP concluded that no evidence suggests that the risk for serious adverse events after receipt of anthrax vaccine is higher in children. The morbidity of inhalation anthrax should be considered when children have been exposed to aerosolized *B. anthracis* spores.

PEP for Previously Unvaccinated Persons

Vaccination as a Component of PEP

Studies have demonstrated not only the persistence of spores in nonhuman primates up to 100 days after inhalation exposure (*95*) but also the potential for long-term spore survival and development of inhalation anthrax after discontinuation of postexposure antimicrobial agents (*93,95*). Because disease can develop long after exposure to spores, animal studies have examined the use of postexposure vaccination in combination with antimicrobial agents. Although the precise correlation between the immune response to vaccination and protection against disease has not been completely defined, several studies (*93,95,102*) have documented that 2- and 3-dose schedules of vaccination, combined with antimicrobial therapy, prevent development of disease in animals. Although the point at which a person develops immunity against anthrax after the first vaccination is unknown, available data indicate that the antibody response to the vaccination administered at week 26 (month 6) is characteristic of a strong anamnestic response, in turn indicating that the vaccine schedule of day 0, week 2, and week 4 effectively primes the immune system against PA.

The available data on human responses to AVA indicate that use of the 3-dose SC regimen (with doses at 0, 2, and 4 weeks) for PEP results in rapid anti-PA antibody production at high levels (*140,143*) and is therefore an additional benefit to the approved antimicrobial therapies. Therefore, ACIP previously recommended that 3 doses of AVA (SC at day 0, week 2, and week 4) be administered in conjunction with antimicrobial therapy to previously unvaccinated persons who have been exposed to aerosolized *B. anthracis* spores (*23*,*24*).

As described, the AVRP clinical trial (*140*) demonstrated that a vaccination schedule of doses administered at 0 and 4 weeks via the IM route elicited a lower antibody response at week 8 than did a schedule of doses administered at weeks 0, 2, and 4 via the SC or IM route (Figure).

Because the clinical significance of the lower immune response to a schedule of doses administered at 0 and 4 weeks is not known, and sex-related differences in antibody levels exist, adherence to a schedule that produces rapid development of high antibody levels is particularly beneficial in a postexposure setting. Therefore, in June 2009, FDA recommended retaining the current PEP protocol (3-dose SC series administered at 0, 2, and 4 weeks in conjunction with antimicrobial therapy for a minimum of 60 days) until additional data are available (J Clifford, FDA, personal communication, June 24, 2009).

After natural, occupational, or bioterrorism-related exposure to aerosolized *B. anthracis* spores, the combination of AVA and antimicrobials is more effective than use of antimicrobials only. Vaccination as a component of PEP is beneficial when antimicrobial PEP is discontinued too soon after exposure. Poor adherence to the prescribed regimen, which has been as low as 42%, minimizes the effectiveness of postexposure antimicrobial therapy (*202*). The bioterrorism events of 2001 also suggested that persons might be exposed to larger amounts of *B. anthracis* spores than those studied in animal models. A possible consequence would be prolonged spore clearance, with increased levels of residual spores at the alveolar surface epithelium and therefore an increased potential for infection when antimicrobial prophylaxis is discontinued after 60 days (*202*).

Because of the potential for short incubation periods with inhalation anthrax, especially when the inhaled dose might be large, and the rapid progression and associated high morbidity and mortality, antimicrobial PEP should be initiated as soon as possible after inhalation exposure to aerosolized *B. anthracis* spores. Vaccination also should be initiated as quickly as possible but will likely occur several days after antimicrobial agent initiation for logistical reasons. To maximize the benefits of vaccine, the first dose should be initiated within 10 days of exposure. Antimicrobial use should continue until the immune response to the priming series has developed, which is expected to be 10--14 days after administration of the third dose of vaccine. PEP recommendations for inhalation exposure to aerosolized *B. anthracis* spores differ from those for a naturally occurring cutaneous or gastrointestinal exposure.

Because AVA is not licensed for postexposure use, administration of AVA as a component of PEP is available under an IND application (IND #10061, held by CDC) and may be made available under an EUA (19--22).† The PEP regimen included in the IND protocol includes children aged 0--17 years. IND protocols require detailed records to be kept; written, informed consent from all participants; data collection; reports to FDA; and follow-up of patients.

The IND mechanism is generally suited to clinical practice and is not easily used during an emergency. The Project BioShield Act of 2004 authorizes the FDA commissioner to issue an EUA during an emergency under certain circumstances (*21*). Under an EUA, medical countermeasures to diagnose, treat, or prevent serious or life-threatening diseases for which no adequate, approved, and available product exists can be disseminated quickly for the protection and safety of the U.S. population. The issuance of an EUA enables large-scale use of a medical countermeasure (*203*) such as AVA as a component of PEP. AVA has been used extensively, including after the bioterrorism events of 2001, with a good safety profile; therefore, on the basis of a review of existing data and expert opinion, ACIP expects that future use of AVA as a component of PEP is likely to have a good safety profile.

Antimicrobial Agents as a Component of PEP

Because limited data are available, the optimal duration of antimicrobial therapy in combination PEP is uncertain. Antimicrobial therapy for 60 days, without vaccine, might prevent inhalation anthrax; however, antimicrobial agents without vaccine might not protect persons from late spore germination. Using the limited available data, FDA licensed a 60-day course of antimicrobials for postexposure use; a shorter course (<60 days) of antimicrobial therapy, even when combined with a 3-dose AVA series, is not approved for use by FDA. In 2006, an expert panel (*204*) discussed whether, based on the limited evidence (*102,139*), the duration of antimicrobial use could be shortened with concurrent receipt of AVA. The panel determined that the available data were too limited to support a regimen of <60 days.

Oral ciprofloxacin, oral doxycycline, and parenteral (IM) penicillin G procaine have been shown to be effective for PEP use in a nonhuman primate model (*93*) and are FDA approved for a 60-day course for inhalation anthrax (postexposure) in all age groups (*205,206*). Ciprofloxacin and doxycycline are equivalent first-line antimicrobial agents for PEP, because they are equally effective and have similar susceptibility profiles among naturally occurring *B. anthracis* isolates (*93,207*). In addition, both have similar safety profiles, with a low rate of anaphylactic reactions (*208,209*).

