Department of Defense

Information About the Anthrax Vaccine and the Anthrax Vaccine Immunization Program (AVIP)

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EXECUTIVE SUMMARY

Anthrax is readily weaponized, highly lethal, and poses a clear threat. For more than three years, the Department of Defense has protected its personnel against anthrax weapons by means of the Anthrax Vaccine Immunization Program (AVIP). The anthrax vaccine, licensed since 1970, protects against anthrax with a safety record like that of other vaccines. A supply shortage has forced a temporary slowdown in the program, but the Defense Department will resume the full AVIP as soon as the shortage resolves.

More than 2.1 million doses of anthrax vaccine have been given to more than 520,000 Service Members since March 1998. Six independent civilian reviews since 1978 unanimously affirm the value of anthrax vaccination. Seventeen human studies involving more than 50,000 vaccine recipients establish the safety profile of anthrax vaccine. Despite an unprecedented level of review by military and civilian scientific experts, no unexpected patterns of adverse events have been detected.

The evidence of vaccine effectiveness against aerosol exposure to anthrax spores is persuasive, based on both human and animal studies. A well-controlled field trial among wool-mill workers showed that anthrax vaccine was 92.5% effective in preventing anthrax infection (jointly against cutaneous and inhalational anthrax). It is unethical to enter human subjects into experiments in which they are exposed to inhalational anthrax spores. But results from studies using non-human primates show that the vaccine is 95% effective in preventing inhalational anthrax, whereas all unvaccinated animals die from anthrax infection.

Previous concerns about production deficiencies in meeting Good Manufacturing Practices have been addressed by the manufacturer and the Food & Drug Administration (FDA), with supplemental testing as an additional quality-control check. As with all vaccines, each lot of anthrax vaccine has passed extensive tests for safety, sterility, purity, and potency before release.

Balancing the low risk of adverse events after vaccination versus the high risk of disease from failing to vaccinate, the scales tip decidedly in favor of immunization. The consequences of unvaccinated Service Members becoming biological warfare casualties would be tragic enough, but the consequences would be graver than their deaths alone. Their individual deaths may jeopardize the capability and survival of entire military units, as well as the success of the military mission.

Just as vaccines are required for school children for the good of the community, anthrax vaccine is mandatory for military personnel as an important force health protection measure. The Secretary of Defense, after assuring a program of high quality, directed the implementation of the Anthrax Vaccine Immunization Program for the Total Force.

It is very important that DoD be recognized as forthright, honest, and credible. The DoD began with an assertive program to inform people about the value of anthrax vaccination. We are steadily enhancing DoD's education efforts by installing a toll-free information line (877-GET-VACC) and an authoritative Internet web site (www.anthrax.osd.mil).

It is the policy of the United States government to protect the Armed Forces against clear biological warfare threats when a safe and effective vaccine is available. The FDA-licensed anthrax vaccine is such a vaccine.

THREAT ASSESSMENT

The biological warfare (BW) threat to U.S. forces is real. At least seven countries, including several hostile to Western democracies - Iran, Iraq, Libya, and North Korea - now possess or are pursuing offensive BW capabilities. Iraq confessed to the United Nations that it loaded anthrax spores into a variety of weapons. Anthrax is within the reach of not only rogue nations, but also transnational terrorist groups. Anthrax tops the DoD biological threat list. When inhaled, anthrax is highly lethal, far more potent than the same quantity of the deadliest chemical warfare agent.

Small amounts of anthrax can produce large numbers of casualties. A 1993 report by the U.S. Congressional Office of Technology Assessment estimated that between 130,000 and 3 million deaths could follow the aerosolized release of 100 kg of anthrax spores upwind of the Washington, DC, area - truly a weapon of mass destruction. The accidental aerosolized release of anthrax spores from a military microbiology facility in Sverdlovsk in the former Soviet Union in 1979 resulted in at least 79 cases of anthrax infection and 68 deaths and demonstrated the lethal potential of anthrax aerosols. An anthrax aerosol would be odorless, invisible, and capable of traveling many miles.

Anthrax is, by far, the easiest biological agent to produce and weaponize. Production of anthrax as a biological weapon does not require special equipment or advanced technology. It is extremely stable and can be stored almost indefinitely as a dry powder. It can be loaded in advance, as a freeze-dried powder, in munitions or disseminated as an aerosol with crude sprayers. While protective clothing and gas masks provide excellent front-line defense, their effective use requires rapid and early detection of the agent. Detection devices are not sufficient to completely protect against the threat. They may not detect an agent in time to warn personnel to don protective gear before exposure would occur.

AVIP BACKGROUND

On December 15, 1997, Defense Secretary William Cohen approved the plan to immunize the Total Force against anthrax, contingent on four conditions: (1) supplemental testing of vaccine lots in the stockpile to assure potency, purity, sterility, and safety, consistent with Food and Drug Administration (FDA) standards; (2) approval of the Services' implementation plans for execution and communication; (3) implementation of a system for fully tracking anthrax vaccinations; and (4) review of the health and medical aspects of the program by an independent expert (former dean of medicine of Yale University and member of the prestigious National Academy of Sciences). Each of these conditions was fulfilled.

Eventually, 2.3 million Service Members, including more than 1 million members of the National Guard and Reserves (the "Selected Reserve"), will receive the FDA-licensed anthrax vaccine. The program also extends to the U.S. Coast Guard. Secretary Cohen and General Henry Shelton, chairman of the Joint Chiefs of Staff, were among the first people vaccinated against anthrax and received all six doses in the anthrax vaccination series.

The Anthrax Vaccine Immunization Program (AVIP) will be implemented in three phases over a seven- to eight-year period. Forces expected to deploy to high-threat areas will be the first immunized against anthrax. This phase, referred to as Phase I, includes Service Members and mission-essential DoD civilians assigned or deployed to areas designated by the Joint Staff as high-threat: Southwest Asia (SWA) and Korea (i.e., Northwest Asia, NWA). Phase I began in March 1998, due to increasing tensions in SWA. Phase I extended to forces deployed to Korea and surrounding waters on August 16, 1998.

Early deploying forces supporting SWA and NWA, both Active Duty and Reserve Component personnel, will be vaccinated in Phase II. Phase II begins once assured production is available from the manufacturer. Phase III will include the remainder of the force and new personnel. As of August 2001, more than 2.1 million doses of anthrax vaccine have been given to over 520,000 Service Members in the DoD Anthrax Vaccine Immunization Program (AVIP).

THE CURRENT SLOWDOWN

Between July 2000 and June 2001, DoD ordered a series of three temporary slowdowns of the AVIP, until additional FDA-approved vaccine becomes available. Vaccination continues for designated special mission units and anthrax vaccine research. Other personnel defer further vaccinations until additional vaccine is available.

Each dose of a vaccine is like climbing a ladder. The first dose of anthrax vaccine begins the process of protection. Anti-anthrax antibodies are detectable in 60% to 84% of people who receive just one dose of vaccine. After two doses, 95% to 100% have detectable antibody concentrations. The full vaccination series is needed for full protection.

The Defense Department assessed the effect of interruptions in the anthrax vaccine schedule in 1992-93. A study was

conducted among 281 Fort Bragg soldiers who had received 1, 2, or 3 doses of anthrax vaccine 18 to 24 months earlier during the Persian Gulf War. These soldiers received one additional dose of anthrax vaccine. From 92% to 100% of these soldiers responded with a ~ 100-fold increase in antibody level. Based on these findings and other knowledge of the human immune system, deferred vaccinations resume where left off. There is no need to start vaccination schedules over from the beginning.

HISTORY OF ANTHRAX VACCINE

The anthrax vaccine given to U.S. forces was licensed by the federal government on November 4, 1970. For more than 30 years, anthrax vaccine has been recommended for at-risk veterinarians, laboratory workers, and others at occupational risk in the U.S. The manufacturer distributed about 68,000 doses of anthrax vaccine between 1974 and 1989. An estimated 150,000 Service Members received 250,000 doses of anthrax vaccine in 1991 during the Persian Gulf War.

The FDA-licensed anthrax vaccine is effective and has an excellent safety record. It is a sterile, non-infectious product made by filtering anthrax bacteria. It is impossible to contract the disease from the vaccine, because an avirulent strain is used.

Immunization with anthrax vaccine requires six doses administered over 18 months to complete the primary series. Doses are administered at 0, 2, and 4 weeks, and 6, 12, and 18 months (where the first dose is given at “week 0”). Yearly boosters are administered thereafter to maintain immunity. Although protection levels increase as shots in the series are given, the entire six-shot series is needed.

EFFECTIVENESS OF ANTHRAX VACCINE

The evidence of effectiveness of the FDA-licensed anthrax vaccine is based upon data from both human and animal research. The vaccine, licensed since 1970, causes the body to produce protective antibodies through a protein called protective antigen (PA). The same protective antigen in the licensed vaccine was involved in the pivotal, placebo-controlled field trial. This study was conducted in a group of wool-mill workers in New Hampshire and Pennsylvania from 1955 to 1959 [Brachman, et al. *American Journal of Public Health* 1962;52:632-45].

Cutaneous anthrax (anthrax contracted through the skin) was an occupational health hazard among wool-mill workers for many years before the study. In the Brachman study, one group of workers was vaccinated, one group received an inert placebo, and another group was simply observed. The study revealed that vaccination resulted in a statistically significant reduction in anthrax infections, compared to those not vaccinated. Vaccinated people developed disease 92.5% less often than those not vaccinated.

During the Brachman study, an outbreak of inhalational anthrax occurred at one of the four mills studied. Five cases of inhalation anthrax occurred among 448 unvaccinated people at that mill, with zero cases among 149 fully vaccinated people. Despite the obvious trend, the number of cases of inhalation anthrax too small for the difference between groups to be statistically conclusive by itself. A follow-on study by the Centers for Disease Control (CDC) from 1962 to 1974 reported 27 cases of cutaneous anthrax among unvaccinated (or only partially vaccinated) workers in or near the mills, compared to zero cases among those fully vaccinated.

In non-human primates, the animals that best mimic humans for inhalational anthrax, the FDA-licensed anthrax vaccine provided 95% protection against a lethal aerosol challenge. In five studies of Rhesus monkeys given either one or two doses of anthrax vaccine, 62 of 65 vaccinated monkeys survived lethal aerosol challenge with hundreds of times the median fatal dose. In these studies, 18 unvaccinated monkeys were challenged and all died (0% survival). Similarly, 114 of 117 vaccinated rabbits (97%) survived inhalational spore challenge, whereas all 28 unvaccinated rabbits died (0% survival).

Although the available human research on vaccine effectiveness against inhalational anthrax is not definitive, the human and animal evidence of effectiveness are very persuasive. Because the occurrence of naturally occurring anthrax (especially inhalational anthrax) is exceedingly low, there is no opportunity to conduct additional human field trials. Anthrax spores are, of course, too lethal to test on humans. Thus, there is no way to conduct human challenge studies of any vaccine or therapeutic agent against inhalational anthrax. For these reasons, the only feasible approach is to rely on the human data available, supplemented by animal research.

SAFETY OF ANTHRAX VACCINE

To date, 17 human studies among more than 520,000 people affirm the safety of anthrax vaccination. These studies involve

short-, intermediate-, and long-term follow-up; both active and passive surveillance; spontaneous and solicited data; and both retrospective and prospective designs. Details about the safety studies are available in a separate document. In aggregate, these multiple studies are the basis for DoD confidence in anthrax vaccine.

Short-Term Safety

Anthrax vaccine is a safe vaccine, with an incidence of side effects after injection similar to other common vaccines. Like any medicine, any vaccine will occasionally cause adverse reactions. Usually these are mild, like a sore arm or "flu"-like symptoms. Symptoms at the injection site often can be treated with over-the-counter antihistamines (for itching) or pain relievers like ibuprofen. Pretreatment of people who developed injection-site reactions may minimize reactions to later doses. Serious reactions are rare, but they can happen with any vaccine.

Our understanding of common side effects after vaccination come from multiple active-surveillance studies stretching from the 1950s to the 1990s. These settings include civilian occupational settings (coordinated by CDC researchers), among U.S. Army research laboratory workers at Fort Detrick, Maryland, and among U.S. military personnel in Korea, Hawaii, North Carolina, and elsewhere.

Based on data obtained during 30 years of experience with anthrax vaccine, we expected up to 30% of men and 60% of women will experience mild adverse effects, most commonly redness and soreness around the injection site. Between 1% and 5% have a local reaction 1" to 5" in diameter. About 1% have larger reactions. Significant events beyond the injection site occur in less than 1% of anthrax vaccine recipients. Women develop injection-site reactions up to twice as often as men, but the reactions typically resolve quickly for both genders. Some vaccine recipients report symptoms that commonly occur among unvaccinated people (e.g., headaches). These rates of adverse reactions are similar to those for other vaccines, including childhood vaccines and other vaccines administered to military personnel (e.g., hepatitis A, typhoid, yellow fever).

For comparison, soreness at the injection site is reported by 56% of adult recipients of hepatitis A vaccine. Headache was reported by 14%. For the typhoid Vi vaccine, 98% report local tenderness, 56% report pain, 24% report malaise, and 11% report headache. The pneumococcal vaccine, recommended vaccine for every American over the age of 65, has a 71% rate for localized soreness. The recently licensed Lyme disease vaccine produced localized pain in 93% of recipients and fever in 2.5%. The hepatitis B vaccine reports a local reaction rate of 17% and a systemic reaction rate of 15% in adults.

To monitor unusual adverse events after anthrax vaccination, DoD directs health-care providers to use the Vaccine Adverse Event Reporting System (VAERS). The Department of Health and Human Services established VAERS in November 1990 as a national surveillance system for vaccines. It is co-managed by the FDA and the CDC. DoD has participated in VAERS since its inception in 1990.

VAERS is considered a passive system, because it relies on health-care providers to report adverse events they see in clinical practice. The strength of VAERS is in recognizing unexpected and rare adverse events. Passive systems like VAERS are known to underreport the true number of adverse events, although they underestimate common events more than rare events. For anthrax vaccine and all other vaccines, DoD *requires* its providers to report through the VAERS system all cases of (1) loss of duty for more than 24 hours; (2) hospitalization for any reaction; and (3) suspected contamination of a vaccine container. In addition, DoD *encourages* health-care professionals to report all adverse events they consider important and clinically relevant, even if the event does not meet the aforementioned criteria. DoD encourages patients who wish to report adverse events directly to VAERS, recognizing that working with a health-care provider tends to improve the quality of data submitted.

In October 1998, DoD requested that the U.S. Department of Health and Human Services (DHHS) establish an Anthrax Vaccine Expert Committee (AVEC) to review VAERS forms related to anthrax vaccine. A distinguished university professor chairs this review committee of civilian physicians with expertise in immunology, internal medicine, neurology, rheumatology, and microbiology. The AVEC independently reviews all anthrax vaccine-related reports. The Committee meets every 3 to 6 weeks, along with nonvoting representatives of DoD, CDC, FDA, and DHHS. The AVEC reviews the quality of the submitted information, evaluates the reported event in the context of expected and unexpected adverse events to vaccines, and assesses the cause-and-effect relationship of the event with anthrax vaccine. The Committee also looks for any significant patterns in the aggregate data. The review performed by the AVEC is unprecedented for a licensed vaccine.

To date, the AVEC reports it found nothing unexpected in the side-effect profile of anthrax vaccine. As of August 7, 2001, the independent Anthrax Vaccine Expert Committee (AVEC) reviewed 1,592 VAERS reports. At this time, more than 2.1 million doses of anthrax vaccine had been administered to over 520,000 people. Fifty-four of the 1,592 reports involved

hospitalization; the civilian panel found that 10 of the 54 certainly or probably were caused by anthrax vaccine. All 10 involved allergic, inflammation reactions at the injection site. Another 157 of the 1,512 reports involved loss of duty of 24 hours or more without hospitalization; the civilian panel found that 88 of the 157 certainly or probably were caused by anthrax vaccine. These 88 reports described injection-site reactions (52 reports), acute allergic reactions (9), various rashes (8), viral-like symptoms (9), or other symptoms.

The FDA-licensed anthrax vaccine was used during the Persian Gulf War to immunize approximately 150,000 American personnel against Iraq's biological weapons. Several national civilian scientific groups, including the Presidential Advisory Committee on Gulf War Veterans' Illnesses, the Institute of Medicine, the National Institutes of Health, and the Defense Science Board, found no evidence to link the FDA-licensed anthrax vaccine with illnesses among Gulf War veterans. These reports can be viewed in their entirety on the Internet and are described in a separate document.

Long-Term Safety

Our leaders respect the concerns expressed by Service Members about the possibility of long-term health effects and want to address these concerns using the most appropriate scientific knowledge and practices. More long-term safety data is already available for anthrax vaccine than for any new vaccine licensed in the 1990s (e.g., hepatitis A, Lyme disease, chicken pox).

More than 2,000 laboratory workers at Fort Detrick, Maryland, have been vaccinated against anthrax and other diseases since the 1940s. Many of these workers received 150 to 200 vaccinations and skin tests; some received more than 300 such injections during their tenure at Fort Detrick. Many received annual booster doses of anthrax and other vaccines for 10 to 20 or more years. The first report of a group of 99 vaccine recipients was published in the *Bulletin of the Johns Hopkins Hospital* in 1958. Two follow-up reports were printed in the *Annals of Internal Medicine* in 1965 and 1974. These studies concluded that long-term follow-up examination "failed to demonstrate any evidence of illness attributable to the immunizations."

An extension of this long-term study is underway to determine, in even greater detail, whether individuals who received multiple vaccines, including anthrax vaccine, during their employment at Fort Detrick demonstrated any adverse health effects over the long term. A total of 570 study and control volunteers have been enrolled in this case-control study begun in 1996. The study methods include a 9-page health history questionnaire, extensive blood tests and urinalysis. Study subjects will be compared to two to three race-, gender-, and age-matched control subjects. Analysis of the data is currently in progress.

An even more far-ranging study involves linking electronic immunization records with hospitalization and outpatient databases maintained by the Defense Medical Surveillance System (DMSS). This study clearly shows that anthrax-vaccinated people are hospitalized slightly less often (one per 35 people per year) than unvaccinated people (one per 28 people per year). Similarly, outpatient medical visits occur as often among anthrax-vaccinated people as those unvaccinated. These findings hold true individually for each organ of the body. Anthrax-vaccinated people are as healthy as (and as sick as) unvaccinated people.

Reproductive Health

According to the CDC's Advisory Committee on Immunization Practices (ACIP), "there is no convincing evidence of risk from vaccinating pregnant women with inactivated virus or bacterial vaccines or toxoids." Similarly, no evidence exists for any other adverse reproductive effect, including effects on fertility, miscarriage, or birth defects. Indeed, the ACIP, the American College of Obstetricians & Gynecologists, the American Academy of Pediatrics, and the American College of Physicians specifically recommend that susceptible women receive some inactivated vaccines during their pregnancy. These vaccines protect against tetanus, influenza, hepatitis B, poliovirus, and meningococcal disease.

Inactivated vaccines licensed by the FDA include anthrax vaccine and many other vaccines that protect children and adults against diseases such as tetanus, hepatitis A, and diphtheria. The FDA does not require, as a condition of licensure, reproductive toxicity studies to determine the effect of these sterile, inactivated vaccines on pregnancy, fertility, or other reproductive outcomes. As a result, the package insert for anthrax vaccine, as well as these other FDA-licensed vaccines, note that animal reproductive studies have not been conducted for the vaccine and that the vaccine has not been evaluated for its potential to impair fertility. This results from the virtual absence of reproductive problems caused by vaccines throughout the 20th century.

Nonetheless, DoD conducted several studies of reproductive implications of anthrax vaccination.

Winn Army Community Hospital studied the reproductive health among 4,092 active-duty women assigned to Fort Stewart or Hunter Army Airfield, where up to 75% of military women received anthrax vaccine from Jan 99 to Mar 00. This cohort developed 513 pregnancies, with 353 births. Vaccinated and unvaccinated women had similar rates of conception (fecundity) and similar rates of giving birth (i.e., not miscarrying). Low-birth-weight offspring and offspring with structural abnormalities were not statistically different in the two groups.

The Center for Healthcare Education & Studies (CHES), Fort Sam Houston, Texas, performed an analysis of reproductive outcomes among wives of anthrax-vaccinated Army soldiers. Wives of vaccinated men were similar to wives of unvaccinated men with respect to admissions for menstrual disorders, infertility, ectopic pregnancy, complications of labor, normal pregnancy, and high-risk pregnancy, delivery of live or stillborn single or twin births, and length of stay.

Even though the FDA-licensed anthrax vaccine is a bacterial vaccine that contains only non-living components of anthrax organisms and is non-infectious, prudent medical practice is to defer immunizations during pregnancy unless clearly needed. Pregnant women should not receive anthrax vaccine unless anthrax exposure occurs or is imminent. Service Members who believe that they may be pregnant should inform their health-care provider. Anthrax vaccination is deferred until the pregnancy is over. Since the vaccine contains no infectious substance, there is no reason for a woman to delay becoming pregnant, nor to stop breast-feeding after receiving a dose of anthrax vaccine. These guidelines are consistent with those of the ACIP, the American College of Obstetricians & Gynecologists, the American Academy of Pediatrics, and the American College of Physicians.

ANTHRAX VACCINE PRODUCTION ISSUES

The State of Michigan opened its first laboratory to manufacture vaccines in Lansing in 1925, receiving federal license #99 to manufacture biological medications. On July 7, 1998, the State of Michigan approved the sale of the United States' only licensed manufacturer of anthrax vaccine to a private-sector company. The organization known as the Michigan Biologic Products Institute (MBPI) was sold effective September 5, 1998, to become BioPort Corporation. The facility's license is now listed as license #1260.

BioPort, whose headquarters remain in Lansing, Michigan, is owned by multiple shareholders. The two main companies that make up BioPort are Intervac, headed by William Crowe and Faud El-Hibri, and Michigan Biologic Products Inc., which is made up of seven managers from the era when the State of Michigan owned the plant, headed by Robert Myers. The former state employees were specifically permitted by the Michigan State Legislature to bid on the sale. The legislators hoped that retaining local management as investors would help keep the plant and its 174 jobs in Michigan. Admiral William Crowe, Jr., is a former chairman of the Joint Chiefs of Staff and the U.S. ambassador to Britain until 1997. Fuad El-Hibri, a US citizen of Lebanese descent, transformed a British government plant for vaccine production into a successful private venture.

As Admiral Crowe testified to the U.S. Congress in October 1999, the government's decision to vaccinate the Armed Forces was made after several years of internal analysis that culminated in a December 1997 decision. These events occurred well before the State of Michigan chose to sell its vaccine-production facilities to BioPort Corporation.

Over the years, the State of Michigan appropriated money to upgrade and expand its existing facility in a staged fashion, as improvements in current Good Manufacturing Practices (cGMPs) were adopted by the U.S. pharmaceutical industry. In January 1993, FDA inspected the anthrax vaccine manufacturing facility as part of a routine program. To improve its operations, the State of Michigan approved renovations for the Lansing facility in July 1993.

In 1994, after the renovation schedule had been approved by Michigan authorities, the FDA conducted a rigorous inspection of Michigan's plasma-derivatives operation. Then, in 1995, the FDA issued a warning letter to Michigan concerning plasma operations and rabies vaccine manufacturing. Findings of a November 1996 inspection showed that corrections to the previous areas had not been completed. The FDA issued a “Notice of Intent to Revoke” (NOIR) letter in March 1997, threatening to begin a multi-step process to revoke Michigan's license to manufacture vaccines. Michigan responded quickly to the NOIR letter, developing a strategic plan for compliance within 30 days. FDA later testified to Congress that Michigan “had made progress in achieving its compliance goals.”

As an additional quality check, the Secretary of Defense ordered DoD to establish a process for supplemental testing of stockpiled vaccine by the manufacturer to assure its sterility, safety, potency and purity. The supplemental testing program reaffirms FDA standards, to assure Service Members and the public that the vaccine stockpile is safe and potent.

Supplemental testing repeats tests required by the FDA for lot release. An independent contractor (Mitretek Systems, Inc., McLean, Virginia) oversees supplemental testing by the manufacturer. Supplemental tests performed by the manufacturer include:

- General Safety: Follows Title 21 Code of Federal Regulations (CFR) section 610.11 guidelines. General safety is determined in the following manner: two animals each of two species (mouse and guinea pig) are given doses of the vaccine and observed for 7 days for adverse effects; and the passing result is that each animal survives the test period, gains weight, and does not show any adverse reaction. Twenty vials per lot are tested for general safety.
- Potency: Follows 21 CFR 610.10 guidelines. Potency is determined in the following manner: three serial dilutions of vaccine are used plus one control group (no vaccine) to vaccinate guinea pigs; 14 days after vaccination, all guinea pigs are injected with known amounts of virulent anthrax; average time to death is calculated for each group; and the passing result is that the test vaccine is no less potent than the reference vaccine. Two vials per lot are tested for potency.
- Sterility: Follows 21 CFR 610.12 guidelines. Sterility testing is performed on the final product to detect the presence of microorganisms. Twenty vials per lot are tested for sterility, using two separate culture media: fluid thioglycollate medium and soybean-casein digest medium.
- Purity: No formal 21 CFR requirements for individual testing of preservatives or additives. Only general requirements for calibration and controls. Purity testing consists of four individual tests for aluminum, benzethonium chloride, and formaldehyde. Five vials per each substance per lot are tested for purity.

The manufacturer closed the anthrax vaccine production line in January 1998 for renovations planned in 1996. The decision to close the facility was part of the manufacturer's facility improvement strategy. It also fulfilled a 1996 DoD assessment that the facility was inadequate to meet expanded demand.

The renovations to the physical plant finished in January 1999. The renovation project cost $3.7 million and included upgrades of the anthrax vaccine manufacturing space, along with the addition of a negative air pressure sink, a reach-in environmental chamber, and a state-of-the-art closed inoculation system. FDA conducted a preliminary on-site inspection of the new facility in November 1999. The week-long visit ended with a report of 30 findings for the manufacturer to resolve before the new facility can be licensed by the FDA. No lot of vaccine will be released from the new facility until the FDA independently validates it.

All lots of anthrax vaccine have been fully tested to FDA standards. No lot of anthrax vaccine has ever left Lansing that has not been current and fully FDA approved. The FDA and DoD work closely with BioPort to resolve any deficiencies in production or record-keeping process at the plant. The FDA and a DoD contractor (Mitretek) review testing of the stockpile of vaccine produced by BioPort for sterility, safety, purity, and potency of each stockpiled lot individually before release. Each lot of vaccine consists of approximately 200,000 doses or 20,000 vials of anthrax vaccine. Each vial contains ten doses.

While the FDA inspection results were significant, the manufacturer's improvements to quality systems, cGMPs, and facilities provide assurance that the current and future anthrax vaccine inventory complies with FDA requirements. BioPort remains vital to U.S. national interests. Maintenance of this critical industrial base is essential to protect Service Members from anthrax weapons.

Over the last few years, several articles in magazines and newspapers have incorrectly reported that certain lots or vials of anthrax vaccine were contaminated. At no time have contaminated lots or vials of anthrax vaccine been shipped to any military facility, nor has such vaccine been administered to our Service Members.

MANDATORY ANTHRAX IMMUNIZATION

DoD policy requires that Service Members, emergency-essential DoD civilian and contractor personnel assigned or rotating to high-threat areas, and those pre-designated for immediate contingency deployment to these areas, will be administered anthrax vaccination first. To set an example for all Service Members, senior defense leaders were among the first to receive anthrax vaccination.

Choosing to be vaccinated is not an isolated decision that can be left solely to the personal choice of individuals. In the military, the risk from being vulnerable to infection affects the capability of the entire military unit and the success of the military mission. Military regulations require many vaccines for military personnel, beginning at basic training. Some vaccines are given to all military personnel, whereas others are given based on occupation or geographic assignment. Military recruits are vaccinated to protect against ten diseases. During the course of military service, Service Members are vaccinated

against 4 to 11 diseases with dozens of injections, depending on assignment, occupation, and underlying health status. For the affected category of personnel at risk, none of these vaccines is optional or voluntary; all are mandatory and provide a basis for a lawful order to a Service Member to be vaccinated.

An analogy is that the risk-versus-risk balance for childhood diseases results in required vaccinations for school children. The risk of not immunizing presents a threat to the health of the community that extends beyond personal health concerns. In 1905, the United States Supreme Court affirmed the right of states to pass and enforce compulsory immunization statutes (Jacobson v. Massachusetts). In 1922, the Supreme Court similarly affirmed laws requiring vaccination before school entry (Zucht v. King).

Service Members who disobey a lawful order to take anthrax vaccination are subject to administrative or disciplinary actions. There is no DoD-wide policy directing a specific disposition when a Service Member refuses a lawful military order. Rather, local military commanders apply the principles in the Uniform Code of Military Justice (UCMJ) and the guidance in the Manual for Courts-Martial and Service regulations that apply to all cases involving refusal to obey a lawful order.

The UCMJ, enacted by Congress over 50 years ago, and the Manual for Courts-Martial provide guidance on how commanders are to resolve misconduct. The commander's disposition decision is based on the facts and circumstances of each individual case. This requires a careful evaluation and balancing of several factors, such as the nature of the offense; the existence of other charges; mitigating or extenuating circumstances; and the character and military service record of the member. Even cases involving similar misconduct may be resolved differently based on a commander's assessment of what will best further the needs of the military and the Service Member. The Manual for Courts-Martial requires commanders to deal with allegations of misconduct in a timely manner at the lowest appropriate level of disposition.

EDUCATION & COMMUNICATION

The DoD has long recognized the importance of a robust and responsive education and communication plan regarding anthrax vaccine. The Department conducts several outreach initiatives, including:

- A toll-free information line (1-877-GET-VACC) to respond to questions about anthrax vaccine and the AVIP (in operation since July 1999).
- A detailed DoD AVIP website at http://www.anthrax.osd.mil.
- A customized email question-and-answer service, at avip@otsg.amedd.army.mil (in operation since August 1999).
- A Speakers Bureau to conduct AVIP open-house forums, staff assistance visits, briefings, press conferences, and training on immunization tracking systems.

THE NEED FOR TOTAL FORCE ANTHRAX IMMUNIZATIONS

The DoD must provide U.S. forces with reasonable levels of protection against battle and non-battle threats to health and well being. Medical protective countermeasures, such as vaccines, are safe and effective ways to protect the health and lives of U.S. Service Members against biological warfare (BW) attack. The anthrax vaccine can be administered well in advance of deployment to high-threat areas. Unlike physical protective devices (e.g., gas masks), anthrax vaccine protects without requiring warning or detection of a BW attack. Anthrax vaccine is the only round-the-clock protection from anthrax weapons.

The risk from not immunizing Service Members against anthrax is not acceptable. The deaths of large numbers of U.S. soldiers, sailors, airmen, or marines is likely, if unvaccinated troops are exposed to this potent and lethal threat. Today's military force, including both active and reserve components, is highly mobile and deployable to high-threat areas on short notice. The risk-versus-risk balance clearly requires Total Force immunization.

In the case of anthrax vaccine, the current FDA-licensed vaccine is not ideal, just as no real vaccine is ideal. Anthrax vaccine was developed in the 1950's and 1960's by the state-of-the-art procedures at that time, and licensed in 1970. Advances in biotechnology and genetic engineering may enable improvements in the vaccine that allow fewer doses or use of highly purified protective antigen. The DoD scientists are pursuing both of these objectives. But, pursuit of licensure of a new anthrax vaccine will take many years. We are unwilling to leave Service Members vulnerable to the threat while waiting for the next-generation vaccine to work its way through research, development, and FDA review.

Today, there is a broad consensus among America's vaccine experts that the FDA-licensed anthrax vaccine is safe and effective for people at high risk of exposure. Six independent civilian panels affirm the safety and effectiveness of anthrax

vaccine:

- Civilian Panel on Review of Bacterial Vaccines & Toxoids, advising the FDA from 1978 to 1985. *Federal Register* 1985;50:51002-117. http://www.anthrax.osd.mil/Site_Files/articles/Indexclinical/Fed_register.htm.
- Armed Forces Epidemiological Board (AFEB), civilian scientists advising the Surgeons General, from 1990 to present. http://www.anthrax.osd.mil/Site_Files/articles/INhttp://www.anthrax.osd.mil/Site_Files/articles/INDEXletters_statemen
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- Advisory Committee on Immunization Practices (ACIP), civilian physicians advising CDC. Advisory Committee on Immunization Practices. Use of anthrax vaccine in the United States. *MMWR-Morbidity & Mortality Weekly Report* 2000;49(RR-15):1-20. http://www.cdc.gov/mmwr/PDF/rr/rr4915.pdf

In addition, the National Academy of Sciences Institute of Medicine (IOM) Committee on the Safety and Efficacy of Anthrax Vaccine began a 2-year review of the subject in October 2000 (http://www4.nas.edu/webcr.nsf/ProjectScopeDisplay/MFUA-H-00-01-A?OpenDocument). There is no objective reason this expert IOM committee will reach differing conclusions than the six panels that preceded it.

CONCLUSION

Anthrax is a deadly biological weapon that represents a real and present danger to U.S. military personnel. The FDA has licensed anthrax vaccine for 30 years as safe and effective in preventing this extremely lethal disease. The Secretary of Defense, after assuring a program of high quality, directed the Anthrax Vaccine Immunization Program for the Total Force. The number of vaccinations given to date exceeds 2.1 million doses, with few serious adverse events. Reports of adverse events are consistent with expectations based on previous research studies and in line with experiences with commonly used vaccines. The evidence of vaccine protection in humans and animals against aerosol exposure to anthrax is persuasive. Concerns about previous deficiencies by the production facility in meeting current Good Manufacturing Practices have been addressed by the manufacturer, FDA, and DoD, and a supplemental testing program on the safety, sterility, purity, and potency of the vaccine. In balancing the risks of immunization versus risks from failing to vaccinate, the scales tip decidedly in favor of immunization. The United States government must protect the Armed Forces against clear biological-warfare threats, whenever safe and effective vaccines are available.

COMMONLY ASKED QUESTIONS & ANSWERS

Q: Why are we getting this vaccine?

A: Anthrax is a lethal biological weapon. Vaccination before exposure is critical to protect us against this weapon.

Q: Is the vaccine all I need to protect against inhalational anthrax?

A: Vaccination is a vital component of Force Health Protection. Being fully vaccinated greatly increases your chances of surviving an exposure to anthrax. Force Health Protection is enhanced through early warning and detection systems, and proper wear of protective gear. Antibiotics play a limited role, but vaccination is essential.

Q: Is this vaccine safe?

A: Yes. As with other vaccines, minor reactions are common. Serious adverse events may occur after any vaccination, but they are rare.

Q: What are the side effects?

A: Like other vaccines, anthrax vaccine may cause burning, soreness, redness, itching, and swelling at the injection site. Up to 30% of men and 60% of women report mild local reactions, but these reactions usually last only a few days. For both genders, between 1% and 5% report reactions of 1 to 5 inches in diameter. Larger reactions occur about once per hundred vaccinees. A lump at the site occurs commonly, usually lasting for a few weeks, before going away on its own, if left alone. Beyond the injection site, from 5% to 35% may notice muscle aches, joint aches, headaches, malaise, rashes, chills, low-grade fever, nausea, or related symptoms. These symptoms usually go away in less than a week.

Any vaccine can cause serious reactions, such as those requiring hospitalization. For anthrax vaccine, they happen less than once per 200,000 doses. Severe allergic reactions occur less than once per 100,000 doses.

Discuss with a health-care provider whether antihistamines or pain relievers before or after vaccination can help reduce bothersome symptoms. Report adverse events to a health-care provider promptly, before receiving additional vaccinations.

Q: What about long-term side effects?

A: After 30 years experience, there are no known long-term side effects to anthrax vaccination. At Fort Detrick, MD, 1,500 laboratory workers have been followed for 10 years or more after anthrax vaccination. None developed unexplained symptoms due to repeated doses of this or other vaccines they received. From this and other monitoring, no patterns of delayed side effects to anthrax vaccine have been found. Monitoring continues.

Q: What if I am pregnant or breast-feeding?

A: A recent study at Fort Stewart found that anthrax-vaccinated women are just as likely to get pregnant as unvaccinated women. And anthrax-vaccinated women are just as likely to successfully give birth as unvaccinated women.

Prudent medical practice defers any vaccination during pregnancy, unless clearly needed. Therefore, pregnant women do not receive the anthrax vaccine, unless anthrax exposure occurs or is imminent. Women who believe they may be pregnant should inform their health-care provider before vaccination. Once pregnancy is confirmed, anthrax vaccinations will be deferred until the woman is no longer pregnant.

The Centers for Disease Control and Prevention (CDC) reports that vaccines are safe for breast-feeding women, causing no harm to children whom breast-feed.

Q: What if I'm planning on having children?

A: The vaccine contains no infectious substance. Therefore, there is no reason to delay child bearing. This applies to both vaccinated men and vaccinated women.

Q: Anthrax vaccine was administered to personnel deployed in the Persian Gulf War. Has the anthrax vaccine been scientifically linked to illnesses among Gulf War veterans?

A: No. Several renowned scientific groups, including the National Academy of Sciences, have addressed this issue and found no evidence to link the FDA-licensed anthrax vaccine with illnesses among Gulf War veterans.

Q: Does anthrax vaccine contain squalene?

A: Squalene is not and has not been added to anthrax vaccine. Squalene is a natural oil produced by the human body and by bacteria. Tests by the Food & Drug Administration (FDA) found squalene in five lots of anthrax vaccine, at minute levels, less than found naturally in the human bloodstream. FDA officials called this squalene "naturally occurring and safe."

Q: What other medical conditions should I inform the medical staff about?

A: If you have an active illness, a chronic illness under medical treatment, or take medication that suppresses the immune system, inform the medical staff before taking any vaccine.

Q: If I feel I'm having a health problem related to vaccination, what should I do?

A: If an adverse event occurs, seek medical care. Any adverse event involving 24 hours or more time lost from duty, or hospitalization, must be reported by your health-care provider using the Vaccine Adverse Events Reporting System (VAERS). We encourage anyone to report a vaccine-associated adverse event of any severity through VAERS. For blank forms, go to http://www.vaers.org or contact VAERS at 1-800-822-7967.

Q: I'm a Reservist/Guard member. If I have an adverse reaction, can I go to a military (DoD or Coast Guard) hospital or clinic?
A: Yes. Adverse events after DoD- or USCG-directed vaccinations are line-of-duty illnesses.

Therefore, a member of the Reserve Component may seek initial treatment and evaluation at any military treatment facility after vaccination given during a period of duty. The member will be examined and provided necessary medical care. Once the condition is stabilized, Line of Duty and/or Notice of Eligibility status will be determined by the member's unit. No treatment beyond that justified to stabilize the condition or emergency is authorized until Service connection is validated. Evaluation does not require being in a duty status, nor DEERS enrollment. For more information, contact your unit representative.

Q: What happens if I am late for a dose?

A. All reasonable steps should be taken to receive each vaccination on or as close as possible to the approved schedule. Do not get vaccinated early. If you are late for a vaccination, get it as soon as possible. There is no increase in side effects from late vaccinations. Getting vaccinated late does not reduce the protection you ultimately develop. But you may not be ideally protected during the interval when your dose is overdue.

Q: Does the vaccine "slowdown" affect me?

A: The slowdown of the program results from a temporary shortage of FDA-released vaccine. During the slowdown, some people who began the vaccination series will have scheduled doses temporarily deferred, to preserve the limited supply for those at highest risk. When the supply of FDA-released vaccine is restored, the full scope of the program will resume.

Q. Does delaying scheduled shots affect the safety or effectiveness of the vaccine?

A. Deferred doses have not been found to increase side effects from any vaccine. There is no reduction in the level of protection achieved, once you complete all doses in the series.

Each dose of anthrax vaccine adds to the anthrax-fighting antibodies in your blood stream. This is like climbing steps on a ladder towards full protection. Data from studies show that delays of 18 to 24 months did not reduce the body's ability to respond to the next dose of anthrax vaccine.

When anthrax vaccine supply is restored, those who deferred any doses will resume vaccinations where they left off. Service Members are not expected to restart the shot series. This is consistent with guidance from the Centers for Disease Control & Prevention's Advisory Committee on Immunization Practices.

Q: Am I required to take the vaccine?

A: Yes. This vaccine, like every other required vaccination, is necessary to prepare you for deployment. Medical exemptions can be granted, if medically appropriate.

Your health and safety are our number one concern.

Anthrax vaccine is safe & effective.

Anthrax is a lethal disease.

The threat is real.

For more information on the Anthrax Vaccine Immunization Program:

Call toll free 1-877-GET-VACC (1-877-438-8222)
www.anthrax.osd.mil

WHAT EVERYONE NEEDS TO KNOW ABOUT THE ANTHRAX VACCINE

1 September 2001

1-877-GET-VACC

www.anthrax.osd.mil

WHAT IS THE THREAT?

Several potential adversaries have biological weapons. These weapons could cause widespread death among unprotected U.S. forces. Anthrax is the biological weapon most likely to be used because it is:

- Highly lethal
- Easy to produce in large quantities
- Relatively easy to develop as a weapon
- Easily spread over a large area
- Easily stored, dangerous for a long time
- Odorless, colorless, tasteless, hard to detect

WHAT IS ANTHRAX?

Anthrax is a disease normally associated with plant-eating animals (sheep, goats, cattle, and swine). It is caused by the bacteria *Bacillus anthracis*. Once common where livestock were raised, it is now controlled through animal vaccination programs in the U.S. and other countries. Anthrax still occurs in countries where animals are not vaccinated, mainly in Africa and Asia.

