INFORMATION PAPER

Military Vaccine Agency
9 January 2009

SUBJECT: Anthrax Infections and Anthrax Vaccine

1. Purpose. To describe anthrax infections and the vaccine to prevent them.

2. Facts.

a. Microbiology. The causative agent of anthrax is named *Bacillus anthracis* and is a large, gram-positive, spore-forming, nonmotile bacillus bacteria. These bacteria use three proteins to make two toxins: lethal toxin and edema toxin. The protein common to both toxins is called protective antigen, or PA. Anthrax bacteria form spores to survive for long periods in the environment. These spores are resistant to heat, light, and harsh environmental conditions. The bacteria can cause three types of disease, depending on how the bacteria enter the body: cutaneous, gastrointestinal, or inhalational anthrax.

b. Disease. The symptoms and incubation period of human anthrax vary depending on the route of transmission of the disease. In general, symptoms begin within 7 days of exposure.

(1) Cutaneous anthrax is the most common form of anthrax reported in humans (>95% of all anthrax cases). It can occur when the bacterium enters a cut or abrasion on the skin, such as when handling contaminated meat, wool, hides, leather or hair products from infected animals or other contaminated materials. Symptoms begin in approximately 1-12 days with an itchy reddish-brown papule on the exposed skin that later develops into blackened eschar with swelling of the surrounding tissue. There are often systemic symptoms associated with cutaneous anthrax such as swollen glands, fever, myalgia, malaise, vomiting and headache. The case fatality rate for cutaneous anthrax is estimated to be 20% without antibiotic treatment.

(2) Gastrointestinal anthrax symptoms usually begin 1-7 days after ingestion of anthrax contaminated meat. There is acute inflammation of the gastrointestinal intestinal tract causing nausea, loss of appetite, vomiting and fever; followed by abdominal pain, vomiting of blood and bloody diarrhea. The pharynx can also be involved causing a sore throat, dysphagia, and fever, lesions at the base of the tongue or tonsils and regional lymphadenopathy. The case fatality rate is unknown but estimated to be 25% to 60%.

(3) Inhalation (pulmonary) anthrax has been reported to occur anywhere from 1 - 43 days after exposure to aerosolized spores. Initial symptoms may include sore throat, mild fever, myalgia, coughing and chest discomfort lasting up to a few days. Secondary symptoms develop abruptly with a sudden onset of fever, acute respiratory distress due to pulmonary edema and pleural effusions, followed by cyanosis, shock and coma.

Meningitis is common. The fatality rate for inhalational anthrax is estimated to be approximately 45% to 90% depending on early diagnosis and aggressive medical interventions.

c. Epidemiology. Anthrax in humans is a rare disease in the United States. It occurs among livestock that ingest or swallow anthrax spores during grazing. It remains unclear whether there are cycles of germination and replication within the soil or if amplification within mammalian hosts serves to maintain the spore population in the soil between cases in animals.

(1) The number of reported human anthrax cases in the United States has steadily declined over the last century. Between 1916 and 1925, the annual average number of cases was 127; between 1948 and 1957, 44 cases; between 1978 and 1987, 0.9 case/year; and between 1988 and 2000, 0.25 case/year. Of the 235 human cases reported from 1955 to 2000, 20 were fatal. Among these cases, 224 had cutaneous lesions (118 on an arm, 65 on the head or neck, 11 on the trunk, 8 on a leg, and 22 at an unknown site) and 11 were inhalational cases. In 2001, there were 22 cases associated with contaminated mail. No cases were reported in the United States from 2002 to 2005. One (1) case of naturally-occurring inhalational anthrax occurred in 2006 and two (2) cases of cutaneous anthrax in 2007. None of the cases were fatal and exposure to anthrax in each case resulted from direct association with djembe drums made from untreated animal hides from West Africa.

(2) Anthrax spores make a potent biological weapon because the spores are hardy and the optimal size to enter and lodge in the lungs if inhaled. Inhalational anthrax is nearly 100% fatal in an unprotected, unvaccinated person who is not treated promptly. The difficulty in detecting an anthrax attack may result in numerous anthrax casualties before adequate countermeasures could be implemented.