Selection of PEP agents should involve consideration of the potential for antimicrobial resistance. Both naturally occurring constitutive and inducible β-lactamase production can be present in *B. anthracis* isolates (*207,210--212*). Because induction of resistance has been previously reported in the nonhuman primate model (*213*), there are concerns that an insufficient dosage could induce penicillin resistance in humans (*49,214,215*). For these reasons, oral penicillins are not considered first-line antimicrobial agents for PEP but may be considered after the antimicrobial susceptibility profile of the organism is known. *B. anthracis* is not susceptible to cephalosporins or trimethoprim-sulfamethoxazole (*207,216,217*).

Although oral amoxicillin is an alternative to the first-line PEP agents when antimicrobial susceptibility profiles demonstrate appropriate sensitivity (minimum inhibitory concentration [MIC] ≤0.125 μg/mL), amoxicillin has not been studied for the prophylaxis or treatment of anthrax, and no safety or efficacy data are available for this indication.

Amoxicillin is not FDA approved for use as a component of PEP and therefore should only be administered under an IND or possibly under an EUA to certain patient groups (e.g., children or pregnant or nursing women) during a declared emergency provided the criteria for issuance have been met.

Because oral amoxicillin has better pharmacokinetics than equivalent doses of oral penicillin V, oral amoxicillin may be used with a less frequent dosing interval, potentially improving adherence to therapy (*218--222*). Compared with oral penicillin, oral amoxicillin has greater pulmonary penetration and is able to maintain a higher concentration above MIC in the target tissues (e.g., pulmonary-associated lymph nodes, tissues, and secretions) for a greater portion of the dosing interval (*223--227*).

Oral amoxicillin at dosages approved for other indications (i.e., 500 mg/kg every 8 hours for adults; 45 mg/kg/day orally in 3 divided doses for children weighing <40 kg) should prevent postexposure inhalation anthrax if the *B. anthracis* strain in question has an amoxicillin MIC <0.125 μg/mL (*225--227*). Amoxicillin-clavulinic acid combinations may be considered for PEP. Because potassium clavulanate does not have a significant impact on the pharmacokinetics of oral amoxicillin, the dosage is based on the amoxicillin component (*228*).

Levofloxacin been shown to be effective for PEP use in a nonhuman primate model (*229*) and is FDA approved for inhalation anthrax (postexposure) in patients aged >6 months (*230*). Short-term (up to 28 days) safety data exist, but extended-use (up to 60 days) data are limited (*231*). Therefore, levofloxacin is recommended as a second-line PEP antimicrobial agent to be reserved for instances in which tolerance issues or drug resistance patterns indicate its use.

Dosing information for recommended antimicrobial agents for PEP is provided (Table 1). For patients unable to tolerate FDA-approved antimicrobial agents, clinicians may consider clindamycin, chloramphenicol, erythromycin, vancomycin, or other fluoroquinolones for PEP, based on in vitro susceptibility results. Administration of these agents would be considered off-label use (i.e., for other than the FDA-approved use) and might require an IND or EUA.

Adverse Events Associated with Antimicrobial PEP

Adverse events associated with the long-term use of antimicrobial PEP include gastrointestinal upset and other conditions that are expected when normal body flora are disrupted by antimicrobial use (*232*). Any antimicrobial agent can have undesirable side effects, including allergic reactions. Patients should be urged to inform public health authorities and their health-care providers of any adverse events that occur. Long-term fluoroquinolone use has been associated with tendinitis and tendon tears (*233*).

During the bioterrorism events of 2001, approximately 10,000 persons were recommended to receive a 60-day regimen of antimicrobial prophylaxis (doxycycline, ciprofloxacin, or amoxicillin) for suspected or confirmed exposure to *B. anthracis* spores. Adverse events that were commonly reported by patients were not serious and included diarrhea, stomach pain, nausea, vomiting, headache, dizziness, and fatigue (*202,234*). No serious adverse events were found to be definitely related to the use of prescribed antimicrobials (*202,234*).

Adverse events associated with ciprofloxacin or doxycycline were not substantially different enough for one therapy to be recommended instead of the other (*178,202*). Among persons who began the 60-day PEP regimen, 21%--41% continued the regimen as prescribed (*202*). Adverse events were a commonly cited reason for discontinuation of antimicrobial PEP; 73 (78%) of the 93 persons in the Washington, DC, postal center who stopped taking antimicrobial PEP cited adverse events as a reason for nonadherence (*235*). Perceived risk for exposure to aerosolized *B. anthracis* was a statistically significant predictor of adherence to PEP (*235*), and according to one study, perceived risk was a stronger predictor of adherence than actual adverse events (*202*).

Antimicrobial Considerations for Pregnant or Breastfeeding Women

Based on limited human clinical information, use of therapeutic doses of ciprofloxacin during pregnancy is unlikely to have a substantial teratogenic risk; however, the actual teratogenic risk from ciprofloxacin use during pregnancy is unknown (*13,236*). Even with these limited data, ciprofloxacin is recommended as the first-line antimicrobial agent of choice for PEP for asymptomatic pregnant or lactating women because of the severity of inhalation anthrax (*237*). Treatment should be changed to amoxicillin if the strain of *B. anthracis* is found to be sufficiently susceptible to penicillin (*237*).

Potential risks associated with the use of tetracycline antimicrobials during pregnancy include dental staining of the fetal primary teeth and possible depressed fetal bone growth and dental enamel defects. Hepatic necrosis has been reported in pregnant women using tetracyclines, although such reports are rare (*13*). Tetracyclines should be used cautiously in asymptomatic pregnant women and only if contraindications to the use of other appropriate antimicrobial agents exist. Penicillins are generally considered to be safe during pregnancy and are not associated with an increased risk for fetal malformation (*238*).

The American Academy of Pediatrics considers ciprofloxacin and tetracyclines (including doxycycline) to be appropriate for breastfeeding women because the amount of drug absorbed by infants is small; however, little is known about the safety of long-term use (*239*). Because of the severity of inhalation anthrax, ciprofloxacin and doxycycline are considered the first-line antimicrobial agents of choice for PEP (*237*) as indicated for adults in these recommendations. Because amoxicillin is known to be safe for infants, this antimicrobial is an option for PEP for breastfeeding mothers when the appropriate conditions described have been met and when the mother has no contraindications to amoxicillin. If an infant is exposed to *B. anthracis* and is receiving PEP, the antimicrobial regimen of the breastfeeding mother should be the same as that of the child, when possible, to minimize infant exposure to multiple drugs. If the drug used by the mother is contraindicated in her infant, the mother should express and discard her breast milk while being treated. Breastfeeding may resume after the mother completes the course of antimicrobial therapy (*204,240,241*).