Inhalational anthrax is the disease that results from breathing in anthrax spores. Under expected battlefield conditions, experts believe you can inhale in one deep breath enough anthrax spores to kill you. Symptoms of inhalational anthrax can begin as early as 24 hours after breathing the spores. Initial symptoms include fever, cough, and weakness. These ultimately progress to breathing problems, shock, and death in almost all cases.

WHY VACCINATE?

Vaccines prevent illness by stimulating the body's natural disease-fighting abilities. They are among the most powerful tools developed by modern medicine to keep people healthy. Vaccines are used routinely in the U.S. to protect against diseases such as tetanus, mumps, measles, whooping cough, and polio. Vaccines also help protect against biological weapons like anthrax.

As part of Force Health Protection, personnel are given other vaccines to protect against naturally occurring diseases when deploying overseas. Examples include typhoid, hepatitis A, and yellow fever.

WHAT IS ANTHRAX VACCINE?

Anthrax vaccine is a sterile liquid made from a strain (type) of the anthrax organism that does not cause disease. The vaccine contains no living or dead anthrax organisms. Vaccination produces antibodies that neutralize the disease-causing protein common to every strain of anthrax. Human anthrax vaccines were developed in England and the U.S. in the 1950s and early 1960s. The anthrax vaccine you will receive was licensed in 1970 by the Food and Drug Administration (FDA) and is produced by BioPort Corporation of Lansing, Michigan under License No. 1260.

The vaccination schedule consists of six doses, with the first three given two weeks apart. The next three doses are given at intervals of five months, six months, and six months after the date of the previous dose. After the sixth dose, booster doses are given every 12 months to maintain immunity.

Anthrax Vaccine has been safely and routinely administered in the U.S. to at-risk veterinarians, laboratory workers, and livestock handlers since 1970.

Anthrax is a highly lethal biological weapon.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NOV 26 1999

The Honorable Dan Burton
House of Representatives
Washington, D.C. **20015**

Dear Mr. Burton:

Thank you for your interest in the anthrax vaccine. This is in response to your letter dated November 3, 1999, co-signed by three of your colleagues, to Dr. Jane E. Henney, Commissioner of the Food and Drug Administration (FDA or the Agency). You raised a number of issues related to the pending license supplement application of BioPort Corporation to produce the anthrax vaccine. Ms. Jarilyn Dupont of my staff has had several conversations with Mr. John Weaver of your staff, on November 12 and November 17, 1999, concerning the status of this response. As was explained to Mr. Weaver, the response provided below is based on information available under the Freedom of Information Act (FOIA) and FDA implementing regulations.

Inspections

As you know, BioPort Corporation, (previously known as Michigan Department of Public Health or Michigan Biologics Products Institute), holds a license to manufacture Anthrax Vaccine Adsorbed. FDA has inspected this facility on many occasions during the past decade, identifying a number of deficiencies requiring correction. Your statement that the anthrax vaccine-specific portion of the manufacturing facility was not physically inspected in 23 years is not accurate. A review of inspection reports from 1972 to 1998 shows that Anthrax Vaccine Adsorbed was covered as part of the inspection on 12 separate occasions either by record review, observation of manufacturing areas or interviews with engineering and manufacturing staff. This information was contained in the written testimony of Dr. Kathryn C. Zoon, Director, Center for Biologics Evaluation and Research (CBER), before the Committee on Government Reform, Subcommittee on National Security, Veterans Affairs and International Relations, on April 29, 1999. In response to Members' questions, Dr. Zoon also stated that FDA did conduct inspections for the anthrax vaccine prior to 1996.

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Product Testing and Specifications

FDA agrees that products must be consistently manufactured to meet specifications prior to product approval. FDA review does include product characterization. Because of the complex manufacturing process for most biological products, each lot of the product undergoes thorough testing for purity, potency, and sterility. Manufacturers may release lots of product only after testing is documented. FDA may require lot samples and protocols showing results of applicable tests to be submitted for review and possible testing by the Agency. The anthrax vaccine manufactured by BioPort is subject to lot release, under which a manufacturer may not distribute a lot of product until CBER releases it. The lot release program is part of FDA's multi-part strategy that helps assure biological product safety by providing a quality control check on product specifications.

Anthrax Vaccine Adsorbed Indications

Dr. Zoon's testimony before the Committee on Government Reform on October 12, 1999, stated that the indication is based on risk. She did not state that the anthrax vaccine is indicated only for individuals at risk for cutaneous exposure to anthrax, nor that the use is for a "limited" population. The labeling for the anthrax vaccine product is enclosed. The labeling for Anthrax Vaccine Adsorbed does not mention route of exposure (e.g., cutaneous), per se. Use of the vaccine for protection against both cutaneous and inhalation anthrax exposure is not inconsistent with the labeling for Anthrax Vaccine Absorbed.

The term "paucity of data," used in the 1997, letter to Dr. Stephen Joseph, then Assistant Secretary of Defense for Health Affairs, from Dr. Michael A. Friedman, then FDA Lead Deputy Commissioner, is used to describe the relatively few reported cases of inhalation anthrax in the efficacy trial. Requiring the anthrax vaccine to be returned to an investigational new drug (IND) status will not generate more human efficacy data, as inhalation anthrax in humans is not amenable to study, due to the low incidence and sporadic occurrence of disease in natural settings. It should be noted that in the United States, in this century, only 18 human cases of inhalation anthrax have been reported (Brachman, P.S. Inhalation anthrax. *Ann N Y Acad Sci* 353:83-93, 1980). This low incidence of naturally occurring inhalation anthrax since introduction of the vaccine makes it impossible to duplicate the findings in the Brachman and the Centers for Disease Control and Prevention (CDC) surveillance data of the 1950's to early 1970's. In the past several years, the Department of Defense (DOD)

In the past several years, the Department of Defense (DOD) has concluded that the threat of biological attack is great enough that troops should be considered part of the high-risk population for which this vaccine is an appropriate prophylactic measure. (This information was provided to Chairman Dan Burton, in a response to an August 11, 1999, letter seeking information on vaccines.) You may wish to contact DOD to discuss its risk assessment.

There is presently no basis for concluding that the anthrax vaccine, a licensed product, when used in accordance with current labeling, should be used pursuant to an IND application or, as requested in your letter, that FDA "place the anthrax vaccine back under IND status."

Data to Support **Indications and Administration Schedule**

There is a misperception that no clinical or scientific studies have been conducted to support the current Anthrax Vaccine Adsorbed-dosing schedule. The currently licensed anthrax vaccine administration schedule was used in the Brachman efficacy trial and CDC IND.

The Brachman et al. trial was used to support the licensure of the anthrax vaccine. This trial was a single-blinded, well-controlled trial conducted in four United States textile mills processing imported goat hair with an 'exposed, susceptible, supervised population." The average incidence of anthrax prior to the study was 1.2 cases per 100 employees per year. The dose administration schedule was the same as the currently licensed vaccine dose administration schedule: 0, 2 and 4 weeks; 6, 12, and 18 months, followed thereafter by annual boosters. Of the 1,249 mill workers, 909 individuals participated in the controlled part of the study. Individuals who received neither vaccine nor placebo served as an unvaccinated observational control. A total of 26 anthrax **cases** occurred during the trial: 21 cutaneous cases and five inhalation cases (four fatal). Of these 26 cases, three (all cutaneous) occurred in anthrax vaccine recipients. One **case** occurred after two doses, one case occurred 13 months after the third dose (fourth dose not given), and one case occurred five months after the third dose. Five cases of inhalation anthrax occurred at one site (the Manchester, New Hampshire goat hair processing plant) during the trial. Two of the inhalation cases were in the placebo group and three inhalation cases were in the unvaccinated group. **No cases of *inhalation anthrax occurred in anthrax vaccine recipients.***

The efficacy level of 92.5 percent, as presented in the major publication of the efficacy trial (Brachman, et. al., 1962 Field evaluation of a human anthrax vaccine. *Am J* Public Health. 52:632-645) includes anthrax cases in the vaccine and placebo groups and is not limited to cutaneous anthrax cases. The efficacy of the anthrax vaccine in this study was calculated to be 92.5 percent. This calculation (92.5 percent) is sometimes erroneously presented as the vaccine efficacy against cutaneous anthrax.

Following the 1957 trial and the five cases of inhalation anthrax in placebo and unvaccinated individuals, the Manchester, New Hampshire goat hair processing plant vaccinated all employees against anthrax (starting in December 1957). The case rate in this plant fell from 8.2 cases per year prior to 1957 to 0.4 cases per year from December 1957 to June 1966, the latter consisting of four cutaneous cases. In July 1966, an employee (unvaccinated) of an adjacent facility (metal fabricator shop) died from inhalation anthrax. The source of the agent was thought to be the adjacent goat hair processing plant. In a follow-up investigation by CDC (January 30 - February 6, 1967), environmental sampling of both facilities identified *B. anthracis* inhalation anthrax (LaForce FM et al.: Epidemiologic study of a fatal case of inhalation anthrax. *Arch* Environ Health 18:798-*805,* 1969).

Under CDC IND, approximately 16,000 doses of the vaccine were administered to approximately 7,000 study participants who were at risk for anthrax. These doses were administered according to the same six-dose schedule that is the approved dosing schedule today.

Furthermore, in CDC surveillance data (1962-1974), 27 cases of anthrax occurred in 'at-risk" industrial settings: *24* cases in unvaccinated individuals, one case after one dose of vaccine and two cases after two doses of vaccine. No cases of anthrax were reported in individuals who received all six doses of anthrax vaccine.

It is interesting to note that CDC publication, *Biosafety in Microbiological and Biomedical Laboratories 4th Edition* (1999), states that laboratory associated cases of anthrax have not been reported in the United States since the late 1950s when the human anthrax vaccine was introduced. Before that date, numerous cases of laboratory associated anthrax, occurring primarily at facilities conducting anthrax research, were reported.

Additional Findings Supporting Anthrax Vaccine Adsorbed

The Public Health Service Act, under which biologicals such as vaccines were licensed in 1970, requires evidence of safety, purity and potency. After the Division of Biologic Standards was transferred from the National Institutes of Health to FDA, expert panels were assigned to review information on biological products, including vaccines that had been licensed prior to the transfer. The review was initiated in order to assess the safety, effectiveness and labeling of products licensed prior to July 1, 1972. Based upon their review of available data, the Advisory Review Panel recommended that marketing of Anthrax Vaccine Adsorbed manufactured by Michigan Department of Public Health be allowed to continue based upon substantial evidence of safety and effectiveness of the product. The safety data from CDC IND, as well as the efficacy data from the Brachman et al. trial, and CDC surveillance data (1962-1974) from "at-risk" industrial settings were the basis for these findings. These findings were published in the Federal Register of December 13, 1985.

Furthermore, data from a well-controlled monkey study has become available since the time of the 1985 Panel report. The efficacy of the Anthrax Vaccine Adsorbed licensed for use in humans also was tested in rhesus monkeys challenged by an aerosol of virulent Bacillus *anthracis* spores. The data from this study suggests vaccine efficacy against inhalation anthrax. It should be noted that monkeys are quite similar to humans with regard to the clinical course and pathological findings following inhalation anthrax.

While these studies cannot prove that the vaccine would be 100 percent effective in a terrorist or wartime situation, they are the only known data on pre-exposure protection currently available against inhalation anthrax.

DOD Vaccine Administration Schedule

In the September 29, 1999, letter to Dr. Sue Bailey, Assistant Secretary of Defense Health Affairs, Dr. Kathryn C. Zoon, Director, CBER, stated in the final paragraph, "We reiterate our previous statement made to DOD on December 16, 1997, that FDA approval of the anthrax vaccine is based on the six-dose regime found in the approved labeling. Because we are unaware of any data demonstrating that any deviation from the approved intervals of doses found in the approved labeling will provide protection from anthrax infection, we strongly recommend that the Anthrax Vaccine Immunization Program follow FDA-approved schedule." Similar information was included in a letter dated

September 28, 1999, to Dr. Sue Bailey from Dr. Jane E. Henney. Copies of both of these letters are enclosed.

DOD has conducted a pilot study, under a BioPort IND, to evaluate several dosing schedules and routes of administration for the anthrax vaccine. This pilot study used full informed consent. The pilot study evaluated anti-protective antigen antibody levels in vaccines. One purpose of the pilot study was to evaluate the feasibility of eliminating the week two dose **as** well as to evaluate differences between the subcutaneous and intramuscular routes of administration. This pilot study was intended to select a dosing schedule(s) for further evaluation in a larger, comparative, statistically definitive study to potentially support a change in the label. In December 1998, DOD met with FDA representatives to discuss such a study. To date, DOD has not yet submitted a definitive study protocol to evaluate and potentially support a change in the dosing schedule for the anthrax vaccine.

Product Expiration Dating

The expiration date of a biological product may be changed pursuant to Title 21, Code of Federal Regulations (CFR) 5610.50, Date of Manufacture, which states in part that the date of manufacture shall be the date of initiation by the manufacturer of the last valid potency test. As stated in 21 CFR §610.53 (b), the dating period for a product shall begin on the date of manufacture, as prescribed in section 610.50. A valid potency assay is required prior to an extension of dating. The expiration date is based on the last valid potency assay.

BioPort's License Application

The content of license applications under FDA review, including the number and characterization of lots, are not releasable under FOIA. Please be assured, however, that FDA will not approve an application until a manufacturer demonstrates that a product can be consistently manufactured under current good manufacturing practices (cGMPs) to meet product specifications. Lots manufactured to support a license application or supplement cannot be sold without approval of the application or supplement and remain subject to FDA lot release requirements as described above.

Proposed rule

In response to your comments on the proposed rule for animal studies, FDA agrees that there needs to be a scientifically verifiable extrapolation from animal data. FDA's Proposed Rule, "New Drug and Biological Drug Products; Evidence Needed to Demonstrate Efficacy of New Drugs for Use Against Lethal or Permanently Disabling Toxic Substances When Efficacy Studies in Humans Ethically Cannot Be Conducted," was published in the October 5, 1999, Federal Register. The docket is open for comment until December 20, 1999. Your letter will be forwarded to the docket so that your comments regarding the proposed rule can be entered into the docket for consideration. After the comment period has closed, FDA will review the comments and determine the appropriate next step in the process. At this time, there is no date for publication of a final rule.

We trust this information responds to your concerns. If you have further questions, please let us know. A similar response has been provided to your co-signers.

Sincerely,

Melinda K. Plaisier
Associate Commissioner
for Legislation

3 Enclosures
"Package Labeling for Anthrax Vaccine Adsorbed"
"September 28, 1999 letter to Dr. Sue Bailey, Assistant Secretary of Defense Health Affairs, from Dr. Jane E. Henney, Commissioner, FDA"
"September 29, 1999, letter to Dr. Sue Bailey, Assistant Secretary of Defense Health Affairs, Dr. Kathryn Zoon, Director, CBER"

cc: Dockets Management Branch

Congress of the United States'

Washington, DC 20515

November 3, 1999

The Honorable Jane E. Henney, M.D.
Commissioner
Food and Drug Administration
14-7 l Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Henney:

We are writing to express our serious concerns regarding the pending license supplement application of BioPort to produce the anthrax vaccine. We strongly urge that each of the items contained in the letter be fully addressed and a response provided to us prior to the approval of BioPort's license supplement application.

As you are aware, in 1997 the Department of Defense mandated the implementation of a force-wide Anthrax Vaccine Immunization Program (AVIP). Since the announcement of this plan to inoculate all 2.4 million members of our Armed Services, FDA documented deficiencies in the manufacturing process have caused widespread and persistent concerns regarding the safety of the vaccine.

Of particular concern is that despite the licensure of the anthrax vaccine in 1970, 23 years passed before your agency physically inspected the anthrax-specific portion of the manufacturing facility. In testimony before the House Government Reform Committee, Dr. Zoon, the Director of FDA's Center for Biologics Evaluation and Research, indicated that two inspections of the production facilities in 1997 and 1998 revealed significant deviations from the Federal Food, Drug, and Cosmetic Act, FDA's regulations, and the standards in the Michigan Biological Product Institute (MBPI) license. Inspection reports of the production facilities following its purchase by BioPort revealed some progress but many remaining deviations. In large part, the significant ongoing deviations prompted the company to close the facility for remodeling rather than face the likelihood of FDA revoking their license.

Given the documented deviations from approved practices in the manufacturing process, it is imperative that the FDA follow it's own prescribed regimen of thorough testing for purity, potency, identity, and sterility. As a prerequisite for approval of the license supplement, the testing must reveal lot-to-lot consistency for the vaccine. Included within the testing requirements, the FDA must ensure lot-to-lot consistency for the antigen level. FDA mandated lot-to-lot consistency will ensure we can accurately measure the efficacy of the vaccine. The lack of clinical data detailing the relationship between antigen levels and the amount of protection provided argues strongly for greater vaccine consistency data so correlates of

No. 99-7003

immunity can be studied. In that regard, please provide information on the status of FDA's request of BioPort to characterize the vaccine. Any failure to characterize the vaccine must preclude the approval of the license supplement application.

We also urge that the FDA place the anthrax vaccine back under Investigational New Drug (IND) status. As Dr. Zoon testified before the Government Reform Committee, the MBPI vaccine was licensed for use by a limited population of individuals at risk for coetaneous exposure to anthrax through infected animals or animal products. The December 13, 1985 Federal Register and the FDA approved package inserts indicate: "Since the risk of exposure to anthrax infection in the general population is slight, routine immunization is not recommended." However, the Department of Defense, in its implementation of the AVIP, is performing a large-scale inoculation for protection against inhalation anthrax. The scope of the vaccination program and the form of exposure anticipated by DoD were not addressed in the initial license. A March 13, 1997, letter from Dr. Michael Friedman, FDA Lead Deputy Commissioner, to Stephen Joseph, then Assistant Secretary of Defense for Health Affairs, acknowledged the "paucity of data regarding the effectiveness of the anthrax vaccine for prevention of inhalation anthrax." This lack of significant data strongly suggests the need for further study under IND status.

Additionally, the data submitted for licensure of initial vaccine did not include scientifically valid support for the current dosing structure. GAO stated that no studies have been conducted to determine the optimum number of doses of the anthrax vaccine. Although annual boosters are recommended, the need for a six-shot regimen and annual booster shots has not been evaluated. There is also no clinical data to accurately conclude that the prescribed regimen provides a consistent level of protective antigen to be efficacious against inhalation anthrax. A September 29, 1999 letter from Dr. Zoon to Dr. Sue Bailey, the Assistant Secretary of Defense for Health Affairs indicated that there is lack of data on the impact of deviations from the approved vaccine regimen. Prior to the approval of the license supplement application, the FDA must scientifically verify the clinical data supporting the six-dose regimen. We would like to be apprised of FDA's plans to accomplish this goal and be provided the clinical data supporting the correlation between the dosage and anti-body levels.

We are also requesting the status of FDA's proposed rule regarding the use of animal data to support claims of human efficacy. Human efficacy information for the current license and the license supplement application is based overwhelmingly upon the application of data from animal anthrax vaccinations and exposure. However, there have been great discrepancies between various animal models regarding the efficacy of the anthrax vaccine. We acknowledge and support the moral argument against human testing to determine the efficacy of the vaccine. At the same time, we must ensure there is a scientifically verifiable extrapolation from animal data that can be applied to humans. It is our understanding the proposed rule would attempt to establish protocols to provide that information. If that rule has not been approved, we would like

Should you have any questions regarding this letter, please do not hesitate to contact us or any member of our staffs. Please provide this information by November 18. Thank you for your consideration of these serious matters. We look forward to your prompt reply.

Sincerely,

Walter B. Jones
Member of Congress

Dan Burton
Member of Congress

Benjamin A. Gilman
Member of Congress

Christopher Shays
Member of Congress

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

September 28, 1999

Sue Bailey, M.D.
Assistant Secretary of Defense
Health Affairs
1200 Defense Pentagon
Room 3E346
Department of Defense
Washington, D.C. 20301-1200

Dear Dr. Bailey:

It was a pleasure meeting with you on August 24 to discuss issues of mutual concern. Subsequent to our meeting, Dr. Kathryn Zoon, Director of FDA's Center for Biologics Evaluation and Research, advised me of additional information that she reviewed related to anthrax vaccination for our military troops.

Dr. Zoon has reviewed information from congressional sources that some troops may not be receiving the vaccine in accordance with the schedule found in the approved labeling. As you are aware this schedule is the only regimen shown to be effective in protecting humans against anthrax and is the only schedule approved by FDA. I have asked Dr. Zoon to communicate our concerns on this important matter to you directly. Thank you in advance for your prompt attention to this.

Sincerely,

Jane E. Henney, M.D.
Commissioner of Food and Drugs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20852-1448

SEP 2 9 1999

Sue Bailey, M. D.
Assistant Secretary of Defense
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1200 Defense Pentagon
Room 3E346
Department of Defense
Washington, DC 20301-1200

Dear Dr. Bailey:

On December 16, 1997, Food and Drug Administration (FDA) officials met with the Department of Defense (DOD) officials to discuss DOD's Anthrax Vaccine Immunization Program (Am). During that meeting, Dr. Ed Martin acting Assistant Secretary of Defense, Health Affairs, briefed Dr. Michael Friedman, Lead FDA Deputy Commissioner on DOD's plan to implement anthrax vaccinations of the U.S. military forces. As part of that briefing, Dr. Martin emphasized that the anthrax vaccine immunization program would not vary from the FDA approved labeling.

Recently, it has come to the agency's attention through congressional sources, that some troops may not be receiving the vaccine in accordance with the schedule found in the approved labeling. As you know, the approved anthrax labeling states that full immunization involves six (6) doses administered over 18 months to complete the primary series Labeling calls for doses of the vaccine to be administered, following the first dose, at 2 and 4 weeks, 6 months, 12 months and 18 months, with yearly boosters thereafter. This schedule is the only regimen shown to be effective in protecting humans against anthrax and is the only schedule approved by FDA Data received by FDA from congressional sources indicate that a number of reserve and active military personnel are receiving their anthrax vaccine doses significantly later than the FDA approved schedule.

WC reiterate our previous statement made to DOD on December 16, 1997 that FDA approval of the anthrax vaccine is based on the six-dose regimen found in the approved labeling. Because we are unaware of any data demonstrating that any deviation from the approved intervals of doses found in the approved labeling will provide protection from anthrax infection, WC strongly recommend that the Anthrax Vaccine Immunization Program follow the FDA approved schedule. We would like to hear from you as soon as possible regarding *this* important *matter.*

Sincerely yours,

Kathryn C. Zoon, Ph.D.
Director
Center for Biologics Evaluation
and Research

ANTHRAX VACCINE ADSORBED

DESCRIPTION

Anthrax Vaccine Adsorbed is a sterile product made from filtrates of microaerophilic cultures of an avirulent, nonencapsulated strain of *Bacillus anthracis* which elaborates the protective antigen during the growth period. The cultures are grown in a synthetic liquid medium and the final product is prepared from the sterile filtered culture fluid. The potency of this product is confirmed according to the U.S. Food and Drug regulations (21 CFR 620.23): Additional Standards for Anthrax Vaccine Adsorbed. The final product contains no more than 2.4 mg aluminum hydroxide (equivalent to 0.83 mg aluminum) per 0.5 cc dose. Formaldehyde, in a final concentration not to exceed 0.02%, and benzethonium chloride, 0.0025%, are added as preservatives.

CLINICALPHARMACOLOGY

Anthrax Vaccine Adsorbed is used in man to promote increased resistance to *Bacillus anthracis* by active immunization (1,2).

INDICATIONS AND USAGE

Immunization with Anthrax Vaccine Adsorbed is recommended for individuals who may come in contact with animal products such as hides, hair, or bones which come from anthrax endemic areas and may be contaminated with *Bacillus anthracis* spores; and for individuals engaged in diagnostic or investigational activities which may bring them into contact with *B. anthracis* spores (1-5). It is also recommended for high risk persons such as veterinarians and others handling potentially infected animals. Since the risk of exposure to anthrax infection in the general population is slight, routine immunization is not recommended.

If a person has not previously been immunized against anthrax, injection of this product following exposure to anthrax bacilli will not protect against infection.

CONTRAINDICATIONS

A history of a severe reaction to a previous dose of anthrax vaccine is a contraindication to immunization with this vaccine.

WARNINGS

1. Any acute respiratory disease or other active infection is generally considered to be adequate reason for deferring an injection.
2. Persons receiving cortico-steroid therapy or other agents which would tend to depress the immune response may not be adequately immunized with the dosage schedule recommended. If the therapy is short termed, immunization should be delayed. If the therapy is long termed, an extra dose of vaccine should be given a month or more after therapy is discontinued.

PRECAUTIONS

1. *General:* Epinephrine solution, 1:1000, should always be available for immediate use in case an anaphylactic reaction should occur, even though such reactions are rare.
2. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* Studies have not been performed to ascertain whether Anthrax Vaccine Adsorbed has carcinogenic action, or any effect on fertility.
3. *Pregnancy:* PREGNANCY CATEGORY C. ANTHRAX VACCINE ADSORBED
   Animal reproduction studies have not been conducted with Anthrax Vaccine Adsorbed. It is also not known whether Anthrax Vaccine Adsorbed can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Anthrax Vaccine Adsorbed should be given to a pregnant woman only if clearly needed.
4. *Pediatric Use:* This antigen should be administered only to healthy men and women from 18 to 65 years of age because investigations to date have been conducted exclusively in that population.

ADVERSE REACTIONS

Local Reactions: Mild local reactions occur in approximately thirty per cent of recipients and consist of a small ring of erythema, 1-2 cm in diameter, plus slight local tenderness(1). This reaction usually occurs within 24 hours and begins to subside by 48 hours. Occasionally, the erythema increases to 3 to 5 cm in diameter. Local reactions tend to increase in severity by the 5th injection and then may decrease in severity with subsequent doses.

Moderate local reactions which occur in 4 per cent of recipients of a second injection are defined by an inflammatory reaction greater than 5 cm diameter.

These may be pruritic. Subcutaneous nodules may occur at the injection site and persist for several weeks in a few persons. A moderate local reaction can occur if the vaccine is given to anyone with a past history of anthrax infection.

More severe local reactions are less frequent and consist of extensive edema of the forearm in addition to the local inflammatory reaction.

All local reactions have been reversible.

Systemic Reactions: Systemic reactions which occur in fewer than 0.2 per cent of recipients have been characterized by malaise and lassitude. Chills and fever have been reported in only a few cases. In such instances, immunization should be discontinued.

DOSAGE AND ADMINISTRATION

Dosage

Primary immunization consists of three subcutaneous injections, 0.5 mL each, given 2 weeks apart followed by three additional subcutaneous injections, 0.5 mL each, given at 6, 12 and 18 months(1).

If immunity is to be maintained, subsequent booster injections of 0.5 mL of anthrax vaccine at one year intervals are recommended.

Administration

1. Use a separate sterile needle and syringe for each patient to avoid transmission of viral hepatitis and other infectious agents.
2. Shake the bottle thoroughly to ensure that the suspension is homogeneous during withdrawal. The rubber stopper should be treated with an appropriate disinfectant and allowed to dry before inserting the needle.
3. This preparation must be given subcutaneously after cleansing the overlying skin with an antiseptic.
4. Follow the usual precautions to avoid intravenous injection.
5. After withdrawing the needle, the injection site may be massaged briefly and gently to promote dispersal of the vaccine.
6. The same site should not be used for more than one injection of this vaccine.
7. Do not syringe-mix with any other product.
8. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Anthrax Vaccine Adsorbed is supplied in 5 mL vials containing 10 doses each.

STORAGE

THIS PRODUCT SHOULD BE STORED AT 2 TO 8 °C (35.6 to 46.4 °F). Do not freeze. Do not use after the expiration date given on the package.

REFERENCES

1. Brachman, P.S., *et. al.* Field Evaluation of a Human Anthrax Vaccine. Amer. J. Pub. Health, *52*:632-645 (1962).
2. Editorial: Vaccine Against Anthrax. Brit. Med. J., *2*:717-718 (1965).
3. Advisory Committee for Immunization Practices. Adult Immunization, Morbidity and Mortality Report, *33*(15):33-34, 1984.
4. Committee on Immunization, *Guide for Adult Immunization, 1985*, Amer. Col. Physicians, Philadelphia, PA (1985).
5. Report of Committee on Infectious Diseases, 19th Edition, Amer. Acad. Pediatrics, Evanston, IL (1982).

These recommendations are prepared by the Michigan Department of Public Health only for the guidance of the physician. They do not replace the experience and judgment of the physician, who should be familiar with the recent pertinent medical literature before administering any biologic product.

Manufactured by
MICHIGAN DEPARTMENT OF
PUBLIC HEALTH
Lansing, Michigan 48909
U.S. License No. 99

Auth.: Act 368, 1978

An anthrax vaccine was evaluated clinically and epidemiologically in an exposed, susceptible, and supervised population. Findings are reported and the authors suggest exposed populations for whom the vaccine is recommended.

FIELD EVALUATION OF A HUMAN ANTHRAX VACCINE

Philip S. Brachman, M.D.; Herman Gold, M.D.; Stanley A. Plotkin, M.D.; F. Robert Fekety, M.D.; Milton Werrin, D.V.M., F.A.P.H.A.; and Norman R. Ingraham, M.D., F.A.P.H.A.

In a series of papers published from 1951-1955[1-6] Wright and colleagues report on the development of an anthrax vaccine. This vaccine was shown to be an effective immunizing agent for laboratory animals and its safety for human use was demonstrated by the successful injection of 600 scientific personnel at Fort Detrick. Its value for human immunization could be established through a field study of a susceptible industrial population known to be chronically exposed to anthrax. This communication reports the data collected in such a study over a four-year period.

Material-Methods

The necessary requirements of a well-defined, exposed, susceptible population among whom cases of anthrax were reported with some regularity could only be met in this country in an industrial area; and thus, epidemiological studies were conducted in various mills where Bacillus anthracis-contaminated raw materials were handled and clinical infections occurred. Four mills located in northeastern United States qualified for inclusion in the evaluation program. All processed raw imported goat hair into a hair cloth interlining used in suit coats. The average yearly incidence of anthrax per 100 employees for these mills was 1.2 cases with a range of from 0.6 to 1.8 as shown in Table 1.

The vaccine was supplied by Dr. G.G. Wright and associates of the U.S. Army Chemical Corps., Fort Detrick, Fredrick, Md. It was produced by growth of the R1-NP strain in 599 medium. R1-NP is a nonencapsulated, nonproteolytic mutant of the Vollum strain of B. anthracis. Protective antigen in the sterile culture filtrates was precipitated and concentrated by addition of 0.1 percent aluminum potassium sulfate (alum). The immunizing properties of various lots of antigen were established by immunization and challenge of rabbits; lots with poor activity were not used in the human evaluation. Details of methods for preparation and testing of the antigen have been presented by Wright, et al.[5]

The employees who had not had anthrax were divided into two numerically equal groups according to their length of employment, age, the department in which they were employed, and the specific job performed. One group received the antigenic material and the other a placebo that consisted of 0.1 percent alum. The employees were not told which material they received. Voluntary cooperation of the employees was solicited and those who refused were removed from the lists. Refusals were distributed in approximately equal proportions among the two groups so that of those initially cooperating, 48 percent were in the vaccine group and 52 percent in the placebo control group.

The immunization schedule used was based upon the results of animal immunization studies. Inoculations consisted of 0.5 ml of either vaccine or placebo given subcutaneously in the deltoid area. The initial series of inoculations consisted of three injections given at two-week intervals, followed by three 0.5 ml booster doses given at six-month intervals. Thereafter, booster inoculations were given at yearly intervals.

The employees of two mills were examined at 24 and 48 hours after each inoculation, and evidence of local or systemic reactions were noted.

A close surveillance was maintained at each mill by means of routine visits and regular environmental sampling programs throughout the study period. The management at each mill was aware of the advantage of a reduced incidence of anthrax infections so that they had an incentive to report all suspicious cases as they occurred. In spite of this close surveillance, one probable case of cutaneous anthrax in a placebo inoculated individual did occur that was not reported. This case is not included in this analysis.

Results

Population

The total populations at the four mills were divided into high- and low-risk groups as defined by the degree of contact with raw materials. It has been

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shown that the incidence of cutaneous anthrax is highest in the bale opening department and gradually decreases through successive departments.[7] The total eligible population at the initiation of the program in each mill was 1,249 individuals, with 47 percent working in high-risk areas and 53 percent working in low-risk areas (Table 2).

The total eligible population continuing through successive inoculations is summarized in Table 3, and shows an initial marked decrease (61 percent) between the initial series and the first booster inoculation. Most of this decrease was the result of the termination of the program at its largest mill (A) midway between the initial series and the first booster, because of an outbreak of inhalation anthrax. All employees were then immunized, which removed from the controlled study 49 percent of the total eligible population. Subsequently, there was a gradual decline (13 percent to 20 percent) following each successive booster inoculation, partly because of the changing nature of the textile business and partly because of the withdrawal of some of the employees from the program. Since the mills entered the program at different times, the respective personnel had received varied numbers of inoculations when the program was terminated at the end of four years.

The inoculees referred to as complete include all those employees who received the prescribed inoculations at the scheduled times; incomplete inoculees include those who missed one or more of the scheduled inoculations, whether placebo or vaccine.

Clinical Data

A total of 26 cases of anthrax were reported among the employees of the four mills during the evaluation program. The occurrence of the cases by month for each mill is summarized in Figure 1. In mills M, P, and S, the cases were reported essentially throughout the entire evaluation period. At mill A, the occurrence of the nine cases during a ten-week period clearly indicates an epidemic.[8,9]

Twenty-one of the cases were cutaneous and five were of inhalation type; four of the latter were fatal. The cases are individually summarized in Table 4. Three of these cases occurred among individuals who had received the vaccine, and the remaining 23 cases occurred among individuals who either had received the placebo inoculations or had not received any inoculations at all (Table 5). Seventeen of these unvaccinated cases received the alum control inocul-

Table 1-Incidence of Anthrax in Four Mills Prior to Initiation of Vaccination Program

Mill	Average Total Employment	Cases of Anthrax 1948 to Initiation of Study*	Cases per 100 Mill Employees Per Year
A	655	63	1.0
M	227	23	1.4
P	148	6	0.6
S	300	38	1.0
	1,330	130	1.2

* Mill A. May, 195 Mill P. May, 1956 Mill M. June, 1955 Mill S. Feb., 1955

Table 2-Participation of Employees in Anthrax Vaccine Evaluation Program

	High Risk					Low Risk					Total				
	Inoculated					Inoculated					Inoculated				
Mill	Vacc.*	Plac.*	Inc.*	Refusal	Total	Vacc.	Plac.	Inc.	Refusal	Total	Vacc.	Plac.	Inc.	Refusal	Total
A	59	60	11	70	200	90	104	24	214	432	149	164	35	284	632
M	42	49	8	8	107	31	42	4	16	93	73	91	12	24	200
P	19	22	15	10	66	22	22	13	21	78	41	44	28	31	144
S	89	95	31	1	216	27	20	10	–	57	116	115	41	1	273
	209	226	65	89	589	170	188	51	251	660	379	414	116	340	1,249

* Vaccinated-Placebo-Incomplete

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ations and are referred to as placebo control cases, and six were uninoculated employees.

The diagnoses of anthrax were based on clinical, bacteriological, pathological, and epidemiological data and are summarized in Table 6. Subcultures of recovered B. anthracis organisms were studied and confirmed in the Anthrax Investigations Unit Laboratory.

Three cases of cutaneous anthrax without bacteriological confirmation are included because in each case the clinical diagnosis was made by a physician who had previously diagnosed many cases, which were subsequently confirmed by bacteriological methods. The single case of fatal inhalation anthrax without laboratory confirmation is a patient whose clinical course paralleled that of three other confirmed cases of fatal inhalation anthrax that occurred at the same time at the same mill.[8,9]

The clinical courses age distributions, sex ratios, length of employment prior to developing anthrax, location of lesions, and over-all departmental attack rates reflect human industrial anthrax as seen in this country.[7,10,11] Twenty-three of the cases occurred among individuals who worked in the high-risk areas, and three occurred in individuals in the low-risk areas.

The immunization histories of the 26 patients are summarized in Table 7. The "complete" vaccinated cases was a 33-year-old female spinner who developed a mild cutaneous lesion five months after receiving the last inoculation of the initial series and just before the regularly scheduled first booster inoculation was due. A smear and culture of the lesion were positive for B. anthracis. Her clinical course was not different from many others previously seen among employees of this mill.

One of the "incomplete" vaccinated cases developed a "typical" cutaneous anthrax a day or two before the scheduled third inoculation of the initial series. A smear and culture were positive for B. anthracis. Since this employee had not received the full complement of the initial series, the failure in protection cannot be charged to the vaccine, therefore, the case is considered to represent an "incomplete" vaccinated case.

The other "incomplete" vaccinated case, a 25-year-old male, had received his initial series in proper order but had not received any subsequent booster inoculations and developed a "typical" cutaneous lesion 13 months after his initial series. A smear and culture from his lesion were positive for B. anthracis.

Two "incomplete" placebo individuals developed anthrax: A 62-year-old female who worked in the drawing department developed her lesion eight months after receiving the last inoculation of her initial series, and a 50-year-old female weaver developed anthrax three months after the last inoculation of an "incomplete" initial series.

The "complete" inoculated placebo cases (15) occurred at all stages of vaccination in decreasing numbers, reflecting the decrease in population for successive inoculations. No cases of anthrax occurred in individuals known to have recovered from a previous confirmed anthrax infection.

The statistical analysis was performed by Dr. R.F. Serfling, chief of the Statistics Section, Epidemiology Branch, Communicable Disease Center. It consisted of calculating the person-months exposure by inoculation status, for each mill, for both the high- and low-risk groups, including only those with "complete" inoculations. The cases of anthrax that occurred in the "complete" inoculated group only were grouped in a similar manner, and the attack rates calculated per 1,000 person-months. Using the attack rates in the placebo groups, the expected number of cases in the vaccinated groups were calculated. The total expected cases for the entire vaccinated group was 13.35. Considering that only one case was actually observed, the effectiveness of the vaccine is calculated to be 92.5 percent (13.35-1) ÷ (13.35) (Table 8).

"Determination of the confidence limit for the estimated effectiveness involved the following computations. Allowing $\pi_{1,}{}^{v}{}_{1}$ to represent, respectively, the risk of infection and the number of person-months exposure in the i^{th} (plant, risk-group, time-period) subgroup, and letting r represent the relative risk of infection if vaccinated, the expected number of vaccinated cases over all groups will equal $r\sum\pi_{1}{}^{v}{}_{1}$. Taking the sum of expected cases in the vaccinated as calculated from the data to be an estimate of $r\sum\pi_{1}{}^{v}{}_{1}$ with r = 1, and considering the observed cases in the vaccinated to be a Poisson variable, the probability of obtaining at least as many vaccinated cases as were observed may be calculated for various values of r." This procedure leads to an estimate of 65 percent as a lower 95 percent confidence limit for effectiveness of the vaccine.[17]

A similar analysis of 81 individuals in the study population who had previously had anthrax was made. By calculating the person-months exposure during the evaluation period and utilizing the attack rates observed for the placebo group (Table 8), 5.73 cases would have been expected in this group; however, no cases were observed. This data suggested that a previous anthrax infection provides some protection against a second anthrax infection.