(3) The anthrax spore attacks of fall 2001 resulted in 11 confirmed inhalational cases and 7 confirmed and 4 suspected cutaneous cases reported from Florida, New York, New Jersey, the District of Columbia, and Connecticut. Of the 11 confirmed inhalational cases there were 5 deaths. Exposure to contaminated mail was the confirmed or apparent source of infection in all patients. More than 32,000 people received short courses of prophylactic antibiotics while potential exposures were evaluated, and among these more than 10,000 people continued to receive antibiotics for 60 or more days with or without post-exposure vaccination as prophylaxis. Exposures may have resulted from opening contaminated letters, from working in buildings with high-speed automated mail-sorting machines, or through contact with cross-contaminated pieces of mail or environments contaminated with spores.

d. Vaccine. Anthrax vaccine is distributed under the brand name *BioThrax* (Emergent Biosolutions, Lansing, Michigan) and reduces disease incidence by 92.5%, based on human and animal data. Anthrax vaccine is an inactivated, acellular vaccine

that principally contains the protective antigen (PA) protein. The Food & Drug Administration (FDA) licensed anthrax vaccine as safe and effective in November 1970. During the Persian Gulf War, an estimated 150,000 personnel received 250,000 doses of vaccine. Between March 1998 and January 2009, more than 2.0 million people received over 8.3 million doses of vaccine under the U.S. Department of Defense's Anthrax Vaccine Immunization Program. The search for new vaccine candidates, as well as therapeutic targets is in various experimental stages.

e. Immunization. Immunizations consist of a series of 5 intramuscular doses administered at 0, 4 weeks, 6, 12, and 18-months, with annual boosters given to sustain immunity. Injections are given in the deltoid region to avoid swelling in the triceps area that could pinch the ulnar nerve.

f. Adverse Events. The CDC sponsored a randomized double-blind clinical trial to evaluate the effect of changing the route of administration of the vaccine from subcutaneous (SC) to intramuscular (IM) and reducing the number of doses on the safety and immunogenicity of BioThrax. The analysis of injection site (local) reactions demonstrated that administration of the vaccine by the IM route, as compared to the SC route, resulted in a statistically significant reduction in reactogenicity (i.e. cutaneous adverse reactions). Injection site adverse reactions, including warmth, tenderness, itching, erythema, induration, edema, and nodule, consistently occurred at lower frequencies and for shorter duration in participants given BioThrax by the IM route. The most common ($\geq$10%) local (injection-site) adverse reactions observed in clinical studies were tenderness, pain, erythema and arm motion limitation. The most common ($\geq$5%) systemic adverse reactions were muscle aches, headache, and fatigue. Women receiving the vaccine reported more systemic reactions than men (fatigue, muscle aches, and headaches) regardless of the route of administration.

g. DoD Policy. Anthrax vaccinations are mandatory for uniformed personnel, emergency essential and comparable employees or contractors deployed (or deploying within 120 days) to U.S. CENTCOM or Korea areas of responsibility (AOR) for 15 or more consecutive days. Anthrax vaccinations are also mandatory for certain uniformed personnel assigned to special units (such as forward deployed forces) and units with biodefense related missions. Uniformed and civilian personnel no longer deployed to U.S. CENTCOM or Korea may continue the series on a voluntary basis. Vaccinations are also voluntary for uniformed and civilian personnel and family members who have received at least one dose previously.

h. Special Considerations. In 1995, Iraq admitted loading anthrax spores into a variety of munitions. The Soviet Union possessed vast quantities of weaponized anthrax, as detailed by former Soviet scientists. Defense intelligence sources suspect other potential adversaries of researching, developing, and/or weaponizing anthrax. Anthrax terror attacks along the eastern coast of the U.S. in fall 2001, killed five people, disrupted government operations, and threatened the U.S. postal delivery service.

j. Independent Reviews. Six independent reviews by civilian physicians and scientists affirm the safety and effectiveness of anthrax vaccine. These include civilian advisors to the Food & Drug Administration, the Centers for Disease Control and Prevention, and the Department of Health & Human Services; plus the Armed Forces Epidemiological Board; the Working Group on Civilian Biodefense convened by Johns Hopkins University; the Cochrane Collaboration (an evidence-based medicine group based in Oxford, England); and the National Academy of Sciences' Institute of Medicine.

3. References.

a. Advisory Committee on Immunization Practices. Use of anthrax vaccine in the United States. *MMWR* 2000; 49(RR-15):1-20. www.cdc.gov/mmwr/preview/mmwrhtml/rr4915a1.htm

b. CDC disease information: www.bt.cdc.gov/agent/anthrax

c. Joint Air Force, Army, Navy, and Coast Guard publication (AR 40–562, BUMEDINST 6230.15A, AFJI 48–110, CG COMDTINST M6230.4F), 29 September 2006, www.vaccines.mil/documents/969r40_562.pdf

d. Multiple resources (e.g., product insert, DoD brochures, informational briefs, Vaccine Information Statements) assembled by Military Vaccine Agency: www.vaccines.mil/anthrax & www.anthrax.mil

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