Antimicrobial Considerations for Children

Although antimicrobials such as ciprofloxacin or doxycycline are typically not administered to children, the severity of anthrax is sufficient that treatment with these antimicrobials is warranted and recommended for children who have been exposed to aerosolized *B. anthracis* spores. Amoxicillin is preferred for antimicrobial PEP in children when susceptibility testing indicates that the *B. anthracis* isolate involved is susceptible to penicillins (i.e., MIC $\leq$0.125 µg/mL for amoxicillin). In these instances, a transition from ciprofloxacin or doxycycline to amoxicillin is recommended for completion of the 60-day PEP antimicrobial regimen (Table 1).

Antimicrobial Considerations for Other Populations

For other specific populations, such as older adults or patients with certain underlying medical conditions (i.e., diabetes or renal failure), standard medical practice should be followed. Additional antimicrobial agents that are not FDA approved for treatment or prevention of anthrax but that may be considered include clindamycin, chloramphenicol, rifampin, vancomycin, and other fluoroquinolones. Health-care providers should consult with public health officials when choosing alternative antimicrobial agents and should consider the antimicrobial susceptibility of the associated strains of *B. anthracis*.

Risk for Exposure to *B. anthracis*

Anthrax exposure is categorized as non--bioterrorism related (i.e., naturally occurring) or bioterrorism related (i.e., intentional). Although naturally occurring anthrax decreased substantially in the United States beginning in 1957 after the initiation of animal vaccination with the Sterne vaccine, persons in certain occupations remain at higher risk for naturally occurring anthrax exposure. In contrast, the risk for bioterrorism-related anthrax is difficult to predict.

General Public

Members of the general public, including pregnant or breastfeeding women, are not at risk for exposure to naturally occurring anthrax but might be exposed through a bioterrorism event that would be time limited, sporadic, and most likely geographically limited, as well as difficult to predict, detect, or prevent (*9*). The target population for a bioterrorism-related release of *B. anthracis* cannot be predicted, and the risk for exposure cannot be reliably calculated. Once a bioterrorism event occurs, exposure and risk for disease development at the individual level are difficult to identify. No data suggest that the risk for developing anthrax is greater for pregnant women who have been exposed to *B. anthracis* than for nonpregnant women who have been exposed. Among children, naturally occurring cases and one confirmed case resulting from exposure during the 2001 bioterrorism events have been reported (*43,242--244*). Data are limited regarding the risk for developing anthrax in children after exposure; however, the risk is assumed to be similar to the risk for adults. Like the general public, medical personnel are not at risk for exposure to naturally occurring anthrax but might be exposed through a bioterrorism event. In general, the risk for acquiring anthrax when caring for infected or contaminated patients is thought to be negligible because no person-to-person transmission or secondary cases of anthrax among medical personnel have been documented. Medical personnel are recommended to routinely follow infection control measures to minimize risk for known nosocomial infections (*245*).

Populations at Risk for Occupational Exposure

Persons who repeatedly enter potentially contaminated areas should use appropriate personal protective equipment (PPE), which is defined in this report as consisting of a powered air-purifying respirator with full-facepiece and high-efficiency particulate air (HEPA) filters, disposable protective clothing with integral hood and booties, and disposable gloves (*246*). However, despite the use of appropriate PPE, exposures during repeated encounters with contaminated areas might occur because PPE is not 100% effective, individual work practices might lead to exposure, breaches in PPE and environmental controls might occur, and some breaches might not be detected (*247,248*).

Persons Handling Animals or Animal Products

Improvements in industrial hygiene standards, mechanization of animal processing, animal disease control, and strict importation guidelines have reduced the risk for exposure to anthrax among manufacturing employees working with animals and animal products such as imported animal hides, furs, bone meal, wool, animal hair, or bristles (6,31).§ Nevertheless, slaughterhouse workers, butchers (*249*), and wool and mohair processors might still be at risk for exposure to *B. anthracis* spores if the industry standards are not upheld.

Inhalation and cutaneous anthrax are occupational hazards primarily for workers who process hides, hair (especially from goats), bone and bone products, and wool (*31,39,43*) and for veterinary, agriculture, and wildlife workers who handle infected animals (*48*). Domestic exposure to *B. anthracis* spores might occur during contact with contaminated bone-meal fertilizer (*40*) or wool yarn (*250*), while making or playing contaminated goat-skin drums (*37,38,44*), and during contact with other domestic products (*31,41*).

Occupational exposure to *B. anthracis* through contact with animals, whether in an agricultural or industrial setting, remains a risk when contact with animals with suspected or confirmed anthrax occurs. However, such human cases are rare (*251*), and cutaneous anthrax is the primary risk. Exposure to *B. anthracis* spores in soil is not considered a substantial risk for human inhalation anthrax because spores are bound to heavy soil particles (*28*).

Persons Working in Laboratories

Multiple types of laboratories might work with *B. anthracis,* including academic (research), military, veterinary, food-testing, and public health laboratories. Direct and indirect contact with contaminated objects, accidental parenteral inoculation, and generation of aerosolized particles are all potential risks for infection. Certain activities increase the risk for exposure, such as working with large volumes and high concentrations of the organism or performing activities that might result in aerosolization, such as vortexing and centrifugation (*252*). In 2006, the Association of Public Health Laboratories website provided guidance to address sample transport, receipt, and screening of unknown environmental samples (*253*).

Persons Working in Postal Facilities

The distribution of letters laden with anthrax spores through the U.S. Postal Service (USPS) in 2001 established the mail as a feasible route of exposure. In the event of another attack through the mail, the risk for exposure to aerosolized *B. anthracis* spores is presumed to be high among staff members in a USPS processing and distribution center who work with mechanical processing equipment that might generate aerosol particles. In response, USPS implemented environmental monitoring to rapidly identify the presence of *B. anthracis* in these centers. Detection of *B. anthracis* using these validated USPS monitors would identify a likely exposure (D Sosin, CDC, personal communication, October 2, 2008) and allow prompt initiation of antimicrobial PEP while laboratory verification is being performed.

Military Personnel

The personnel who have been determined by DoD to be at risk for exposure to *B. anthracis* spores include military personnel being deployed to areas designated by DoD as posing a high risk for anthrax exposure, other select military units with unique missions, civilians deemed to be essential emergency personnel in designated locations, and contractors assigned to higher risk areas who are performing mission-essential services (*254,255*).