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Table 3-The Population Remaining in the Evaluation Program Following Successive Inoculations

	Inoculations					
	Complete		Incomplete	None	Total Eligible	
	No.	Percent Decrease			No.	Percent Decrease
Primary Series	793		116	340	1,249	
		51				61
Booster: 1	390		56	47	493	
		16				16
2	327		65	23	415	
		19				13
3	265		69	24	358	
		28				20
4	190		73	24	287	

Table 4-Summary of Cases of Anthrax in the Evaluation Population

Date of Onset	Name	Age	Employer	Depart-ment	Length of Employment (Years)	Vaccine Status*	Site of Lesion
1. 3-14-55	A.C.	24	S	Spinning	4-1/2	V-I	hand
2. 3-30-55	J.K.	36	S	Carding	4	P-C	nose
3. 5-19-55	G.W.	30	S	Spinning	4	P-C	finger
4. 5-27-55	V.V.	48	S	Spinning	16	P-C	hand
5. 9-4-55	M.S.	33	S	Spinning	9-1/2	V-C	leg
6. 11-1-55	E.S.	27	S	Spinning	3	P-C	forearm
7. 11-18-55	M.G.	53	S	Spinning	10	P-C	cheek
8. 1-31-56	M.V.	33	S	Spinning	4	U	finger
9. 6-15-56	H.K.	38	S	Carding	6	P-C	wrist
10. 8-10-56	C.P.	55	M	Spinning	8-1/2	P-C	finger
11. 12-18-56	E.S.	43	S	Spinning	7	P-C	forearm
12. 2-15-57	N.J.	40	S	Carding	6	P-C	neck
13. 2-18-57	S.W.	62	P	Drawing	τ	P-I	arm
14. 5-20-57	A.I.	63	P	Carding	τ	P-C	cheek
15. 8-27-57	T.T.	60	A	Carding	6	U	inhalation
16. 9-1-57	A.J.	49	A	Carding	1-1/2	U	inhalation
17. 9-2-57	E.C.	65	A	Weaving	11	P-C	inhalation
18. 9-9-57	L.L.	46	A	Carding	2	P-C	inhalation
19. 10-3-57	V.K.	64	A	Weaving	7	P-C	finger
20. 10-10-57	H.T.	35	A	Carding	7	U	forehead
21. 10-15-57	R.P.	50	A	Weaving	2	P-I	wrist
22. 10-30 57	A.L.	33	A	Carding	(2-1/2 mo.)	U	inhalation
23. 11-5-57	C.S.	61	A	Carding	(2-1/2 mo.)	U	chest
24. 11-11-58	M.G.	55	M	Combing	5	P-C	cheek
25. 3-31-59	D.J.	39	M	Spinning	6	P-C	forearm
26. 3-27-59	J.W.	25	P	Picking	1-1/2	V-I	forearm
Median		45			5-1/2		

* P-placebo
V-vaccine
U-uninoculated
C-complete
I-incomplete

τ Not known

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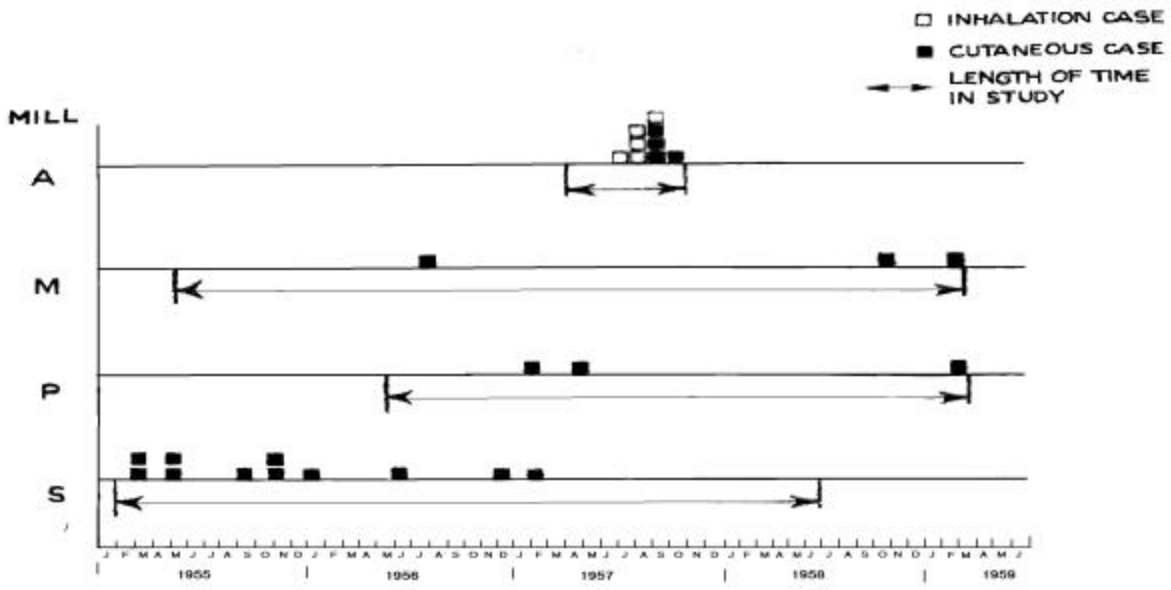

Figure 1-Occurrence of Cases of Anthrax in Four Mills During Vaccine Evaluation Studies, January, 1955-March, 1959

Reactions

Objective criteria for evaluation of local reactions are summarized in Table 9. These consisted of the determination of two indexes based upon observations following inoculations of employees at two of the mills. The first index is the erythema value based upon the measured area of local erythema observed, and the second is the reaction index based upon all objective findings, including erythema, induration, and edema.

The average erythema value and the average reaction index for all vaccinated persons, following successive inoculations is summarized in Figure 2 and shows that both values gradually rose through the fifth inoculation and then declined. This decline was not related to the withdrawal from the program of those who had the more severe local reactions.

The typical reaction was mild and did not cause any interruption of work. A small ring of erythema

Table 5-Cases of Anthrax Occurring at Each Mill During Evaluation Program

Mill	Complete Inoculations		Incomplete Inoculations	No Inoculations	Total
	Vaccine	Placebo	Vaccine	Placebo	
A	–	3	–	1	5	9
M	–	3	–	–	–	3
P	–	1	1	1	–	3
S	1	8	1	–	1	11
Total	1	15	2	2	6	26

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Table 6-Diagnostic Criteria for the 26 Cases of Anthrax that Occurred During the Evaluation Period

	Clinical Data	Smear	Culture	Pathology
Vaccinated Cases: (3)				
Cutaneous				
Complete 1	+	+	+	
Incomplete 2	+	+	+	
Placebo Control Cases: (17)				
Cutaneous (15)				
12	+	+	+	
3	+	ND	ND	
Inhalation (2)				
Fatal 1	+	ND	ND	ND
Recovery 1	+*	–	–	
Uninoculated Control Cases (6)				
Cutaneous (3)				
2	+	–	–	
1	+	+	+	
Inhalation (all fatal)				
2	+	+	+	+
1	+	–	–	+

\+ Positive
– Negative
ND Not done
* Serological data also positive

1-2 cm in diameter, with slight local tenderness, was noted commonly with 24 hours after vaccination. In general, all signs and symptoms disappeared within the next 24 to 48 hours. In many cases, this minimal degree of local reaction would not have been noticed by the inoculee had not his arm been examined at 24 to 48 hours after inoculation. In a few instances, the area of erythema increased between 24 and 48 hours to an area of from 3 to 5 cm in diameter which then disappeared. Pruritus and a small area of induration were the next most common local reaction. Most severe local reactions were characterized by edema, erythema greater than 5 x 5 cm, induration, and considerable local warmth, tenderness, and pruritus. A few inoculees developed small, firm, painless nodules at the site of the injections, which persisted

Table 7-Occurrence of Anthrax Cases During the Evaluation Program by Immunization Status

	Complete Inoculations		Incomplete Inoculations		No Inoculations*
	Vaccine	Placebo	Vaccine	Placebo	
1st Series	1	6	2	2	5
1st Booster	–	4	–	–	1
2nd Booster	–	1	–	–	–
3rd Booster	–	2	–	–	–
4th Booster	–	2	–	–	–
Total	1	15	2	2	6

* Listed according to what their inoculation status would have been had they entered the inoculation program.

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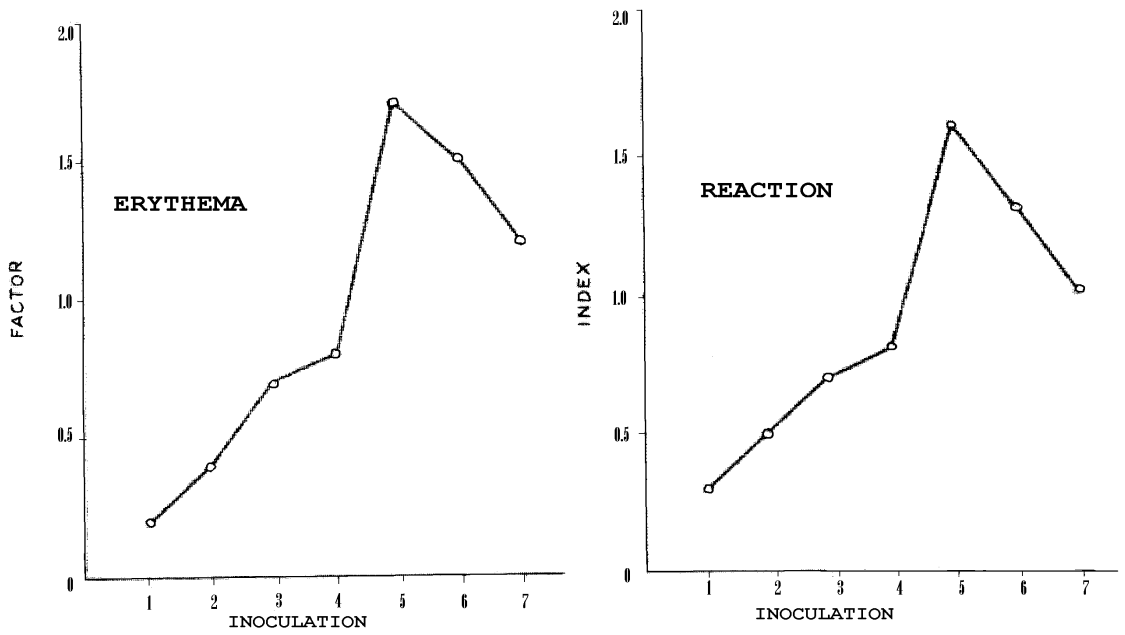

Figure 2-Average Erythema Factor and Reaction Index per Person Following Anthrax Vaccination

for several weeks. It was our impression that antihistamines were effective in giving relief from symptoms, especially pruritus.

The total incidence of the more moderate local reactions is summarized in Figure 3. The most prominent local reactions were those associated with the development of local edema (4+). Figure 3 shows that 21 individuals experienced 29 such reactions. None of these reactions were noted following the first inoculation but 4 percent of the vaccinees developed this degree of reaction after the second inoculation. Following a decline, the incidence rose to a peak of 7 percent after the sixth inoculation, and then fell to 2 percent after the seventh inoculation.

Half of these edema-producing reactions were maximum at 24 hours, and the remainder at 48 hours. Three individuals experienced edema extending from the deltoid to the mid-forearm and, in one case, to the wrist, with a definite collection of fluid in the bursa of the elbow. This extensive edema disappeared within three to five days. Once an individual had an edema-producing local reaction, he had an 88 percent chance of having a less severe reaction following subsequent inoculations. These individuals were scattered throughout all departments in the mill and had worked for varying periods of time before being immunized. A total of six working days were lost as a result of these edema-producing reactions.

Confirmed systemic reactions were not seen except for two individuals who experienced, along with edema-producing local reactions, some malaise of 24 hours' duration. Reactions to the alum material were seen in three individuals. These reactions, however, were mild as compared to the edema-producing reactions in vaccinated individuals.

The development of local reactions was not related to the particular batch of vaccine used or to the length of employment of the individual, the department in which he was employed, or the type of work in which he engaged. There were two individuals who inadvertently received the first injection of the vaccine, even though they had had clinical cutaneous anthrax 7 and 14 years previously. Both of these individuals experienced severe local reactions at 24 and 48 hours, with edema, induration, erythema, and pruritus. They received no further inoculations. The patient in mill A who had inhalation anthrax and recovered was vaccinated several months later without any untoward reaction. These are the only three individuals in this series who received the vaccine following a clinical anthrax infection.

Discussion

In 1946, Gladstone reviewed the literature on the

(7)

Table 8-Calculation of Effectiveness of the Anthrax Vaccine

Period Number*	Risk Group	Length of Exposure (Months)	Person-Months Exposure by Vaccine Status and Mill: Vaccinated – Mill A	Mill M	Mill P	Mill S	Sub-Total	Not Vaccinated (Placebo) – Mill A	Mill M	Mill P	Mill S	Sub-Total
1	High	6	372	281	99	483	1,185	384	270	120	513	1,287
2		6	–	189	63	423	675	–	237	87	429	753
3		6	–	150	42	381	573	–	216	54	366	636
4		12	–	240	42	588	870	–	390	42	588	1,020
5		12	–	204	–	306	510	–	306	–	306	612
	Subtotal		372	1,014	246	2,181	3,813	384	1,419	303	2,202	4,308
1	Low	6	450	177	120	144	891	534	243	114	96	987
2		6	–	156	84	117	357	–	219	75	72	366
3		6	–	138	54	87	279	–	186	39	63	288
4		12	–	234	48	132	414	–	312	24	90	246
5		12	–	180	–	120	300	–	264	–	66	330
	Subtotal		450	885	306	600	2,241	534	1,224	252	387	2,397
	Grand Total		822	1,899	552	2,781	6,054	918	2,643	555	2,589	6,705

			Anthrax Cases by Vaccine Status and Mill: Vaccinated – Mill A	Mill M	Mill P	Mill S	Sub-Total	Not Vaccinated (Placebo) – Mill A	Mill M	Mill P	Mill S	Sub-Total
1	High	6	–	–	–	1	1	1	–	–	3	4
2		6	–	–	–	–	–	–	1	1	2	4
3		6	–	–	–	–	–	–	–	–	1	1
4		12	–	–	–	–	–	–	–	–	2	2
5		12	–	–	–	–	–	–	2	–	–	2
	Subtotal		–	–	–	1	1	1	3	1	8	13
1	Low	6	–	–	–	–	–	2	–	–	–	2
2		6	–	–	–	–	–	–	–	–	–	–
3		6	–	–	–	–	–	–	–	–	–	–
4		12	–	–	–	–	–	–	–	–	–	–
5		12	–	–	–	–	–	–	–	–	–	–
	Subtotal											
	Grand Total		–	–	–	1	1	3	3	1	8	15

* Represents sequential periods of exposure between inoculations except that period 5 is the 12-month interval following the last inoculation.

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Table 8-(Continued)

Period Number	Risk Group	Length of Exposure (Months)	Attack Rate per 1,000 Person-Months by Vaccine Status and Mill: Vaccinated Mill A	Vaccinated Mill M	Vaccinated Mill P	Vaccinated Mill S	Not Vaccinated (Placebo) Mill A	Not Vaccinated (Placebo) Mill M	Not Vaccinated (Placebo) Mill P	Not Vaccinated (Placebo) Mill S
1	High	6	–	–	–	2.07	2.60	–	–	5.85
2		6	–	–	–	–	–	4.22	11.49	4.66
3		6	–	–	–	–	–	–	–	2.73
4		12	–	–	–	–	–	–	–	3.40
5		12	–	–	–	–	–	6.54	–	–
1	Low	6	–	–	–	–	3.75	–	–	–
2		6	–	–	–	–	–	–	–	–
3		6	–	–	–	–	–	–	–	–
4		12	–	–	–	–	–	–	–	–
5		12	–	–	–	–	–	–	–	–

Period Number	Risk Group	Length of Exposure (Months)	Expected Cases in Vaccinated by Comparison Group and Mill: Not Vaccinated Mill A	Not Vaccinated Mill M	Not Vaccinated Mill P	Not Vaccinated Mill S	Not Vaccinated Sub-Total
1	High	6	0.97	–	–	2.83	3.80
2		6	–	0.80	0.72	1.97	3.49
3		6	–	–	–	1.04	1.04
4		12	–	–	–	2.00	2.00
5		12	–	1.33	–	–	1.33
	Subtotal		0.97	2.13	0.72	7.84	11.66
1	Low	6	1.69	–	–	–	1.69
2		6	–	–	–	–	–
3		6	–	–	–	–	–
4		12	–	–	–	–	–
5		12	–	–	–	–	–
	Subtotal		1.69	–	–	–	1.69
	Grand Total		2.66	2.13	0.72	7.84	13.35

$$\text{Estimated effectiveness} = \frac{\text{Expected Cases Minus Observed Cases}}{\text{Expected Cases}}$$

High-risk group only: $\frac{11.66-1}{11.66} = 91.4\%$

Low-risk group only: $\frac{1.69-0}{1.69} = 100\%$

High-risk and low-risk groups combined: $\frac{13.35-1}{13.35} = 92.5\%$

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characterization of immunizing antigens extracted from Bacillus anthracis cultures or anthrax lesions.[12] He described the elaboration of the protective antigen from B. anthracis organisms grown in serum. In 1947, Watson, et al., reported on the separation of two factors from the edema fluid of anthrax lesions: one of these factors was used for successful immunization of animals.[13] Heckly and Goldwasser (1949) and Boor (1955) recovered the protective antigen after incubation of B. anthracis in special culture media.[14,15] All of these preparations of the protective antigen were used to successfully immunize laboratory animals (including sheep).

Wright's protective antigen was elaborated by the growth of a selected B. anthracis strain in a chemically defined medium. Darlow, Belton, and Henderson reported the development of a similar vaccine in 1956.[16]

The evaluation of the Wright vaccine demanded a susceptible population that was exposed to B. anthracis and that was under adequate medical supervision. These criteria were satisfied in the four goat hair processing mills selected for this study. The statistical analysis of the data indicates that the vaccine was effective in protecting against cutaneous anthrax infections. When inhalation anthrax is considered, the limited experience with this form of the disease makes the data less significant in showing effectiveness of the vaccine.

The occurrence of the single vaccinated case five months after the initial series may indicate that the immunity resulting from the initial three inoculations had fallen significantly by that time. This possibility is further substantiated by a report that the only cases of anthrax among the immunized people in the Biological Laboratories of the U. S. Army Chemical Corps at Fort Detrick occurred in two employee, five months after the initial series.[18] It appears that a booster response occurs after the first booster inoculation, raising immunity to protective levels which are stable for at least six months. The single case in the incompletely immunized individual, 13 months after the initial series, further supports the importance of the first booster inoculations in securing adequate protective levels. Serological investigations of antibody titers utilizing the agar-gel precipitin method are currently in progress.[19] Darlow and colleagues, using their own vaccine, immunized human subjects by giving two subcutaneous inoculations ten days apart followed by a booster inoculation one year later.[16] They then demonstrated a booster response by using the rabbit-skin toxin-neutralization method.

Systemic or local reactions following vaccination were a minor problem. The incidence of 0.2 percent systemic reactions, representing malaise in two individuals, compares favorably with that found by Wright[5] and Darlow.[16]

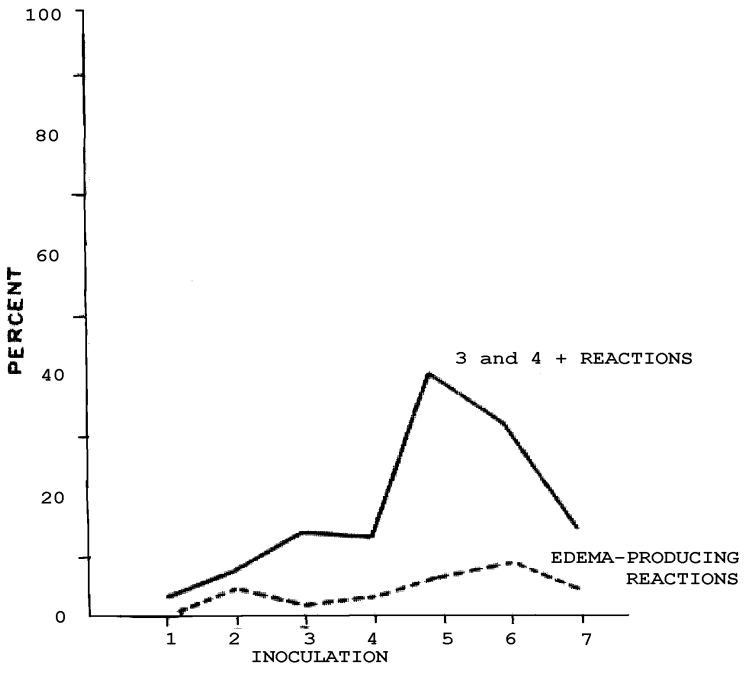

Figure 3-Percent of Immunized Persons Who Had Significant Reactions Following Inoculations **(10)**

The detection of local reactions was overemphasized because of the close surveillance maintained for 48 hours after vaccination. A gradual increase in the severity of local reactions was noted through the fifth inoculation followed by a decline. The edema reaction, however, peaked after the sixth inoculation and then decreased in incidence. The total incidence of all local reactions from the mildest to the most severe was 35 percent; however, the most severe or edema-producing local reactions occurred in only 2.8 percent of the vaccinations. The latter figure corresponds to that reported by Wright. Although Wright noted some increased reactivity associated with certain lots of vaccine, the same correlation could not be made in this study.

In Darlow's series, the reactions seen were mild with an over-all reaction rate of 20 percent. Darlow states that six different batches of vaccine were used without evidence of variation in potency or reactivity among them. Darlow also noted the development of lymphadenopathy and lymphangitis in several individuals, signs that were not encountered in our series. He also described the development of small, painless persistent nodules, of doubtful significance, at the site of inoculation. Similar nodules were noted in some of the inoculees in this series but were not recorded.

The increase in incidence and severity of the local reactions indicates an allergic component. Wright and Darlow came to the same conclusion. Treatment of the severe local reactions, especially of pruritus, with antihistamines was followed by fairly prompt relief. The decline in reactivity following the sixth and seventh inoculations may indicate some desensitization of the recipients. Darlow also noted in some people the development of mild local reactions at the site of a previous inoculation even though given in the opposite arm; we did not encounter this phenomenon.

There are various occupational groups in whom use of the vaccine is indicated. In this country, immunization should be recommended for people who work with imported wool, hair (especially goat hair), bristles, hides, bone meal, and any materials reclaimed from animal products industries. Anthrax is rare among stevedores and truckers who have brief and sporadic but intimate contact with these materials. The cases that do occur, however, are not uncommonly quite severe so that immunization of these groups is desirable but would be more difficult to accomplish. Veterinarians practicing in certain "anthrax districts" in this country should be vaccinated just as they recommend vaccination of cattle in these areas. Laboratory workers who have contact with B. anthracis should also be protected by vaccination.

The world incidence of human anthrax has recently been estimated to range from 20,000 to 100,000 cases annually.[20] The majority of these cases are agriculturally associated, and are reported from southern European, African, and Asian countries. It would be difficult to vaccinate the rural susceptibles in many of these countries because of the prevalent nomadic conditions and the inadequate medical facilities available. The necessity of giving multiple inoculations is also a factor that would contribute to the difficulties of implementing an anthrax vaccination program. Currently, an improved vaccine prepared by Dr. Wright is being evaluated through serological testing and by use in an exposed, susceptible population. If the new vaccine should prove more potent, a less strenuous immunization schedule may be applicable.

Table 9-Criteria for Evaluation of Local Reactions

Erythema Value			
1 (+) —1	to	99	____^{2} mm
2 (+) —101	to	399	____^{2} mm
3 (+) —400	to	1,599	____^{2} mm
4 (+) —1,600+			____^{2} mm

Reaction Index*		
0—No reaction		
1—1 · 2 (+)	E or I alone	Minimal
2—3 · 4 (+)	E or 1 · 2 + E & I	Mild
3—3 · 4 (+)	E & I or Ed	Moderate
4—3 · 4 (+)	E & I & Ed	Marked reaction

* E— Erythema
I— Induration
Ed— Edema

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Summary

An anthrax vaccine was clinically and epidemiologically evaluated in an exposed, susceptible, supervised population. Twenty-six cases occurred among the population during the evaluation period. Four cases occurred in individuals who had incomplete inoculations. Of the remaining 22 cases, 15 occurred in placebo-inoculated employees, six in uninoculated employees, and one in a vaccine-inoculated employee. The data indicates that the vaccine has an effectiveness of 92.5 percent with a lower 95 percent confidence limit of 65 percent.

Individual reactions to the vaccine was a relatively minor problem. Edema-producing local reactions occurred following 2.8 percent of all inoculations. There was evidence that the local reactions had an allergic basis, with reactivity increasing through the fifth inoculation, following which they decreased. Systemic reactions were rare with only 0.2 percent of inoculations followed by noticeable symptoms.

There are various exposed population groups in whom use of the vaccine is recommended. Specifically, these include persons who handle imported hair, wool, hides, or bone meal, in addition to veterinarians in "anthrax districts." Selected use in other countries is also recommended, though implementation would be difficult.

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This paper was presented before the Epidemiology Section of the American Public Health Association at the Eighty-Eighth Annual Meeting in San Francisco, Calif., November 2, 1960.

Report from the Communicable Disease Center, Public Health Service, U.S. Department of Health, Education, and Welfare, Atlanta, Ga.

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The following text is taken verbatim from the December 13, 1985, issue of the *Federal Register*, reporting the findings of an independent civilian advisory panel that considered the evidence for the safety and efficacy of vaccines available in the 1970s. The end of the document reports FDA's actions in response to the panel's recommendations. The entire report is 115 pages long (pages 51002 through 51117). All the sections that discuss anthrax vaccine are reprinted in their entirety below.

Department of Health and Human Services Food and Drug Administration

Federal Register

Vol. 50, No. 240

Friday, December 13, 1985, Part II

[Excerpt from page 51002]

Under section 601.25, FDA assigned responsibility for the initial review of each of the biological product categories to a separate independent advisory panel consisting of qualified experts to ensure objectivity of the review and public confidence in the use of these products. Each panel was charged with preparing an advisory report to the Commissioner which was to:

1. Evaluate the safety and effectiveness of the biological products
2. Review labeling of the biological products
3. Identify the biological products under review that are safe, effective, and not misbranded. The advisory report includes recommendations classifying products into one of three categories.

Category I designates those biological products determined by the Panel to be safe, effective, and not misbranded. The Panel's statement may include any condition relating to active components, labeling, tests required prior to release of batches, product standards, or other conditions necessary or appropriate for their safety and effectiveness.

Category II designates those biological products determined by determined by the Panel to be unsafe, ineffective, or misbranded.

Category III designates those biological products determined by the Panel not to fall within either Category I or II on the basis of the Panel's conclusion that the unavailable data are insufficient to classify such biological products, and for which further testing is therefore required. These biological products in Category III for which continued licensing, manufacturing, and marketing during the period of further testing are recommended are designated as Category IIIA. Those biological products in Category III for which suspension of the product licenses pending submission of additional data are recommended are designated as Category IIIB. The recommendation for either Category IIIA or IIIB is based on assessment of the present evidence of safety and effectiveness of the product and the potential benefits and risks likely to result from the continued use of the product for a limited period of time, while questions raised concerning the products are being resolved by further study.

[Excerpt from page 51003]

The Panel appointed by FDA to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of bacterial vaccines, toxoids, related antitoxins, and immune globulins included the following individuals:

Panel Chairman, Gene H. Stollerman, M.D., Professor and Chairman, Department of Medicine, University of Tennesee College Memphis, TN 38163 (now Professor of Medicine, Boston University Medical Center);

Geoffery Edsal, M.D. (deceased), Professor Emeritus of Microbiology (Harvard School of Public Health and London School of Hygiene and Tropical Medicine);

Theodore C. Eickhoff, M.D., Professor of Medicine, Head, Division of Infectious Diseases, University of Colorado Medical Center, Denver, CO 80262;

John C. Feeley, Ph.D., Chief, Bacterial Immuniology Branch (now Assistant Director for Laboratory Sciences, Bacterial Disease Division), Centers for Disease control, Atlanta, GA 30333;

Hjordis M. Foy, M.D., Ph.D. Associate Professor (since July 1, 1976, Professor) Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, WA 98195;

Edward A. Mortimer, Jr., M.D., Chairman of the Department of Pediatrics, School of Medicine, University of New Mexico, Albuquerque, NM 87131. (Since February 1, 1975, Professor and Chairman of the Department of Community Health and Professor of Pediatrics, School of Medicine, Case Western University, Cleveland, OH 44106.)

Jay P. Sanford, M.D., Professor, Department of Internal Medicine, University of Texas, Southwestern Medical School at Dallas, Dallas, TX 75235. (Since June 1, 1975, Dean, School of Medicine, Uniformed Services University, Bethesda, MD 20014.).

The Panel was convened on July 12, 1973, in an organizational meeting. Working meetings were held on: July 12, September 24-25, November 9-10, December 13-14, 1973; February 13-14, April 9-10, June 13-14, September 12-13, November 7-8 1974; January 13-14, February 24-25.

Two nonvoting liaison representatives served on the Panel. Ms. Laryl Lee Delker, nominated by the Consumer Federation of America, served as the representative. John Adams, Ph.D., of the Pharmaceutical Manufacturers Association, nominated by a number of producers with products under review by the Panel, served as the industry representative. Karl Bambach, Ph.D., substituted for Dr. Adams during his absences. Morris Schaefer, M.D., Ph.D., participated in the Panel meetings in his capacity as Director of the Office of Scientific Advisors and Consultants, FDA. Jack Gertzog, Deputy Director, Office of Scientific Advisors and Consultants, FDA, served as Executive Secretary of the Panel. Margaret Pittman, Ph.D., was selected by the panel as a consultant. Over 120 persons requested an opportunity or were otherwise invited to appear before the Panel and present their views on one or more of the vaccines and related matters. Every person who requested an opportunity was heard by the Panel. The names of these persons are on file with the Dockets Management Branch.

[Excerpt from page 51058]

Anthrax Vaccine, Adsorbed

Anthrax is an acute bacterial disease caused by *Bacillus anthracis*. The reservoir is any of several species (cattle, sheep, goats, horses, pigs) and the organism produces extremely resistant spores which

may persist in soil and contaminate animals or their products. The disease is primarily an occupational hazard for industrial workers who process hides, hair (especially goat), bone meal, and wool, as well as veterinarians and agricultural workers who may contact infected animals.

Most infections are cutaneous; if untreated they may spread to regional lymph nodes and may cause a fatal septicemia. Primary inhalation and gastrointestinal infections do occur, but with low frequency, and are highly fatal.

Description of Product

Anthrax vaccine is an aluminum hydroxide adsorbed, protective, proteinaceous, antigenic fraction prepared from a nonencapsulated mutant of the Vollum strain of *Bacillus anthracis*. It contains no more than 0.83 mg aluminum per 0.5 mL dose, 0.0025 percent benzethonium chloride as a preservative, and 0.0037 percent formaldehyde, which is believed to act as a stabilizer.

The product is tested according to the Public Health Service regulations for biological products and specific additional standards for anthrax vaccine. In addition to tests for general safety and sterility, the product is subjected to a potency assay of its protective antigen in guinea pigs, which are challenged with virulent *Bacillus anthracis*.

Indications and Contraindications

Immunization with this vaccine is indicated only for certain occupational groups with risk of uncontrollable or unavoidable exposure to the organism. It is recommended for individuals in industrial settings who come in contact with imported animal hides, furs, wool hair (especially goat hair), bristles, and bone meal, as well as in laboratory workers involved in ongoing studies on the organism.

Contraindications to its use include:

1. A history of clinical anthrax infection which may enhance the risk of severe reactions.
2. Severe systemic reactions with marked chills and fever following a prior injection - in this case further attempts at immunization should be abandoned.
3. The presence of acute respiratory disease or other febrile illnesses in order not to confuse the cause of further fever.
4. Therapy with corticosteroids or other immunosuppressive agents - in this case immunization should be deferred until such therapy has been completed. If on a long-term therapy, a more intensive immunization schedule should be considered.

Safety

In general, safety of this product is not a major concern, especially considering its very limited distribution and the benefit-to-risk aspects of occupational exposure in those individuals for whom it is indicated. Local reactions are typically mild, with erythema and slight local tenderness for 24 to 48 hours. Some individuals may have more severe local reactions, with edema, erythema greater than 5 x 5 cm, induration, local warmth, tenderness, and pruritus. Only a few systemic reactions with marked chills and fever have been recorded. All reactions reported have been self-limited.

Efficacy

The best evidence for the efficacy of anthrax vaccine comes from a placebo-controlled field trial conducted by Brachman (Ref. 1) covering four mills processing raw imported goathair into garment underlinings. The study involved approximately 1,200 mill employees of whom about 40 percent

received the vaccine and the remainder received the placebo or nothing. The average yearly incidence of clinical anthrax in this population was 1 percent. During the evaluation period, 26 cases of anthrax occurred. Twenty-one had received no vaccine, four had incomplete immunization and one had complete immunization. Based upon analysis of attack rates per 1000 person-months, the vaccine was calculated to give 93 percent (lower 95 percent confidence limit=65 percent) protection against cutaneous anthrax based upon comparison with the control group. Inhalation anthrax occurred too infrequently to assess the protective effect of the vaccine against this form of the disease.

The Center for Disease Control has continued to collect data on the occurrence of anthrax in at-risk industrial settings. These data were summarized for the period 1962 to 1974. Twenty-seven cases were identified. Three cases were not mill employees, but worked in or near mills; none of these cases were vaccinated. Twenty-four cases were mill employees; three were partially immunized (one with 1 dose, two with 2 doses); the remainder (89 percent) being unvaccinated. Therefore, no cases have occurred in fully vaccinated subjects while the risk of infection has continued. These observations lend further support to the effectiveness of the product.

Special Problems

Anthrax vaccine poses no serious special problems other than the fact that its efficacy against inhalation anthrax is not well documented. This question is not amenable to study due to the low incidence and sporadic occurrence of the disease. In fact, the industrial setting in which the studies above were conducted is vanishing, precluding any further clinical studies.

In any event, further studies on this vaccine would receive low priority for available funding.

Recommendations

The Panel believes that [page 51059] there is sufficient evidence to conclude that anthrax vaccine is safe and effective under the limited circumstances for which this vaccine is employed.

Reference

1. Brachman, P.S., H. Gold, S.A. Plotkin, R. Fekety, M. Werrin, and N.R. Ingraham, "Field Evaluation of a Human Anthrax Vaccine," American Journal of Public Health, 52:632-645, 1962.

SPECIFIC PRODUCT REVIEW

Anthrax Vaccine Adsorbed Manufactured by Bureau of Laboratories, Michigan Department of Public Health

1. *Description*. Anthrax vaccine adsorbed is an aluminum hydroxide adsorbed preparation of protective antigen of *Bacillus anthracis*. The product is prepared from a microaerophilic culture of an avirulent, nonproteolytic, nonencapsulated strain. The product contains 0.83 mg of aluminum per single human dose (0.5 mL) and is preserved with 0.0025 percent benzethonium chloride. Not more than 0.0037 percent formaldehyde is added as a stabilizer.
2. *Labeling*.
   A. *Recommended use / indications*. This product is intended solely for immunization of high risk of exposure industrial populations such as individuals who contact imported animal hides, furs, bone meal, wool, hair (especially goat hair), and bristles. It is also recommended for laboratory investigators handling the organism. Primary immunization consists of 6 subcutaneous 0.5 mL injections at 0, 2, and 4 weeks and 6, 12, and 18 months. Subsequent

boosters at yearly intervals are recommended.

B. *Contraindications*. Prior anthrax infection is an absolute contraindication. Immunization should be avoided in acute respiratory disease or other active infections. Corticosteroid therapy should be avoided in acute respiratory disease or other active infections. Corticosteroid therapy may suppress response. Further immunization should be discontinued in those rare individuals who suffer severe systemic reactions.

3. *Analysis* -
   A. Efficacy
      i. *Animal*. This product meets Federal requirements<.
      ii. *Human.*The vaccine manufactured by the Michigan Department of Public Health has not been employed in a controlled field trial. A similar vaccine prepared by Merck Sharp & Dohme for Fort Detrick was employed by Brachman (Ref. 1) in a placebo-controlled field trial in mills processing imported goat hair. This vaccine appeared 93 percent protective (lower 95 percent confidence level = 65 percent protective) against cutaneous anthrax. No meaningful assessment of its value against inhalational anthrax is possible due to its low incidence. The Michigan Department of Public Health vaccine is patterned after that of the Merck Sharp & Dohme with various minor production changes. It has been distributed by the Center for Disease Control since 1966, first as an investigational new drug and since 1972 as a licensed product. A review of the Center for Disease Control data pertinent to this product for the period 1962 to 1974 in at risk industrial settings indicates that no cases have occurred in fully immunized workers (see Generic Statement).
4. *Safety*.
   A. *Animal*. This product meets Federal requirements.
   B. *Human.*Accumulated data for the Center for Disease Control suggests that this product is fairly well tolerated with the majority of reactions consisting of local erythema and edema. Severe local reactions and systemic reactions are relatively rare.
5. *Benefit / risk ratio*. This vaccine is recommended for a limited high-risk of exposure population along with other industrial safety measures designed to minimize contact with potentially contaminated material. The benefit-to-risk assessment is satisfactory under the prevailing circumstances of use.
6. *Labeling.*The labeling seems generally adequate. There is a conflict, however, with additional standards for anthrax vaccine. Section 620.24(a) (21 CFR 620.24(a)) defines a total primary immunizing dose a 3 single doses of 0.5 mL. The labeling defines primary immunization as 6 doses (0, 2, and 4 weeks plus 6, 12, and 18 months).
7. *Critique.*This product appears to offer significant protection against cutaneous anthrax in fully immunized subjects. This is adequately established by the controlled field trial of the very similar Merck Sharp & Dohme experimental vaccine and by the Center for Disease Control surveillance data conducted on industrial high-risk settings.
8. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling revisions in accordance with this Report are recommended.

Reference

(1) Brachman, P.S., H. Gold, S.A. Plotkin, R. Fekety, M. Werrin, and N.R. Ingraham, "Field Evaluation of a Human Anthrax Vaccine," American Journal of Public Health, 52:632-645, 1962.

[Excerpt from page 51104]

A. Regulatory Categories

1. The Panel recommended that bacterial vaccines and toxoids be grouped into regulatory categories as follows:

    a. Category I

    1. Licensed biological products determined to be safe and effective and not misbranded [and may continue in interstate commerce]: Collagenase, Advance Biofactures Corp., License No. 383; Tetanus Immune Globulin (Human), Armour Pharmaceutical Co., License No. 149; BCG Vaccine, Botulism Antitoxin (Types A, B, and E), Botulism Antitoxin (Type E), Tetanus Toxoid, Connaught Laboratories, Ltd., License No. 73; Plague Vaccine, Tetanus Immune Globulin (Human), Cutter Laboratories, Inc., License No. 8; Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Eli Lilly & Co., License No. 56; BCG Vaccine, Glaxo Laboratories, Ltd., License No. 337; Diphtheria Antitoxin, Diphtheria Toxoid Adsorbed, Tetanus Toxoid Adsorbed, Istituto Sieroterapico Vaccinogeno Toscano Sclavo, License No.238; Cholera Vaccine, Tetanus Immune Globulin (Human), Lederle Laboratories, Division American Cyanamid Co., License No. 17; Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus and Pertussis Toxoids Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Immune Globulin (Human), Tetanus Toxoid Adsorbe, Typhoid Vaccine, Massachusetts Public Health Biologic Laboratories, License No. 64; Tetanus Immune Globulin (Human), Merck Sharp and Dohme, Division of Merck & Co., Inc., License No. 2; Anthrax Vaccine Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Pertussis Vaccine Adsorbed, Typhoid Vaccine, Michigan Department of Public Health, License No. 99; Tetanus Immune Globulin (Human), Parke-Davis, Division of Warner-Lambert Co., License No. 1: Tetanus Immune Globulin (Human), Travenol Laboratories, Inc., Hyland Therapeutics Division, License No. 140; BCG Vaccine, University of Illinois, License No. 188; and Cholera Vaccine, Tetanus Immune Globulin (Human), Typhoid Vaccine (acerone inactivated), Typhoid Vaccine (heat-phenol inactivated), Wyeth Laboratories, Inc.., License No.3.
    2. Biological products also recommended for category I but for which product license has been revoked at the manufacturers request subsequent to the Panel's review. Diphtheria Toxoid, Connaught Laboratories, Ltd., License No. 73; Tetanus Toxoid, Cutter Laboratories, Inc., License No. 8; Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (with aluminum phosphate), Tetanus Immune Globulin (Human), Dow Chemical Co., License No. 110; Cholera Vaccine, Pertussis Vaccine, Typhoid Vaccine, Eli Lilly & Co., License No. 56; Streptokinase-Streptodornase (Varidase, Topical), Lederle Laboratories, Division American Cyanamid Co., License No. 17; Cholera Vaccine, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Diphtheria Antitoxin, Merril-National Laboratories, Division of Richardson-Merrell, Inc., License No. 101; Tetanus Immune Globulin (Human), Michigan Department of Public Health, License No., 99; Tetanus Immune Globulin (Human), Oesterrichisches Institut fuer Haemoderivate GmbH, License No. 258; Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Parke-Davis, Division of Warner-Lambert Co., License No. 1; and Pertussis Vaccine, Typhoid Vaccine, Texas Department of Health Resources, License No. 121.

A list of all voluntarily revoked products reviewed by the Panel, with the date of the license revocation, is on file with FDA's Dockets Management Branch (address above). No further regulatory or administrative action is necessary for these products.

Merrell-National Laboratoriers, Division of Richardson-Merrell, Inc., transferred its manufacturing processes and facilities for manufacturing Diphtheria and Tetanus Toxoids and Pertussis Vaccine

Adsorbed, and Diphtheria Antitoxin to Connaught Laboratories, Inc. Connaught Laboratories was issued License No. 711 on January 3, 1978, FDA advises that all comments and recommendations directed to the Merrell-National products apply equally to the products now manufactured by Connaught Laboratories, Inc.

FDA agrees with the Panel's findings and recommendations for these products, and hereby proposes to adopt its conclusions, including proposed labeling revisions concerning the intended use of the products. Comments or additional data on this classification are invited.

a. *Category II. Biological products determined to be unsafe or ineffective or to be misbranded and which should not continue in interstate commerce:*

Streptokinase-Streptodornase Varidase-buccal tablet, intramuscular, and oral tablet dosage forms), Lederle Laboratories, Division American Cyanamid Co., License No. 17.

Lederle Laboratories was licensed for the manufacture and sale of five forms of Streptokinase-Streptodornase: topical, topical jelly, buccal tablet, intramuscular, and oral tablet. The topical form was recommended for Category I, the topical jelly for Category IIIA, and the buccal tablet, intramuscular, and oral tablet for Category IIIB. At the request of the manufacturer, the product license for the[page 51105] manufacture and sale of all forms of Streptokinase-Streptodornase has been revoked. Accordingly, no further FDA action is necessary.

CLINICAL GUIDELINES

FOR MANAGING ADVERSE EVENTS AFTER VACCINATION

February 2001 edition

To view slides showing the Algorithm for Adverse Events After Vaccination

To download PowerPoint slides showing the Algorithm for Adverse Events After Vaccination

To download Word document version of the Clinical Practice Guidelines

1. Purpose: To help medical personnel individually manage and document adverse events after vaccination. Based on clinical experience with adverse-drug-reaction management with vaccines in general, treatment and reporting recommendations are offered here. Adapt these guidelines to individual clinical cases, according to the judgment and scope-of-practice of the health-care provider.

2. Adverse Events After Vaccination: Most people tolerate vaccination without significant side effects. But adverse events may occur vaccination, sometimes requiring treatment to relieve symptoms. Although many side effects respond to self-medication, people experiencing a reaction should advise a health-care provider before the next dose of the same vaccine. Several studies indicate that women are more likely than men to experience temporary injection-site reactions and systemic symptoms that typically resolve on their own.

a. *Injection-site reactions*, such as redness and swelling. These reactions are not unusual. Antibiotics are not typically warranted to treat injection-site reactions. Anthrax vaccine, administered subcutaneously, is associated with a high frequency of nodules (also called knots or lumps). Although mild to moderate local reactions can be self-medicated, worsening local reactions should be reported to a health-care provider and documented in the medical record, before the next dose.

b. *Systemic events* such as immediate hypersensitivity, fever, or muscle aches. Systemic events are less common than injection-site reactions, and may or may not be caused by the vaccine. Systemic events may appear later after vaccination than injection-site reactions.

c. Some events are caused by vaccination. Others simply coincide in time and may be unrelated to the vaccine. The frequency of the events listed in the attached tables is not uniform. Some are common, while others are rare, if they occur at all. Events may occur that are not listed. Regardless, it is paramount for health-care providers to provide the best care possible for the person in need, regardless of causality. Identify and document clinical problems that follow vaccination before the next dose. Vaccination should be considered in the differential diagnosis, as biologically appropriate. When planning future actions, assess the risk-benefit ratio for continued vaccination versus medical exemption.

d. While most reactions after vaccination require no treatment, some people may need further evaluation, therapy, and/or exemption from further doses of the vaccine. Document all adverse events requiring pre-vaccination treatment, post-vaccination treatment, relief from work, hospitalization, or other medical care on the Service's clinical-encounter form. Report as discussed below.

3. Treatment Guidelines—See algorithms depicted in Figures 1, 2, and 3, plus companion tables with text-based details. Based on published literature and clinical experience, these guidelines are divided into two major groups: injection-site reactions and systemic events. Consider relevant footnotes. Patients may present with symptoms corresponding to more than one category.

4. VAERS Reporting:

a. Adverse events after vaccination are reported to the Vaccine Adverse Event Reporting System (VAERS) using Form VAERS-1. DoD and the Coast Guard require submission of Form VAERS-1, *at a minimum*, for adverse events after vaccination that involve hospitalization, a life-threatening event (such as anaphylaxis), loss of duty of 24 hours or longer, or an event related to suspected contamination of a vaccine vial. These are minimum requirements. Clinicians are encouraged to report all other clinically relevant adverse events after administration of any vaccine or medication to VAERS or MedWatch.

b. Clinicians who file Form VAERS-1 are not making a determination that the two events are causally linked. Ideally, initial VAERS forms should be submitted by primary-care providers, with follow-up VAERS forms filed by subspecialists as additional information comes to light. Anyone identifying a qualifying case, and uncertain whether a Form VAERS-1 was submitted previously, should submit one.

c. If the patient considers his or her adverse event significant and due to the vaccine, the clinician should file a Form VAERS-1 report. Vaccine recipients may complete VAERS forms themselves and submit them directly to the FDA. Reporting by a health-care provider is preferred, to enhance the quality and completeness of the clinical data reported.

d. Form VAERS-1 may be downloaded from the Service surveillance centers, or from http://www.anthrax.osd.mil/Site_Files/vaers/vaers.htm. Additionally, one may obtain VAERS forms by contacting VAERS at 1-800-822-7967 http://www.vaers.org.

e. Attach pertinent information from the vaccine recipient's medical record to the Form VAERS-1 report. Forward the original Form VAERS-1 and attachments to VAERS, P.O. Box 1100, Rockville, MD 20849-1100. At the same time, send a copy of the Form VAERS-1 and attachments through the local Preventive Medicine or Preventive Health Officer, as applicable, to the Service surveillance center (Annex A). Reports also should be submitted to the local pharmacy-and-therapeutics (P&T) committee, because institutions have an accreditation requirement to encourage adverse-drug-reaction reporting. Do not delay reporting while awaiting a P&T committee meeting. Pharmacists can assist in filing Form VAERS-1.

f. The Department of Defense forwards all Form VAERS-1 reports to the FDA and the CDC without screening or restriction. All Form VAERS-1 reports on anthrax vaccine are reviewed for causality by an independent civilian committee, known as the Anthrax Vaccine Expert Committee (AVEC), under the auspices of the U.S. Department of Health and Human Services.

g. Granting administrative exemptions is a non-medical function, usually controlled by an individual's unit. Granting medical exemptions is a medical function performed by a credentialed health-care provider. Medical exemptions should be applied only when medically warranted. If the case is complex or not readily definable, a clinical summary should be sent to the regional clinical subject matter expert or group for

review. Medical records of Service Members who disagree with a given provider or consultant's recommendations regarding the exemption should be referred for a second opinion to a provider or consultant group with experience in vaccine adverse reaction management. Review exemptions periodically to confirm continued applicability.

5. Referrals:

a. If additional clinical consultation is needed to assess a patient's condition, the primary-care provider should first perform the initial clinical work-up appropriate to the presenting symptoms. Temporary medical exemptions may be granted by primary-care providers pending referral to a subspecialist appropriate to the individual's clinical condition (e.g., dermatology, neurology, otolaryngology, rheumatology, allergy/immunology).

b. Subspecialists may grant indefinite medical exemptions. Multidisciplinary consultations may be appropriate in some circumstances.

6. Exemption Codes: Use the following exemption codes for electronic tracking of vaccinations (exemption code table).

a. Good medical practices for the management of an adverse drug reaction apply to the evaluation of any adverse event after vaccination. Good medical practices also apply to the medical-decision process for granting exemptions or continuing to vaccinate in the face of an adverse event potentially linked to vaccine administration.

b. Medical Exemption Codes:

Code	Meaning	Explanation or Example	Duration
MI	Medical, Immune	Evidence of immunity (e.g., serologic antibody test); documented previous infection (e.g., chickenpox)	Indefinite
MR	Medical, Reactive	Severe adverse reaction after immunization (e.g., anaphylaxis). Code can be reversed if an alternate form of prophylaxis is available. Probably warrants VAERS report	Indefinite
MT	Medical, Temporary	Pregnancy, hospitalization, temporary immune suppression, convalescent leave, any temporary contraindication to immunization	Specified period
MP	Medical, Permanent	HIV infection, pre-existing allergy, permanent immune suppression. Can be reversed if the condition changes.	Indefinite

MD	Medical, Declined	Declination of optional vaccines (not applicable to anthrax vaccine), religious waivers	Indefinite
MS	Medical, Supply	Exempt due to lack of vaccine supply	Indefinite

c. Administrative Exemption Codes:

Code	Meaning	Explanation or Example	Duration
AD	Administrative, Deceased	Service member is deceased	Indefinite
AL	Administrative, Emergency Leave	Service member is on emergency leave	Max 1 month
AM	Administrative, Missing	Missing in action, prisoner of war	Indefinite
AP	Administrative, PCS	Permanent change of station	Max 3 months
AR	Administrative, Refusal	UCMJ Actions	Until resolution
AS	Administrative, Separation	Discharge, separation, retirement	
AT	Administrative, Temporary	AWOL, legal action pending	Max 3 months

7. Acknowledgements & Revisions:

a. This revision, the second edition of these guidelines, is issued by the Anthrax Vaccine Immunization Program (AVIP) Agency, within the Office of The Army Surgeon General, Falls Church, Virginia. The guidelines were developed based on published literature and clinical consensus, beginning at the Biological Warfare Defense Immunizations Conference, 25-27 May 1999. The major authors of this document are LTC Phillip Pittman, COL Renata Engler, LTC Bryan Martin, LTC John Grabenstein, along with clinicians from the medical departments of the U.S. Army, Navy, Marine Corps, Air Force, and Coast Guard.

b. This document will be revised periodically, based on clinical experience and epidemiological data. This document provides general guidelines to adapt to individual clinical cases, according to the judgment and scope-of-practice of each health-care provider.

c. Forward suggestions for improvements to this document to LTC John D. Grabenstein, Anthrax Vaccine Immunization Program Agency, fax 703-681-4692, e-mail john.grabenstein@amedd.army.mil. Medical command channels will disseminate revisions periodically, which will be posted on the AVIP website, www.anthrax.osd.mil.

8. Selected Bibliography on Anthrax & Other Vaccines:

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Annex A. Service Surveillance Centers

Army Medical Surveillance Activity

Bldg T-20, Rm 213 (Attn: MCHB-EDS)

6825 16th Street, N.W.

Washington, DC 20307-5000

Phone: 202-782-0471 (DSN 662)

Fax: 202-782-0612

http://amsa.army.mil/AMSA/amsa_home.htm

Navy Environmental Health Center

2510 Walmer Ave

Norfolk, VA 23513-2617

Phone: 757-462-5500 (DSN 253), after hours 757-621-1967

Fax: 757- 444-9691

http://www-nehc.med.navy.mil/

Air Force Force Health Protection and Surveillance Branch

Institute for Environment, Safety and Occupational Health (ESOH) Risk Analysis

2513 Kennedy Circle

Brooks AFB, TX 78235-5123

Phone: 210-536-5454 (DSN 240)

Fax: 210-536-6841

http://iera.satx.disa.mil/iera/index.html

Coast Guard Headquarters Directorate of Health and Safety

Commandant (G-WKH)

2100 Second Street SW

Washington, DC 20593

Phone: 202-267-1098

Fax: 202-267-4338

Table 1A: Localized Reactions (LR) After Vaccination: February 2001

(Note: The probability of events listed in these tables is not uniform. Some are quite common. Others occur rarely, if at all)

Adverse Event Definitions & Evaluation	Treatment & Management	Future Doses	Comments
Local (Injection-Site) Reactions (LR) typically involve changes at the injection site with contiguous spread. Signs of inflammation (e.g., itching, redness, heat, swelling) may be present, with occasional bruising. Record specific observations, along with a photo, if needed to preserve the image. Biopsy may be warranted in some cases (e.g., scaling, crusting).	Remote electronic consultation (e.g., telephonic, e-mail, telemedicine) can be used to request assistance. Reassure vaccine recipient that local reactions typically resolve and do NOT result in long-term disease. Although some of these reactions may mimic cellulitis, antibiotic therapy is not warranted for post-vaccination inflammation.	Unless LR was very large or complicated, Service Member usually can proceed with subsequent doses. Credentialled health-care providers may make clinical decisions to alleviate future discomfort for individual Service Members who develop large or persistent injection-site reactions.[8]	Most local reactions require no treatment. Topical or oral treatment to control symptoms depends on reaction severity. Complications may warrant consultation with a specialist. May benefit from treatment and/or pretreatment programs.[1,2] VAERS reporting discussed in text.
Subcutaneous Nodules (LR1): • Usually painless with no redness or heat at the site • Usually present within 1-2 days of the injection, may persist for weeks, gradually dissipating	Record size (in mm) of nodule in longest diameter and duration of palpable presence. Usually requires no treatment. Reassure vaccine recipient that these are common and	Proceed with subsequent doses at different site (e.g., contralateral side, antero-lateral thigh). Anthrax: For unusually large, bothersome or persistent nodules, consider route.	Do not inject into or through nodule. If painful, consider topical corticosteroid cream or ointment applied 2 to 3 times per day for as long as symptoms persist. Dermatology consult if persistent (> 4 to 6 months).

	will resolve spontaneously.		
Local Redness or Swelling (LR2): • < 30 mm in longest diameter • "Mild"	Usually requires no treatment. Resolves within < 72 hours in most cases. Reassure.	Proceed with subsequent doses.	May benefit from topical steroid therapy or antihistamines, if itching is present.[1]
Local Redness or Swelling 30 to 50 mm (LR3): • 30 to 50 mm in longest diameter • "Mild"	May warrant treatment. Rash management noted in LR8.	Proceed. Consider topical corticosteroids and/or antihistamines just after injection.[1,2]	May benefit from topical corticosteroids and/or antihistamines just after injection.[1,2]

Table 1B: Localized Reactions (LR) After Vaccination: February 2001

(Note: The probability of events listed in these tables is not uniform. Some are quite common. Others occur rarely, if at all)

Adverse Event Definitions & Evaluation	Treatment & Management	Future Doses	Comments
Local Redness or Swelling 50 to 120 mm, but NOT extending below elbow (LR4): • Patient may exhibit concern about progression and risk from next injection • "Moderate"	Treat with topical therapy, analgesics, antihistamines to prevent complications or progression. May benefit from short course of oral prednisone, if symptoms persist or worsen. Consider consultation with next level of care.[7] Rash management noted in LR8.	Consider consultation with next level of care,[7] before proceeding with next dose. Consider pre-treatment options. Anthrax: Consider route.[8]	Consider treatment before or at time of next vaccination.[1,2,3] Avoid simultaneous vaccination.
Local Redness or Swelling > 120 mm without complications	Rash management noted in LR8.	Consider consult with next level of care.[7]	If repeats or worsens, consider temporary

(LR5): • "Large – Simple"		Temporary exemption may be warranted. Consider pretreatment options.[1,2] Anthrax: Consider route and/or interval.[8]	exemption, pending consultation. Consider pretreatment.[1,2,3] Encourage submission of Form VAERS-1. Avoid simultaneous vaccination.
Local Redness or Swelling > 120 mm or extending below elbow (LR6): • "Large – Complicated" • Peri-articular soft-tissue swelling, soreness, stiffness may be present • May occur with systemic symptoms Note: May see swelling at or below wrist. Consider possibility of gravitational settling of edema.	Provide treatment by physician. Consider potent topical and/or oral corticosteroids to prevent complications or progression.[1] Seek consultation, as needed. If reaction occurs after ≥ 2 doses, may be immune (i.e., a "hyper-responder," although booster doses may still be needed). Rash management noted in LR8.	Give temporary exemption, pending consultation. Anthrax: Consider route and/or interval.[8] Avoid simultaneous vaccination.	If repetitive or worsening, may merit a temporary exemption from subsequent vaccination, pending consultation. Benefit-risk ratio may merit pretreatment trial.[1,2,3] Encourage submission of Form VAERS-1.

Table 1C: Localized Reactions (LR) After Vaccination: February 2001

(Note: The probability of events listed in these tables is not uniform. Some are quite common. Others occur rarely, if at all)

Adverse Event Definitions & Evaluation	Treatment & Management	Future Doses	Comments
Numbness, Burning, or Tingling At or Distal to Injection Site (LR7_): • 7a. Prolonged lack of sensation (numbness, hypesthesia, anesthesia) near or over injection site • 7b. Burning or painful sensation	Record detailed description, size of area affected. No specific treatment. Usually resolves in < 1 to 2 weeks. Reassure. May benefit from topical corticosteroids.	Reinforce avoiding injection over triceps. Proceed with subsequent doses at different site, to avoid ulnar nerve. Anthrax:	Value of topical anti-inflammatory therapy not established. Encourage submission of Form VAERS-1. Avoid simultaneous vaccination.

(dysesthesia) near or over injection site • 7c. Tingling, altered, cold, or other sensation without stimulus (paresthesia) near or over injection site • 7d. Any unusual sensation distal to injection site If physical exam and/or nerve studies establish diagnosis of focal neurologic disease (e.g., ulnar nerve neuropathy, see SE14.		Consider route. [8]	
Focal Rash At or Near Injection Site (LR8): • May involve vesicles or papules	May treat with topical steroid cream and new-generation antihistamine.[1] May be associated with LR3, LR4, LR5, LR6, or other categories.	After rash resolves, continue doses. Give temporary exemption, pending consultation. Obtain photo and consider biopsy.	If etiology is not clear or rash is slow to resolve, consult with dermatologist. Avoid simultaneous vaccination.
Other Events At or Near Injection Site (LR-xx)	Treat according to clinical condition. Seek consultation, as appropriate.	Base decision on complete medical evaluation and consideration of benefit-risk ratio.	

Table 2A: Systemic Events (SE) After Vaccination: February 2001

(Note: The probability of events listed in these tables is not uniform. Some are quite common. Others occur rarely, if at all)

Adverse Event	Treatment & Management	Future Doses	Comments

Definitions & Evaluation			
Systemic Events (SE): Symptoms and signs of illness after vaccination. Any reaction that does not involve the injection site. Temporal relationship does NOT prove a cause-effect relationship, particularly if multiple vaccines were given and/or other specific diagnoses of illness have occurred.	Health-care provider should provide appropriate diagnostic evaluation. In some cases, give pretreatment to avert symptoms with next vaccination, to avoid morbidity, but allowing for continued vaccination.	If mild and self-limited, may proceed with next dose. Avoid multiple vaccines in one session for this patient, if possible. Credentialled health-care providers may make clinical decisions to alleviate future discomfort for individual Service Members who develop substantial or persistent reactions.[8]	VAERS reporting discussed in text.
Myalgias and/or Arthralgias (SE1a) **Arthritis** (SE1b) • Primary • Secondary (exacerbation of existing condition)	Acetaminophen or NSAIDs may be administered. Pretreatment may be necessary.	Subsequent doses can usually be given. Anthrax: For symptoms persisting > 96 h, seek specialty consultation; consider route.[8]	If persistent, start work-up to rule out other etiologies. Consult, if needed. VAERS report encouraged when symptoms persist > 48 hours.

Table 2B: Systemic Events (SE) After Vaccination: February 2001

(Note: The probability of events listed in these tables is not uniform. Some are quite common. Others occur rarely, if at all)

Adverse Event Definitions & Evaluation	Treatment & Management	Future Doses	Comments
Mild "Viral"-Like Symptoms (SE2a): At least three of the following, lasting < 96 hours:	Options include antihistamines and analgesics to prevent complications or progression.	Proceed with next dose, in most cases..[2,4] For fever > 102.5° F	Consider treatment before or at time of next vaccination,

• Fever (100° to 102.5° F (adolescent/adult) or 104° F (children)) [oral equivalent] • Anorexia • Nausea • Myalgia • Arthralgia • Malaise • Fatigue • Light-headedness (colloquial "dizziness," but not true vertigo. See also SE19b) • Headache (including photophobia or aching eyes) But without (or only one) symptom referable to either the respiratory (SE17) or gastrointestinal tract (SE18). May be associated with moderate or large local reactions. Usually resolves spontaneously with no treatment or with analgesics and rest. ========== **"Flu"-like or "Viral"-like**, not otherwise specified (SE2b)		(adolescent / adult) or 104° F (children) [oral equivalent], consider benefit-risk ratio for continuing doses if patient or provider is concerned about risk with future doses.	particularly if large local reaction as well.[1,2,4]
Severe and/or Prolonged Nonspecific Symptoms (sometimes called severe or prolonged "viral"-like illness) (SE3) • Includes temperature > 102.5° F (adolescent/adult) or 104° F (children) [oral equivalent] • Includes temperature > 100.5° F and/or systemic symptoms lasting > 96 hours	May benefit from short course of oral prednisone, if not stabilized. May warrant consultation.[5] Evaluate for coincident disease, treat appropriately. High temperatures warrant consultation.	Consult with next level of care. Consider temporary exemption, pending consultation. If unexplained by other causes, may warrant contraindication.	VAERS report encouraged, if no other cause identified. Avoid simultaneous vaccination.

Table 2C: Systemic Events (SE) After Vaccination: February 2001

(Note: The probability of events listed in these tables is not uniform. Some are quite common. Others occur rarely, if at all)

Adverse Event Definitions & Evaluation	Treatment & Management	Future Doses	Comments
Headaches (SE4): • Usually bitemporal without migraine features, "tension" type or dominant feature of "flu"-like syndrome • Usually resolve in several days	Acetaminophen 650 to 1000 mg orally every 4 to 6 hours or ibuprofen 600 to 800 mg orally every 8 hours (or other non-steroidal anti-inflammatory drugs, NSAIDs); can start this treatment 1 hour before next dose.[5]	Proceed with next dose, unless worsening pattern. Anthrax: For symptoms persisting > 96 h, consider route.[8]	Pretreatment generally effective. If pattern worsens, give temporary exemption, pending consultation with neurology. If referred, neurologist should submit follow-up VAERS.
Nausea and/or Vomiting (SE5): • No other signs or symptoms of anaphylaxis • Usually resolves without treatment • Can be vasovagal	Usually resolves without treatment, but standard anti-emetics and even (sedating) antihistamines may provide relief.	Proceed with next dose, with precautions for a vasovagal reaction. Anthrax: For symptoms persisting > 96 h, consider route.[8]	Not reproducible from one injection to the next on initial observations, unless part of vasovagal reaction. Typically, no predictive value for more serious reaction.
Syncope or Near-Syncope (Fainting, Light-headedness) Shortly After Vaccination (SE6): • May be accompanied by prolonged malaise • Fainting or near-fainting with signs of vasovagal reaction (diaphoresis, nausea, vomiting, usually bradycardia, widening pulse pressure and/or frank hypotension) • May result in a fall with	Position in sitting or supine position with legs elevated, head down. • Rarely requires atropine to reverse profound bradycardia • Encourage hydration as soon as stabilized and before future injections • Advise that future	Proceed, but with precautions as outlined under treatment. Anthrax: If syncope or near-syncope was related to pain or burning at injection site after injection, consider route.[8]	Occurs in about 1% of healthy, fit adults. Procedures when giving injections of any kind should anticipate this reaction, to avoid traumatic injury.

secondary injury • Asking people before vaccination about this predisposition may avoid injury	injections be given in supine position		

Table 2D: Systemic Events (SE) After Vaccination: February 2001

(Note: The probability of events listed in these tables is not uniform. Some are quite common. Others occur rarely, if at all)

Adverse Event Definitions & Evaluation	Treatment & Management	Future Doses	Comments
Tinnitus (SE7): • New onset ringing in the ears developing within less than 1 to 2 weeks after an injection • Other cause unlikely (e.g., neurogenic hearing loss from noise injury)	Therapy for nasal congestion may help in some cases. If symptoms persist > 1 to 2 weeks, consult with ear-nose-throat (ENT) specialist.	Consider temporary exemption, pending routine consultation with specialist.	No well-defined association with any vaccine recognized at this time. If event recurs with later dose, give temporary exemption, pending consultation.
Focal or Limited Skin Reaction, <u>not</u> near most recent injection site (SE8): Take photo while acute (or have local dermatologist and/or allergist evaluate)	Treat as indicated. Consult with dermatology, if symptoms persist.	Subsequent doses can usually be given.	May be a rash, erythema, bruising, swelling, etc., at a distance from most recent injection site, such as at previous injection site. May be unrelated to vaccination.
Generalized Skin Reaction (pruritic or non-pruritic), not suggestive of anaphylaxis (SE9): • Maculopapular or target lesions • Must involve skin sites remote from injection site, not just on	Cetirizine 10 mg daily or other second-generation antihistamines. Consider high-dose prednisone (50 to 60 mg daily for 5 to 7 days with rapid taper) if severe.[1,2]	Consider temporary exemption, pending routine consultation with specialist.	In rare circumstances, additional vaccine doses may result in a more serious generalized skin reaction. Additional doses should be given with caution after expert evaluation and consideration of benefit/risk

the injection arm • Take photo while acute (or have local dermatologist and/or allergist evaluate)	If rash is early erythema multiforme, Stevens-Johnson, or toxic epidermal necrolysis, see section SE10. Longer therapy may be needed. Note: accurate diagnosis may call for skin biopsy.		ratio. Encourage submission of Form VAERS-1.

Table 2E: Systemic Events (SE) After Vaccination: February 2001

(Note: The probability of events listed in these tables is not uniform. Some are quite common. Others occur rarely, if at all)

Adverse Event Definitions & Evaluation	Treatment & Management	Future Doses	Comments
Diffuse Blistering Dermatitis and/or Mucositis (SE10): • Erythema multiforme • Stevens-Johnson syndrome • Toxic epidermal necrolysis • Others (fixed drug eruptions, etc.)	Treat acutely, record visually with photo; immediate dermatology and allergy consultation for full treatment program and follow-up. Accurate diagnosis may call for skin biopsy.	Give temporary exemption, pending consultation.	Submit Form VAERS-1. There are no safety data for challenge dosing and/or desensitization of these types of potentially life-threatening skin reactions.
Anaphylaxis, Generalized Allergic Reaction: onset typically within the first few hours after vaccination (SE11): • **Anaphylaxis:** Watery eyes, nasal congestion, general itching, hives, coughing, throat tightness, wheezing, short of	Potentially life-threatening allergic reaction, treat immediately with epinephrine. Oral corticosteroid therapy prevents delayed-phase anaphylaxis, which can also become life threatening. Admit to hospital if laryngeal edema or other life-threatening condition is	Give temporary exemption, pending consultation with allergist.	Submit Form VAERS-1. Seek allergy consult.[4] Review benefit-risk ratio carefully with patient. Consult patient regarding treatment options and further vaccination under controlled desensitization conditions. Avoid simultaneous vaccination.

breath, light-headed, rapid heart rate, hypotension, anxiety reaction ("sense of doom"), nausea, vomiting, diarrhea, loss of bladder or bowel control with loss of consciousness • **Generalized rash, itching and shortness of breath:** Treat as anaphylaxis, unless immediate evidence of other cause.	present. Physician or physician assistant evaluation required.		
Angioedema/Swelling – Diffuse or distant from injection site, with or without pruritus within 2 weeks of vaccination (SE12): • If onset immediate (within ~ 2 hours after injection) may be early cutaneous presentation of serious anaphylactic reaction (see SE11) • If delayed onset (typically within 2 to 3 weeks), consider serum sickness	If initial manifestation is consistent with anaphylaxis, treat as in SE11. If onset > 4 hours, consider treating with corticosteroids and anti-histamines for 5 to 7 days. Note risk of relapse of serum sickness, if steroids are tapered too quickly. Evaluate with CBC, ESR, CRP, LFTs, and UA. Store serum sample before steroid therapy.	Give temporary exemption, pending consultation with allergist.	Submit Form VAERS-1. Seek allergy consult.[4] Review benefit-risk ratio carefully with patient. Consult patient regarding treatment options and further vaccination under controlled desensitization conditions.

Table 2F: Systemic Events (SE) After Vaccination: February 2001

(Note: The probability of events listed in these tables is not uniform. Some are quite common. Others occur rarely, if at all)

Adverse Event Definitions & Evaluation	Treatment & Management	Future Doses	Comments
Neurologic Disease, Severe (SE13):	Consult with neurology for diagnosis and treatment. Some cases may benefit from	Give temporary exemption,	Submit Form VAERS-1. Consider risk for recurrent reaction before administering

Possible diagnoses include: • Peripheral neuropathy, nonfocal • Encephalopathy • Guillain-Barré syndrome • Progressive focal neurologic disease (see also SE14) Assumes no other etiologic factor	rapid treatment with high-dose intravenous immunoglobulin.	pending consultation with neurology.	additional doses.
Focal Neurologic Disease (SE14): • Cranial nerve palsy • Neuropathy/neuritis • Radiculopathy • Paresthesias / blepharospasms • Optic neuritis • Ulnar nerve neuropathy (if diagnosis based on physical exam and/or nerve studies. If by symptoms only, give precedence to LR7 group)	Consider compression or trauma to ulnar nerve due to act of injection. Perform clinical work-up. Consult with neurology.	Give temporary exemption, pending consultation with neurology. Emphasize injection in deltoid rather than triceps area.	Submit Form VAERS-1. If persistent, specific treatment may be necessary after neurology consultation.
Prolonged Fatigue (> 60 days)[6] (SE15): < 50% functionality (work, recreation, school), compared to before vaccination • Loss of exercise tolerance • Non-restful sleep a frequent feature • Reduced concentration, decreased memory, as seen in many other chronic illnesses and/or depression	Treat and consult appropriately before 60-day threshold. Consult with specialty center with expertise in chronic fatigue and related syndromes.	Give temporary exemption, pending consultation.	Currently no recognized association with any vaccine. Cases are often eventually linked with other diagnoses. Close follow-up and sequential evaluations may be warranted. Submit Form VAERS-1.

Table 2G: Systemic Events (SE) After Vaccination: February 2001

(Note: The probability of events listed in these tables is not uniform. Some are quite common. Others occur rarely, if at all)

Adverse Event Definitions & Evaluation	Treatment & Management	Future Doses	Comments
Acute Anxiety Response (SE16):	Educate. Reassure. Treat according to clinical condition.	Anthrax: If response related to burning at injection site or related events, consider route.[8]	Some personnel may benefit from psychiatry consultation to assist with diagnosis and management.
Respiratory Illness (SE17): symptoms such as cough, coryza, congestion, sore throat and rhinorrhea with or without accompanying systemic symptoms	Treat symptomatically. If symptoms persist $\geq$ 2 weeks, consider other etiologies.	Proceed with next dose, in most cases.[2,4]	Contrast with SE2a. Some patients may jointly experience SE17 and SE2a.
Gastrointestinal Illness (SE18): symptoms such as vomiting and/or diarrhea, with or without accompanying systemic symptoms (e.g., loose stool, abdominal pain, gas, indigestion). Note that category SE5 includes uncomplicated nausea and/or vomiting.	Treat symptomatically. Treat symptomatically. If symptoms persist $\geq$ 2 weeks, consider other etiologies.	Proceed with next dose, in most cases.[2,4]	Contrast with SE2a. Some patients may jointly experience SE18 and SE2a.
Dizziness (SE19a) **"True" Vertigo** (SE19b) • Dysequilibrium characterized by spinning or impulsion, often with nystagmus	An agent such as meclizine or scopolamine may help symptoms of vertigo.	As clinically appropriate.	
Idiosyncratic Response(s) to Live	As clinically appropriate.	As clinically	

Vaccine(s) (SE20), for example: • Rash after measles, rubella, varicella vaccines • Fever after yellow-fever vaccine • Abdominal cramps, diarrhea after oral typhoid vaccine		appropriate.	
Other Systemic Events (SE-xx)	Treat according to clinical condition. Seek consults, as appropriate.	Base decision on complete medical evaluation and consideration of benefit-risk ratio.	

Notes February 2001

1 - Treatment program for moderate to large local reactions:

- Apply topical corticosteroid cream or ointment at least 2 to 3 times per day until reaction has resolved. Rarely requires oral corticosteroids (e.g., prednisone at 1 mg/kg or 50 to 60 mg per day for 3 to 4 days, tapering off by 10 to 20 mg per day over the next 2 to 4 days). Avoid unprotected sun exposure at the treated sites and use sunscreen aggressively.
- If itching is present, use second-generation antihistamines such as fexofenadine (*Allegra*®) 60 mg twice daily or cetirizine (*Zyrtec*®) 10 mg daily. If not available, use first-generation antihistamines, recognizing sedating side effects.
- If swelling extends below elbow, a sling may be useful. Some vaccine recipients may benefit from an ice pack within first 24 hours.

2 - Pretreatment program to prevent future large local reactions:

- If localized itching was a dominant feature, pretreat with a second-generation antihistamine such as fexofenadine (*Allegra*®) 60 mg twice daily (at least 2 doses prior to the next injection) or cetirizine (*Zyrtec*®) 10 mg daily (at least 2 doses before next injection), continuing for 48 to 72 hours after the injection (longer if local reaction persists or reflares). If not available, use first-generation antihistamines, recognizing their sedating side effects.
- Avoid unprotected sun exposure at the treated site for at least 1 to 2 weeks and use sunscreen aggressively. For at least 3 to 4 days, avoid strenuous exercise using the arm that has received the vaccination.

3 - Comment: Some vaccine recipients will tolerate these types of reactions less well than others, and may be apprehensive about the health risk from the next injection. Careful education and/or willingness to consult with specialists may prevent unnecessary polarization or potential refusal of subsequent vaccinations. Because most of these vaccine recipients can receive additional doses safely, it is important to

avoid unnecessary indefinite exemptions, considering the threat and mortality risk of weaponized anthrax.

4 - Prototype Allergy-Immunology Evaluation: Anthrax vaccine skin testing (full-strength prick test, 1:1,000 then 1:100 volume/volume dilution intradermal) with both prick and intradermal histamine (histamine base: prick test 1 mg/ml, intradermal 0.1 mg/ml) and diluent controls (sodium chloride 0.9%). If patient understands risks and benefits of further vaccination and seeks desensitization, provide progressive dose challenge without pretreatment initially, treat any reactions appropriately, and pretreat subsequent doses as needed. Save serum from before and 3 to 4 weeks after procedure, to evaluate immune response later. Serum can be sent to central repository or local medical treatment facility (MTF) serum bank. Use generic consent form for serum collection for patient care, but specifying permission for subsequent use of sera for anonymous retrospective research.

5 - Treatment program for mild to moderate systemic events: Symptomatic treatment to prevent recurrence of adverse events has been very effective for many vaccines, including anthrax vaccine.

6 - Prolonged fatigue linked to vaccination is extremely rare, and has not been characterized as a well-defined vaccine-related adverse event. However, if the patient so desires, Form VAERS-1 may be filed. In many cases, other diagnoses are made when more extensive evaluation and follow-up occurs.

7 - Next level of care indicates review by provider with more specialized scope of practice.

8 – Route and Interval: DoD and USCG policy is to administer anthrax vaccine using the subcutaneous route, as described in the manufacturer's product labeling ("package insert"). This policy, however, does not preclude a physician or other credentialled health-care provider from making clinical decisions to alleviate future discomfort for an individual Service Member who developed a large or persistent injection-site reaction or experienced a significant systemic event after an earlier dose of anthrax vaccine. Information to be given to these Service Members appears on the following page.

According to the guidelines of the Advisory Committee on Immunization Practices (**ACIP. Use of anthrax vaccine in the United States. *MMWR* 2000;49(RR-15)(Dec 15):1-20**, http://www.cdc.gov/mmwr/PDF/rr/rr4915.pdf or http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4915a1.htm):

"At this time, ACIP cannot recommend changes in vaccine administration because of the preliminary nature of this information. However, the data in this report do support some flexibility in the route and timing of anthrax vaccination under special circumstances. As with other licensed vaccines, no data indicate that increasing the interval between doses adversely affects immunogenicity or safety. Therefore, interruption of the vaccination schedule does not require restarting the entire series of anthrax vaccine or the addition of extra doses."

Regarding immunogenicity considerations in individualizing medical treatment: "Because of the complexity of a six-dose primary vaccination schedule and frequency of local injection-site reactions (see Vaccine Safety), studies are under way to assess the immunogenicity of schedules with a reduced number of doses and with intramuscular (IM) administration rather than subcutaneous administration. Immunogenicity data were collected from military personnel who had a prolonged interval between the first and second doses of anthrax vaccine in the U.S. military anthrax vaccination program. Antibody to PA was measured by enzyme-linked immunosorbent assay (ELISA) at 7 weeks after the first dose. Geometric mean titers increased from 450 µg/mL among those who received the second vaccine dose 2 weeks

after the first (the recommended schedule, n = 22), to 1,225 for those vaccinated at a 3-week interval (n = 19), and 1,860 for those vaccinated at a 4-week interval (n = 12). Differences in titer between the routine and prolonged intervals were statistically significant ($p < 0.01$)."

Regarding immunogenicity and safety considerations in individualizing medical treatment: "…a small randomized study was conducted among military personnel to compare the licensed regimen (subcutaneous injections at 0, 2, and 4 weeks, n = 28) and alternate regimens (subcutaneous [n = 23] or intramuscular [n=22] injections at 0 and 4 weeks). Immunogenicity outcomes measured at 8 weeks after the first dose included geometric mean IgG concentrations and the proportion of subjects seroconverting (defined by an anti-PA IgG concentration of $\geq$ 25 µg/mL). In addition, the occurrence of local and systemic adverse events was determined. IgG concentrations were similar between the routine and alternate schedule groups (routine: 478 µg/mL; subcutaneous at 0 and 4 weeks: 625 µg/mL; intramuscular at 0 and 4 weeks: 482 µg/mL). All study participants seroconverted except for one of 21 in the intramuscular (injections at 0 and 4 weeks) group. Systemic adverse events were uncommon and similar for the intramuscular and subcutaneous groups. All local reactions (i.e., tenderness, erythema, warmth, induration, and subcutaneous nodules) were significantly more common following subcutaneous vaccination. Comparison of the three vaccination series indicated no significant differences between the proportion of subjects experiencing local reactions for the two subcutaneous regimens but significantly fewer subcutaneous nodules ($p < 0.001$) and significantly less erythema ($p = 0.001$) in the group vaccinated intramuscularly (P. Pittman, personal communication, USAMRIID, Ft. Detrick, MD)."

ANTHRAX VACCINE IMMUNIZATION PROGRAM

INFORMATION PAPER

1 February 2001

SUBJECT: Route of Administration for Anthrax Vaccine

1. PURPOSE. To describe an alternate route for administrating anthrax vaccine.

2. FACTS.

a. The US government license (approved by the Food and Drug Administration (FDA)) for anthrax vaccine is based on injecting the vaccine subcutaneously, about ½-inch under the skin. Subcutaneous (SC) injections place the vaccine in fatty tissue between the skin and underlying muscle. The anthrax vaccine was 92.5% effective in preventing anthrax infection when injected subcutaneously in a key study (Brachman, 1962; FDA, 1985).

b. In a small study, people given anthrax vaccine SC or IM were compared for antibody levels and side effects. The two groups developed roughly the same amount of antibodies. But people vaccinated by the SC route were more likely to develop tenderness, redness, warmth,

swelling, or lumps at the injection site, compared to people vaccinated by the IM route. Other information shows that anthrax-fighting antibody levels are somewhat higher when the intervals between anthrax vaccinations are prolonged a few weeks longer than usual. These data come from the US Army Medical Research Institute of Infectious Diseases (USAMRIID), Fort Detrick, MD (ACIP, 2000).

c. Although it is DoD policy to follow the FDA-approved method of SC injections, this policy does not prevent a physician or other authorized health-care provider from making a clinical decision to use an IM injection in a special case. A special case could be to alleviate future discomfort for an individual Service Member who developed a large or persistent injection-site reaction or experienced a significant systemic event after an earlier dose of anthrax vaccine given by SC injection. In such a special case, IM administration is not prohibited if the health-care provider believes the injection will provide appropriate vaccine protection and reduce side effects, and informs the patient of the special circumstances.

d. The independent civilian panel known as the Advisory Committee on Immunization Practices reported that available data "do support some flexibility in the route and timing of anthrax vaccination under special circumstances. As with other licensed vaccines, no data indicate that increasing the interval between doses adversely affects immunogenicity or safety."

3. REFERENCES.

a. Brachman PS, Gold H, Plotkin SA, Fekety FR, Werrin M, Ingraham NR. Field evaluation of a human anthrax vaccine. *American Journal of Public Health* 1962;52:432-45. http://www.anthrax.osd.mil/site_files/articles/indexclinical/brachman.pdf.

b. Food & Drug Administration. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review. *Federal Register* 1985;50:51002-117. http://www.anthrax.osd.mil/Site_Files/articles/Indexclinical/Fed_register.htm.

c. Advisory Committee on Immunization Practices. Use of anthrax vaccine in the United States. *Morbidity & Mortality Weekly Report* 2000;49(RR-15):1-20. www.cdc.gov/mmwr/PDF/rr/rr4915.pdf.

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Approved by COL Randolph

Anthrax

Frequently Asked Questions

What is anthrax?

Anthrax is an acute infectious disease caused by the spore-forming bacterium *Bacillus anthracis*. Anthrax most commonly occurs in wild and domestic lower vertebrates (cattle, sheep, goats, camels, antelopes, and other herbivores), but it can also occur in humans when they are exposed to infected animals or tissue from infected animals.

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Why has anthrax become a current issue?

Because anthrax is considered to be a potential agent for use in biological warfare, the Department of Defense (DoD) has begun mandatory vaccination of all active duty military personnel who might be involved in conflict.

How common is anthrax and who can get it?

Anthrax is most common in agricultural regions where it occurs in animals. These include South and Central America, Southern and Eastern Europe, Asia, Africa, the Caribbean, and the Middle East. When anthrax affects humans, it is usually due to an occupational exposure to infected animals or their products. Workers who are exposed to dead animals and animal products from other countries where anthrax is more common may become infected with *B. anthracis* (industrial anthrax). Anthrax in wild livestock has occurred in the United States.

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How is anthrax transmitted?

Anthrax infection can occur in three forms: cutaneous (skin), inhalation, and gastrointestinal. *B. anthracis* spores can live in the soil for many years, and humans can become infected with anthrax

by handling products from infected animals or by inhaling anthrax spores from contaminated animal products. Anthrax can also be spread by eating undercooked meat from infected animals. It is rare to find infected animals in the United States.

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What are the symptoms of anthrax?

Symptoms of disease vary depending on how the disease was contracted, but symptoms usually occur within 7 days.

Cutaneous: Most (about 95%) anthrax infections occur when the bacterium enters a cut or abrasion on the skin, such as when handling contaminated wool, hides, leather or hair products (especially goat hair) of infected animals. Skin infection begins as a raised itchy bump that resembles an insect bite but within 1-2 days develops into a vesicle and then a painless ulcer, usually 1-3 cm in diameter, with a characteristic black necrotic (dying) area in the center. Lymph glands in the adjacent area may swell. About 20% of untreated cases of cutaneous anthrax will result in death. Deaths are rare with appropriate antimicrobial therapy.

Inhalation: Initial symptoms may resemble a common cold. After several days, the symptoms may progress to severe breathing problems and shock. Inhalation anthrax is usually fatal.

Intestinal: The intestinal disease form of anthrax may follow the consumption of contaminated meat and is characterized by an acute inflammation of the intestinal tract. Initial signs of nausea, loss of appetite, vomiting, fever are followed by abdominal pain, vomiting of blood, and severe diarrhea. Intestinal anthrax results in death in 25% to 60% of cases.

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Where is anthrax usually found?

Anthrax can be found globally. It is more common in developing countries or countries without veterinary public health programs. Certain regions of the world (South and Central America, Southern and Eastern Europe, Asia, Africa, the Caribbean, and the Middle East) report more anthrax in animals than others.

Can anthrax be spread from person-to-person?

Direct person-to-person spread of anthrax is extremely unlikely to occur. Communicability is not a concern in managing or visiting with patients with inhalational anthrax.