Persons Involved in Emergency Response Activities

Environmental Investigators and Remediation Workers

Conducting remediation of *B. anthracis*-contaminated areas can pose a risk for exposure to *B. anthracis* spores. Repeated occupational exposures might occur during environmental investigation or remediation efforts after identification of anthrax cases, regardless of whether the event is bioterrorism related. However, certain features of a bioterrorism event might result in higher risk for exposure during remediation activities. The characteristics of an intentionally dispersed strain of *B. anthracis* (e.g., antimicrobial resistance or dispersion capabilities) might differ from those of a naturally occurring strain. The level of environmental contamination resulting from intentionally dispersed strains, and therefore the potential for exposure at lower infective doses, might be significantly greater than the level of contamination that would result from naturally occurring strains. Because animal studies indicate that the incubation period for inhalation anthrax might be inversely related to the dose of *B. anthracis* spores (*95,107,108*), exposure to higher levels of spores may result in more rapid disease onset, with limited time for initiating PEP.

Emergency and Other Responders

Persons involved in emergency response activities might include persons who work in police departments, fire departments, hazardous material units, and the National Guard, as well as other government responders. These persons might perform site investigations, respond to suspicious substance reports (also known as white powder incidents), and perform other related activities such as evacuation procedures or other activities critical to the maintenance of infrastructure.

The risk for potential exposures associated with responder activities varies depending on the situation. Although the risk for exposure to aerosolized *B. anthracis* spores is likely low, secondary aerosolization of previously settled spores might occur during the performance of certain activities (*63*). Because the location and dissemination of the organism as a result of a bioterrorism attack cannot be predicted, the risk for exposure to aerosolized *B. anthracis* spores in association with emergency response activities cannot be quantified.

Recommended Uses of Anthrax Vaccine

AVA may be used 1) via the licensed schedule to prevent infection by priming the immune system before exposure to *B. anthracis* (pre-event or preexposure vaccination) and 2) after exposure to aerosolized *B. anthracis* spores under an IND or possibly under an EUA (PEP vaccination) (Tables 2 and 3). Recommendations for the use of AVA differ for pre-event or preexposure vaccination and postexposure vaccination. For pre-event or preexposure vaccination, ACIP recommends 5 IM doses administered at day 0, week 4, and months 6, 12, and 18, followed by annual boosters. To elicit the most substantial and rapid immune response possible among previously unvaccinated persons in a postexposure setting, PEP vaccination should be administered as a 3-dose SC series (at 0, 2, and 4 weeks) in conjunction with a 60-day course of appropriate antimicrobial agents.

Pre-event and Preexposure Vaccination

By priming the immune system before exposure to *B. anthracis* spores, pre-event and preexposure vaccination might provide more protection than antimicrobial agents alone to persons at risk for occupational exposure to *B. anthracis,* including protection for persons exposed to large inocula, protection if the public health infrastructure cannot ensure immediate availability or timely delivery of postevent antimicrobial agents, and potential benefits if bioengineered strains were released, limiting antimicrobial PEP effectiveness. The potential benefits from pre-event and preexposure vaccination should be weighed against the resource requirements to implement and maintain the vaccination schedule, as well as the potential adverse events associated with vaccination. Decisions for pre-event vaccination should be made based on a calculated risk assessment. In the absence of such an assessment, vaccination may be considered based on an estimated/presumed risk-benefit assessment. Depending on the occupational activities of the vaccine recipient, pre-event or preexposure vaccination might not eliminate the need for appropriate personal protective equipment.

General Public

Because the location and timing of a bioterrorism attack cannot be predicted, the risk-benefit profile for pre-event vaccination for the general public is low, and pre-event vaccination is not recommended. Preventing the morbidity and mortality associated with a deliberate release of *B. anthracis* depends on public vigilance, early detection and diagnosis, appropriate treatment, and rapid administration of PEP.

Special Populations

Pregnant and Breastfeeding Women

In a pre-event setting, in which the risk for exposure to aerosolized *B. anthracis* spores is presumably low, vaccination of pregnant women is not recommended and should be deferred until after pregnancy. Breastfeeding is neither a precaution nor a contraindication to vaccination, and vaccination does not need to be deferred in a pre-event setting if the occupation of the breastfeeding mother poses a risk for exposure to *B. anthracis*.

Children

In a pre-event setting, in which the risk for exposure to aerosolized *B. anthracis* spores is presumably low, vaccination of children is not recommended.

Medical Personnel

Pre-event vaccination is not recommended for medical personnel. If exposed to aerosolized *B. anthracis* spores during a bioterrorism event, they should receive PEP in accordance with ACIP recommendations.

Populations at Risk for Occupational Exposure

Persons Handling Animals or Animal Products

Routine preexposure vaccination for persons who handle animals or animal products is recommended only for persons for whom previously discussed standards and restrictions are insufficient to prevent exposure to *B. anthracis* spores. Preexposure vaccination is not recommended for persons who routinely have contact with animal hide drums or animal hides; other preventive measures are available.

Routine vaccination of U.S. veterinarians and animal husbandry technicians is not recommended because of the low incidence of animal anthrax cases in the United States. However, vaccination might be recommended for veterinarians and other persons considered to be at high risk for anthrax exposure if they handle potentially infected animals in research settings or in areas with a high incidence of enzootic anthrax cases.

Laboratorians

Preexposure vaccination is recommended for laboratorians at risk for repeated exposure to fully virulent *B. anthracis* spores, such as those who 1) work with high concentrations of spores with potential for aerosol production; 2) handle environmental samples that might contain powders and are associated with anthrax investigations; 3) routinely work with pure cultures of *B. anthracis*; 4) frequently work in spore-contaminated areas after a bioterrorism attack; or 5) work in other settings where repeated exposures to *B. anthracis* aerosols may occur.

Persons Working in Postal Processing Facilities

Because of biodetection systems in postal processing centers, contamination of mail with *B. anthracis* spores is likely to be detected rapidly, allowing postexposure therapy to be initiated immediately. Therefore, persons who work in these facilities are not recommended to receive pre-event vaccination.

Military Personnel

Military personnel determined by DoD to have a calculable risk for exposure to aerosolized *B. anthracis* spores are recommended to receive preexposure vaccination. DoD has exclusionary criteria for employees, including an exclusion for pre-event vaccination of pregnant women (*256,257*).

Environmental Investigators and Remediation Workers

Vaccination is recommended for persons who, as part of their occupation, might repeatedly enter areas contaminated with *B. anthracis* spores.

Emergency and Other Responders

Emergency and other responders are not recommended to receive routine pre-event anthrax vaccination because of the lack of a calculable risk assessment. However, responder units engaged in response activities that might lead to exposure to aerosolized *B. anthracis* spores may offer their workers voluntary pre-event vaccination. The vaccination program should be carried out under the direction of a comprehensive occupational health and safety program.