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Is there a way to prevent infection?

In countries where anthrax is common and vaccination levels of animal herds are low, humans should avoid contact with livestock and animal products and avoid eating meat that has not been properly slaughtered and cooked. Also, an anthrax vaccine has been licensed for use in humans. The vaccine is reported to be 93% effective in protecting against anthrax.

What is the anthrax vaccine?

The anthrax vaccine is manufactured and distributed by BioPort, Corporation, Lansing, Michigan. The vaccine is a cell-free filtrate vaccine, which means it contains no dead or live bacteria in the preparation. The final product contains no more than 2.4 mg of aluminum hydroxide as adjuvant. Anthrax vaccines intended for animals should not be used in humans.

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Who should get vaccinated against anthrax?

The Advisory Committee on Immunization Practices has recommend anthrax vaccination for the following groups:

- Persons who work directly with the organism in the laboratory
- Persons who work with imported animal hides or furs in areas where standards are insufficient to prevent exposure to anthrax spores.
- Persons who handle potentially infected animal products in high-incidence areas. (Incidence is low in the United States, but veterinarians who travel to work in other countries where incidence is higher should consider being vaccinated.)
- Military personnel deployed to areas with high risk for exposure to the organism (as when it is used as a biological warfare weapon).

Pregnant women should be vaccinated only if absolutely necessary.

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What is the protocol for anthrax vaccination?

The immunization consists of three subcutaneous injections given 2 weeks apart followed by three additional subcutaneous injections given at 6, 12, and 18 months. Annual booster injections of the vaccine are recommended thereafter.

Are there adverse reactions to the anthrax vaccine?

Mild local reactions occur in 30% of recipients and consist of slight tenderness and redness at the injection site. Severe local reactions are infrequent and consist of extensive swelling of the forearm in addition to the local reaction. Systemic reactions occur in fewer than 0.2% of recipients.

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How is anthrax diagnosed?

Anthrax is diagnosed by isolating *B. anthracis* from the blood, skin lesions, or respiratory secretions or by measuring specific antibodies in the blood of persons with suspected cases.

Is there a treatment for anthrax?

Doctors can prescribe effective antibiotics. To be effective, treatment should be initiated early. If left untreated, the disease can be fatal.

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Where can I get more information about the recent Department of Defense decision to require men and women in the Armed Services to be vaccinated against anthrax?

The Department of Defense recommends that servicemen and women contact their chain of command on questions about the vaccine and its distribution. The anthrax Vaccine Immunization Program in the U.S. Army Surgeon General's Office can be reached at 1-877-GETVACC (1-877-438-8222). http://www.anthrax.osd.mil

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Centers for Disease Control and Prevention
National Center for Infectious Diseases
Division of Bacterial and Mycotic Diseases

Control of Communicable Diseases Manual

James Chin, MD, MPH, Editor

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ANTHRAX ICD-9 022; ICD-10 A22

(Malignant pustule, Malignant edema, Woolsorter disease, Ragpicker disease)

1. Identification —An acute bacterial disease that usually affects the skin, but which may very rarely involve the oropharynx, mediastinum or intestinal tract. In cutaneous anthrax, itching of an exposed skin surface occurs first, followed by a lesion that becomes papular, then vesicular and in 2-6 days develops into a depressed black eschar. The eschar is usually surrounded by moderate to severe and very extensive edema, sometimes with small secondary vesicles. Pain is unusual and, if present, is due to edema or secondary infection. The head, forearms and hands are common sites of infection. The lesion has been confused with human orf (see Orf virus disease). Untreated infections may spread to regional lymph nodes and to the bloodstream with an overwhelming septicemia. The meninges can become involved. Untreated cutaneous anthrax has a case-fatality rate between 5% and 20%, but with effective antibiotic therapy, few deaths occur. The lesion evolves through typical local changes even after the initiation of antibiotic therapy.

Initial symptoms of inhalation anthrax are mild and nonspecific and may include fever, malaise and mild cough or chest pain; acute symptoms of respiratory distress, x-ray evidence of mediastinal widening, fever and shock follow in 3-5 days, with death shortly thereafter. Intestinal anthrax is rare and more difficult to recognize, except that it tends to occur in explosive food poisoning outbreaks; abdominal distress is followed by fever, signs of septicemia and death in the typical case. An oropharyngeal form of primary disease has been described.

Laboratory confirmation is made by demonstration of the causative organism in blood, lesions or discharges by direct polychrome methylene blue (M'Fadyean)-stained smears or by culture or inoculation of mice, guinea pigs or rabbits. Rapid identification of the organism by using immunodiagnostic testing, ELISA and PCR may be available in certain reference laboratories.

2. Infectious agent—*Bacillus anthracis,* a Gram-positive, encapsulated, spore forming, nonmotile rod.

3. Occurrence—Primarily a disease of herbivores; humans and carnivores are incidental hosts. Anthrax is an infrequent and sporadic human infection in most industrialized countries. It is an occupational hazard primarily of workers who process hides, hair (especially from goats), bone and bone products and wool; and of veterinarians and agriculture and wildlife workers who handle infected animals. Human anthrax is endemic in those agricultural regions of the world where anthrax in animals is common; these include countries in South and Central America, southern and eastern Europe, Asia and Africa. New areas of infection in livestock may develop through introduction of animal feed containing contaminated

bone meal. Environmental events such as floods may provoke epizootics. Anthrax is considered a leading potential agent in bioterrorism or biowarfare and, as such, could present in epidemiologicaily unusual circumstances.

4. Reservoir—Animals (normally herbivores, both livestock and wildlife) shed the bacilli in terminal hemorrhages or spilt blood at death. On exposure to the air, the vegetative forms sporulate, and the spores of ***B.*** *anthracis,* which are very resistant to adverse environmental conditions and disinfection, may remain viable in contaminated soil for many years. ***B. anthracis*** is a soil commensal in many parts of the world. Bacterial growth and spore density in soil are enhanced by flooding or other ecological conditions. Soil can also be contaminated by vultures, which spread the organism from one area to another after feeding on anthrax infected carcasses. Dried or otherwise processed skins and hides of infected animals may harbor the spores for years and are the fomites by which the disease is spread worldwide.

5. Mode of transmission—Cutaneous infection is by contact with tissues of animals (cattle, sheep, goats, horses, pigs and others) dying of the disease; possibly by biting flies that had partially fed on such animals; by contact with contaminated hair, wool, hides or products made from them, such as drums, brushes or rugs; or by contact with soil associated with infected animals or contaminated bone meal used in gardening. Inhalation anthrax results from inhalation of spores in risky industrial processes— such as tanning hides and processing wool or bone—where aerosols of ***B. anthracis*** spores may be produced. Intestinal and oropharyngeal anthrax arise from ingestion of contaminated undercooked meat; there is no evidence that milk from infected animals transmits anthrax. The disease spreads among grazing animals through contaminated soil and feed; among omnivorous and carnivorous animals through

contaminated meat, bone meal or other feeds; and among wildlife from feeding on carcasses infected with anthrax. Accidental infections may occur among laboratory workers.

In 1979, an outbreak of largely inhalation anthrax occurred in Yekaterinburg (Sverdlovsk), Russia, in which 66 individuals were documented to have died of anthrax and 11 infected persons were known to have survived; many other cases are presumed to have occurred, investigations disclosed that the cases occurred as the result of a plume emanating from a biological research institute and led to the conclusion that the outbreak had resulted from an accidental aerosol generated in work related to biological warfare studies.

6. Incubation period—From 1 to 7 days, although incubation periods up to 60 days are possible. (In the Sverdlovsk outbreak, incubation periods extended up to 43 days.)

7. Period of communicability—Transmission from person to person is very rare. Articles and soil contaminated with spores may remain infective for decades.

8. Susceptibility and resistance—Uncertain; there is some evidence of inapparent infection among people in frequent contact with the infectious agent; second attacks can occur, but reports are rare.

9. Methods of control—

A. Preventive measures:

1) Immunize high risk persons with a cell-free vaccine prepared from a culture filtrate containing the protective antigen (available in the USA from the Bioport Corporation, 3500 N. Martin Luther King, Jr., Boulevard, Lansing MI 48909). **Evidence indicates that this vaccine is effective in preventing cutaneous and inhalational anthrax; it is recommended for laboratory workers who routinely work with *B. anthracis* and workers who handle potentially contaminated industrial raw materials. It may also be used to protect military personnel against potential exposure to anthrax used as a biological warfare agent. Annual booster injections are recommended if the risk of exposure continues.** [Emphasis added]

2) Educate employees who handle potentially contaminated articles about modes of anthrax transmission, care of skin abrasions and personal cleanliness.

3) Control dust and properly ventilate work areas in hazardous industries, especially those that handle raw animal materials. Maintain continuing medical supervision of employees and provide prompt medical care of all suspicious skin lesions. Workers should wear protective clothing and have adequate facilities for washing and changing clothes after work. Locate eating facilities away from places of work. Vaporized formaldehyde has been used for terminal disinfection of textile mills contaminated with ***B. anthracis.***

4) Thoroughly wash, disinfect or sterilize hair, wool and bone meal or other feed of animal origin prior to processing.

5) Do not sell the hides of animals exposed to anthrax or use their carcasses as food or feed supplements (i.e., as bone or blood meal).

6) If anthrax is suspected, do not necropsy the animal but aseptically collect a blood sample for culture. Avoid contamination of the area. If a necropsy is inadvertently performed, autoclave, incinerate or chemically disinfect/fumigate all instruments or materials.

Because the anthrax spores may survive for decades if the carcasses are buried, the preferred disposal technique is to incinerate the carcasses at the site of death or to remove them to a rendering plant, ensure no contamination en route to the plant. Should these methods be impossible, deeply bury carcasses at the site of death, if possible; do not bum them on

open fields. Decontaminate soil seeded by carcasses or discharges with 5% lye or anhydrous calcium oxide (quicklime). Deeply buried carcasses should be covered with quicklime.

7) Control effluents and trade wastes from rendering plants that handle potentially infected animals and those from factories that manufacture products from hair, wool, bones or hides likely to be contaminated.

8) Promptly immunize and annually reimmunize all animals at risk. Treat symptomatic animals with penicillin or tetracyclines; immunize these animals after cessation of therapy. They should not be used for food until a few months have passed. Treatment in lieu of immunization may be used for animals exposed to a discrete source of infection, such as contaminated commercial feed.

B. Control of patient, contacts and the immediate environment:

1) Report to local health authority: Case report obligatory in most states and countries, Class 2A (see Communicable Disease Reporting). Also report to the appropriate livestock or agriculture authority. Even a single case of human anthrax, especially of the

inhalational variety, is so unusual that it should be reported immediately to both public health and law enforcement authorities for consideration of a bioterrorist source.

2) Isolation: Standard precautions for the duration of illness for cutaneous and inhalation anthrax. Antibiotic therapy sterilizes a skin lesion within 24 hours, but the lesion progresses through its typical cycle of ulceration, sloughing and resolution.

3) Concurrent disinfection: Of discharges from lesions and articles soiled therewith. Hypochlorite is sporicidal and good when organic matter is not overwhelming and the item is not corrodable; hydrogen peroxide, peracetic acid or glutaraldehyde may be alternatives; formaldehyde, ethylene oxide and cobalt irradiation have been used. Spores require steam sterilization, autoclaving or burning to ensure complete destruction. Fumigation and chemical disinfection may be used for valuable equipment. Terminal cleaning.

4) Quarantine: None.

5) Immunization of contacts: None.

6) Investigation of contacts and source of infection: Search for history of exposure to infected animals or animal products and trace to place of origin. In a manufacturing plant, inspect for adequacy of preventive measures as outlined in 9A, above. As mentioned in 9B1, a potential bioterrorist source may need to be ruled out for all human cases of anthrax, especially for those cases with no obvious occupational source of infection.

7) Specific treatment: Penicillin is the drug of choice for cutane-

ous anthrax and is given for 5-7 days. Tetracyclines, erythromycin and chloramphenicol are also effective. The U.S. military recommends parenteral ciprofloxacin or doxycycline for inhalational anthrax; the duration of therapy is not well defined.

C. Epidemic measures: Outbreaks may be an occupational hazard of animal husbandry. The occasional epidemics in the USA are local industrial outbreaks among employees who work with animal products, especially goat hair. Outbreaks related to handling and consuming meat from infected cattle have occurred in Asia, Africa and the former Soviet Union.

D. Disaster implications: None, except in case of floods in previously infected areas.

E. International measures: Sterilize imported bone meal before use as animal feed. Disinfect wool, hair and other products when indicated and practical.

F. Bioterrorism measures: During 1998, more than two dozen anthrax threats were made in the USA. None of these threats was real. The general procedures in the USA for dealing with these civilian threats include the following:

1) Anyone who receives a threat about dissemination of anthrax organisms should notify the local office of the Federal Bureau of investigation (FBI) immediately.

2) In the USA, the FBI has primary responsibility for the investigation of such biological threats, and all other agencies are to cooperate and provide assistance as requested by the FBI.

3) Local and state health departments should be notified also and be ready to provide any public health management and follow-up that may be needed.

4) Persons who may have been exposed to anthrax are not contagious, so quarantine is not appropriate.

5) Persons who may have been exposed should be advised to await laboratory results and need not be placed on chemoprophylaxis. If they become ill before laboratory results are available, they should immediately contact their local health department and proceed to a predetermined emergency care unit, where they should inform the attending staff of their potential exposure.

6) If the threat of exposure to aerosolized anthrax is credible or confirmed, persons at risk should begin postexposure prophylaxis with both an appropriate antibiotic (fluoroquinolones are the drugs of choice; doxycycline is an alternative) and vaccine. Postexposure immunization with an inactivated, cell-free anthrax vaccine is indicated in conjunction with

chemoprophylaxis following a proven biologic incident. Immunization is recommended because of the uncertainty of when or if inhaled spores may germinate. Postexposure immunization consists of three injections: as soon as possible after exposure and at 2 and 4 weeks after exposure. This vaccine has not been evaluated for safety and efficacy in children less than 18 years of age or adults 60 [sic] years of age or older.

7) All first responders should follow local protocols for incidents involving biological hazards.

8) Responders can be protected from anthrax spores by donning splash protection, gloves and a full face respirator with high-efficiency particle air (HEPA) filters (Level C) or self-contained breathing apparatus (SCBA) (Level B).

9) Persons who may have been exposed and are potentially contaminated should be decontaminated with soap and copious amounts of water in a shower. Usually no bleach solutions are required. A 1:10 dilution of household bleach (i.e., a final hypochlorite concentration of 0.5%) should be used only if there is gross contamination with the agent and an inability to remove the materials through soap and water decontamination. The use of bleach decontamination is recommended only after soap and water decontamination, and the solution should be rinsed off after 10 to 15 minutes.

10) All persons who are to be decontaminated should remove their clothing and personal effects and place all items in plastic bags, which should be labeled clearly with the owner's name, contact telephone number and inventory of the bag's contents. Personal items may be kept as evidence in a criminal trial or returned to the owner if the threat is unsubstantiated.

11) If the suspect envelope or package associated with an anthrax threat remains sealed (not opened), then first responders should not take any action other than notifying the FBI and packaging the evidence. Quarantine, evacuation, decontamination and chemoprophylaxis efforts are NOT indicated if the envelope or package remains sealed. For incidents involving possibly contaminated letters, the environment in direct contact with the letter or its contents should be decontaminated with a 0.5% hypochlorite solution following a crime scene investigation. Personal effects may be decontaminated similarly.

12) Technical assistance can be provided immediately by contacting the National Response Center at 800-424-8802 or the local Weapons of Mass Destruction Coordinator of the FBI.

February 05, 1999 / 48(04);69-74

Bioterrorism Alleging Use of Anthrax and Interim Guidelines for Management -- United States, 1998

From October 30 through December 23, 1998, CDC received reports of a series of bioterroristic threats of anthrax * exposure. Letters alleged to contain anthrax were sent to health clinics on October 30, 1998, in Indiana, Kentucky, and Tennessee. During December 17-23 in California, a letter alleged to contain anthrax was sent to a private business, and three telephone threats of anthrax contamination of ventilation systems were made to private and public buildings. All threats were hoaxes and are under investigation by the Federal Bureau of Investigation (FBI) and local law enforcement officials. The public health implications of these threats were investigated to assist in developing national public health guidelines for responding to bioterrorism. This report summarizes the findings of these investigations and provides interim guidance for public health authorities on bioterrorism related to anthrax.

Indiana

The threatening letter was opened by an administrative assistant, who called 911; police, fire, emergency medical services (EMS), and hazardous materials units (HAZMAT) (i.e., first responders) were sent to the clinic, and the local FBI office was contacted. The letter was sealed in a plastic bag and collected by FBI. All 31 adults who were in the building when the letter was opened were considered possibly exposed to Bacillus anthracis spores and were detained for approximately 3 hours.

First responders in consultation with public health officials in the Marion County Health Department (MCHD) decontaminated the potentially exposed persons in a temporary shelter constructed on the scene. HAZMAT personnel used full protective gear with self-contained respirators (level A protection). The 31 occupants placed their clothing and personal effects in plastic bags and showered using soap and water plus a dilute bleach solution. The desktop where the letter was opened was washed with a 5% hypochlorite solution (i.e., standard household bleach). All 31 persons were transported to local emergency departments (EDs) to receive oral chemoprophylaxis with ciprofloxacin (500 mg twice daily); some underwent additional decontamination (i.e., showered again with soap and water) as required by hospital policy.

Public health officials from the MCHD collected contact information from all persons and informed them they would be notified when results from laboratory testing were available; arrangements also were made for counseling. The letter was taken by FBI to the Indiana State Department of Health Laboratory, where cultures for B. anthracis were negative. The next day, FBI transported the letter to the United States Army Medical Research Institute for Infectious Diseases (USAMRIID), U.S. Department of Defense, in Ft. Detrick, Maryland, where direct fluorescent antibody testing and culture were negative.

Kentucky

The letter was opened by an administrative assistant; the assistant called the postal inspector and was advised to put the letter in a plastic bag. The postal inspector contacted the local FBI office and went to the clinic. FBI contacted the assistant fire chief who sent police, fire, EMS, and a HAZMAT unit to the clinic.

Jefferson County Health Department personnel recommended that the staff member and the postal inspector shower with soap and water at the clinic and obtain oral chemoprophylaxis (ciprofloxacin 500 mg twice daily) at a local ED. The Kentucky State Department for Public Health, FBI's Weapons of Mass Destruction Office, and USAMRIID advised that decontamination and oral chemoprophylaxis were not necessary for five other adults in the center who may have been exposed to the letter. The desktop where the envelope had been opened was decontaminated with a hypochlorite solution.

The letter was taken by FBI to a biosafety level 3 facility at the University of Louisville Hospital Clinical Microbiology Laboratory, where phase microscopy revealed no spores consistent with B. anthracis, and cultures were negative. The next day, FBI transported the letter to USAMRIID, where direct fluorescent antibody testing and culture were negative.

Tennessee

The letter was opened by an administrative assistant, who called the local police department; officers took custody of the letter and placed it in a plastic bag. A clinic administrator contacted CDC seeking advice about preventive health measures. CDC notified the local FBI field office and the Tennessee Department of Health regarding the threat. FBI took the letter from the local police

department to USAMRIID, where tests were negative for B. anthracis. The administrative assistant and the responding police officer, both of whom had direct contact with the letter, received chemoprophylaxis.

California

During December 17-23, 1998, four threats alleging use of anthrax were reported in greater metropolitan Los Angeles. The response to all four threats involved the police and fire departments, EMS, HAZMAT, FBI, the County of Los Angeles Department of Health Services (CLADHS), the California Department of Health Services, and CDC.

The first threat was a letter mailed to a private business; all 28 adults considered at risk for exposure to B. anthracis were decontaminated at the scene and given chemoprophylaxis. The letter was transported by FBI to a CLADHS biosafety level 3 laboratory and cultured for B. anthracis; all cultures were negative.

In the second threat, a telephone caller to a government building claimed to have contaminated the building's air-handling system. Approximately 95 adults received chemoprophylaxis. First responders, FBI, and CLADHS jointly decided not to decontaminate involved persons.

In the third threat, a telephone caller to 911 claimed to have contaminated the air-handling system of a federal building with B. anthracis; 1200-1500 persons (at least one of whom was pregnant) and two children potentially were exposed. Contact information for potentially exposed persons was collected for follow-up. No one was decontaminated on the scene, and chemoprophylaxis was not recommended; all potentially exposed persons were asked to go home, wipe down the interiors of their potentially contaminated vehicles with a solution of one part bleach to 10 parts water, place their clothing in a plastic bag until results from laboratory testing were known, and then shower. Environmental samples taken from the air ducts of the building were cultured for B. anthracis at CLADHS; all cultures were negative.

In the fourth incident, an anonymous telephone caller to 911 claimed to have contaminated the air-handling system of an office building occupied by approximately 200 persons. FBI was contacted; the threat was deemed to have low credibility. FBI in conjunction with CLADHS decided that neither decontamination nor chemoprophylaxis was warranted. Environmental samples tested at CLADHS were negative for B. anthracis.

Reported by: Marion County Health Dept, Indianapolis; Indiana State Dept of Health. Jefferson County Health Dept, Louisville; Kentucky Dept for Public Health. Knox County Health Dept, Knoxville; Tennessee Dept of Health. County of Los Angeles Dept of Health Svcs, Los Angeles; California Dept of Health Svcs. Council of State and Territorial Epidemiologists, Atlanta, Georgia. Federal Bur of Investigation, Washington, DC. US Army Medical Research Institute for Infectious Diseases, US Dept of Defense, Ft. Detrick, Maryland. Office of Emergency Preparedness, US Dept of Health and Human Svcs. Emergency Response Coordinating Group, National Center for Environmental Health; Meningitis and Special Pathogens Br, Div of Bacterial and Mycotic Diseases, National Center for Infectious Diseases; and an EIS Officer, CDC.

Editorial Note

Editorial Note: Anthrax is an acute infectious disease caused by the spore-forming bacterium B. anthracis. It occurs most frequently as an epizootic or enzootic disease of herbivores (e.g., cattle, goats, and sheep), which acquire spores from direct contact with contaminated soil. Humans usually become infected through contact with or ingestion or inhalation of B. anthracis spores from infected animals or their products (e.g., goat hair). Human-to-human transmission has not been documented.

Although all the threats alleging use of anthrax described in this report were hoaxes, they demonstrate settings where bioterrorism can occur and the potential public health impact. These threats required prompt action by health, law enforcement, and laboratory personnel. Coordination and communication across agencies are necessary to protect the public and first responders from credible biologic warfare and bioterrorism agents such as anthrax.

The spore form of B. anthracis is durable and can be delivered as an aerosol (1). The incubation period for anthrax is 2-60 days. Inhalation causes the most serious form of human anthrax, and although contemporary experience in humans is limited, mortality may be high even with appropriate therapy (T.V. Inglesby, D.A. Henderson, J.G. Bartlett, et al., Working Group for Civilian Biodefense, personal communication, 1998). The likelihood of developing cutaneous disease is low after exposure of B. anthracis spores to intact skin. The risk for "secondary" anthrax through reaerosolization appears to be low in settings where B. anthracis spores were released unintentionally or were present at low levels (2). In situations where the threat for transmission of B. anthracis spores is deemed credible, decontamination of skin and potential fomites (e.g., clothing or desks) may be considered to reduce the risk for cutaneous and gastrointestinal forms of disease.

Planning for Response to Threats

The public health response to bioterrorism requires communication and coordination with first responders and law enforcement

officials. State and local health departments should work with these groups to ensure that local disaster preparedness plans address bioterrorism; define the roles of each agency, including protection of first responders; and are tested through simulations. FBI has jurisdiction for bioterrorism response but recognizes the need to conduct epidemiologic investigations, define at-risk groups, and rapidly implement potentially life-saving medical and public health responses. When bioterrorism alleging use of anthrax or other agents occur, the local emergency response system should be activated by dialing 911 in most communities; in communities without 911 systems, local law enforcement authorities should be notified. The local FBI field office and local and state public health authorities also should be notified.

FBI will coordinate the collection of evidence (e.g., letters, packages, or air-handling system samples) and deliver materials to an FBI or U.S. Department of Defense laboratory for testing. To guide decision-making, test results identifying B. anthracis should be available as soon as possible, at least within 24-48 hours. Efforts are under way to assess and enhance the capabilities of state and local health department laboratories to fulfill the need for rapid analysis. Planning for laboratory testing should be part of bioterrorism preparedness by state and local public health, law enforcement, and first responder authorities in consultation with federal officials.

Public health officials, working with law enforcement and first response personnel, should determine the need for decontamination and postexposure prophylaxis. In most of the recent hoaxes purporting anthrax exposure, immediate postexposure decontamination and prophylaxis have not been indicated because of the lack of credibility of the threat. Public health officials should collect contact information for potentially exposed persons for notification of laboratory results or other follow-up. Potentially exposed persons should be given information about the signs and symptoms of illnesses associated with the biologic agent and about whom to contact and where to go should they develop illness.

Recommendations for Postexposure Prophylaxis

Postexposure prophylaxis for exposure to B. anthracis consists of chemoprophylaxis and vaccination. Oral fluoroquinolones are the drugs of choice for adults, including pregnant women (T.V. Inglesby, D.A. Henderson, J.G. Bartlett, et al., Working Group for Civilian Biodefense, personal communication, 1998; 3) (Table_1). If fluoroquinolones are not available or are contraindicated, doxycycline is acceptable. Children should receive prophylaxis with oral ciprofloxacin or oral doxycycline (T.V. Inglesby, D.A. Henderson, J.G. Bartlett, et al., Working Group for Civilian Biodefense, personal communication, 1998; 3) (Table_1). Prophylaxis should continue until B. anthracis exposure has been excluded.

Postexposure vaccination with an inactivated, cell-free anthrax vaccine (Bioport Corporation, formerly Michigan Biologic Products Institute **) is indicated in conjunction with chemoprophylaxis following a proven biologic incident (T.V. Inglesby, D.A. Henderson, J.G. Bartlett, et al., Working Group for Civilian Biodefense, personal communication, 1998; 4). Postexposure vaccination consists of three injections: as soon as possible after exposure and at 2 and 4 weeks after exposure. Anthrax vaccine can be requested through CDC. Although this vaccine is now being administered routinely to U.S. military personnel, routine vaccination of civilian populations is not recommended. This vaccine has not been evaluated for safety and efficacy in children aged less than 18 years or adults aged greater than 60 years.

If decontamination is appropriate, persons should remove their clothing and personal effects, place all items in plastic bags, and shower using copious quantities of soap and water (5). Plastic bags with personal effects should be labeled clearly with the owner's name, contact telephone number, and inventory of the bag's contents. Personal items may be kept as evidence in a criminal trial or returned to the owner if the threat is unsubstantiated. For incidents involving possibly contaminated letters, the environment in direct contact with the letter or its contents should be decontaminated with a 0.5% hypochlorite solution (i.e., one part household bleach to 10 parts water) following a crime scene investigation. Personal effects may be decontaminated similarly.

CDC and other offices in the U.S. Department of Health and Human Services are working with state and local health departments, federal agencies, and nongovernmental organizations to improve the public health capacity to address bioterrorism and develop locality-specific response plans. CDC also can assist public health officials with decision-making if a threat occurs alleging the use of a biologic agent.

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5. U.S. Army Medical Research Institute for Infectious diseases/CDC/Food and Drug Administration. Medical response to biological warfare and terrorism {Satellite broadcast}. Atlanta, Georgia: US Department of Defense/US Department of Health and Human Services, CDC, September 22-24,1998.

Infection caused by the bacterium Bacillus anthracis. ** Use of trade names and commercial sources is for identification only and does not imply endorsement by CDC or the U.S. Department of Health and Human Services.

Table_1

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 1. Recommended postexposure prophylaxis for exposure to Bacillus anthracis*

Drug	Adults	Children+
Oral fluroquinolones		
One of the following:		
Ciprofloxacin	500 mg twice daily	20-30 mg per kg of body mass per day divided every 12 hours
Levofloxacin	500 mg once daily	Not recommended
Ofloxacin	400 mg twice daily	Not recommended
If fluoroquinolones are not available or are contraindicated		
Doxycycline	100 mg twice daily	5 mg per kg of body mass per day divided every 12 hours

* Prophylaxis should continue until exposure to B. anthracis has been excluded. If exposure is confirmed, prophylaxis should continue for 4 weeks and until three doses of vaccine have been administered or for 8 weeks if vaccine is not available.

\+ Use of tetracyclines and fluoroquinolones in children has well-known adverse effects; these risks must be weighed carefully against the risk for developing life-threatening disease. If a release of B. anthracis is confirmed, children should receive oral amoxicillin 40 mg per kg of body mass per day divided every 8 hours (not to exceed 500 mg three times daily) as soon as penicillin susceptibility of the organism has been confirmed.

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Page converted: 02/04/99

ANTHRAX VACCINE

WHAT YOU NEED TO KNOW

1 What is anthrax?

Anthrax is a serious disease that can affect both animals and humans. It is caused by bacteria called *Bacillus anthracis*. People can get anthrax from contact with infected animals, wool, meat, or hides. In its most common form, anthrax is a skin disease that causes skin ulcers and usually fever and fatigue. Up to 20% of these cases are fatal if untreated.

When *B. anthracis* is inhaled, as when used as a biological weapon, it is much more serious. The first symptoms may include a sore throat, mild fever and muscle aches. But within several days these symptoms are followed by severe breathing problems, shock, and often meningitis (inflammation of the brain and spinal cord covering). Once symptoms appear, this form of anthrax is almost always fatal, despite treatment with antibiotics.

2 What is anthrax vaccine?

Anthrax vaccine protects against anthrax disease. The U.S. vaccine does not contain actual *B. anthracis* cells and it does not cause anthrax disease. Anthrax vaccine was licensed in 1970.

Based on limited but convincing evidence, the vaccine protects against both cutaneous (skin) and inhalational anthrax.

3 Who should get anthrax vaccine and when?

People 18 to 65 years of age potentially exposed to large amounts of *B. anthracis* bacteria on the job, such as laboratory workers.

Military personnel who may be at risk of anthrax exposure from weapons.

The basic vaccine series consists of **6** doses.

- The first three doses are given at two-week intervals.
- Three additional doses are given, each one 6 months after the previous dose.

Annual booster doses are needed for ongoing protection.

If a dose is not given at the scheduled time, the series does not have to be started over. Resume the series as soon as practical.

Anthrax vaccine may be given at the same time as other vaccines.

4 Some people should not get anthrax vaccine or should wait

Anyone who has had a serious allergic reaction to a previous dose of anthrax vaccine should not get another dose.

Anyone who has recovered from cutaneous (skin) anthrax should not get the vaccine.

Pregnant women should not be routinely vaccinated with anthrax vaccine. This is merely a precaution. There is no evidence that the vaccine is harmful to either a pregnant woman or her unborn baby. Vaccination *may* be recommended for pregnant women who have been exposed, or are likely to be exposed, to anthrax.

There is no reason to delay childbearing after either the man or the woman gets anthrax vaccine.

Vaccines, including anthrax vaccine, are safe to give to breast-feeding women.

5 What are the risks from anthrax vaccine?

Getting anthrax disease is much more dangerous than any risk from the vaccine.

Like any medicine, a vaccine is capable of causing serious problems, such as severe allergic reactions. The risk of anthrax vaccine causing serious harm, or death, is extremely small.

Mild Problems

- Soreness, redness, or itching where the shot was given (about 1 out of 10 men, about 1 out of 6 women)
- A lump where the shot was given (about 1 person out of 2)
- Muscle aches or joint aches (about 1 person out of 5)
- Headaches (about 1 person out of 5)
- Fatigue (about 1 out of 15 men, about 1 out of 6 women)
- Chills or fever (about 1 person out of 20)
- Nausea (about 1 person out of 20).

Moderate Problems

- Large areas of redness where the shot was given (up to l person out of 20).

Severe Problems

- Serious allergic reaction (very rare - less than once in 100,000 doses).

As with any vaccine, other severe problems have been reported. But these events appear to occur no more often among anthrax vaccine recipients than among unvaccinated people.

There is no evidence that anthrax vaccine causes sterility, birth defects, or long-term health problems.

Independent civilian committees have not found anthrax vaccination to be a factor in unexplained illnesses among Gulf War veterans.

6 What if there is a moderate or severe reaction?

What should I look for?

Any unusual condition, such as a severe allergic reaction or a high fever. If a severe allergic reaction occurred, it would happen within a few minutes to an hour after the shot. Signs of a serious allergic reaction can include difficulty breathing, weakness, hoarseness or wheezing, a fast heart beat, hives, dizziness, paleness, or swelling of the throat.

What should I do?

- Call a doctor, or get the person to a doctor right away.
- Tell your doctor what happened, the date and time it happened, and when the vaccination was given.
- Ask your health care provider to file a Vaccine Adverse Event Reporting System (VAERS) form if you have *any* reaction to the vaccine, or call VAERS yourself at **1-800-822-7967.**

7 How can I learn more?

- Ask your doctor or other health care provider. They can give you the vaccine package insert or suggest other sources of information.

- Contact the Centers for Disease Control and Prevention (CDC):
  - Call **1-800-232-2522** (English)
  - Call **1-800-232-0233** (Español)

  - Visit the CDC's website at **http://www.cdc.gov/ncidod/dbmd/diseaseinfo/anthrax_g.htm**

- Contact the U.S Department of Defense (DoD):
  - Call **1-877-438-8222**
  - Visit the DoD website at **www.anthrax.osd.mil**

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention
National Immunization Program

Anthrax

Clinical Features

Human anthrax has three major clinical forms: cutaneous, inhalation, and gastrointestinal. Cutaneous anthrax is a result of introduction of the spore through the skin; inhalation anthrax, through the respiratory tract; and gastrointestinal anthrax, by ingestion.

Etiologic Agent

Bacillus anthracis, the etiologic agent of anthrax, is a large, gram-positive, nonmotile, spore-forming bacterial rod. The three virulence factors of *B. anthracis* are edema toxin, lethal toxin and a capsular antigen. *B. anthracis* is considered to be a likely agent for use in acts of biological terrorism.

Incidence

In the United States, incidence is extremely low. Gastrointestinal anthrax is rare but may occur as explosive outbreaks associated with ingestion of infected animals. Worldwide, the incidence is unknown, though *B. anthracis* is present in most of the world.

Sequelae

If untreated, anthrax in all forms can lead to septicemia and death. Early treatment of cutaneous anthrax is usually curative, and early treatment of all forms is important for recovery. Patients with gastrointestinal anthrax have reported case- fatality rates ranging from 25% to 75%. Case-fatality rates for inhalational anthrax are thought to approach 90 to 100%.

Transmission

For humans, the source of infection in naturally acquired disease is infected livestock and wild animals or contaminated animal products. Human-to-human transmission is extremely rare and only reported with cutaneous anthrax.

Risk Groups

Cutaneous anthrax is the most common manifestation of infection with *B. anthracis*. Inhalation (pulmonary) anthrax occurs in persons working in certain occupations where spores may be forced into the air from contaminated animal products, such as animal hair processing. Occupational risk groups include those coming into contact with livestock or products from livestock, e.g., veterinarians, animal handlers, abattoir workers, and laboratorians.

Surveillance

For both livestock and humans, anthrax is a notifiable disease in the United States.

Trends

Among humans, there has been no increase in naturally acquired infection in the United States. Recently, considerable attention has been focused on the potential for *B. anthracis* to be used in acts of biologic terrorism.

Challenges

Because *B. anthracis* has a high probability for use as an agent in biologic terrorism, CDC is expanding epidemiologic and diagnostic laboratory capacities and technologies. This capacity building, includes local and state health department training. In addition, there are gaps in our understanding of the immunology of anthrax and protection against anthrax via vaccination. Also, post-exposure prophylaxis against anthrax requires further investigation.

Opportunities

Identify, transfer to CDC laboratories, test, and improve as needed, rapid diagnostic technologies developed for rapid identification of *B. anthracis* in

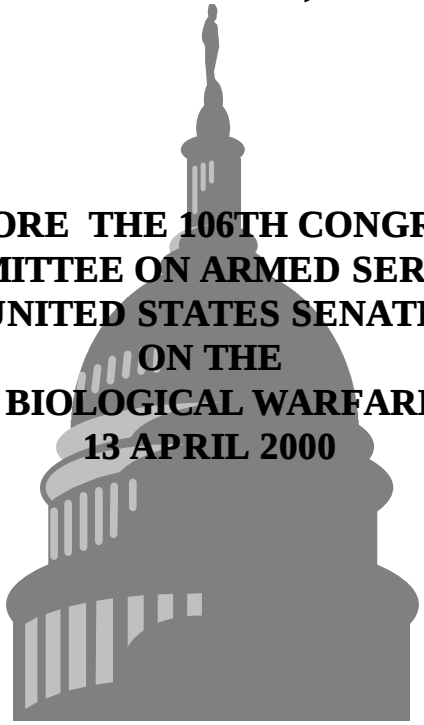
Department of Defense (DoD) laboratories.

December 2000

This page last reviewed March 06, 2001

Centers for Disease Control and Prevention
National Center for Infectious Diseases
Division of Bacterial and Mycotic Diseases

STATEMENT OF
REAR ADMIRAL LOWELL JACOBY
DIRECTOR OF INTELLIGENCE,
JOINT STAFF, J2



BEFORE THE 106TH CONGRESS
COMMITTEE ON ARMED SERVICES
UNITED STATES SENATE
ON THE
ANTHRAX BIOLOGICAL WARFARE THREAT
13 APRIL 2000

Mr. Chairman, distinguished Members of the Committee, thank you for inviting me to testify. I am pleased to present an unclassified intelligence overview of the anthrax threat.

Overview

The Intelligence Community assesses that anthrax is the leading biological warfare threat agent. The potential for terrorist use of this agent is also of concern to us based on the relative ease with which it can be produced. Anthrax is considered an anti-personnel biological warfare agent. However, it also has economic warfare applications for anti-agricultural use against livestock.

What is Anthrax?

Anthrax is a naturally occurring disease of herbivores like sheep, cattle, and goats. This disease occurs worldwide, and particularly in areas where animals are not routinely vaccinated, such as in Asia and Africa. A spore forming bacteria causes the disease. In the spore form, the bacteria are resistant to environmental effects and demonstrate a high level of stability.

There are three modes of exposure. One form occurs usually on the hands and forearms of persons working with infected livestock. Mortality rate ranges up to 25%. The gastrointestinal form is contracted by ingestion of insufficiently cooked contaminated meat. The mortality rate can range up to 70%. The third way anthrax is contracted is by inhalation of anthrax spores. The fatality rate is virtually 100%. Because airborne anthrax spores have the

ability to infect large numbers over a large coverage area, inhalational anthrax is the primary concern for biological warfare.

In inhalation anthrax, the spores are inhaled into the lungs and migrate to the lymph nodes in the cavity between the lungs. Once in the lymph nodes, the spores germinate and produce toxins, which cause massive internal tissue destruction and swelling. The bacteria can also enter the blood and cause blood poisoning. The first symptoms can appear one to several days after inhalation, and include general flu-like symptoms, fever and fatigue. Severe respiratory distress and then death will occur in 24-36 hours.

Anthrax – An Ideal Organism for Biological Warfare

Anthrax is an ideal organism for biological warfare use. Anthrax is 100% lethal if not treated before symptoms appear. There is no effective treatment available once symptoms have occurred. This is a critical issue for troops since there is no indication of exposure to anthrax until after the symptoms have appeared – and then it is too late.

Anthrax spores can be produced in large quantities with basic biological techniques. It grows easily and can be used as a dry powder or as slurry (slush) for aerosol spray. Anthrax spores can be stored for decades without losing their viability. They can be delivered by missiles, rockets, artillery, and sprayers. Anthrax can be stored in filled munitions, as well as in dry or liquid bulk.

Anthrax particles can be achieved in the 1-5 micron range, which is optimal for suspending absorbed biological warfare agent in an aerosol cloud

and carrying it over long distances. This range also represents the optimal particle size for inhalation exposure.

The equipment for anthrax spore production is dual use. Illegal production can be concealed in legitimate production industries. Additionally, legitimate public health and veterinarian needs for vaccines and bio-pesticides can camouflage agent production.

Anthrax is considered a cost-effective alternative to other weapons of mass destruction methods. A smaller quantity is required for the same area of coverage when compared to other weapons of mass destruction means. For comparison, for 120 square kilometers of coverage, you would need one-megaton yield of nuclear material, 158 metric tons of a chemical agent, and only 6.5 kilograms of anthrax. Anthrax is 100,000 times more lethal than chemical agents.

Vulnerabilities

With no advance warning of an anthrax attack, we will have no indication that the attack has occurred. Anthrax has no smell, no taste, no color, and no odor. The aerosol cloud of anthrax will not be detected.

Weaponization Conditions

In order for anthrax to be used as an effective biological warfare agent, it must be weaponized. Optimal delivery involves release of the agent in a particle cloud suspended in air (aerosol), light wind conditions and dispersion in non-daylight hours to minimize the dilution of the aerosol cloud and light induced degradation of the agent.

The aerosol anthrax particles would remain suspended in air and travel with the wind currents for a considerable distance. If disseminated at night near the ground or water surface, they can be expected to form a cloud with the potential to remain relatively intact for several hours while slowly moving across the terrain or water surface. Except for a short time in the immediate vicinity of the release, the aerosol will not be visible, and would be inhaled without the victim's knowledge. It is this profile which makes it impossible for our troops to assume a reactive protective posture.

Even with appropriate data to assess a cloud's predicted path of movement, it would be difficult at best given varying weather and terrain effects. Air stability, temperature, relative humidity, pollutants, cloud coverage, and precipitation all affect biological warfare agent duration and effectiveness. It is traditional to expect a biological warfare attack in the early morning and late evening when air stability is optimal and direct sunlight is minimal. As the agent aerosol is transported away from the site of initial dissemination, it is subject to gradual dilution by dispersion, as well as to decay resulting from the effects of sunlight and other environmental factors.

Dissemination Means

Anthrax can be disseminated by a wide variety of means. Missiles, rockets, artillery, aerial bombs, and sprayers mounted on aircraft, cars, boats, as well as hand-held sprayers, make effective dissemination means.

In the case of less efficient biological warfare delivery means, such as bulk-fill missile warheads or artillery shells that detonate on impact, the area

of coverage for each kilogram of agent will be reduced. Even though a significant percentage (as high as 95%) of the agent may not be effectively aerosolized by bulk-fill weapons, the resulting exposure hazard in the immediate area of the attack could have significant operational impact. Given this scenario, we would still expect an infected area of 1 square kilometer per kilogram, and some downwind exposure hazard for several kilometers.

Scenarios for Use

United States forces face a growing possibility of exposure to biological agents in situations over a wide range of contingencies. At one end of the spectrum is deliberate, high-concentration agent exposure resulting from an enemy missile attack on a military facility. At the other end is low-concentration agent release caused by an accident at a foreign biological warfare research and development facility that impacts our forces engaged in peacekeeping operations.

The Threat

At least 10 countries have or are developing a biological warfare capability. Several of these countries are suspected of developing anthrax as a biological warfare agent. As offensive biological warfare programs proliferate and expand, the exposure threat presented by some biological agents may well become comparable to that attributed to the endemic disease hazards (for example, diphtheria, influenza, and tetanus) for which our active-duty and reserve personnel are now routinely vaccinated.

Iraq

Iraq admitted to weaponizing anthrax. They declared 10 Al-Husayn Missiles, 50 R-400 bombs, and 3 MIG-21 with spray tanks. They also acknowledged research on 155mm artillery shells, artillery rockets, and aerosol generators. Iraq claimed to have destroyed these munitions, but to date UN monitors have not been able to verify these claims. Iraq also declared 8,500 liters (2,245 gallons) of concentrated anthrax, as well as several other biological warfare agents.

Al Hakam, a confirmed biological warfare Anthrax and Botulinum toxin production facility in Iraq, was destroyed in 1996 by UNSCOM. Iraq had maintained that it was a legitimate civilian facility designed to produce single-cell proteins and bio-pesticides. Al Hakam's remote location and the security involved in its construction suggested that it was intended to be a biological warfare production facility from the outset.

Experts conclude that Iraq retains sufficient technology components, data, and scientific expertise to resume development and production of biological weapons. Although the UNSCOM inspections severely curtailed Iraqi WMD programs, even a small residual force of operational biological warfare missiles would pose a serious threat to neighboring countries and U.S. military forces in the region.

Iran

Iran has a growing biotech industry, significant pharmaceutical experience, and the overall infrastructure to support its biological warfare

program. It continues to pursue dual-use biotech equipment and expertise from Russian and other sources, ostensibly for civilian reasons. Iran has had a limited capability to employ biological warfare agents since at least 1986.

Syria

We assess Syria is pursuing development of a biological warfare program and has the biotechnical infrastructure capable of supporting limited agent development. Syria's mature chemical warfare program likely is a source of biological weaponization technologies.

Libya

Libya's biological warfare program most likely has not advanced beyond the research and development stage, although they may be capable of producing small quantities of biological warfare agent.

North Korea

Although little is known on North Korea's biological warfare program, we suspect they are capable of producing and weaponizing several biological warfare agents, which include anthrax, cholera and plague.

Former Soviet Union

Since the inception of the biological warfare program prior to the Second World War, the Soviet Ministry of Defense systematically improved their biological warfare weapons characteristics and production capabilities for anthrax. During the peak of the cold war, the Soviet Union had the capability to produce thousands of tons of anthrax agent. Anthrax was considered the 'backbone' of the Former Soviet Union's offensive biological warfare program.

Biological warfare in the Former Soviet Union has received substantial press coverage over the past two years, to include a book entitled Biohazard by Dr. Ken Alibek, the Former Soviet Union's former Director of the premier anthrax facility located in Stepnogorsk, Kazahkstan. These books detail many events surrounding the capabilities of the Former Soviet Union with regard to biological warfare agents, facilities, and weaponization.

Former Soviet Union biological warfare scientists have detailed the Soviet research and development of anthrax as a biological warfare agent. The 1979 Sverdlovsk anthrax accident confirmed the Soviet Union's production on the bacteria, as well as the lethality of an anthrax aerosol cloud. Even prior to this accident, a leak from an alleged defective reactor in the Kirov bacteriological facility spread anthrax into the city's sewer system. Although no deaths were reported, an apparent new strain, more virulent than the original was isolated in the sewer rats several years later.

We also know that the research goals of the Soviet biological warfare program included the development of antibiotic resistance strains, and that this was likely accomplished by the early 1990's. To date, no information corroborates development of a vaccine-resistant strain of anthrax biological warfare agent.

Through scientific literature analysis, we have observed a continuing robust Russian research, development, and production effort on the anthrax organism. The difficulty is determining whether this ongoing effort at facilities

formerly associated with anthrax biological warfare agent work, is for legitimate purposes or a continuation of offensive related activity.

According to Russia's 1992 declaration of past biological warfare activity to the Biological and Toxin Weapons Convention (BWC), Russia admitted that anthrax was an agent researched at Soviet Ministry of Defense facilities and its 'effectiveness was evaluated'. While the declaration states that 'only models of biological ammunition and spray devices were ever developed', Dr. Alibek and others claim that by the mid 1980s, the Soviets had perfected delivery of anthrax as a biological warfare agent using a wide range of delivery systems, to include ballistic missiles.

Although the Former Soviet Union program has certainly been downsized and restructured from the era where thousands of scientists engaged in biological warfare development, the current status of all facilities is not known, nor do we know the whereabouts of former biological warfare scientists previously engaged in offensive activity.

China

China continues to maintain an offensive biological warfare program. They possess a sufficiently advanced biotech infrastructure to allow development of biological warfare agents. Additionally, its munitions industry is capable of weaponizing of biological warfare agents.

Terrorism

Anthrax is also a potential terrorist weapon because of its relative ease of production. It does not require conventional military equipment or personnel

for production or dissemination. Aerosol generators and spray equipment needed for dissemination is commercially available, as are easily concealed portable devices. These items could be used by terrorists in attacks against military or civilian targets. Devices as simple as insecticide spray cans can be used to introduce anthrax into heating, ventilating, and air conditioning systems. Nevertheless, terrorists contemplating anthrax attacks face technological challenges.

The Aum Shinrikyo sect reportedly had anthrax, and claimed to have attempted dissemination of anthrax during several 1993 attacks in Tokyo using improvised sprayers on buildings and trucks. They had difficulties with clogged sprayers and the anthrax itself, but demonstrated the scientific capability necessary to work with anthrax as a biological warfare agent.

Currently, while some international terrorist groups are interested in developing the capability to use biological agents, other than the Aum Shinrikyo's past incidents, there are no confirmed indications that other groups are specifically developing anthrax. International terrorist group activities have primarily focused on chemical rather than biological materials.

Conclusions

In conclusion, anthrax represents the primary biological warfare threat to United States forces and interests. It is the most widely adopted agent in foreign biological warfare programs. An attack will likely come with little to no warning with potential catastrophic impact. Because of this, anthrax deserves its reputation as an effective and deadly biological warfare agent.

Thank you again for the opportunity to testify before this committee. I will be pleased to respond to any questions you may have now, or may wish to provide later.

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Prepared Testimony on Anthrax Vaccination Immunization Program, Submitted To Senate Armed Services Committee

Deputy Secretary of Defense Rudy de Leon, Senate Armed Services Committee, United States Senate, Thursday, April 13, 2000

INTRODUCTION

Chairman Warner and Distinguished Committee Members, I am honored to appear before your Committee today to address your questions on the Department of Defense (DOD) Anthrax Vaccine Immunization Program (AVIP). I am Rudy deLeon, Deputy Secretary of Defense. I am accompanied by the Honorable David Oliver, Principal Deputy Under Secretary of Defense, Acquisition and Technology, Lieutenant General Ronald R. Blanck, Surgeon General of the Army, and Major General Randy L. West, Special Advisor for Biological Defense, Office of the Secretary of Defense. At your request, our testimony will specifically address the anthrax threat, the safety and efficacy of the anthrax vaccine, an update on the immunization program and program reports on the procurement of new vaccine.

THE THREAT

General - Currently, about a dozen nation states are known to possess, or have in development, a biological warfare capability. The is also evidence that a small number of terrorist groups appear to be interested in biological agents. The production of biological warfare agents does not require specialized equipment or advanced technology. When comparing equal amounts of biological and chemical warfare agents, the biological agent is far more potent. Small quantities of biological agents can produce large numbers of casualties. Biological agents can be delivered through a number of means including aerial bombs, artillery shells, long-range missiles, agricultural sprayers, and spray tanks carried by aircraft, ships, boats or even automobile. Many of the materials and equipment that are used to produce biological warfare agents are available from legitimate sources and intended for other uses such as pharmaceuticals or biopesticides. This makes it difficult to limit the spread of biological warfare technologies and capabilities.

Anthrax Itself - Anthrax is an infectious disease caused by the bacterium Bacillus anthracis and is spread by contact with infected animals, handling infected products, eating infected meat, or inhaling weapon-dispersed anthrax spores. Of all known biological warfare agents, anthrax spores are the top choice in biological weapons for "germ warfare." Several of the countries that have or are developing offensive biological warfare capabilities are most likely working with anthrax. Iraq has admitted to producing and weaponizing anthrax. The anthrax accident at Sverdlovsk in 1979 illustrated Russia's military research with the organism.

Anthrax Facts - Compared to many other pathogens with BW potential, anthrax cultures are relatively easy to obtain. Large quantities of the bacterium can be produced in readily obtainable fermentation vessels. The organism can convert to a spore form that can be stored as bulk agent or in filled munitions. When disseminated in air, the spores remain viable much longer than other types of infectious agents. The size of the spores (approximately 1-micrometer) is such that when inhaled, they tend to be retained in the lung. The effects are usually lethal unless rapid diagnosis is made and a combination of appropriate medical measures is administered immediately. One deep breath can inhale enough spores to result in fatality. Initial symptoms can begin as early as 1 to 3 days after exposure and mimic a common cold or the flu. For the vast majority of inhalation anthrax victims, it is too late for help, once symptoms occur. Post-exposure vaccination or antibiotic treatment for these victims will not likely be effective. The vaccination must be administered prior to symptom onset, in order to be effective.

Anthrax is a deadly and stealth disease that is colorless, odorless, and tasteless, making it very difficult to detect. And, if detection does not occur, there may not be enough time to warn, prepare or diagnose so that effective medical treatment can be administered. If untreated, death is almost certain and, depending on the exposure, can occur within 1 to 5 days after symptoms first begin. Lethality approaches 100% for unvaccinated persons who are contaminated and do not receive antibiotics, before symptoms appear.

Anthrax is considered an effective biological weapon because:

- Spores can be produced in large quantities using basic knowledge of biology.
- Spores can be stored for years without losing viability.
- Spores can be easily spread in the air by missiles, rockets, artillery, aerial bombs & sprayers.

SAFETY AND EFFICACY

The Department is using a vaccine that is proven both safe and effective for individuals at risk of exposure to anthrax spores. The anthrax vaccine has been licensed since 1970 and utilized for decades. It has proven to be a safe vaccine. The vaccine was also re-assessed in the 1980s when responsibility for biological medicine transferred from the National Institutes of Health's Division of Biological Standards to the FDA. Other independent civilian review panels have also recognized the value of anthrax vaccine, including the Armed Forces Epidemiological Board. Twenty-nine plus years of usage and a decade of increased scrutiny confirms the vaccine's safety and has increased our confidence in its efficacy.

Coordinated Surveillance for Anthrax Vaccine Safety - The Department of Defense conducts an aggressive, multi-faceted surveillance program to assess vaccine safety. In fact, the safeguards for vaccine administered to DOD personnel meet or exceed every standard for vaccine administration to the civilian population. Our program includes a wide variety of activities that can be grouped into three main scientific method categories: clinical studies of vaccine recipients; database analysis of vaccine recipient automated medical records; and spontaneous reports.

DOD distinguishes between adverse events adverse reactions. Adverse events are adverse outcomes, for which a cause-and-effect relationship with an exposure (to a medication or vaccine) has not yet objectively been determined. An adverse event becomes an adverse reaction once objective evidence is available to establish a cause-and-effect link between an exposure and an adverse outcome. Table A lists some of the criteria proposed many years ago by famed epidemiologist Sir Austin Bradford Hill that help us make the determination of causal association.

Table A: Causal Association Criteria

Adapted from: Rothman KJ, Greenland S. Modern Epidemiology, 2nd ed. Philadelphia: Lippincott-Raven, 1998:24-28.

The CDC publication, Epidemiology and Prevention of Vaccine-Preventable Disease, 6th ed., January, 2000, discusses the most reliable and conclusive ways to establish causal relationships for vaccine adverse events — and they are relatively few. Causal links between a vaccine and an adverse event may be established if they produce a unique laboratory result, a unique clinical syndrome, or if an epidemiological study shows vaccinated persons are more likely than unvaccinated persons to experience the adverse event.

Numerous clinical studies have been conducted on the safety of the anthrax vaccine. Among them are twelve clinical studies using more than 16,000 vaccine recipients. The known adverse events from anthrax vaccine as demonstrated by these and other studies include local injection site reactions, headache, slight fever, joint pain, and fatigue.

Additional Long -Term Study – While the DOD leadership, its physicians and its research experts are confident of the safety and efficacy of the anthrax vaccine, they are aware of and respect the concerns expressed by a small number of service members about possible long-term health effects. The Department wants to address these concerns using the best, most appropriate scientific knowledge and practices. We will continue demonstrating an ongoing commitment to ensuring the health of our men and women as we implement the AVIP.

To that end, the Anthrax Vaccine Immunization Program Agency convened a team of civilian and military medical experts to design a set of studies to assess the long-term safety of the anthrax vaccine, in response

to requests from Service Members, their families and recommendations of the General Accounting Office. In designing these studies, we have drawn from the accumulated experience of some of the nation's best vaccine researchers at CDC and FDA.

A new long term study is also underway to determine whether individuals who received multiple vaccines, including the anthrax vaccine, during their past employment at Ft. Detrick, MD demonstrated any adverse health effects over the long term. A total of 570 study and control volunteers have been enrolled in this case-controlled study that began in 1996. All volunteers signed an approved informed consent document. The study media included a 9-page health history questionnaire, extensive blood tests and urinalysis. The questionnaire queries mental and physical conditions of progeny as well as the health of volunteers. Study end points include symptoms, symptom complexes (including the Gulf War Illness complex of symptoms), diseases, abnormal laboratory and urine tests. Study subjects will be compared to race, gender, and age-matched control subjects to determine if any long-term medical effects exist among this unique group of study subjects. Analysis of the data from the extensive health history questionnaire and numerous laboratory tests is currently in progress.

We have also initiated a $20 million multi-year research study, under the auspices of the CDC, with the collaboration from the Department of Defense, the Food and Drug Administration, and the National Institutes of Health. This four- objective comprehensive effort will examine risk factors for adverse events, including gender reaction differences, alternate routes of administration, reduced dosage schedule, and immunogenicity build-up and retention. In addition, we are looking at instituting a network for improving the quality of vaccine heath care delivery in the DoD.

Member Concerns - The Department strongly encourages all members who have received the vaccine and feel they have had a negative reaction to report it through the Vaccine Adverse Event Reporting System (VAERS). Not only are members encouraged to submit a report but families or anyone personally aware of a situation can as well. We listen. We are concerned. This has included listening to many members on a one-to-one basis. Members of my staff have personally met with dozens of service members who have voiced concern for the reactions the members believe they have experienced, and talked to or corresponded with many, many more.

Education & Communication – When we spoke to the members on a one-on-one basis we realized that improvements in the program were needed and we have begun them. We want this program to be the best it can be. To do this we have initiated the research I mentioned earlier and have published polices for both administrative and medical exemption. Now, personnel with 180 days or less left before separating from the service, may elect to not receive the vaccine. In addition, there is a written medical waiver policy for personnel who have experienced what could be adverse reactions. While waivers have always been available, they have been reiterated in the waiver policy. The Department is also committed to fully educating our Service Member population and their families on the purpose and value of anthrax vaccination in an unprecedented manner. We use each of the following communications media to accomplish this goal:

◆ A sophisticated anthrax specific website www.anthrax.osd.mil with multiple layers of information and methods for communicating with our Service Member population, their families, and other DOD beneficiaries and concerned members of the American public.

◆ Three Service - specific anthrax websites hyper-linked to all known military and civilian websites discussing anthrax, biological weapons, health care, domestic preparedness, terrorism, VAERS reporting, preventive medicine, infectious disease, etc.

◆ Quad-fold information sheets individually tailored for Service Members, Family Members and Civilians. DOD has provided each Service Member receiving the vaccine with printed silent training aides since administering the first doses in March 1998. The current quad-fold brochure explains the threat of biological weapons, the benefits of anthrax vaccination and the known risks from the vaccine. The Quad-fold also includes information aimed specifically at Reserve Component personnel accessing care.

◆ DOD Leaders Briefing required to be given to all Service Members prior to receiving the anthrax immunization. Distributed by each Service and prominently posted on the www.anthrax.osd.mil website.

◆ DOD Health Care Providers Briefing given to all DOD health care providers administering the anthrax vaccine — who then serve as teachers, coaches, mentors for supervisors, commanders, Service Members and their families. Distributed by each Service and prominently posted on the www.anthrax.osd.mil website.

◆ Open House/Speakers Bureau briefings and open educational forums for all Service Members and their families.

- A 1.877.GETVACC telephone hotline.

◆ A variety of anthrax vaccine 'silent training aids'. These highly visible training aids emphasize the key themes of the anthrax threat, safety and efficacy of the vaccine, adverse event reporting, etc.

◆ Armed Forces Information Service news media, local installation print, radio and television news service initiatives.

◆ A state-of-the-art Anthrax Education CD-ROM is in development and it will provide Service Members, their families, supervisors, commanders and health care providers with tailored, multimedia information on the anthrax threat, safety and efficacy of the vaccine, signs, symptoms and prevention of the anthrax disease.

◆ An Anthrax Vaccine Immunization Program Videotape explaining the threat, safety, efficacy of the vaccine. The video features prominent civilian and Government scientists and vaccine experts explaining and endorsing the vaccine.

◆ DOD is currently collaborating with CDC to array this information in the format of a Vaccine Information Statements (VISs) the standard vaccine information format that civilian health care providers around the country give America's children, adolescents, and adults during routine vaccinations (e.g. measles, polio, tetanus).

◆ Clinical Practice Guidelines for Management of Adverse Events After Any Vaccination that are based on a consensus panel of civilian and military physicians experienced both in immunology and the general provision of health care.

Our anthrax vaccine program is one of the most studied, reviewed and examined programs in the Defense Department. The most current are reviews by the General Accounting Office and the Inspector General. We are aware of the issues raised in these studies and are taking steps to address them. There is concern for the stockpile and we, as a Department, are addressing the issue objectively with interim requirement dosage supply contingency plans being developed. We are also aware of the financial condition of the anthrax vaccine manufacturer BioPort Corporation. The company, and its management, have improved over the past quarter and seem determined to continue in that direction.

Another issue is FDA licensing. The need for FDA approval of BioPort's Supplemental Biologics Application License (BLA) is also an area of media and opponent attention. We expect BioPort to achieve FDA approval of the BLA Supplement for assured production of the vaccine this calendar year. Continuing the program uninterrupted until FDA approves the BLA supplement requires FDA release approval of additional lots previously manufactured by Michigan Biologic Products Institute (MBPI). BioPort has submitted information on several lots and we are optimistic sufficient amounts will be released to continue Phase I uninterrupted.

PROCUREMENT AND PROGRAM

Anthrax Vaccine Adsorbed is produced by the BioPort Corporation of Lansing, Michigan, which is the only FDA licensed establishment for the Anthrax Vaccine Adsorbed. BioPort's facility has been licensed to manufacture the anthrax vaccine since 1970.

In the fall of 1998, BioPort became the sole licensed producer of the anthrax vaccine via a privatization process initiated by the State of Michigan. In September 1998, BioPort was awarded a contract for production of the anthrax vaccine. In August 1999, DOD renegotiated the contract and provided extraordinary contractual relief under authority of PL 85-804.

This action was necessary to preserve the company's financial viability and ensure uninterrupted production of the anthrax vaccine. The necessity to renegotiate BioPort's contract resulted from poor accounting of production costs prior to privatization and a lack of adequate resources. Even though, during state ownership the Michigan taxpayers subsidized the Defense Department's procurement of Anthrax vaccine, BioPort discovered that more work was required to bring the facility up to the state of the art, and that, the vaccine

cost more to produce than anticipated. The Defense Contract Audit Agency verified the need for the extraordinary contractual relief and a recent DOD IG report validated that it had been done in accordance with Federal Acquisition Regulations. The Department of Defense continues to work with BioPort, the only FDA licensed manufacturer of the anthrax vaccine, to ensure the viability of the facility with the production capability to provide a sufficient supply of the vaccine to meet Department of Defense requirements. If BioPort enters into bankruptcy, the immunization program to protect the U.S. service members is at risk and our warfighters will be vulnerable to the extremely lethal and present danger of anthrax exposure resulting from biowarfare or bioterrorism.

SUMMARY

Our Service men and women in at least two major theaters go to work everyday in areas where bioweapons could be delivered at any time. There is a limited availability of Bio-detectors and sensitivity is a concern. Protective clothing and equipment are available, but they cannot be comfortably used for long periods of time. Antibiotics are available, but must be used in the first few hours of exposure, before initial symptoms appear. Those same service personnel would also be incapacitated with severe diarrhea for a period of time. The superior form of protection is vaccination.

Our personnel deserve our best and fullest protection. The FDA licenses the current vaccine for that full protection with the complete six-shot regimen. We cannot wait until the balloon goes up to begin the vaccination. Being vaccinated may very well save the life of thousands of America's men and women in uniform, should some state or terrorist organization elect to employ what we know they are already capable of using. It would be a dereliction of duty to have the anthrax vaccine capability we presently have and not make it part of the arsenal of protection that we provide to our servicemen and women. We hope anthrax is never used as a weapon, but if it is, we must be ready!

Protecting the Total Force Against Anthrax

Statement by

Charles L. Cragin

Principal Deputy Assistant Secretary of Defense for Reserve Affairs

To

Subcommittee on National Security, Veterans Affairs,

and International Relations

Committee on Government Reform

U.S. House of Representatives

September 29, 1999

Mr. Chairman, distinguished members of the Committee.

I welcome the opportunity to be here today to discuss the Department of Defense's efforts to protect the Total Force, and in particular the members of our Reserve components, against the very real and growing threat of weaponized anthrax. This vital force protection issue deserves your full attention, careful deliberation and continuing support.

My statement begins with a brief overview of the rationale behind the Department's decision to implement the Anthrax Vaccine Immunization Program (AVIP). It then addresses the impact of the AVIP on the recruiting, retention, readiness and morale of our National Guard and Reserve forces; the criteria used to select Reserve component (RC) units for enrollment in the AVIP; and the factors considered in setting definitive dates for RC units to begin inoculations. In addition, this statement discusses the operation of the AVIP tracking system; the accuracy of the Defense Eligibility and Enrollment Reporting System (DEERS) data; and the extent of enrolled RC compliance with the FDA-approved immunization regimen.

Why We Are Protecting the Total Force against Anthrax

The Gulf War and the recent air campaign over Kosovo were both prime illustrations of the awesome technological and military superiority of our armed forces. However, these advantages may also prove to be our greatest weaknesses, prompting future adversaries to strike with asymmetrical or non-conventional means, which may include chemical or biological weapons.

Today, at least 10 countries, including Iraq and North Korea, now have—or are attempting to acquire or produce—these deadly, insidious weapons. When it comes to germ warfare, anthrax remains the weapon of choice. In the words of Secretary of Defense William S. Cohen, anthrax "is very easy to weaponize and almost always deadly."

In an effort to protect our military personnel from the anthrax threat, the Department of Defense has begun immunizing the Total Force with the anthrax vaccine. Over the next seven years, 1.4 million active duty personnel and some 900,000 members of the Selected Reserve will be immunized.

For those who inhale anthrax but have not been vaccinated, death is the ultimate and predictable outcome. For the unvaccinated, the onset of clinical symptoms means that most will die, despite the most heroic, state of the art, post-exposure medical intervention and treatment. But much of this death can be prevented by vaccination—in fact, the anthrax vaccine provides our men and women in uniform with their best chance of survival.

The anthrax vaccine is as safe as most common vaccines. It has had an excellent safety record since it was first licensed and approved by the Food and Drug Administration (FDA) in 1970. In fact, before Secretary Cohen authorized the use of a single dose, he ordered supplemental testing of the vaccine, further ensuring the vaccine's safety.

I have taken four in the series of six anthrax shots as required by the FDA for best protection. Secretary Cohen, General Henry H. Shelton,

the Chairman of the Joint Chiefs of Staff, and numerous other senior military and civilian leaders, including the Chiefs of all the Reserve components, have done the same, and they too are on their way to being protected against this threat.

The anthrax vaccination protection program was unanimously recommended by the Chairman and the Joint Chiefs of Staff. Vaccination is a requirement for all service members and must remain so—voluntary participation is not an option, for it would result in having only part of our force protected and would open the way for uncertainty and unacceptable risk in battle. When our personnel go into battle, they need to know that all, and not merely some, of those who serve with them have full protection from weaponized anthrax. A voluntary program would mean a less well protected force, which would create unnecessary vulnerabilities for our troops, endanger mission accomplishment, and impact the overall combat effectiveness of our personnel.

What we are doing today is no different from what we have always tried to do: we are taking prudent measures to protect the Total Force. We routinely vaccinate military personnel against many diseases, including tetanus, diphtheria, influenza, hepatitis A, measles, mumps, rubella, polio, and yellow fever. Like the anthrax vaccine, the vaccinations for these diseases are FDA-approved and effective. The anthrax vaccine will protect our men and women in uniform from yet another disease—a disease that will kill, a disease that can be used as a weapon.

If we were to deny our military personnel protection from anthrax, we would be denying them the protection they need to undertake the critical missions they are called upon to perform. Just as we would not deny them helmets and flack jackets, we cannot send them into battle without protection from anthrax. In short, we have an obligation to give our personnel the best protection available from all anticipated threats—anthrax is one of those threats; and the vaccine offers safe and effective protection.

Our men and women in uniform, their families, the American public and the Congress rightly expect the Department of Defense to meet the highest standards of force health protection and ensure that those who defend our nation are equipped to meet the threats that they may face on the battlefield. Failing to provide our personnel with protection against anthrax would be the equivalent of failing to fulfill our solemnly sworn duty to protect them on the battlefield. We have no alternative other than to proceed with this program—it is the right thing to do, and we have a moral obligation to see it through.

Recruiting, Retention, Readiness and Morale

Mr. Chairman, we view the recruiting, retention, readiness and morale of our service members, both active and reserve, as paramount to the viability and sustainability of our military forces. Our personnel are our most precious resource. Throughout the military services and across the nation, we are working tirelessly to recruit our nation's best and brightest and retain them in the service of their country.

Over the past weeks and months, I have had many conversations with the Chiefs of the Reserve components to discuss the impact that the anthrax protection program is having on our forces. In addition, I travel nearly every weekend, around the world and here at home, to visit with National Guard and Reserve personnel—and anthrax protection has been a topic in our discussions. Let me give you a sense of what our personnel and their leaders are telling me.

First and foremost, we must be aware that, except in a very small number of cases, the anthrax vaccination program is not the determining factor behind a member's decision to withdraw from military service. However, we must also acknowledge that, in some cases, concern about the program can, has been and will continue to be a factor in the decision of some service members to leave the force.

Reservists decide to leave military service for many reasons, including pressures or demands related to their civilian jobs or employers; the recent high optempo that all of our personnel have had to endure in the aftermath of the Cold War, and the resulting strains on family relationships; service-related illnesses or injuries; and the fact that some people may simply no longer find military service rewarding or challenging. To these very disparate factors we must also add the tremendous impact of today's booming economy and the temptations, both monetary and professional, which may draw our people away from continued military service and into the civilian sector.

These combined forces, rather than the prospect of anthrax vaccination, help explain why we continue to face challenges in the recruiting and retention realms. We should not look to a single-factor explanation, such as concern about anthrax vaccinations, to account for the decline in recruiting and retention that has generally characterized the Total Force in recent years. According to the Chiefs of the Reserve components, recent recruiting and retention trends do not show any substantial increase or decrease attributable to the anthrax vaccination program. And although the military recruiting market has posed significant challenges to all Services, both active and reserve, in the past few years, we currently see no appreciable impact as a result of implementation of the anthrax vaccination program.

As for the readiness of our Reserve components, we have not seen a sufficient number of refusals, or departure of personnel, attributable to concern over the anthrax vaccine that would degrade, impair or compromise mission capability or operational readiness. As a matter of fact, in the past few days, I have spoken personally with the commanding officers of many of the units that have been experiencing personnel challenges regarding anthrax, and each of them has assured me unequivocally that their units remain fully mission capable and ready for service.

Despite the current negligible impact of the anthrax protection program on readiness, the Department of Defense continues to monitor the situation carefully and constantly. If or when anthrax vaccinations are cited by a service member as a reason for leaving or seeking reassignment, or if they indicate their intent to refuse the shot, reserve commanders in the field make conscientious efforts to educate and inform their personnel about the nature and purpose of the protection program. The commander's goal is to help their personnel fully understand and appreciate the nature of the threat and the necessity of vaccination. Some commanders provide education and counseling over a 3 month period to ensure relevant information is presented in a non-confrontational manner, allowing time for reluctant members to make a reasoned decision concerning their participation. These efforts are being undertaken within a very challenging administrative framework, especially in light of the fact that most commanders can plan on only sixteen hours a month (or one drill weekend) in which to formally communicate with their personnel.

Admittedly, the Department's efforts to inform and educate reserve personnel about the anthrax protection program were not initially as robust as they should have been. That matter is now being addressed and, towards that end, we are working hard to better educate our service members about the nature of the anthrax threat and provide them with credible and convincing information about the vaccine's safety and efficacy. Increasingly, as the anthrax protection effort matures, we are reaching out to service members well before their initial vaccination and providing a range of educational and information tools. We are also communicating directly with them, both shortly before and at the time of vaccination. Our communication effort is becoming increasingly broad in scope, sophisticated in its approach and flexible in terms of its implementation. We are endeavoring to be more responsive to the needs of individual units and components; and our efforts regularly include commanders' calls, briefings, brochures, videos, the Internet, and a toll-free "877" phone line to answer questions and address concerns.

As I have said, the anthrax vaccine is safe, effective and FDA-approved. To further support these facts, we are making our personnel aware of independent assessments. We are providing them with information from the Food and Drug Administration, the Centers for Disease Control, the Institute of Medicine, the Presidential Advisory Committee on Gulf War Illnesses, and the Airline Pilots Association, among others. More independent assessments will be forthcoming.

To provide our reserve service members with additional assurance, Dr. Sue Bailey (Assistant Secretary of Defense for Health Affairs) and I have disseminated a policy which ensures that we take care of our people if they have any vaccine-related health problems. The memorandum reinforces existing policy and directs commanders of medical treatment facilities (MTF) to provide full access to reserve component personnel at Department of Defense MTFs for evaluation and treatment of adverse events potentially related to any DoD-directed immunizations, to include anthrax. Reserve service members can also refer to their own physicians if they choose. We plan to develop additional educational information to help civilian physicians who may be unfamiliar with the vaccine. The bottom line is that if there is a vaccine-related health problem, we are committed to taking care of the service member and have made extensive provisions to provide the necessary and appropriate medical support.

Our efforts to nurture and sustain Total Force awareness about the safety and efficacy of the anthrax protection program are now being combined with ongoing measures to enhance command emphasis, provide thorough and comprehensive medical support, and furnish independent assessments to our personnel. Our objective is to address, credibly and convincingly, the concerns of reservists as we move forward in protecting them from the threat of weaponized anthrax. And despite the media attention and scrutiny that this issue sometimes receives, I can say to you with complete confidence that, overall, the program has not significantly affected the readiness and morale of our reserve forces. Nor has it had a significant impact on our ability to recruit and retain personnel in the Reserve components.

While it is true that some service members have concerns about the anthrax protection program, we are working tirelessly to alleviate those concerns through an intensive educational and leadership outreach effort. The vast majority of our personnel currently requiring vaccination have taken the anthrax shots. Many have done so because they realize that the anthrax vaccine is the best option and the right choice for protecting our forces from a valid threat. Within this context, we have not been able to convince everyone about the wisdom and necessity of this course of action and, as a result, we have lost some valuable people. We may lose more in the future. Although that would be regrettable, it would not be nearly as tragic as the losses we would incur in the event of an anthrax attack against unvaccinated personnel.

Criteria Used to Select RC Units for Enrollment in AVIP

All military personnel are not being immunized immediately, due largely to limited production capabilities and stockpiles. Initial immunization is a priority for personnel deploying to the Korean peninsula or Southwest Asia (SWA), which includes Kuwait, Saudi Arabia, Bahrain, Jordan, Qatar, Oman, United Arab Emirates, Yemen, and Israel. Second priority goes to those who are on mobility status and who have the potential to deploy early to high-threat areas. The lowest priority—and, consequently, the last to begin the immunization program—will be the remainder of our personnel. Reserve forces are included in all three groups.

Accordingly, the Department's anthrax effort has three phases:

- Phase I. Forces assigned or rotating to high threat areas of SWA and the Korean peninsula

(Accelerated phase began March 1998)

- Phase II. Early deploying forces (C to C+35) into high threat areas of SWA and the Korean peninsula

  (Projected start of 2nd quarter of FY 2000)

- Phase III. Remainder of Total Force, accessions, and program sustainment

  (Projected start of 2003)

Selected Reserve units and individuals will be scheduled for vaccination based on where they fit into these three phases. For example, National Guard or Reserve personnel who are deployed or are expected to delpoy early to Southwest Asia or the Korean peninsula are in Phase I, and would begin their shots before deploying. This includes many Air National Guard and Air Force Reserve pilots and air crews who are rotating in and out of high threat areas. The majority of Selected Reserve units will be vaccinated in Phase III, beginning in 2003.

As part of this process of phased immunization, on March 30, 1999, the Department announced the implementation of the "One Day Policy," which states that all Service members and DoD emergency essential civilians and contractors deploying to a high-threat area for any period of time, even one day, must initiate the anthrax vaccination regimen. Ideally, personnel should at least receive the first three vaccinations in the series before deploying.

As a result largely of the One Day Policy, more than 27,000 Selected Reserve component personnel in nearly all of the 54 states and territories have already begun anthrax vaccinations (see chart below). Overall, nearly 340,000 men and women in uniform have received over 1.1 million shots.

Reserve Component Vaccinations (As of September 24, 1999)

Reserve Component	Total Individuals (At Least 1 Vaccination)	SELRES End Strength (July 1999)
Army SELRES	2,388	202,126
Army Guard SELRES	2,824	356,438
Navy SELRES	1,981	90,842
Air Force SELRES	8,781	71,033
Air Guard SELRES	10,486	105,866
Marines SELRES	710	40,583
Coast Guard SELRES	16	8,151
Total	27,186	875,039

Tracking and Reporting Anthrax Inoculations

Anthrax vaccination data for the Total Force can be found in the Defense Enrollment Eligibility Reporting System (DEERS), which serves as the Department's master repository for such information. Let me take a moment to lay out the process by which vaccinations are tracked, and what is being done to streamline and improve that process.

We currently have a "triple-redundancy" system that records vaccinations in three key places – "yellow" shot cards carried by individual personnel; individual medical records used by health care providers; and automated data systems for commanders. Each service maintains its own tracking system (MEDPROS for Army; SAMS for Navy, Marines and Coast Guard; RSTARS for Naval Reserve; and MITS for Air Force)* —each of which feeds into DEERS. If information is not entered properly or in a timely fashion, the accuracy of tracking data contained within DEERS can be impacted. As a result of data entry errors and the time lag in getting data transmitted, DEERS data slightly

lags behind the Service systems that supply data to DEERS. Nevertheless, I can report with confidence that the tracking systems used by individual services are more current and complete than DEERS, and they continue to provide commanders with the information they need to track vaccinations.

In an effort to address the challenge of ensuring that service-specific tracking data is accurately reflected in DEERS, we are in the process of merging all service-specific systems into one comprehensive, streamlined and easy-to-use automated system. This merger entails a tremendous amount of work and a significant amount of time, but the payoffs in force health protection tracking will be profound and long-lasting.

Our interim tracking systems are functioning much more proficiently than in the past, but the new comprehensive system will help us perform even better. This common system will feed data directly into DEERS, be available to any unit with access to the Internet, be easy to use, and support the commander's tracking of the personnel in his unit who need shots.

Although DEERS currently (and consistently) indicates significant shortfalls in our efforts to meet vaccination timelines, closer analysis of overdue shot tracking data reveals a more complex picture. The Reserve components actually fall within the 70 to 90 percent range with regard to shots being administered within 30 days of the due date. Most of the "overdues" are the result of tardiness in reporting, rather than lack of timeliness of vaccination. A case in point is the Connecticut Air National Guard. Though the data shows it to be in excess of 90 percent overdue, only five percent of the state's Air Guard personnel are actually overdue for shots. The discrepancy is primarily due to data recording and transmission problems.

Though we are working hard to ensure the timeliness of vaccinations and are doing far better than in the past, we have not consistently met our own stringent standards. We are working aggressively to bring all the Reserve components up to the 90 percent standard. Throughout the entire force, both active and reserve, we are improving the timeliness of vaccinations and their reporting through a concerted effort by commanders at the national, state and unit level. We have analyzed why the "overdues" are as high as they are. We have sorted out "data reporting" issues from "shots in arms" issues. And we have launched aggressive efforts to address both sets of issues. In short, we are working assiduously to resolve the outstanding challenges, and the Reserve Chiefs and I assure you that this situation will continue to improve.

RC Compliance with the FDA-Approved Protocol

The anthrax vaccine has a stringent FDA-approved shot protocol, which presents unique challenges to the Reserve components. While active duty personnel are available for vaccination virtually any day throughout the year, the availability of reservists varies throughout the month. Coupling that with the availability of medical personnel makes strict compliance with the FDA-approved protocol a very demanding challenge for our service members and commanders alike. In addition, many reserve units are very small, located in isolated communities, and less likely to have computers and other equipment that are compatible with the automated tracking systems. Small units may also have limited or no refrigerated storage for the anthrax vaccine. Many units, especially those in the Army National Guard and Army Reserve, do not have medical resources embedded within their organizations. These create tremendous challenges with regard to our efforts to comply with the FDA-approved protocol for the vaccine.

Although these challenges are not easily surmounted, we intend to do just that and conform to the protocol. Towards that end, we have negotiated contracts with non-military health agencies, the Department of Veterans Affairs, and Federal Occupational Health organizations to provide shots to Army National Guard and Army Reserve units. As I mentioned earlier, we have also ensured that the Department's military treatment facilities provide evaluation and care when a reservist has a vaccine-related health concern. In addition, we are assisting small units in finding ways to handle vaccine storage, and we are ensuring that even the most isolated units can have their shots recorded and tracked on a timely and accurate basis. We are arranging alternative times (which fall within the approved protocol) and, in some cases, alternative sites for reservists to get their shots. We are committed to meeting the FDA-approved protocol for shots, and we intend to fulfill that commitment.

Conclusion

In many respects, the future of Total Force health protection depends upon how well we implement the anthrax vaccination program. This program will set the tone and tenor of future efforts—efforts that will very likely need to be undertaken repeatedly in the next millennium, as our adversaries seek new and more effective ways to counter our military and strategic superiority. Faced with our awesome technological prowess and the skill and determination of our personnel, future adversaries may look to other forms of attack. The lethality and

accessibility of anthrax may very well prove highly tempting as a means of moderating or neutralizing our forces in the field.

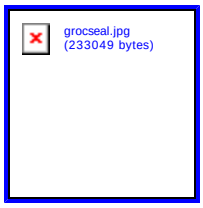
As a result, the Department of Defense has made a leadership commitment to provide our personnel with all the means at our disposal to protect them from any known threats. The anthrax threat is real and growing; and the vaccine offers safe and effective protection. In recent months, and in direct response to many of the challenges that I have discussed here today, the Department of Defense has re-engineered its methods for providing force health protection. This has required a high level of commitment from the Department's senior military and civilian leadership.

We have made substantial improvements in educating our personnel and their families. We have imposed quality controls that vigorously track the flow of the vaccine, from production to vaccination. We have upgraded the level of medical support and information for those with vaccine-related concerns. Most importantly, we have made this a "commanders" program, one in which leaders of the Total Force, from service chiefs on down to the unit level, have direct responsibility and accountability for ensuring that this new force health protection initiative is implemented in a timely and responsible manner.

Mr. Chairman, we are strongly committed to reducing the threat to our forces posed by weaponized anthrax. We intend to meet that threat by providing our personnel with a safe, effective and FDA-approved vaccine.

It is imperative that we continue to meet our responsibilities—to our service members, to the nation and to the Congress—within the realm of force health protection. We have a moral obligation in this regard, and we would be derelict in our duty if we were to decide not to protect our forces from anthrax. Failure to implement this protection program could have profound consequences: sending our men and women in uniform into battle unprotected could result in unacceptable (and preventable) losses and prompt the outrage of the nation.