Delayed Doses

Available data on AVA dosages suggest that increasing the interval between doses does not decrease the ultimate serologic response achieved or adversely affect the safety profile. Therefore, as with other vaccines, interruption of the vaccination schedule does not require restarting the entire series or the addition of extra doses (*199*).

PEP

PEP should be used for previously unvaccinated persons after exposure to aerosolized *B. anthracis* spores, whether the exposure is naturally occurring, occupationally related, or intentional. To elicit the most substantial and rapid immune response possible for previously unvaccinated persons in a postexposure setting, vaccination should be administered as recommended in conjunction with appropriate antimicrobial agents (Tables 1 and 2).

PEP After Inhalation Exposure

General Adult Population

ACIP recommends a postexposure regimen of 60 days of appropriate antimicrobial prophylaxis combined with 3 SC doses of AVA (administered at 0, 2, and 4 weeks postexposure) as the most effective protection against inhalation anthrax for previously unvaccinated persons aged ≥18 years who have been exposed to aerosolized *B. anthracis* spores.

After exposure to aerosolized *B. anthracis* spores, antimicrobial therapy should be initiated as soon as possible. Ideally, the first dose of vaccine should be administered within 10 days. Because AVA is not licensed for postexposure use, the vaccine will likely be made available either through an IND or an EUA during a public health emergency.

In general, the peak serologic response to anthrax vaccine occurs 10--14 days after the third dose. To ensure continued protection, persons for whom vaccination has been delayed should extend antimicrobial use to 14 days after the third dose, even though this practice might result in use of antimicrobials for >60 days. Antimicrobials should not be used for <60 days in previously unvaccinated persons who have been exposed to aerosolized *B. anthracis* spores.

Pregnant Women

In a postevent setting that poses a high risk for exposure to aerosolized *B. anthracis* spores, pregnancy is neither a precaution nor a contraindication to PEP. Pregnant women at risk for inhalation anthrax should receive AVA and 60 days of antimicrobial therapy as described.

Breastfeeding Women

In a postevent setting that poses a high risk for exposure to aerosolized *B. anthracis* spores, breastfeeding remains neither a precaution nor a contraindication to PEP. Breastfeeding women at risk for inhalation anthrax should receive AVA and 60 days of antimicrobial therapy as described.

Children

The use of AVA in children is not contraindicated in a postevent setting that poses a high risk for exposure to aerosolized *B. anthracis* spores. During such an event, public health authorities will determine whether, under the existing IND protocol, to offer vaccine to children aged 0--17 years. Under this IND protocol, 3 doses of vaccine would be administered in conjunction with 60 days of appropriate antimicrobial therapy.

PEP After Repeated Occupational Exposures

The combination of pre-event vaccine and appropriate PPE effectively protects fully vaccinated persons who work in occupations that might result in repeated exposure to aerosolized *B. anthracis* spores (Table 4).

Antimicrobial PEP is not needed for fully vaccinated workers who wear appropriate PPE while working in environments contaminated with *B. anthracis* spores unless the PPE is disrupted. However, fully vaccinated workers who prefer additional protection may consider antimicrobial PEP under the direction of their occupational health program

A 30-day course of antimicrobial PEP is recommended for partially vaccinated workers (Table 4), fully vaccinated workers who do not wear PPE, and fully vaccinated workers whose PPE has been disrupted; these workers should continue with their licensed vaccination regimen.

A 60-day course of antimicrobial PEP is recommended for previously unvaccinated workers. These workers also should begin receiving AVA as soon as possible using the PEP schedule of 3 SC doses.

PEP After Naturally Occurring Cutaneous or Gastrointestinal Exposure

Vaccination is not recommended after cutaneous or gastrointestinal exposures that pose no risk for inhalation exposure. When a naturally occurring cutaneous exposure occurs, appropriate medical and public health personnel should be notified, and affected persons should be monitored for development of a spot, pimple, or boil-like lesion, especially in the exposed areas. For persons who experience a naturally occurring gastrointestinal exposure, such those who eat meat from an undercooked carcass of an anthrax-infected animal, antimicrobial PEP for 7--14 days may be considered.

Contraindication and Precautions for Use of AVA

The following contraindication and precautions are relevant for both preexposure and postexposure settings (*137*).

Contraindication

Although anaphylaxis after anthrax vaccination is extremely rare and no anaphylaxis deaths associated with AVA have been reported (CDC, unpublished data, 2010), an anaphylactic reaction can be life-threatening. Therefore, AVA is contraindicated for persons who have experienced an anaphylactic reaction after a previous dose of AVA or any of the vaccine components.

Precautions

- **Latex allergy:** Because the vaccine vial stopper contains dry, natural rubber, caution should be used when administering the vaccine to persons with a latex allergy (*137*). Epinephrine solution (1:1000) should be available for immediate use in the event that an anaphylactic reaction occurs.
- **History of anthrax disease:** A history of anthrax disease might increase the potential for severe local adverse reactions after AVA administration (*137*).
- **Impaired immune response:** Patients with an impaired immune response might not be adequately immunized after administration of AVA (*137*).

- **Moderate or severe acute illness:** In a standard preexposure vaccination program, vaccination of persons with moderate or severe acute illness should be postponed until after recovery (*137*). In a postevent setting, the risks of administering vaccine to a person who has been exposed to anthrax but has moderate or severe acute illness should be weighed against the benefits of vaccination. Vaccine may be administered to persons who have a mild illness with or without a low-grade fever.

Reporting Adverse Events

Adverse events that occur after administration of anthrax vaccine should be reported to VAERS, regardless of whether the reporter considers the vaccine to be the cause of the event. Information about VAERS and how to report vaccine adverse events is available at http://vaers.hhs.gov. Adverse events that occur after administration of antimicrobial agents should be reported to the FDA MedWatch program at http://www.fda.gov/medwatch.

Current and Future Research

Research priorities for future studies on the currently licensed anthrax vaccine should include immunogenicity; additional evaluations of the dosing schedule (including the maximum time between boosters); additional long-term human safety studies; the number of vaccine doses required for PEP; the optimal duration of antimicrobial use in postexposure settings; antimicrobial susceptibility and treatment studies; optimal alternative antimicrobial agents for children, older adults (aged >65 years), and pregnant women; and the safety of anthrax vaccine in clinical toxicology studies among pregnant animals. Future research should include the groups for whom AVA is currently licensed, as well as children, older adults, and pregnant women. These research questions also should be addressed as new potential anthrax vaccines are identified and considered for use in humans.