Thank you very much.



ANTHRAX VACCINATION IMMUNIZATION PROGRAM

Proven Protection Against a Documented Threat

STATEMENT BY

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Honorable David Oliver
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Submitted To

SENATE COMMITTEE ON ARMED SERVICES

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INTRODUCTION

Chairman Warner and Distinguished Committee Members, I am honored to appear before your Committee today to address your questions on the Department of Defense (DOD) Anthrax Vaccine Immunization Program (AVIP). I am Rudy deLeon, Deputy Secretary of Defense. I am accompanied by the Honorable David Oliver, Principal Deputy Under Secretary of Defense, Acquisition and Technology, Lieutenant General Ronald R. Blanck, Surgeon General of the Army, and Major General Randy L. West, Special Advisor for Biological Defense, Office of the Secretary of Defense. At your request, our testimony will specifically address the anthrax threat, the safety and efficacy of the anthrax vaccine, an update on the immunization program and program reports on the procurement of new vaccine.

THE THREAT

General - Currently, about a dozen nation states are known to possess, or have in development, a biological warfare capability. The is also evidence that a small number of terrorist groups appear to be interested in biological agents. The production of biological warfare agents does not require specialized equipment or advanced technology. When comparing equal amounts of biological and chemical warfare agents, the biological agent is far more potent. Small quantities of biological agents can produce large numbers of casualties. Biological agents can be delivered through a number of means including aerial bombs, artillery shells, long-range missiles, agricultural sprayers, and spray tanks carried by aircraft, ships, boats or even automobile. Many of the materials and equipment that are used to produce biological warfare agents are available from legitimate sources and intended for other uses such as pharmaceuticals or biopesticides. This makes it difficult to limit the spread of biological warfare technologies and capabilities.

Anthrax Itself - Anthrax is an infectious disease caused by the bacterium *Bacillus anthracis* and is spread by contact with infected animals, handling infected products, eating infected meat, or inhaling weapon-dispersed anthrax spores. Of all known biological warfare agents, anthrax spores are the top choice in biological weapons for "germ warfare." Several of the countries that have or are developing offensive biological warfare capabilities are most likely working with anthrax. Iraq has admitted to producing and weaponizing anthrax. The anthrax accident at Sverdlovsk in 1979 illustrated Russia's military research with the organism.

Anthrax Facts - Compared to many other pathogens with BW potential, anthrax cultures are relatively easy to obtain. Large quantities of the bacterium can be produced in readily obtainable fermentation vessels. The organism can convert to a spore form that can be stored as bulk agent or in filled munitions. When disseminated in air, the spores remain viable much longer than other types of infectious agents. The size of the spores (approximately 1-micrometer) is such that when inhaled, they tend to be retained in the lung. The effects are usually lethal unless rapid diagnosis is made and a combination of appropriate medical measures is administered immediately. One deep breath can inhale enough spores to result in fatality. Initial symptoms can begin as early as 1 to 3 days after exposure and mimic a common cold or the flu. For the vast majority of inhalation anthrax victims, it is too late for help, once symptoms occur. Post-exposure vaccination or antibiotic treatment for these victims will not likely be effective. The vaccination must be administered prior to symptom onset, in order to be effective.

Anthrax is a deadly and stealth disease that is colorless, odorless, and tasteless, making it very difficult to detect. And, if detection does not occur, there may not be enough time to warn, prepare or diagnose so that effective medical treatment can be administered. If untreated, death is almost certain and, depending on the exposure, can occur within 1 to 5 days after symptoms first

begin. Lethality approaches 100% for unvaccinated persons who are contaminated and do not receive antibiotics, before symptoms appear.

Anthrax is considered an effective biological weapon because:

- Spores can be produced in large quantities using basic knowledge of biology.
- Spores can be stored for years without losing viability.
- Spores can be easily spread in the air by missiles, rockets, artillery, aerial bombs & sprayers.

SAFETY AND EFFICACY

The Department is using a vaccine that is proven both safe and effective for individuals at risk of exposure to anthrax spores. The anthrax vaccine has been licensed since 1970 and utilized for decades. It has proven to be a safe vaccine. The vaccine was also re-assessed in the 1980s when responsibility for biological medicine transferred from the National Institutes of Health's Division of Biological Standards to the FDA. Other independent civilian review panels have also recognized the value of anthrax vaccine, including the Armed Forces Epidemiological Board. Twenty-nine plus years of usage and a decade of increased scrutiny confirms the vaccine's safety and has increased our confidence in its efficacy.

Coordinated Surveillance for Anthrax Vaccine Safety - The Department of Defense conducts an aggressive, multi-faceted surveillance program to assess vaccine safety. In fact, the safeguards for vaccine administered to DOD personnel meet or exceed every standard for vaccine administration to the civilian population. Our program includes a wide variety of activities that can be grouped into three main scientific method categories: clinical studies of vaccine recipients; database analysis of vaccine recipient automated medical records; and spontaneous reports.

DOD distinguishes between adverse events adverse reactions. Adverse events are adverse outcomes, for which a cause-and-effect relationship with an exposure (to a medication or vaccine) has not yet objectively been determined. An ***adverse event*** becomes an ***adverse reaction*** once objective evidence is available to establish a cause-and-effect link between an exposure and an adverse outcome. Table A lists some of the criteria proposed many years ago by famed epidemiologist Sir Austin Bradford Hill that help us make the determination of causal association.

Table A: Causal Association Criteria

1. How strong is the association between the exposure and the outcome?
2. What is the quality of the evidence for an association?
3. Is there a dose-response relationship?
4. Is there consistency among several studies?
5. Is there a specific cause for the effect observed?
6. Did the cause exist before the effect occurred?
7. Is the outcome plausible, given what we know about biology?

Adapted from: Rothman KJ, Greenland S. Modern Epidemiology, 2nd ed. Philadelphia: Lippincott-Raven, 1998:24-28.

The CDC publication, *Epidemiology and Prevention of Vaccine-Preventable Disease*, 6th ed., January, 2000, discusses the most reliable and conclusive ways to establish causal relationships for vaccine adverse events — and they are relatively few. Causal links between a vaccine and an adverse event may be established if they produce a unique laboratory result, a unique clinical syndrome, or if an epidemiological study shows vaccinated persons are more likely than unvaccinated persons to experience the adverse event. Numerous clinical studies have been conducted on the safety of the anthrax vaccine. Among them are twelve clinical studies using more than 16,000 vaccine recipients. The known adverse events from anthrax vaccine as demonstrated by these and other studies include local injection site reactions, headache, slight fever, joint pain, and fatigue.

Additional Long -Term Study – While the DOD leadership, its physicians and its research experts are confident of the safety and efficacy of the anthrax vaccine, they are aware of and respect the concerns expressed by a small number of service members about possible long-term health effects. The Department wants to address these concerns using the best, most appropriate scientific knowledge and practices. We will continue demonstrating an ongoing commitment to ensuring the health of our men and women as we implement the AVIP.

To that end, the Anthrax Vaccine Immunization Program Agency convened a team of civilian and military medical experts to design a set of studies to assess the long-term safety of the anthrax vaccine, in response to requests from Service Members, their families and recommendations of the General Accounting Office. In designing these studies, we have drawn from the accumulated experience of some of the nation's best vaccine researchers at CDC and FDA.

A new long term study is also underway to determine whether individuals who received multiple vaccines, including the anthrax vaccine, during their past employment at Ft. Detrick, MD demonstrated any adverse health effects over the long term. A total of 570 study and control volunteers have been enrolled in this case-controlled study that began in 1996. All volunteers signed an approved informed consent document. The study media included a 9-page health history questionnaire, extensive blood tests and urinalysis. The questionnaire queries mental and physical conditions of progeny as well as the health of volunteers. Study end points include symptoms, symptom complexes (including the Gulf War Illness complex of symptoms), diseases, abnormal laboratory and urine tests. Study subjects will be compared to race, gender, and age-matched control subjects to determine if any long-term medical effects exist among this unique

group of study subjects. Analysis of the data from the extensive health history questionnaire and numerous laboratory tests is currently in progress.

We have also initiated a $20 million multi-year research study, under the auspices of the CDC, with the collaboration from the Department of Defense, the Food and Drug Administration, and the National Institutes of Health. This four-objective comprehensive effort will examine risk factors for adverse events, including gender reaction differences, alternate routes of administration, reduced dosage schedule, and immunogenicity build-up and retention. In addition, we are looking at instituting a network for improving the quality of vaccine heath care delivery in the DoD.

Member Concerns- The Department strongly encourages all members who have received the vaccine and feel they have had a negative reaction to report it through the Vaccine Adverse Event Reporting System (VAERS). Not only are members encouraged to submit a report but families or anyone personally aware of a situation can as well. We listen. We are concerned. This has included listening to many members on a one-to-one basis. Members of my staff have personally met with dozens of service members who have voiced concern for the reactions the members believe they have experienced, and talked to or corresponded with many, many more.

Education & Communication – When we spoke to the members on a one-on-one basis we realized that improvements in the program were needed and we have begun them. We want this program to be the best it can be. To do this we have initiated the research I mentioned earlier and have published polices for both administrative and medical exemption. Now, personnel with 180 days or less left before separating from the service, may elect to not receive the vaccine. In addition, there is a written medical waiver policy for personnel who have experienced what could be adverse reactions. While waivers have always been available, they have been reiterated in the waiver policy. The Department is also

committed to fully educating our Service Member population and their families on the purpose and value of anthrax vaccination in an unprecedented manner. We use each of the following communications media to accomplish this goal:

◆ A sophisticated anthrax specific website www.anthrax.osd.mil with multiple layers of information and methods for communicating with our Service Member population, their families, and other DOD beneficiaries and concerned members of the American public.

◆ Three Service - specific anthrax websites hyper-linked to all known military and civilian websites discussing anthrax, biological weapons, health care, domestic preparedness, terrorism, VAERS reporting, preventive medicine, infectious disease, etc.

◆ Quad-fold information sheets individually tailored for Service Members, Family Members and Civilians. DOD has provided each Service Member receiving the vaccine with printed silent training aides since administering the first doses in March 1998. The current quad-fold brochure explains the threat of biological weapons, the benefits of anthrax vaccination and the known risks from the vaccine. The Quad-fold also includes information aimed specifically at Reserve Component personnel accessing care.

◆ DOD Leaders Briefing required to be given to all Service Members prior to receiving the anthrax immunization. Distributed by each Service and prominently posted on the www.anthrax.osd.mil website.

◆ DOD Health Care Providers Briefing given to all DOD health care providers administering the anthrax vaccine — who then serve as teachers, coaches, mentors for supervisors, commanders, Service Members and their families. Distributed by each Service and prominently posted on the www.anthrax.osd.mil website.

◆ Open House/Speakers Bureau briefings and open educational forums for all Service Members and their families.

◆ A 1.877.GETVACC telephone hotline.

◆ A variety of anthrax vaccine ‘silent training aids’. These highly visible training aids emphasize the key themes of the anthrax threat, safety and efficacy of the vaccine, adverse event reporting, etc.

◆ Armed Forces Information Service news media, local installation print, radio and television news service initiatives.

◆ A state-of-the-art Anthrax Education CD-ROM is in development and it will provide Service Members, their families, supervisors, commanders and health care providers with tailored, multimedia information on the anthrax threat, safety and efficacy of the vaccine, signs, symptoms and prevention of the anthrax disease.

◆ An Anthrax Vaccine Immunization Program Videotape explaining the threat, safety, efficacy of the vaccine. The video features prominent civilian and Government scientists and vaccine experts explaining and endorsing the vaccine.

◆ DOD is currently collaborating with CDC to array this information in the format of a Vaccine Information Statements (VISs) the standard vaccine information format that civilian health care providers around the country give America’s children, adolescents, and adults during routine vaccinations (e.g. measles, polio, tetanus).

◆ Clinical Practice Guidelines for Management of Adverse Events After Any Vaccination that are based on a consensus panel of civilian and military physicians experienced both in immunology and the general provision of health care.

Our anthrax vaccine program is one of the most studied, reviewed and examined programs in the Defense Department. The most current are reviews by the General Accounting Office and the Inspector General. We are aware of the issues raised in these studies and are taking steps to address them. There is concern for the stockpile and we, as a Department, are addressing the issue objectively with interim requirement dosage supply contingency plans being developed. We are also aware of the financial condition of the anthrax vaccine manufacturer BioPort Corporation. The company, and its management, have improved over the past quarter and seem determined to continue in that direction.

Another issue is FDA licensing. The need for FDA approval of BioPort's Supplemental Biologics Application License (BLA) is also an area of media and opponent attention. We expect BioPort to achieve FDA approval of the BLA Supplement for assured production of the vaccine this calendar year. Continuing the program uninterrupted until FDA approves the BLA supplement requires FDA release approval of additional lots previously manufactured by Michigan Biologic Products Institute (MBPI). BioPort has submitted information on several lots and we are optimistic sufficient amounts will be released to continue Phase I uninterrupted.

PROCUREMENT AND PROGRAM

Anthrax Vaccine Adsorbed is produced by the BioPort Corporation of Lansing, Michigan, which is the only FDA licensed establishment for the Anthrax Vaccine Adsorbed. BioPort's facility has been licensed to manufacture the anthrax vaccine since 1970.

In the fall of 1998, BioPort became the sole licensed producer of the anthrax vaccine via a privatization process initiated by the State of Michigan. In September 1998, BioPort was awarded a contract for production of the anthrax vaccine. In August 1999, DOD renegotiated the contract and provided extraordinary contractual relief under authority of PL 85-804.

This action was necessary to preserve the company's financial viability and ensure uninterrupted production of the anthrax vaccine. The necessity to renegotiate BioPort's contract resulted from poor accounting of production costs prior to privatization and a lack of adequate resources. Even though, during state ownership the Michigan taxpayers subsidized the Defense Department's procurement of Anthrax vaccine, BioPort discovered that more work was required to bring the facility up to the state of the art, and that, the vaccine cost more to produce than anticipated. The Defense Contract Audit Agency verified the need for the extraordinary contractual relief and a recent DOD IG report validated that it had been done in accordance with Federal Acquisition Regulations. The Department of Defense continues to work with BioPort, the only FDA licensed manufacturer of the anthrax vaccine, to ensure the viability of the facility with the production capability to provide a sufficient supply of the vaccine to meet Department of Defense requirements. If BioPort enters into bankruptcy, the immunization program to protect the U.S. service members is at risk and our warfighters will be vulnerable to the extremely lethal and present danger of anthrax exposure resulting from biowarfare or bioterrorism.

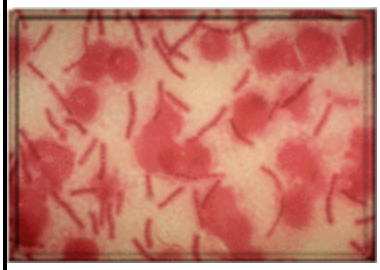
SUMMARY

Our Service men and women in at least two major theaters go to work everyday in areas where bioweapons could be delivered at any time. There is a limited availability of Bio-detectors and sensitivity is a concern. Protective clothing and equipment are available, but they cannot be comfortably used for long periods of time. Antibiotics are available, but must be used in the first few hours of exposure, before initial symptoms appear. Those same service personnel would also be incapacitated with severe diarrhea for a period of time. The superior form of protection is vaccination.

Our personnel deserve our best and fullest protection. The FDA licenses the current vaccine for that full protection with the complete six-shot regimen. We cannot wait until the balloon goes up to begin the vaccination. Being vaccinated may very well save the life of thousands of America's men and women in uniform, should some state or terrorist organization elect to employ what we know they are already capable of using. It would be a dereliction of duty to have the anthrax vaccine capability we presently have and not make it part of the arsenal of protection that we provide to our servicemen and women. We hope anthrax is never used as a weapon, but if it is, we must be ready!

THE BACTERIA

WHAT YOU NEED TO KNOW



Anthrax is an infectious bacterial disease spread by contact with infected animals, handling infected products, eating infected meat, or breathing weapon-dispersed anthrax spores.

METHOD OF DELIVERY

Projectiles Missiles, Artillery shells

Sprayers Aircraft, Trucks,

Hand-held aerosols

Why is it a threat?

Anthrax spores are the top choice in biological weapons for "germ warfare."

Anthrax is effective as a biological weapon because:

- Anthrax is almost always DEADLY if not treated early.
- Spores can be produced in large quantities using basic knowledge of biology.
- Spores can be stored for decades without losing viability.
- Spores can be easily spread in the air by missiles, rockets, artillery, aerial bombs & sprayers.

We KNOW there are potential adversaries developing it as a weapon.

- **At least 7 of our potential adversaries have worked to develop an offensive biological warfare capability using anthrax.**
- **Iraq has admitted to producing and weaponizing anthrax.**

There is no indication of exposure.

- **There is no cloud or color.**
- **There is no smell.**
- **There is no taste.**
- **There is no indication of an attack when dispersed by aerosol spray.**

Defense Secretary William Cohen holds a 5-pound bag of sugar to show the amount of the biological weapon anthrax that could destroy half the population of Washington, D.C.

Bacillus Anthracis

Anthrax is the easiest biological agent to manufacture.

Cutaneous Anthrax

There is no effective treatment for unvaccinated victims of inhalational anthrax.

- **Antibiotics will suppress infection only if administered early after exposure – usually within the first 24 - 48 hours.**
- **By the time symptoms develop, it is highly likely death will occur despite the best efforts of modern medical science.**
- **99% lethal to unprotected individuals.**

What it is:

- **Anthrax is produced by the bacteria *Bacillus anthracis*. A tough protective coat allows the bacteria to survive for decades as spores.**
- **Anthrax is dangerous because, it is:**
- **Highly lethal**
- **One of the easiest biological agents to manufacture**
- **Relatively easy to develop as a weapon**
- **Easily spread in the air over a large area**
- **Easily stored and dangerous for a long period**

- **Three types of Anthrax diseases:**
    - **Cutaneous Anthrax - caused by contact with infected animals or contaminated animal products.**
    - **Gastrointestinal Anthrax - caused by ingestion of contaminated meat.**
    - **Inhalation Anthrax - caused by inhalation of anthrax spores **MOST DEADLY - BIGGEST THREAT****

Incubation period - 1 to 6 days

Symptoms of inhalation anthrax include:

- **Flu-like aches & pains**

- **Fever, malaise, fatigue, cough and mild chest discomfort followed by severe difficulty breathing**

Diagnosed by:

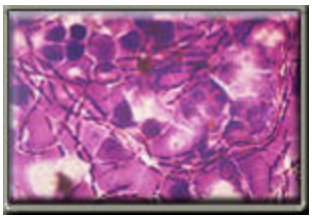
- **Isolating the bacteria from blood, other body fluids or skin lesions**

- **Blood culture, measuring specific antibodies late in the course of the disease**

Treatment:

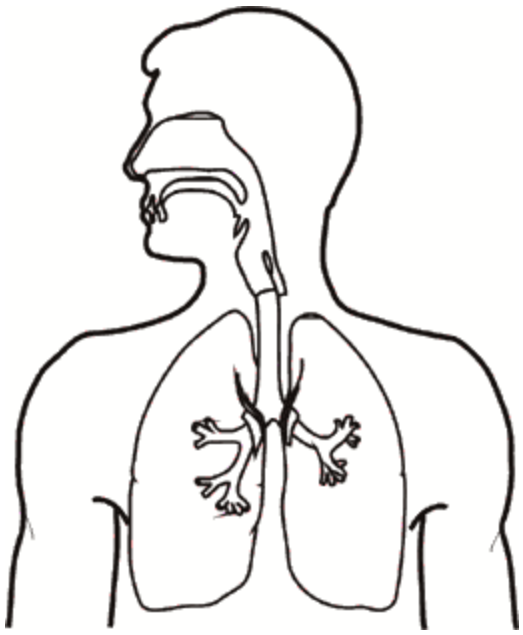
- **Treatment is usually not effective after symptoms are present.**
- **High dose antibiotic treatment – can lower the death rate slightly.**

What it does:



How it works: The airborne anthrax spores are inhaled and lodge in the lungs. There, they move to local lymph nodes, multiply and produce toxins that spread through the body via the bloodstream.

- **The disease occurs when spores enter lungs, migrate to the lymph nodes, change to the bacterial forms, multiply, and produce toxins.**
- **These toxins cause bleeding and destruction of structures in the middle of the chest (medical term: hemorrahgic necrotizing mediastinitis).**
- **Shock and death occur within 24-36 hours**



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Background Briefing

Thursday, August 5, 1999
Subject: Anthrax Vaccine Contract Briefing
Presenter: Senior Defense and Army Officials

Mr. Bacon: Hello. I have a whole team of briefers coming to talk to you about anthrax. The main topic today is the renegotiation of a contract with Bioport, the company that makes the anthrax vaccine, and this is all on background attributable to either senior Army or defense officials.

The briefing will be basically in three parts. The first part will be a brief description from the Joint Staff of the threat and the military requirements from a warfighter's standpoint for the anthrax vaccine.

Second, we will have two briefers from the Army who administer this program as the executive agent, to talk about the contract renegotiation and what's been achieved and why.

Then we'll have a representative from Health Affairs, a doctor and flag officer talk about the health aspects of the vaccine. He will be able to answer your questions on adverse reactions or anything else that you may have that you need answered. Obviously, the Army briefers will be able to answer your questions on the contract itself.

The first briefer, even though this is on background, is well known to you because he's been here many times before. He will be followed by the following briefer who is the head of the team who renegotiated the contract here.

Q: Why can't this be on the record?

Mr. Bacon: This is pretty technical stuff and I thought it would be a freer flow, more of a dialogue, if we did it this way.

Q: But (inaudible) the program part of the problem here with...

Mr. Bacon: I think this will be a highly credible briefing and you'll get all your questions answered.

Q: There won't be any names attached to it, though.

Mr. Bacon: We're going to do it this way, and there will be future opportunities to talk about that. Let me just, again – for the bonafides here... this is also part of the Army team who is involved in the negotiations. Then finally, the Health Affairs, and doctor who will be here with you. Then we also have from the Army Surgeon General's office another doctor who will also be able to answer questions if they should arise.

With that we'll turn it over to the first briefer.

Briefer: Good afternoon. I really want to talk to you today about the operational imperatives of the anthrax vaccination program. As Ken said, we've got some technical experts here and some medical experts to really answer your questions on – if you would – the inner workings of the program itself, but I really want to talk to you about the imperatives, the need for a vaccination against this threat.

As you know, or if you don't know, there's ten countries that we know have this capability to kill our troops. I mean that's the bottom line.

When you think about threat as an operational commander, and I'll relate my experiences as a commander, we do all we can do to ensure the safety of our troops. I'd like to relate vaccination to force protection, because that's exactly the way any good commander would view it. When we put troops in harm's way, we

don't give them the choice of wearing a kevlar helmet or not wearing a kevlar helmet. We know there's a threat and we protect them accordingly. If we're putting soldiers or Marines, Special OPS, whatever that may be into a certain type of environment, close combat in a built-up area, we would normally require them to wear body armor. It protects them from direct-fire and indirect-fire.

When we put a soldier, a sailor, an airman, a marine into an area where there is a known threat, in this case we're talking about anthrax, we want to equip that trooper so he or she can survive against that threat, to do the best we can do.

So when I look at vaccination, I look at that as an attempt to give that soldier, sailor, airman, Marine the best chance they can to survive whatever threat or whatever condition they're in.

I'll go back to an operation that I was a line commander in when we went into Haiti. It was originally going to be a combat operation. It was called Restore Democracy, and it evolved to Uphold Democracy. One of the big concerns was the disease problems in Haiti. I spent as much time as an operational commander then making sure that every soldier – and I was commanding an Army unit – that was going in on that deployment into Haiti had all of the vaccinations that they needed to make sure that they were medically ready and fit to be able to encounter that threat.

The threat of anthrax is there. We absolutely have to have our troops prepared to handle that threat.

Let me paint a picture for you. Fighting is tough. It's a team issue. Soldiers, sailors, airmen, Marines rely on each other.

If you were to take a unit on a battlefield in this environment that happened to be exposed to the anthrax threat – those that were vaccinated survive. Those that were not vaccinated, the medical evidence is within a couple of days they're close to being incapacitated, and as you have been told before, this terrible agent, in fact, is worse than Ebola. You have in the high 90s fatality rate.

So now we took a unit, and you can look at any size, whether it's a battalion, a company, whatever it may be. You just reduced the fighting effectiveness of that unit by 50 percent.

So not only do you have the difficulty of the evacuation of these troops that have been exposed to this terrible agent. You now have taken a unit that was a fit fighting force and you've reduced it 50 percent and now it in fact can be in harm's way for a period of time because of other threats, and also it no longer is an effective fighting force towards the accomplishment of your mission.

So this is about force protection, and that's all it's about. And giving our soldiers, sailors, airmen, Marines, the opportunity to survive on a very, very lethal battlefield.

I've got to tell you, personally it would be irresponsible and it's unconscionable that we would take a trooper into that threat area and not be vaccinated. That's not a choice of the soldier as to whether he or she is not, because it's a matter of being part of that team. And I would have great difficulty coming to one of you, for those of you who are old enough to have children of military age and look you in the eye and tell you that your soldier died or your son died or your daughter died because they weren't vaccinated. I'd have grave difficulty with that. And as a leader, I can't fathom that we would ever take a trooper into that threat environment without being vaccinated.

That's really the operational commander's feeling, and that's what we're really talking about here.

I'll be glad to answer some operational questions, then I'll turn it over to the experts who are technical.

Q: Sir, if the enemy knows that all your troops are vaccinated and they use a different agent that's not anthrax, then what do you do?

A: I'm going to let the chemical experts answer that question when they come up here and talk about that. There are some solutions there.

Let me make a comment, though. Our protection issue, force protection issue, is just not the vaccination. We also have a program going on to try and detect different agents. Also you get protection from the use of your chemical protective gear because it actually filters out the spores.

However, when you go back to that, if you were in an environment where you actually use the protective masks, if you inhaled it before you got the mask on and you weren't vaccinated, it's like not having the mask. Period. But I'll let somebody else talk about the other agents.

Q: If for some reason this program were stopped, what signal would that send to your adversaries, and how might that affect potential use? Does it raise the value of their stockpile of material?

A: You can look at it several ways. I would tell you that it sends a strong signal to your adversary that he or she might be more inclined to use it. So I can't fathom, like I said, taking soldiers, sailors, airmen, or Marines into an environment where we're not vaccinated against this threat where it's a known threat.

Clearly if you're not going to protect yourself from it, it makes that capability seem or appear to be or in fact will be much greater.

Q: Since you and the other people here are advocating this program, have you had your anthrax shots yet?

A: I've had the first three. I get the fourth one here in another five months. I have great confidence in it.

We have a very sophisticated vaccination program, and have had. I've been vaccinated... I've been in early deploying units all my life so I've been vaccinated many times. In fact, I've learned to keep my shot records with me so I didn't have to take the yellow fever shot as many times as I've had to over the years because I couldn't, because it hurts. But I've never had yellow fever.

So I have total confidence in it. It's 30 years old. We don't seem to get this blow-back on our other vaccines, but I'll let the docs talk about that.

Q: Why do you think that is? Why so much trouble with this one in particular?

A: I think a lot of it has to do with the Internet age. There's this tremendous amount of information out there that our youngsters can go right to the net and pull down information, and in fact there's a lot of disinformation on the Internet. Very, very aggressive, I think, disinformation about the program. We have a different generation today and they have that access to that.

Q: What do you say to those that have trouble, whether it's valid or not in your mind, what do you say to them that say, 'I don't want to do it?'

A: First of all, you need a very, very strong education program, and we owe our troopers that and we give them that. And we're doing it all the time. But the bottom line is it's not a voluntary program. It should not be a voluntary program. Again, I'll go back to this team effort. If you're going to go into combat you don't want to wear your helmet, I'm sorry. You're going to wear your helmet. We know there's a threat there and you can lose your life.

Q: You equated the anthrax vaccine to the kevlar helmet and your flack jacket and that sort of thing. Before those were given to the troops they were thoroughly tested and you knew what protection they provided.

What the (inaudible) seems even among the medical profession of this vaccine is that it was not tested with the long term consequences or (inaudible) utilization or its effectiveness against the kind of germ distribution that you're going to face in a combat situation which is airborne.

A: Let me let Mike talk to you about the medical piece of it, but I want to clarify something. I also consider yellow fever, hepatitis, plague, diphtheria, all of the other vaccinations that we take also equal to the kevlar helmet and to any issue. I also look at the fact that we go in and do as much work as we can in medical surveillance to determine types of diseases and other things we have in a given area to force protection. I mean you can look at each of the activities that we go through to try and make it as safe as possible, and that's kind of an oxymoron when you're thinking about combat, to give our soldiers the most protection that we can. So it's not just anthrax versus those, it's all of the pieces of force protection. Anthrax vaccination being one piece of that.

Q: What do you know about the folks whose religion prohibits vaccinations? They're just not allowed...

A: I'll defer that also to the experts on that.

A: I'll try to answer that briefly. I am from Health Affairs, I am a doc, and I've been involved with this for some time now. I was recently, until the last few weeks, involved with sending out troops, providing protection in the field, so I've been concerned about this not only from an operator's point of view but now for the last several weeks from the policy point of view.

There are exemptions. There's medical exemptions and there's a process for religious exemption for people who don't take vaccinations. We have them scattered throughout the services. We can get you as much information on that process or how may people avail themselves of that and those sorts of things.

I'd like to take exception to your assertion that we haven't proven this as effective. We have. Period.

You can't ever have an absolute 100 percent certainty in science, and especially medical science. We bring scientific methods to the art of medicine. So every doctor that you've ever seen is always to a small extent playing the probabilities.

We know this. We know that in a relatively small human study of occupational exposure, that the vaccine, in lower doses than we give now was effective. Period. I'll show you that study. We know that in primate studies, which is our nearest biological kin, we have overwhelming evidence that the vaccine is effective against inhalation anthrax.

Now I can raise the probability by experimenting on humans, but there's no ethical experiment that I or anybody else can think of that would prove this to a higher degree than what we have now. Because to really know, you would have to take two groups of people and give some of them a placebo so they thought they were getting vaccinated, and some of them the vaccine, then challenge them with lethal doses of the anthrax and there would have to be enough lethal doses that all of the placebo, all of the untreated would contract the disease. Then to see how many of the people who had the vaccine did not.

I wouldn't volunteer for that. That's the only way we can prove it to any further extent than what we have now. We know when we did the primates, I think they were Rhesus monkey studies, we found the antibody levels that were protective; we know that with our vaccine we get antibody levels in humans that are even higher than that. So to say that it is not effective is unsupportable.

Q: ...primate tests conducted (inaudible) widely known (inaudible)...

A: Well it is widely known, and I can give you those studies and they were done in the '90s.

Q: Can you compare the kind of reactivity that you're getting to the injections, how many people have been vaccinated from skin rash to flu symptoms, anything else.

A: Yes, sir. I can give you a site picture of that.

May I ask that we hold that for a moment, because we may be getting the cart ahead of the horse and we wanted to bring out the topic of the day and then I'm supposed to be kind of wingman to help answer those kind of questions so if we could do that I'd appreciate it and then I'm very happy to come back up and continue.

Briefer: Good afternoon. I want to follow up on the issue of the premises of providing protection to the total force. The only way you're going to do that is to have a source of that vaccine. We have a problem in this country. We only have one single source of the anthrax vaccine.

Prior to Secretary Cohen's decision to immunize the total force, the State of Michigan subsidized the production of anthrax vaccine at a state-owned facility called MBPI, Michigan Biological Product Institute.

Both the government and the state believed that $4.36 was a practical and reasonable price to charge for the production of one dose of anthrax vaccine or per dose of vaccine.

In June of '98, the State of Michigan in a business decision made a decision to sell MBPI to the highest bidder. Bioport was the highest bidder. They consummated that sale in September of '98 at a total price of approximately $25 million.

What's important to understand about that sale is, we call it a novation, but it really wasn't a novation. It was the people who were there that worked for the state, the facilities were the same. They simply brought in new

management to take over that contract. Indeed, they renegotiated that contract with DoD at a price of approximately about $4.36.

Six months into the contract, Bioport made a discovery. That discovery was that the $4.36 did not cover all of the costs to maintain and operate that facility. Let me give you an example.

There were state employees that were on the state payroll that worked at MBPI. Grounds and maintenance facilities, janitors, one example. The utilities – state owned, under the state payroll, not under MBPI. Maintenance of the facilities, again, a state payroll price, not under the MBPI. So you can see the discrepancies here.

Bioport had a choice at that time. They came to the Department of Defense and requested an exceptional, extraordinary exception or relief on this contract. We put a team together and for two months we studied what options and alternatives we had at that time to help Bioport.

After two months of extensive study, findings were presented to a contract arbitration board. That board concurred and believed that Bioport was in fact in financial distress. It also made a decision at that time what we needed to do was go back and renegotiate the contract.

We also in DoD wanted, at that time, to make sure there would be a continuous and uninterrupted supply of anthrax vaccine to ensure our soldiers, sailors, airmen and Marines would have that force protection.

What I want to do right now is bring up the task force leader who provided the lead for the government on negotiating this contract and give you the specifics of what we negotiated or renegotiated.

Briefer: Good afternoon.

As the other briefer said, we spent the last several months working this issue. It is important that we restructure this contract because we must have this vaccine to protect our troops.

There were three major key elements that we renegotiated. One was an increase in price from $4.36 to $10.64. That increased the total contract by $24.1 million.

The second key factor was that we will be providing advance payments against future production. We'll be providing $18.7 million of the $24.1 million to Bioport prior to completion of production. But they will repay that at $4.60 every time they bill a dose to us.

In order to protect our investment we put in several safeguards. First and foremost, we will have liens on all of Bioport's assets. We will also have a renegotiation provision so that nine months into this contract we can look at it again, reassess the price and determine if the price is appropriate.

We have established a special bank account that requires that the government contracting officer sign off on all withdrawal of funds to Bioport.

We will be putting several people on the ground at the Bioport facility in Michigan to oversee the effort between now and the end of the new contract, next year in December.

The Defense Contract Audit Agency will do a follow-up audit in six to nine months to ensure that Bioport is working as we expected.

One other aspect that we did with this contract was authorized them to use government-furnished equipment that is now in the plant so they could go for commercial sales. So eventually this company will not be dependent on the Department of Defense as its sole provider of funding.

I'll be happy to answer any questions.

Q: Can you give some of the figures about how much... what's the total value of this contract? How much we've already spent on anthrax vaccines, how much is anticipated? How much money are we talking about all together here?

A: The total value of this contract now, from the beginning of September of '98 to December of 2005 is $49.8

million.

Q: How does that compare with what you've already spent in the past on the anthrax vaccine?

A: This is the first time that we have had a contract for significant production. I don't have the answer specifically of how much we spent in the past. I can get you that.

Q: So you've doubled the price basically, from whatever it was to $49; it's a $24 million increase.

A: Yeah.

Q: It does seem like an extraordinarily large jump to a layman, even if the janitors are paid at a different wage.

A: I understand that. But there was approximately, as far as we can tell, about $5 million that Michigan actually was paying that was not being credited to this account. That's the first thing.

The second thing is, when Bioport took over – and you have to remember this is a small, brand new company, and all companies have startup problems – when they took over this company, the state-run facility was in the middle of renovating the production suite. There were some delays in that. So consequently, they're not getting paid as soon as they had expected.

In addition, they had expected to be able to sell more commercially than they were able to. So they had fewer revenues than they expected.

Q: How many doses does the $49.8 million buy?

A: Approximately 5.3 million.

Q: That's a reduction in the amount of doses, is that correct? You're getting less vaccine out of this contract...

A: We are getting less vaccine because the contract called for a total, a larger stockpile than we actually needed. What we had put on contract was their maximum capability which is not really a reasonable thing to do. After the new management took over they looked at it and said a normal pharmaceutical company does not count on 100 percent production. What they count on is about 75 percent production.

So what we're looking at now is about 75 percent production and it still meets Department of Defense needs.

Q: Can you talk to the safeguards to guarantee the government's financial investment in this company. What about, are there any safeguards in this contract to guarantee the quality or effectiveness of the vaccine?

A: Just as normal. This contract change did not affect that. No lot is releasable without FDA approval.

Q: You're getting 5.3 million doses instead of how many?

A: We were getting 7.6.

Q: The quality assurances, one of the reasons for the sale was Michigan didn't want to pay to make the improvements that were required by FDA (inaudible) the lab was inspected. Have the inspections been completed in the testing to determine whether it can now release the new doses?

A: Not yet. We expect that they will submit their first request for inspection early next month, and then the FDA will come in and inspect the new production suite.

Q: You're still using the untested vaccine?

A: No, as the gentleman said, this vaccine has been tested and this contract change does not affect that.

Q: (inaudible)

A: I'll have to refer that.

Q: Can I ask another contract question, please? Can you just tell us what the profit structure is in this, if any, per dose? In other words, is this new price straight covering of costs or is it...

A: It's just covering costs. There is no profit in this.

Q: What percentage of the anthrax vaccination... what percentage of Bioport's business is the anthrax?

A: It's the majority of it right now. I don't know what the exact percentage is, but it is... They are almost a one product...

Q: ...question about negotiating with these folks. The other briefer said a moment ago that Bioport made the discovery six months into the contract. Actually at a congressional hearing some time ago the President of the company, if I recall correctly, said that he knew all along that most likely Bioport would not be able to make that price and that something would have to be done later on.

How were you able to negotiate and determine this was a trustworthy company to negotiate with after that experience?

A: We sent the Defense Contract Audit Agency in there three times in the last month and they audited the financial capabilities of the company, they audited the accounting system, and then the audited specifically this request and this price increase.

And they determined that the accounting system, that they were in financial trouble and that this company would not survive unless we increased the price.

Q: My point is that they seemed to know all along they were going to have to come back, that something like this was going to happen all along. How can you know you can trust them now?

A: I don't know what was said. I don't know exactly what you're referring to. But I believe that they did not know exactly what the price should be because of the things we said; then the other things of the commercial sales that did not materialize; and then the delays in the production suite.

Q: ...know what the cost of this stuff is?

A: Yes, we have done... Frankly, we have spent the last two months almost in Michigan. I've been in Michigan more than I've been here and the DCAA has been also.

Q: This is a non-profit profitmaking company?

A: They will be able to make a profit on their commercial sales.

Q: If anybody buys it.

A: If anybody buys it. But there's no profit included in our price.

Q: So the incentive to them, just to clarify this point, is that they continue to produce this vaccine, the government covers their costs of production, they get to stay in business, and they have the potential to make a profit with other customers, and without this help they'd probably not remain in business. Am I reading this correctly?

A: That's correct. But let's not forget that the key here is that we get our vaccine.

Q: One more point. When you mentioned the window, nine months, where you could renegotiate the contract, is that, would that renegotiation take place if it was determined that the actual cost of producing the vaccine was lower or higher than projected?

A: Correct.

Q: Would it be adjusted to cover, again, the actual cost?

A: Yes.

Q: Are there any (inaudible) penalties in this contract if they don't meet the contract standards?

A: There are performance requirements but there are no standard incentives that you're thinking about. The important thing is that this company maintain its financial viability so that we can get our vaccine. However, we have provisions in the contract that our needs are met first. They can't sell it to anyone else until our needs are met.

Q: What is your latest thinking about whether or not it's practical or viable to even begin to look for a second supplier, a competitive supplier?

A: Actually the Department of Defense is looking into that and it's going to make an analysis. But the problem is that it takes six, seven, eight years before we could bring another producer on board, so we can't wait that long.

Q: There's just nobody else in the United States that...

A: They're the only licensed manufacturer.

Q: What about other countries? Are there...

A: There's no one else that's licensed by the FDA.

Q: ...in Iraq. (Laughter)

Q: There were other companies that bid on this, and I realize that Michigan made the sale, not the Pentagon. But who are those other companies, and how did this company end up in the hands of this holding corporation that's based in the Caribbean and apparently doesn't have a lot of resources to sustain itself? How did that happen? Have you explored that at all?

A: I really wasn't involved. That was completely between the State of Michigan and Bioport. I can't really answer that.

Q: The other bidders, are they potential, as you look at other producers for this thing?

A: There were only two bidders. Bioport was only one of two bidders, as I understand it.

Q: Who was the other one?

A: I don't remember the name. Sorry. I wasn't involved in it.

Q: Bioport I think said they wanted to keep 70,000 doses for commercial sales earlier this year. Is that allowed under this renegotiation?

A: Yes, it is. Assuming that they meet our requirements, our cumulative requirements every month first.

Q: And how much profit can they expect to make off of that? Would they be selling it for the same... I can't imagine that...

A: No, they will be selling it for a higher price.

Q: And is DoD paying all of their overhead so that anything that they sell is pure profit?

A: Actually if they sell commercially... and what we've done is negotiate a quantity and an amount... If they sell above that amount, then we will get a percentage of that back if they sell it.

Q: Can you put some numbers on that, please? How much are they expected to produce for DoD a month?

A: I can't do it by month. I could look it up...

Q: ...quantity?

A: It's in the contract. I just don't remember off the top of my head. I'm sorry. But in total... First they have to meet our requirements every month and that is laid out in detail. I'm sorry, I just don't have that. But in total, they cannot, they will give us a credit back if they sell over 300,000 at a price greater than $30 a dose.

Briefer: We're the medical health team representing the Army as the executive agent and the policy.

The first one that's sort of hanging in the background and I think needs a direct answer is the FDA having to shut the plant down for renovations. That's another one of those urban legends or something that just keeps cropping up.

We planned to shut the plant down to modernize it because the manufacturing techniques and the size of the cooking vats and all of those sorts of things were insufficient for what we needed. It was plenty sufficient for veterinarians and agricultural workers, but we greatly upscaled the whole program and had to have modernization of the factory. It was not an FDA requirement, it was a planned upgrade.