Research on AVA and Future Anthrax Vaccines: Immunogenicity, Schedule, and Route

Research is ongoing to address priority topics, including identification of quantitative immune correlates of protection in relevant animal species and defining the quantitative relationship between the vaccine-elicited immune response in these animal species and humans. Completion of the ongoing AVRP clinical trial should provide a definitive clinical evaluation of the effects of reducing the number of AVA doses (*140*).

Information regarding the efficacy and safety of AVA in children and older adults also is needed, as is additional information regarding the safety and efficacy of AVA when used during pregnancy. Future research should include trials to obtain this information and to develop dosage recommendations for children. In addition, research to further develop both the recombinant PA (rPA) vaccines and the next generation of anthrax vaccines should continue.

Postexposure Prophylaxis

Studies in animals indicate that the combination of antimicrobials and vaccination is very effective for preventing systemic *B. anthracis* infection. When using a combined approach the immune system benefits from the acute-phase antimicrobial protection provided against germinating spores and vegetative cells of *B. anthracis* while gaining enough time to complete immunological priming and establish anamnestic capability (i.e., immunological memory) (*93*). The effectiveness of vaccination might allow the antimicrobial course to be shortened from the recommended 60 days to as few as 14 days (*102*). Definitive, pivotal human studies to evaluate the magnitude and duration of the human immune response to anthrax vaccines when combined with antimicrobials have not been conducted. Additional research is needed to determine the optimal duration of antimicrobial administration in conjunction with the optimal doses of vaccine.

Long-Term Safety of AVA

The FDA final order for use of AVA emphasizes the need to continue postmarketing safety studies (*135*), and the IOM reports document the need for additional long-term follow-up of vaccine recipients (*152,169*). VAU continues to conduct research to address these issues through a combination of studies, including continued screening of the VAERS database for identification of potential long-term adverse events, hypothesis testing research studies using the DMSS database (*170*), and assessments of new safety signals identified from VAERS or other sources.

Alternative Anthrax Vaccines

The rPA vaccines contain the purified protein of an avirulent, non--spore-forming strain of *B. anthracis* (*258*). Although recent phase 1 dose-escalation studies comparing rPA with AVA for reactogenicity, immunogenicity, and dosing range of rPA have been conducted (*258,259*), problems with vaccine formulation have delayed the start of phase 3 trials. One formulation demonstrated that immune responses of participants receiving rPA with adjuvant were not statistically significantly different from the responses of those receiving AVA (*258*). Evidence indicates that rPA candidate vaccines might cause fewer local adverse events than AVA administered subcutaneously (*259*). However, licensure of new anthrax vaccine will likely not occur for several years.

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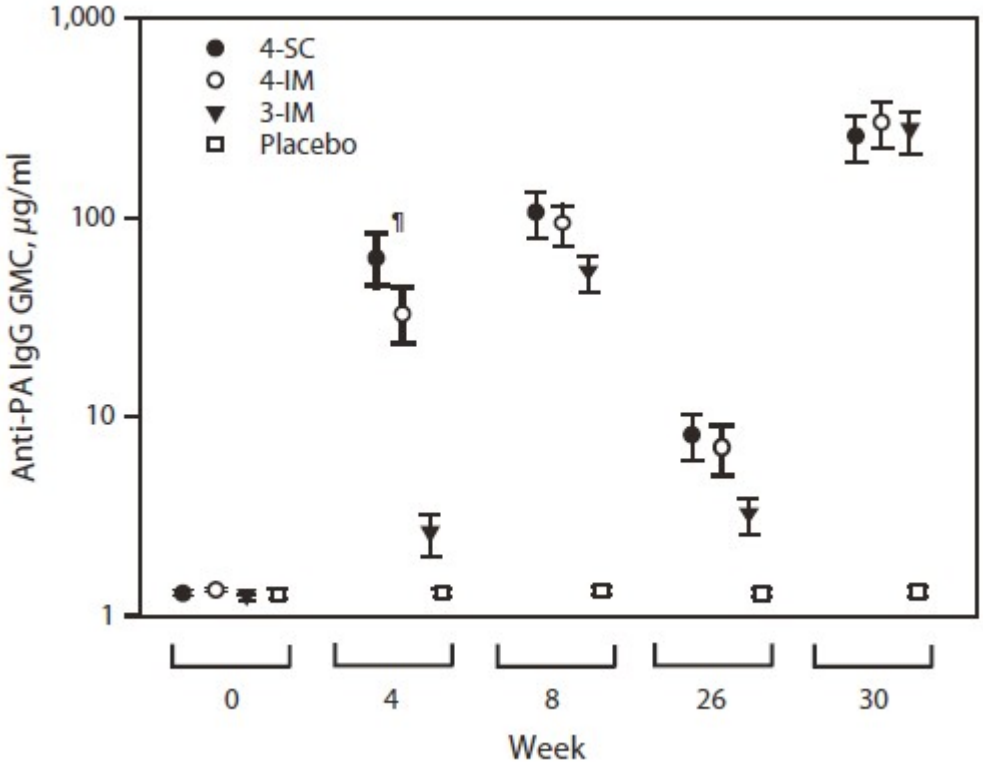
* Sanitary control of animal byproducts (except casings), and hay and straw, offered for entry into the United States, 9 C.F.R. Pt. 95.

† Protection of Human Subjects, 21 C.F.R. Pt. 50.

§ Sanitary control of animal byproducts (except casings), and hay and straw, offered for entry into the United States, 9 C.F.R. Pt. 95.

FIGURE. Scatter plot of levels of the anti--protective antigen immunoglobulin G geometric mean concentration (anti-PA IgG GMC) among participants in the Anthrax Vaccine Research Program (AVRP) phase 4 clinical trial,* by vaccine regimen group† and week§



Source: Marano N, Plikaytis BD, Martin SW, et al. Effects of a reduced dose schedule and intramuscular administration of anthrax vaccine adsorbed on immunogenicity and safety at 7 months: a randomized trial. JAMA 2008;300:1532--43.

* Interim analysis of the AVRP clinical trial.

† CDC submitted data to the Food and Drug Administration from the interim analysis of the first 1,005 enrolled participants who, at the time of the analysis, had received 4 doses of anthrax vaccine adsorbed by the subcataneous (SC) route (4-SC group) or the intramuscular (IM) route (4-IM group) or 3 doses by the IM route (3-IM group).

§ Serological noninferiority analyses of antibody responses at week 8 and month 7 (week 30) were performed (i.e., responses to injections up to week 4 and month 6 [week 26], respectively). GMCs were one of three primary serological end points. Analysis of variance models were constructed to analyze log-transformed antibody data. Models allowed for the longitudinal nature of the data and included adjustments for study site, age group, sex, race, and significant interactions.

¶ 95% confidence intervals.

Alternate Text: This figure above shows a scatter plot of levels of the anti–protective anti¬gen immunoglobulin G geometric mean concentration (anti-PA IgG GMC) among 1,005 participants in the Anthrax Vaccine Research Program phase 4 clinical trial, by week (0, 4, 8, 26 [month 6], and 30 [month 7]) and vaccine regimen group. CDC submitted data to the Food and Drug Administration from the interim analysis of the first 1,005 enrolled participants who, at the time of the analysis, had received 4 doses of anthrax vaccine adsorbed by the sub¬cutaneous (SC) route (4-SC group) or the intramuscular (IM) route (4-IM group) or 3 doses by the IM route (3-IM group). Serological noninferiority analyses of antibody responses (anti-PA IgG GMC) demonstrated the noninferiority of both the 3-IM regimen and the 4-IM regimen to the originally licensed schedule at month 7.

TABLE 1. Recommended initial antimicrobial agent and anthrax vaccine adsorbed (AVA) dosages for postexposure prophylaxis (PEP) after exposure to aerosolized *Bacillus anthracis* spores

Population	Antimicrobials for 60-day* PEP	AVA dosage and route†
Adults (18--65 yrs)	*One of the following for 60 days:* Ciprofloxacin,§ 500 mg orally twice daily Doxycycline, 100 mg orally twice daily	3-dose subcutaneous (SC) series: first dose administered as soon as possible, second and third doses administered 2 and 4 wks after the first dose
Pregnant women¶	*One of the following for 60 days:* Ciprofloxacin, 500 mg orally twice daily Doxycycline, 100 mg orally twice daily Amoxicillin,** 500 mg every 8 hrs	3-dose SC series; first dose administered as soon as possible, second and third doses administered 2 and 4 wks after the first dose
Children	*One of the following for 60 days:*	Recommendations for use of AVA in

(<18 yrs)††	Ciprofloxacin,§,††,§§ 15 mg/kg every 12 hrs Doxycycline,††,¶¶ (maximum of 100 mg/dose) >8 yrs and >45 kg: 100 mg every 12 hrs >8 yrs and ≤45 kg: 2.2 mg/kg every 12 hrs ≤8 yrs: 2.2 mg/kg every 12 hrs Amoxicillin,**,*** 45 mg/kg/day orally divided into 3 daily doses given every 8 hrs; each dose should not exceed 500 mg	children are made on an event-by-event basis.

* Antimicrobials should continue for 14 days after administration of the third dose of vaccine.

† AVA used for PEP must be administered subcutaneously.

§ Levofloxacin is a second-line antimicrobial agent for PEP for persons aged ≥6 mos with medical issues (e.g., tolerance or resistance to ciprofloxacin) that indicate its use. *Children:* 16 mg/kg/day divided every 12 hrs; each dose should not exceed 250 mg. *Adults:* 500 mg every 24 hrs. Safety data on extended use of levofloxacin in any population for >28 days are limited; therefore, levofloxacin PEP should only be used when the benefit outweighs the risk.

¶ The antimicrobial of choice for initial prophylactic therapy among pregnant women is ciprofloxacin. Doxycycline should be used with caution in asymptomatic pregnant women and only when other appropriate antimicrobial drugs are contraindicated. Although tetracyclines are not recommended during pregnancy, their use might be indicated for life-threatening illness.

** If susceptibility testing demonstrates an amoxicillin MIC ≤0.125 μg/mL, oral amoxicillin should be used to complete therapy.

†† Use of tetracyclines and fluoroquinolones in children can have adverse effects. These effects must be weighed carefully against the risk for developing life-threatening disease. If exposure to *B. anthracis* is confirmed, children may be treated initially with ciprofloxacin or doxycycline as prophylaxis. However, amoxicillin is preferred for antimicrobial PEP in children when susceptibility testing indicates that the *B. anthracis* isolate is susceptible to penicillins.

§§ Each ciprofloxacin dose should not exceed 500 mg, or 1 g/day.

¶¶ In 1991, the American Academy of Pediatrics (AAP) amended the recommendation to allow treatment of young children with tetracyclines for serious infections such as Rocky Mountain spotted fever for which doxycycline might be indicated. Doxycycline is preferred for its twice daily dosage and low incidence of gastrointestinal side effects.

*** Because of the lack of data on amoxicillin dosages for treating anthrax (and the associated high mortality rate), AAP recommends a higher dosage of 80 mg/kg/day, divided into 3 daily doses; each dose should not exceed 500 mg. If this higher dosage of amoxicillin is used, recipients should be carefully monitored for side effects from long-term treatment.

TABLE 2. Recommended preexposure and postexposure vaccination schedules for anthrax vaccine adsorbed

Type of prophylaxis	Schedule	Route	Dose
Preexposure	5 doses (0 wks, 4 wks, 6 mos, 12 mos, and 18 mos) Annual booster to maintain immunity	Intramuscular	0.5 mL

Postexposure*	3 doses (0, 2, and 4 wks)†,§	Subcutaneous	0.5 mL

* For previously unvaccinated persons.

† In conjunction with 60-day antimicrobial postexposure prophylaxis.

§ Administered under an Investigational New Drug (IND) protocol or an Emergency Use Authorization (EUA).

TABLE 3. Recommendations for use of anthrax vaccine adsorbed, by type of population

Population	**Pre-event***	**Postexposure prophylaxis (PEP)†**
General public	Not recommended	Recommended
Special populations in the general public		
Pregnant women	Not recommended	Recommended
Breastfeeding women	Not recommended	Recommended
Children (aged <18 yrs)	Not recommended	Determined on an event-by-event basis
Medical professionals	Not recommended	Recommended
Populations at risk for occupational exposure		
Persons who handle animals or animal products	Not routinely recommended§	Recommended
Persons who perform certain types of laboratory work	Recommended¶	Based on pre-event vaccination status
Persons who work in postal facilities	Not recommended	Recommended
Military personnel	As recommended by the Department of Defense	As recommended by the Department of Defense
Persons involved in environmental investigations or remediation efforts	Recommended	Based on pre-event vaccination status

Persons involved in emergency response activities**	Not routinely recommended; may be offered on a voluntary basis under the direction of a comprehensive occupational health and safety program	Recommended

* Five 0.5-mL doses administered intramuscularly at 0 wks, 4 wks, 6 mos, 12 mos, and 18 mos; annual boosters are required to maintain immunity.

† Three 0.5-mL doses administered subcutaneously at 0, 2, and 4 wks after exposure to aerosolized *Bacillus anthracis* spores for persons who have not completed the pre-event vaccination schedule.

§ Recommended only if handling potentially infected animals in research settings or in areas with a high incidence of enzootic anthrax or when standards and restrictions are insufficient to prevent exposure to *B. anthracis* spores.

¶ Laboratorians who work 1) with high concentrations or pure cultures of *B. anthracis* spores, 2) with environmental samples associated with anthrax investigations, or 3) in spore-contaminated areas or other settings with exposure to aerosolized *B. anthracis* spores. Laboratorians who do not work in these settings are not recommended for pre-event vaccine.

** Persons involved in emergency response activities might include persons who work in police departments, fire departments, hazardous material units, and the National Guard, as well as other government responders. These persons might perform site investigations, respond to suspicious substance reports (also known as white powder incidents), and perform other related activities, such as evacuation procedures or other activities critical to the maintenance of infrastructure.

TABLE 4. Postexposure prophylaxis (PEP) for persons with repeated occupational exposures to aerosolized *Bacillus anthracis* spores, by preexposure anthrax vaccine adsorbed vaccination status

Vaccination status	Vaccination recommendation	Duration of antimicrobial PEP*
No previous vaccine	Use PEP schedule of 3 subcutaneous doses (0, 2, and 4, wks); resume the licensed vaccination schedule† at 6 mos	60 days; continue for 14 days after the third dose of vaccine, even if initial vaccine administration is delayed and therefore antimicrobial is used for >60 days
Partially vaccinated§	Continue with licensed vaccination schedule†	At least 30 days after any type of disruption of respiratory protection¶
Fully vaccinated**	Continue with annual boosters as scheduled	At least 30 days after any type of disruption of respiratory protection¶

* Because antimicrobial PEP is the primary intervention, do not delay initiation if vaccine is not available.

† Licensed vaccination schedule: 5 doses intramuscularly (IM) (0 wks, 4 wks, 6 mos, 12 mos, and 18 mos), with annual boosters thereafter.

§ Partially vaccinated persons have either received <5 IM priming doses or have not received all annual boosters indicated by the licensed vaccination schedule.

¶ Because respiratory protection can be disrupted in numerous ways (e.g., a face-seal leak in a respirator or not wearing personal protective equipment when entering an area presumed to be uncontaminated that is later determined to be contaminated) and such disruptions are not always detected, the threshold for assuming such a disruption has occurred should be extremely low.

** Fully vaccinated workers have completed the 5-dose IM series and have received all annual booster doses indicated by the licensed vaccination schedule.

Examination

Select the ***best*** answer to each of the following items. Mark your responses on the Answer form.

1. Anthrax is a zoonotic disease caused by the spore-forming bacterium *Bacillus anthracis*.

a. True
b. False

2. The disease most commonly occurs in wild and domestic mammals (e.g., _____, camels, antelope, and other herbivores).

a. cattle
b. sheep
c. goats
d. All of the above

3. Anthrax occurs in humans when they are exposed to infected animals or tissue from infected animals or when they are directly exposed to *B. anthracis* spores.

a. True
b. False

4. Vaccines against anthrax were first developed as early as 1880 and used in livestock. An acellular product for human use was developed in _____ and used in the first U.S. efficacy study of human anthrax vaccine.

a. 1948
b. 1954
c. 1960
d. 1971

5. *B. anthracis* is a _____, spore-forming, nonmotile rod.

a. facultatively anaerobic
b. gram-positive
c. encapsulated
d. All of the above

6. The major virulence factors of *B. anthracis* include: _____.

a. an antiphagocytic capsule
b. lethal toxin
c. edema toxin
d. All of the above

7. Today, *B. anthracis* is considered one of the most serious biowarfare or bioterrorism agents because of the ability of the spores _____.

a. to persist in the environment
b. the ability of the aerosolized spores to readily cause infection via respiratory (inhalation) exposure
c. the high mortality of resulting inhalation anthrax
d. All of the above

8. *B. anthracis* spores can remain viable and infective in soil for decades, during which time they serve as a potential source of infection for grazing livestock that might become infected when they ingest or inhale the spores.

a. True
b. False

9. The largest recent epidemic of human anthrax occurred in _____during 1978--1980 and involved 9,445 cases, including 141 (1.5%) deaths (*5*).

a. China
b. Ukraine
c. Zimbabwe
d. None of the above

10. Of the _____ naturally occurring human anthrax cases reported to CDC during 1955--2007, 232 (96%) were cutaneous, 10 (4%) were inhalation, and none were gastrointestinal (CDC, unpublished data, 2010).

a. 100
b. 187
c. 208
d. 242

11. In 2001, _____ confirmed or suspected human cases of anthrax occurred in the eastern United States (referred to as the bioterrorism events of 2001 in this report) when *B. anthracis* spores were sent through the mail in powder-containing envelopes to news media companies and U.S. congressional leaders. Eleven of the 22 cases were inhalation anthrax, and 11 were cutaneous; 20 of the cases occurred in mail handlers or persons exposed to buildings where contaminated mail was processed or received. Five persons with inhalation anthrax died.

a. 10
b. 12
c. 22
d. None of the above

12. WHO experts have estimated that 50 kg of *B. anthracis* spores released upwind of a population center of 500,000 persons could result in 95,000 deaths and 125,000 hospitalizations (*56*), and a release of 100 kg of spores upwind of the Washington, DC, metropolitan area would result in an estimated 130,000 to _____deaths (*57*).

a. 900,000
b. 1 million
c. 3 million
d. None of the above

13. *B. anthracis* enters the host in the form of spores at the epidermis (cutaneous anthrax), the gastrointestinal epithelium (gastrointestinal anthrax), or the lung mucosa (inhalation anthrax). It is unknown whether *B. anthracis* has an active invasive process, and the symptoms and incubation period vary depending on the route of exposure to the spores.

a. True
b. False

14. In practice, *B. anthracis* is readily identifiable using a range of standard microbiological tests, including Gram stain, cell and colony morphology, sensitivity of the gamma phage of McCloy, and production of the γ-linked poly-d-glutamic acid (γDGA) capsule in blood or under culture in _____% carbon dioxide.

a. 15
b. 20
c. 25
d. None of the above

15. Inhalation anthrax is a systemic infection caused by inhalation of *B. anthracis* spores. The mediastinal lymph nodes are most often the nidus of bacterial proliferation. Inhalation anthrax has historically accounted for 5% of all anthrax cases in the United States.

a. True
b. False

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