The other question that has been kind of hanging since right at the beginning was, 'Why use this when if you use this somebody would then attack you with something else'?

This is classic deterrence. The answer is, we try to deter the known and most dangerous threats. If we can make it harder for an enemy to attack us, if we can make him use his second best gun, his third best weapon, then we do that. We have our people wear kevlar vests. They don't stop all sorts of ordnance, but they stop some, and they stop the ones that are easier to use. So that's I think the question is the deterrence of using a vaccine under the envelope of force health protection which is our overarching plan – to try to use every means we have from detection to deterrence to mitigation to masks to protective gear, on and on and on, because no one thing is perfect. But all of them put together increases the odds of survival of each and every soldier.

Q: Do you believe a bio threat (inaudible) that this strand of anthrax is the most likely, the easiest to weaponize, the most stable? Can you run through...

A: Anthrax, if you want to use a biological weapon of mass destruction, is the weapon of choice. It's sturdy. It's easy to find. It's easy to grow in massive quantities. When you get it in massive quantities, it's easy to get it to turn into a spore form which is sort of like a seed which is very, very resistant to the usual things that inactivate or kill bacteria and viruses. It's easy to weaponize in a variety of weapons, both terrorists' and using rather conventional delivery systems. And the unfortunate thing is that the first indication you may have of it is when people begin to die.

Q: Are there other strains of anthrax that you can – as a weapons designer – you slightly alter that and therefore bypass your vaccine?

A: There are a couple of answers to that. One is, it's theoretically possible to alter anthrax so that our vaccine would not be effective against it. It's theoretically possible. Nobody has one that we know of. And it would not be an easy trick. So even if that existed perhaps in the hands of an enemy, it would not make it any less valuable against another who didn't have that, who was using one of the common strains.

Also, this is a vaccine, and it's a vaccine against the inner poison of anthrax that makes anthrax deadly. So if you change anthrax, you have to change that. If you change the anthrax to make it resistant to our vaccine, you have to change the very thing about anthrax that is anthrax. If you do that, you have something, but you don't have anthrax anymore.

So we think that the idea of a strain that's resistant is very unlikely, and we think the idea of somebody altering this into something else is possible – both these things are possible – but they're not very likely.

Q: I want to go back to your statement that you planned to shut down the plant. The GAO testified at the congressional hearing that the state decided to get out of the anthrax business when FDA came in and inspected them and they weren't prepared to make the financial commitment to make the improvements that

were necessary.

A: There's been a great deal of confusion about that, and that may be worth another day altogether. At that time, Michigan did a number of things.

In each of the areas of operation they had difficulties with the Food and Drug Administration. In the area of the anthrax vaccine production, and step in if I say anything that's not exactly right, they had some bookkeeping difficulties. There were no issues that FDA had with the purity, the strength, any of the things that they want when that vaccine rolls out at the end, but there were bookkeeping difficulties. They dinged them for that. But there was nothing about what was going on in the anthrax production that made them shut down to do that. It was an upgrade of the plant because of the modernization and increased production requirements.

Q: Do you think, in your opinion, is the resistance to taking the anthrax vaccine and the opposition by some to it, which it was said earlier it's a disinformation campaign... Is that just hysteria?

A: I think the answer to the last part is no. It's not hysteria. I think we have people who develop symptoms and illnesses that have had the anthrax vaccination. We know – and the third question I was going to get to in a moment also bears on that. People are having side effects. But I think that a great deal of the fear of it is being stoked by people who simply want the vaccine program stopped. A great deal of the misinformation we have is misinterpretation and different presentations of the kind of things like the safety that we talked about earlier.

It's very clear – I'm sorry, the efficacy.

It's very clear that this is efficacious.

Q: What are the side effects that you can reasonably connect to this vaccine as opposed to just other illness that people may have and think they're connected to the vaccine?

A: Let me try and answer that. I don't think there's anything unique about this vaccine and the side effects, the normal expected side effects we see when we immunize servicemembers. And we're not aware of any systemic or large number of unique, in fact we're not aware of anything that we could say is specifically attributed as a trend to the vaccine. We have seen a handful of individuals with longer term illnesses and conditions that we're continuing to evaluate that may be associated, when you consider that we have vaccinated 320,000 servicemembers. But when you talk about soreness in the arm, fever, that's actually very much a profile for most vaccines to one extent or another.

Q: Are there more severe than that? Are there people who are crippled because of this? Are there people who...

A: We're not aware of anyone who's crippled...

Q: ...reactions that you are getting? Is it three people?

A: It's on the order of three to five people. We've had one individual we think may have a long term pulmonary problem. We've had a couple of individuals that have had total body rashes that have resolved. We have seen a couple of individuals complaining about autoimmune type of conditions that we haven't fully evaluated yet – aches and pains, arthritis, those kinds of things.

A: If I can put this into a little bit of historical perspective, when we first started the best information we had from the experience in the field of using this in smaller numbers, was that the side effects, including the lumps and bumps and aches and pains and fevers, were extraordinarily low. So we gave you that information. I stood on this podium and said it's really, really low.

As we have gained experience, we have found that those sort of local, self-limited, and actually harmless reactions are much higher than we thought. We have initiated two ongoing surveys of large numbers of people so that we can get an exact handle on that and know exactly what to tell our folks in what to expect. The unexpected and the unknown is a lot more fearful and dismaying than knowing you're going to get a lump on your arm and it's going to hurt for a couple of days.

The rest of the answer is – I mentioned earlier that in medicine it's using the science to advance the art...

There's always the question of the unknown, the unexpected.

For example, recently vaccinations against rota viruses, I believe, were found to be associated with an increased number of intussusception, which is a bowel problem, and that was stopped.

We have set up both active and passive sentinel systems where we're trying very, very hard, and paying a great deal of attention, to make sure that we are not inadvertently creating some disease with this vaccine that was not known to be associated with the vaccine before.

The answer to your question is, so far we have not found any association that we would not expect to see in just the background population that we're dealing with.

Q: Is the kind of reaction, can you compare it to diphtheria, tetanus? When I take my routine shots that everybody takes before they go overseas or to Africa, how does the anthrax shot compare to the side effects that you get from any of these other more accepted...

A: I think it would be best to answer that by saying we are seeing more local, self-limited site reactions than we thought we would.

Q: More sore arms, more rashes.

A: More bumps on the arm. My arm was sore one time. I had a bump on my arm another time. Another time I had nothing. Self limiting.

Q: They go away.

Q: They don't require any or minimal, you know, two aspirins and see me in the morning kind of things.

What we are continuing to monitor and have sentinel systems looking for is some disease line intussusception following rota virus vaccination. That we haven't seen. But we are very vigilant for that. So we're seeing more of the local reactions but we have not... With a million vaccinations more or less, and 300,000 people, we now have a pretty good sample, and we probably would start seeing things by now if we had associations, and we don't.

And if we do see anything we will obviously take the appropriate steps because this is a force health protection measure and we'll do whatever needs to be done if this turns out not to be that.

Q: So what percentage of the people who are getting the shots are coming up with some sort of reaction on their arm? Twenty percent, 40 percent?

A: The data I'm aware of would say closer to the order of 40 to 50 percent would have something. They'll have some soreness, redness. The number that are going to have systemic illness with fevers, they're going to have to be hospitalized, are still extremely small. Much less than 40 to 50 percent.

Q: So 100, 1,000 people out of your million shots, out of your 320,000?

A: I don't have a number for you of that order. We looked at two small subsets. The numbers that have got fevers were probably in the 7 to 10 percent. If you want to extrapolate that.

Q: How much do you think the kickback on this program stems from the lingering problems with the Gulf War syndrome? A lot of the people who are testifying on the Hill are saying to the congressman, are reporting symptoms quite similar to, that fall within the, if you want to call it a syndrome, from the Gulf War. Is there a feedback relationship between these two?

A: I think medicine is based on trust. If for whatever reason, in any individual's mind he loses trust in his medicine, in his doctor, or he loses trust in his government, then those sorts of feelings will fall on more fertile ground. Maybe in some people's cases that's so, but we might be feeling repercussions of that. Our job is to regain that trust and make sure that our message is clear, that we're protecting our people, that we're doing everything we possibly can to make sure we're not harming them with the thing we give them to protect them. If we're digging out of a hole from Gulf War syndrome suspicions, we just have to keep digging out.

A: I think the numbers of individuals who are presenting with those kind of symptom complexes, if we could use that, that someone might try to label as Gulf War syndrome, are so small by comparison to the vast number of servicemembers that we've already immunized, 320,000 plus, that I think it's a little bit of a stretch to say this is exactly the same thing as those individuals that came out of the Gulf and are ill and the ones that are working their way through there. So I'm leery to try to make that kind of connection.

Q: What is your latest statistic on how many servicemembers have refused the vaccine?

A: We don't have a formal tracking mechanism where we query and require commanders in the field to report back to us the numbers. Our best estimate is around 200 soldiers, sailors, airmen and Marines total, plus or minus, and I don't want to get fixed on that number, but that's a rough approximation.

Q: Just to clarify, that's both the active and the Reserve?

A: Right.

Q: My other question, I don't know if it's best addressed to you two gentlemen, but perhaps. What is the current policy now on disciplinary action for those who do refuse? Is there a military-wide, department-wide policy? Is it left up to individual commanders? What happens...

A: It's a refusal to follow a lawful order, and that's a number [violation] in the UCMJ and it's left a great deal to the individual commander's discretion as to what he does about it.

Q: Is there any thinking that this is a problem that's serious enough that some additional policy needs to be made on disciplinary action? Have you given any consideration to that? Implementing some specific department-wide policy?

A: We would have to pass on that. That's at a pay grade level well beyond ours. And here he comes. (Laughter)

Mr. Bacon: The answer is I'm not aware that any specific... We have approximately 200 people out of 320,000 who have received this vaccine have come into the disciplinary system. It's a small number. There is some indication that, in fact, some soldiers have said that they refused to take the vaccine because they didn't want to deploy to some place such as Korea where they would be required to have this vaccine.

So sometimes there can be various reasons why people refuse to take the vaccine, even to avoid a deployment.

I don't think that this problem is large enough to warrant restudying the penalties of the disciplinary system. I think the system is perfectly...

Q: ...on the Hill. You've got two pieces of legislation...

Mr. Bacon: We're not disciplining the people on the Hill.

Q: But you've got to deal with them. There are two pieces of legislation introduced in the House, a growing number of cosponsors. And they're holding more and more hearings. Any information (inaudible) to try to stop the legislation that might cut...

Mr. Bacon: The answer is yes, we're engaging fully with people on the Hill. We're giving them threat briefings, we're giving them medical briefings. We're answering their questions the same way we're answering your questions here, and we will do that thoroughly and aggressively.

The point is, I believe most people on the Hill when they understand this vaccine and they understand the threat that our military people are facing today will say not to give people this vaccine would be irresponsible. It would be like sending people into combat without helmets. To make vaccine use voluntary would be irresponsible because it could lead to the hollowing out of units where one soldier lives and the person next to him dies. That is not an intelligent way to go into battle.

The whole point here is to protect our soldiers, sailors, airmen and Marines in the most thorough possible way, and that's why we have made the vaccine use mandatory.

We have a problem, which is General Craddock is coming on here by phone in five minutes. We'd be glad to run out the clock right up to 2:00 o'clock if you have more questions on this. But I just want to announce that we have to end at 2:00 because he will then be on the phone from Kosovo.

So if there are two or three more questions we can take them quickly. Otherwise we'll give you a five minute break and come back at 2:00 o'clock.

Anything else?

Thank you very much.

STATEMENT OF

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FOR CHEMICAL/BIOLOGICAL DEFENSE

DEPARTMENT OF DEFENSE

ANTI-BIOLOGICAL WAREFARE AGENT

VACCINE ACQUISITION PROGRAM

ON

APRIL 14, 2000

BEFORE THE

SUBCOMMITTEE ON PERSONNEL

SENATE ARMED SERVICES COMMITTEE

FIELD HEARING AT PINE BLUFF ARSENEL, ARKANSAS

I. Introduction

Good afternoon, Mr. Chairman and distinguished members. I am honored to appear before your committee today to discuss the capacity of the civilian pharmaceutical industry to manufacture and supply vaccines to protect against bioterrorism and bioweapons. I am Dr. Anna Johnson-Winegar, Deputy Assistant to the Secretary of Defense for Chemical and Biological Defense, and I am accompanied today by MG John Doesburg, Commanding General of Soldier Biological and Chemical Command. At your request, my testimony will specifically address the Biological Defense Joint Vaccine Acquisition Program (JVAP).

II. The Biological Threat

The biological weapons threat is serious and potentially increasing in diversity and frequency. Currently, there are over 10 countries with known or suspected biological weapons programs. In addition, there are a number of non-national groups with access to such weapons. Assessing the threat is complicated by several interrelated changes, including the proliferation of weapons, technological advances, unstable political regimes, shifting regional power balances, and the increasing threat of terrorism. The threat will be exacerbated with continued and more frequent deployment of U.S. forces worldwide. The countries that are of greatest concern to the United States are located in regions in which the U. S. has well defined national security interests. Therefore, it is of paramount importance that we continue to maintain a credible, robust capability to protect our forces and provide them capabilities to operate effectively in a biologically contaminated environment.

The Department of Defense's (DoD) biological defense program is threat-driven, not technology-driven. This is because the products created by the program are for defensive purposes. The biological threat motivates the user to identify requirements and the capability needed, which, in turn, forms the basis for requirements for the research and acquisition community. The requirements are therefore generated to meet user identified materiel shortcomings. Vaccines are the most effective and least costly medical protection from biological agents and there has been significant progress within the area of biological defense vaccine policy and development. The DoD has established policy, responsibilities, and procedures for stockpiling biological agent vaccines and determined which personnel should be immunized and when the vaccines should be administered. The DoD has also identified biological agents that constitute critical threats and determined the amount of vaccine that should be stocked for each threat.

III. History and Chronology of the Biological Defense Vaccine Program

During Operation Desert Shield/Storm (ODSS) the enemy threat posed by Iraq

created an immediate requirement for vaccines against biological warfare agents (BD vaccines), specifically anthrax and botulinum vaccines. The Anthrax Vaccine Adsorbed (AVA) is the only BD vaccine licensed by the U.S. Food and Drug Administration (FDA). The DoD recognizes the FDA licensure as the standard that determines if a vaccine is pure, safe, and effective for its intended use. Under its regulations as promulgated in Title 21 of the Code of Federal Regulations (CFR), the FDA licenses both the biologic production and storage establishments. Only the FDA Commissioner may waive the regulatory requirements of Title 21 of the CFR.

AVA is produced by BioPort Corporation of Lansing, Michigan, which is the only FDA licensed establishment for the production, testing and storage of Anthrax Vaccine Adsorbed. BioPort's facility has been licensed to manufacture the anthrax vaccine since 1970. The facilities and operations of BioPort were previously owned by the State of Michigan under the Michigan Department of Public Health until the passage of State of Michigan Public Act in December of 1996 (and amended in 1998) requiring privatization through sale. A temporary organization, the Michigan Biologics Products Institute, operated the facilities until the finalized sale to BioPort in September of 1998.

The Center for Biologics Evaluation and Research of the FDA lists 16 licensed vaccine establishments. Nine have primary facilities in the United States. Despite a large national pharmaceutical-manufacturing base in the U.S., there was little interest by U.S. commercial firms in producing biological defense products, including the AVA, for the DoD for several reasons. First, major pharmaceutical firms typically expect their products to produce in excess of $200 million in annual sales. At most, DoD will provide a small piece of this revenue expectation.

Second, the AVA vaccine places limits on the manufacturing infrastructure. As AVA utilizes a spore-bearing organism fermentation process, Title 21 CFR, Sections 600.10 and 600.11, require all capital facilities, to include production equipment and buildings associated with spore-bearing production, to be solely dedicated to the production of that one item. This adversely affects capital costs and severely limits alternative investment options since the equipment and facility can never be used to produce any other product in the future.

Third, there are concerns by U.S. commercial pharmaceutical firms that supporting DoD in this business area is inherently high risk because of changing requirements and inconsistent support for programs. Therefore, the manufacturer cannot predict quantities and schedules.

Fourth, the Biological and Toxin Weapons Convention of 1973 that addresses the issue of biological weapons has potential implications for commercial manufacturers of BD vaccines. Under the terms of a monitoring and compliance Protocol that is now being negotiated for that Treaty, it is possible that international inspectors may occasionally visit vaccine production facilities. The United States government is committed to ensuring that provisions be included in any such Protocol that assure that any visited facility will be able to protect proprietary information from disclosure during such a visit. However, commercial companies have expressed concerns that proprietary information unrelated to the BD vaccine manufacturing process might be disclosed, and they are generally leery of hosting outside inspectors. There would be less concern about such disclosure if the facility were government-owned, since the contractor operator would not be undertaking activities that were unrelated to BD vaccine manufacturing.

Several studies were conducted to examine the commercial capabilities to produce biological defense vaccines and to develop options for short and long-term production. These studies assessed whether a dedicated Government Owned/Contractor Operated (GOCO) or Contractor Owned/Contractor Operated (COCO) facility should be constructed to provide the additional capacity. Each option has advantages and disadvantages associated with production, operating costs, licensure requirements, staffing, and management. Representatives from the pharmaceutical industry, academia, and not-for-profit organizations discussed these issues of concern. Discussions led by representatives from the Food and Drug Administration (FDA) and the Pharmaceutical Research and Manufacturers Association revealed that the required production capacity was limited for BD vaccines, with current Good Manufacturing Practices (cGMP) and other regulatory compliance issues. Central to their concerns was the reality that producing BD vaccines for DoD is high risk due to issues of liability and licensure, and would require compensation for and/or protection from these risks. In addition, the FDA normally requires vaccine developers to demonstrate the safety and efficacy of each

vaccine in human clinical trials. For BD vaccines, safety can be established. However, since it is unethical to deliberately expose people to biological warfare (BW) agents, efficacy in humans can only be inferred from animal studies since there is no or limited naturally occurring disease in human populations.

Despite the initial recommendation that a dedicated production facility should be established to produce BD vaccines, the senior leadership in DoD and Congress were not convinced of the need for a dedicated facility or the most cost-effective approach. A Vaccine Production Facility Task Force worked with the Joint Staff to validate the vaccine requirement and propose alternate solutions. The U.S. Army Medical Research and Development Command requested support from the U.S. Army Health Facility Planning Agency (HFPA) at the Office of the Surgeon General to plan and construct a GOCO vaccine production facility and money was placed in the President's Budget for design and construction. In December 1993, the MILCON planning effort was suspended pending completion of a cost and feasibility study on other alternatives for acquiring BD vaccines. In 1994 the Joint Program Office for Biological Defense was chartered and part of their responsibility was to ensure DoD had an adequate vaccine acquisition capability. A cost/benefit analysis in 1994 concluded that a COCO approach was the most cost-effective, particularly if existing facilities could be used or renovated for production. In 1995, a draft Request for Proposal (RFP) for BD vaccine production was released for comment. Responses indicated that industry was more concerned with the legal and regulatory processes associated with these unique medical products rather than the production capacity issue. Four companies expressed an interest in the actual production of BD vaccines.

Based on industry responses and the economic study, a revised acquisition strategy was developed. After evaluating several options, the DoD approved the Joint Vaccine Acquisition Program (JVAP), which relies on a prime systems contractor to integrate all of the processes associated with developing, licensing, producing, storing, testing and conducting post-marketing surveillance of medical BD products. Subcontracting is accomplished on an as-needed basis. The contractor serves as the responsible agent to the FDA for product licensure. The JVAP provides government oversight of the contractor to the Joint Program Office for Biological Defense (JPO-BD).

DoD awarded a prime systems contract to DynPort LLC in November 1997. This contract begins with the development and licensure of three vaccines: Q fever, tularemia, and vaccinia, and the storage of the current stockpile of investigational BD vaccines. The contract includes options for the development and licensure of ten other BD vaccines, to include a next generation anthrax vaccine, which are programmed for development and licensure by FY 2010.

IV. **Future recommendations**

There are multiple risks associated with having a sole-source commercial BD vaccine production facility. The DoD needs a mechanism for maximum flexibility for each vaccine product and not be locked into a contract with specific deliverables and specific production rates. As the threat changes, there may be a need to respond quickly and provide for a rapid surge capacity to meet increased production requirements for U. S. military personnel and, potentially, our domestic partners, such as the Department of State, or other essential DoD civilian and contractor personnel in a high-threat area. While there is currently no policy for the use of BD vaccines in these individuals, the possibility exists that additional requirements may be addressed at a future time, thereby increasing the number of doses required.

The Department of Defense continues to explore alternatives for vaccine production capabilities. We recognize the need to update the information on manufacturing interest of BD vaccines from the commercial sector, as well as revalidating the threat list and our capability to meet our requirements. Any decision to establish a Department of Defense alternative vaccine production facility must consider multiple factors, including the economic cost benefit analysis of a GOCO in comparison to commercial vaccine manufacturing companies. The site selection would be based on a best value determination considering a number of factors. Availability of a secure siting location, adequacy of available workforce in the area, linkage to a technical community suitable to support the facility, cost of construction and operation, existing infrastructure such as power, water, sewer and roads, and compatibility of other on-going installation missions are some of the factors that would influence the best value determination. Upon

site selection, a full and open contracting process would be utilized to design, construct and operate the facility.

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Use of Anthrax Vaccine in the United States

Recommendations of the Advisory Committee on Immunization Practices

Advisory Committee on Immunization Practices Membership List, October 2000

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Summary

These recommendations concern the use of aluminum hydroxide adsorbed cell-free anthrax vaccine (Anthrax Vaccine Adsorbed [AVA], BioPort Corporation, Lansing, MI) in the United States for protection against disease caused by Bacillus anthracis*. In addition, information is included regarding the use of chemoprophylaxis against* B. anthracis*.*

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)(*2*). 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* (*3--5*). Depending on the route of infection, anthrax disease can occur in three forms: cutaneous, gastrointestinal, and inhalation (*2*).

B. anthracis spores can remain viable and infective in the soil for many years. During this time, they are a potential source of infection for grazing livestock, but generally do not represent a direct infection risk for humans. Grazing ruminants become infected when they ingest these spores. Consequently, humans can become infected with *B. anthracis* by skin contact, ingestion, or inhalation of *B. anthracis* spores originating from animal products of infected animals. Direct skin contact with contaminated animal products can result in cutaneous anthrax. Ingestion of infected and undercooked or raw meat can result in oropharyngeal or gastrointestinal forms of the disease. Inhalation of aerosolized spores associated with industrial processing of contaminated wool, hair, or hides can result in inhalation anthrax. Person-to-person transmission of inhalation anthrax has not been confirmed.

Estimation of the true incidence of human anthrax worldwide is difficult because reporting of anthrax cases is unreliable (*6*). However, anthrax occurs globally and is most common in agricultural regions with inadequate control programs for anthrax in livestock. In these regions, anthrax affects domestic animals, which can directly or indirectly infect humans, and the form of anthrax that occurs in >95% of cases is cutaneous. These regions include South and Central America, Southern and Eastern Europe, Asia, Africa, the Caribbean, and the Middle East (*6*). The largest recent epidemic of human anthrax occurred in Zimbabwe during 1978--1980; 9445 cases occurred, including 141 (1.5%) deaths (*4*).

In the United States, the annual incidence of human anthrax has declined from approximately 130 cases annually in the early 1900s to no cases during 1993--2000. The last confirmed case of human anthrax reported in the United States was a cutaneous case reported in 1992. Most cases reported in the United States have been cutaneous; during the 20th century, only 18 cases of inhalation anthrax were reported, the most recent in 1976 (*7*). Of the 18 cases of inhalation anthrax reported in the United States since 1950, two occurred in laboratory workers. No gastrointestinal cases have been reported in the United States.

Anthrax continues to be reported among domestic and wild animals in the United States. The incidence of anthrax in U.S. animals is unknown; however, reports of animal infection have occurred among the Great Plains states from Texas to North Dakota (*8--10*).

In addition to causing naturally occurring anthrax, *B. anthracis* has been manufactured as a biological warfare agent, and concern exists that it could be used as a biological terrorist agent. *B. anthracis* is considered one of the most likely biological warfare agents because of the ability of *B. anthracis* spores to be transmitted by the respiratory route, the high mortality of inhalation anthrax, and the greater stability of *B. anthracis* spores compared with other potential biological warfare agents (*11--14*). Anthrax has been a focus of offensive and defensive biological warfare research programs for approximately 60 years. The World Health Organization estimated that 50 kg of *B. anthracis* released upwind of a population center of 500,000 could result in 95,000 deaths and 125,000 hospitalizations (*15*).

The infectious dose of *B. anthracis* in humans by any route is not precisely known. Based on data from studies of primates, the estimated infectious dose by the respiratory route required to cause inhalation anthrax in humans is 8,000--50,000 spores (*7,16,17*). The influence of the bacterium strain or host factors on this infectious dose is not completely understood.

Primary and secondary aerosolization of *B. anthracis* spores are important considerations in bioterrorist acts involving deliberate release of *B. anthracis*. Primary aerosolization results from the initial release of the agent. Secondary aerosolization results from agitation of the particles that have settled from the primary release (e.g., as a result of disturbance of contaminated dust by wind, human, or animal activities.) In the generation of infectious aerosols, the aerosol is composed of two components that have differing properties: particles larger than 5 microns and particles 1--5 microns in diameter. Particles >5 microns in diameter quickly fall from the atmosphere and bond to any surface. These particles require large amounts of energy to be resuspended. Even with use of highly efficient dissemination devices (i.e., devices able to disseminate a high concentration of agent into the environment), the level of environmental contamination with the larger, bound particles is estimated to still be too low to represent a substantial threat of secondary aerosolization (*18--20*). Particles 1--5 microns in diameter behave as a gas and move through the environment without settling. Environmental residue is not a concern from this portion of the aerosol (*21*).

Disease

The symptoms and incubation period of human anthrax vary depending on the route of transmission of the disease. In general, symptoms usually begin within 7 days of exposure (*1*).

Cutaneous

Most (>95%) naturally occurring *B. anthracis* infections are cutaneous and occur when the bacterium enters a cut or abrasion on the skin (e.g., when handling contaminated meat, wool, hides, leather, or hair products from infected animals). The reported incubation period for cutaneous anthrax ranges from 0.5 to 12 days (*1,6,22*). Skin infection begins as a small papule, progresses to a vesicle in 1--2 days, and erodes leaving a necrotic ulcer with a characteristic black center. Secondary vesicles are sometimes

observed. The lesion is usually painless. Other symptoms might include swelling of adjacent lymph glands, fever, malaise, and headache. The case-fatality rate of cutaneous anthrax is 20% without antibiotic treatment and <1% with antibiotic treatment (*1,23,24*).

Gastrointestinal

The intestinal form of anthrax usually occurs after eating contaminated meat and is characterized by an acute inflammation of the intestinal tract. The incubation period for intestinal anthrax is suspected to be 1--7 days. Involvement of the pharynx is characterized by lesions at the base of the tongue or tonsils, with sore throat, dysphagia, fever, and regional lymphadenopathy. Involvement of the lower intestine is characterized by acute inflammation of the bowel. Initial signs of nausea, loss of appetite, vomiting, and fever are followed by abdominal pain, vomiting of blood, and bloody diarrhea (*25*). The case-fatality rate of gastrointestinal anthrax is unknown but is estimated to be 25% --60% (*1,26,27*).

Inhalation

Inhalation anthrax results from inspiration of 8,000--50,000 spores of *B. anthracis*. Although the incubation period for inhalation anthrax for humans is unclear, reported incubation periods range from 1 to 43 days (*28*). In a 1979 outbreak of inhalation anthrax in the former Soviet Union, cases were reported up to 43 days after initial exposure. The exact date of exposure in this outbreak was estimated and never confirmed, and the modal incubation period was reported as 9--10 days. This modal incubation period is slightly longer than estimated incubation periods reported in limited outbreaks of inhalation anthrax in humans (*29*). However, the incubation period for inhalation anthrax might be inversely related to the dose of *B. anthracis* (*30,31*). In addition, the reported administration of postexposure chemoprophylaxis during this outbreak might have prolonged the incubation period in some cases. Data from studies of laboratory animals suggest that *B. anthracis* spores continue to vegetate in the host for several weeks postinfection, and antibiotics can prolong the incubation period for developing disease (*28--30,32*). These studies of nonhuman primates, which are considered to be the animal model that most closely approximates human disease, indicate that inhaled spores do not immediately germinate within the alveolar recesses but reside there potentially for weeks until taken up by alveolar macrophages. Spores then germinate and begin replication within the macrophages. Antibiotics are effective against germinating or vegetative *B. anthracis* but are not effective against the nonvegetative or spore form of the organism. Consequently, disease development can be prevented as long as a therapeutic level of antibiotics is maintained to kill germinating *B. anthracis* organisms. After discontinuation of antibiotics, if the remaining nongerminated spores are sufficiently numerous to evade or overwhelm the immune system when they germinate, disease will then develop. This phenomenon of delayed onset of disease is not recognized to occur with cutaneous or gastrointestinal exposures.

Initial symptoms can include sore throat, mild fever, and muscle aches. After several days, the symptoms can progress to severe difficulty breathing and shock. Meningitis frequently develops. Case-fatality estimates for inhalation anthrax are based on incomplete information regarding the number of persons exposed and infected. However, a case-fatality rate of 86% was reported following the 1979 outbreak in the former Soviet Union, and a case-fatality rate of 89% (16 of 18 cases) was reported for inhalation anthrax in the United States (*8,28,29*). Records of industrially acquired inhalation anthrax in the United Kingdom, before the availability of antibiotics or vaccines, document that 97% of cases were fatal.

PATHOGENESIS

B. anthracis evades the immune system by producing an antiphagocytic capsule. In addition, *B. anthracis* produces three proteins --- protective antigen (PA), lethal factor (LF), and edema factor (EF) --- that act in binary combinations to form two exotoxins known as lethal toxin and edema toxin (*33--35*). PA and LF form lethal toxin; PA and EF form edema toxin. LF is a protease that inhibits mitogen-activated protein kinase-kinase (*36*). EF is an adenylate cyclase that generates cyclic adenosine monophosphate in the cytoplasm of eukaryotic cells (*37,38*). PA is required for binding and translocating LF and EF into host cells. PA is an 82 kD protein that binds to receptors on mammalian cells and is critical to the ability of *B. anthracis* to cause disease. After binding to the cell membrane, PA is cleaved to a 63 kD fragment that subsequently binds with LF or EF (*39*). LF or EF bound to the 63KD fragment undergoes receptor-mediated internalization, and the LF or EF is translocated into the cytosol upon acidification of the endosome.

After wound inoculation, ingestion, or inhalation, spores infect macrophages, germinate, and proliferate. In cutaneous and gastrointestinal infection, proliferation can occur at the site of infection and the lymph nodes draining the infection site. Lethal toxin and edema toxin are produced and respectively cause local necrosis and extensive edema, which is a major characteristic of the disease. As the bacteria multiply in the lymph nodes, toxemia progresses, and bacteremia may ensue. With the increase in toxin production, the potential for widespread tissue destruction and organ failure increases (*40*).

CONTROL AND PREVENTION

Reducing the Risk for Exposure

Worldwide, anthrax among livestock is controlled through vaccination programs, rapid case detection and case reporting, and

burning or burial of animals suspected or confirmed of having the disease. Human infection is controlled through reducing infection in livestock, veterinary supervision of slaughter practices to avoid contact with potentially infected livestock, and restriction of importation of hides and wool from countries in which anthrax occurs. In countries where anthrax is common and vaccination coverage among livestock is low, humans should avoid contact with livestock and animal products that were not inspected before and after slaughter. In addition, consumption of meat from animals that have experienced sudden death and meat of uncertain origin should be avoided (*1,4*).

Vaccination

Protective Immunity

Before the mechanisms of humoral and cellular immunity were understood, researchers demonstrated that inoculation of animals with attenuated strains of *B. anthracis* led to protection (*41,42*). Subsequently, an improved vaccine for livestock, based on a live unencapsulated avirulent variant of *B. anthracis*, was developed (*43,44*). Since then, this vaccine has served as the principal veterinary vaccine in the Western Hemisphere.

The use of livestock vaccines was associated with occasional animal casualties, and live vaccines were considered unsuitable for humans. In 1904, the possibility 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 (*45,46*). This led to exploration of the use of filtrates of artificially cultivated *B. anthracis* as vaccines (*47--51*) and thereby to the human anthrax vaccines currently licensed and used in the United States and Europe today. The first product --- an alum-precipitated cell-free filtrate from an aerobic culture --- was developed in 1954 (*52,53*). Alum is the common name for aluminum potassium sulfate. This vaccine provided protection in monkeys, caused minimal reactivity and short-term adverse events in humans, and was used in the only efficacy study of human vaccination against anthrax in the United States. In the United States, during 1957--1960, the vaccine was improved through a) the selection of a *B. anthracis* strain that produced a higher fraction of PA under microaerophilic conditions, b) the production of a protein-free media, and c) the use of aluminum hydroxide rather than alum as the adjuvant (*50,51*). This became the vaccine approved for use in the United States --- anthrax vaccine adsorbed (AVA [patent number 3,208,909, September 28, 1965]).

Passive immunity against *B. anthracis* can be transferred using polyclonal antibodies in laboratory animals (*54*); however, specific correlates for immunity against *B. anthracis* have not been identified (*55--57*). Evidence suggests that a humoral and cellular response against PA is critical to protection against disease following exposure (*49,57--59*).

Anthrax Vaccine Adsorbed

AVA, the only licensed human anthrax vaccine in the United States, is produced by BioPort Corporation in Lansing, Michigan, and is prepared from a cell-free filtrate of *B. anthracis* culture that contains no dead or live bacteria (*60*). The strain used to prepare the vaccine is a toxigenic, nonencapsulated strain known as V770-NP1-R (*50*). The filtrate contains a mix of cellular products including PA (*57*) and is adsorbed to aluminum hydroxide (Amphogel, Wyeth Laboratories) as adjuvant (*49*). The amount of PA and other proteins per 0.5mL dose is unknown, and all three toxin components (LF, EF, and PA) are present in the product (*57*). The vaccine contains no more that 0.83 mg aluminum per 0.5mL dose, 0.0025% benzethonium chloride as a preservative, and 0.0037% formaldehyde as a stabilizer. The potency and safety of the final product is confirmed according to U.S. Food and Drug Administration (FDA) regulations (*61*). Primary vaccination consists of three subcutaneous injections at 0, 2, and 4 weeks, and three booster vaccinations at 6, 12, and 18 months. To maintain immunity, the manufacturer recommends an annual booster injection. The basis for the schedule of vaccinations at 0, 2, and 4 weeks, and 6, 12, and 18 months followed by annual boosters is not well defined (*52,62,63*; Table 1).

Because of the complexity of a six-dose primary vaccination schedule and frequency of local injection-site reactions (see Vaccine Safety), studies are under way to assess the immunogenicity of schedules with a reduced number of doses and with intramuscular (IM) administration rather than subcutaneous administration. Immunogenicity data were collected from military personnel who had a prolonged interval between the first and second doses of anthrax vaccine in the U.S. military anthrax vaccination program. Antibody to PA was measured by enzyme-linked immunosorbent assay (ELISA) at 7 weeks after the first dose. Geometric mean titers increased from 450 µg/mL among those who received the second vaccine dose 2 weeks after the first (the recommended schedule, n = 22), to 1,225 for those vaccinated at a 3-week interval (n = 19), and 1,860 for those vaccinated at a 4-week interval (n = 12). Differences in titer between the routine and prolonged intervals were statistically significant ($p < 0.01$).

Subsequently, a small randomized study was conducted among military personnel to compare the licensed regimen (subcutaneous injections at 0, 2, and 4 weeks, n = 28) and alternate regimens (subcutaneous [n = 23] or intramuscular [n=22] injections at 0 and 4 weeks). Immunogenicity outcomes measured at 8 weeks after the first dose included geometric mean IgG concentrations and the proportion of subjects seroconverting (defined by an anti-PA IgG concentration of $\geq$25 µg/mL). In addition, the occurrence of local and systemic adverse events was determined. IgG concentrations were similar between the routine and alternate schedule groups (routine: 478 µg/mL; subcutaneous at 0 and 4 weeks: 625 µg/mL; intramuscular at 0 and 4 weeks: 482 µg/mL). All study participants seroconverted except for one of 21 in the intramuscular (injections at 0 and 4 weeks) group. Systemic adverse events were uncommon and similar for the intramuscular and subcutaneous groups. All local reactions (i.e., tenderness, erythema,

warmth, induration, and subcutaneous nodules) were significantly more common following subcutaneous vaccination. Comparison of the three vaccination series indicated no significant differences between the proportion of subjects experiencing local reactions for the two subcutaneous regimens but significantly fewer subcutaneous nodules ($p<0.001$) and significantly less erythema ($p = 0.001$) in the group vaccinated intramuscularly (P. Pittman, personal communication, USAMRIID, Ft. Detrick, MD).

Larger studies are planned to further evaluate vaccination schedule and route of administration. At this time, ACIP cannot recommend changes in vaccine administration because of the preliminary nature of this information. However, the data in this report do support some flexibility in the route and timing of anthrax vaccination under special circumstances. As with other licensed vaccines, no data indicate that increasing the interval between doses adversely affects immunogenicity or safety. Therefore, interruption of the vaccination schedule does not require restarting the entire series of anthrax vaccine or the addition of extra doses.

Vaccine Efficacy

The efficacy of AVA is based on several studies in animals, one controlled vaccine trial in humans (*64*), and immunogenicity data for both humans and lower mammalian species (*47,49,57,65*). Vaccination of adults with the licensed vaccine induced an immune response measured by indirect hemagglutination in 83% of vaccinees 2 weeks after the first dose and in 91% of vaccinees who received two or more doses (*57,65*). Approxi mately 95% of vaccinees seroconvert with a fourfold rise in anti-PA IgG titers after three doses (*57,65*). However, the precise correlation between antibody titer (or concentration) and protection against infection is not defined (*57*).

The protective efficacy of the alum-precipitated vaccine (the original form of the PA filtrate vaccine) and AVA (adsorbed to aluminum hydroxide) have been demonstrated in several animal models using different routes of administration (*49--52,57,62,63,66--69*). Data from animal studies (except primate studies) involve several animal models, preparations, and vaccine schedules and are difficult to interpret and compare. The macaque model (Rhesus monkeys, *Macaca mulatta)* of inhalation anthrax is believed to best reflect human disease (*31*), and the AVA vaccine has been shown to be protective against pulmonary challenge in macaques using a limited number of *B. anthracis* strains (*52,62,70--73*) (Table 2).

In addition to the studies of macaques, a study was published in 1962 of an adjuvant controlled, single-blinded, clinical trial among mill workers using the alum-precipitated vaccine --- the precursor to the currently licensed AVA. In this controlled study, 379 employees received the vaccine, 414 received the placebo, and 340 received neither the vaccine nor the placebo. This study documented a vaccine efficacy of 92.5% for protection against anthrax (cutaneous and inhalation combined), based on person time of occupational exposure (*64*). During the study, an outbreak of inhalation anthrax occurred among the study participants. Overall, five cases of inhalation anthrax occurred among persons who were either placebo recipients or did not participate in the controlled part of the study. No cases occurred in anthrax vaccine recipients. No data are available regarding the efficacy of anthrax vaccine for persons aged <18 years and >65 years.

Duration of Efficacy

The duration of efficacy of AVA is unknown in humans. Data from animal studies suggest that the duration of efficacy after two inoculations might be 1--2 years (*57,62,72*).

Vaccine Safety

Data regarding adverse events associated with use of AVA are derived from information from three sources. These sources are a) prelicensure investigational new drug data evaluating vaccine safety, b) passive surveillance data regarding adverse events associated with postlicensure use of AVA, and c) several published studies (*64,74,75*).

Prelicensure Adverse Event Surveillance

Local Reactions. In AVA prelicensure evaluations, 6,985 persons received 16,435 doses: 9,893 initial series doses and 6,542 annual boosters (*74*). Severe local reactions (defined as edema or induration >120 mm) occurred after 1% of vaccinations. Moderate local reactions (defined as edema and induration of 30 mm--120 mm) occurred after 3% of vaccinations. Mild local reactions (defined as erythema, edema, and induration <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 (*64*).

Systemic Reactions. In AVA 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 (*74*). In the study of the alum precipitated precursor to AVA, systemic reactions occurred in 0.2% of vaccine recipients (*64*).

Postlicensure Adverse Event Surveillance

Data regarding potential adverse events following anthrax vaccination are available from the Vaccine Adverse Event Reporting System (VAERS) (*75*). From January 1, 1990, through August 31, 2000, at least 1,859,000 doses of anthrax vaccine were distributed in the United States. During this period, VAERS received 1,544 reports of adverse events; of these, 76 (5%) were serious. A serious event is one that results in death, hospitalization, or permanent disability or is life-threatening. Approximately 75% of the reports were for persons aged <40 years; 25% were female, and 89% received anthrax vaccine alone. The most frequently reported adverse events were injection-site hypersensitivity (334), injection-site edema (283), injection-site pain (247), headache (239), arthralgia (232), asthenia (215), and pruritis (212). Two reports of anaphylaxis have been received by VAERS. One report of a death following receipt of anthrax vaccine has been submitted to VAERS; the autopsy final diagnosis was coronary arteritis. A second fatal report, submitted after August 31, 2000, indicated aplastic anemia as the cause of death. A causal association with anthrax vaccine has not been documented for either of the death reports. Serious adverse events infrequently reported (<10) to VAERS have included cellulitis, pneumonia, Guillain-Barré syndrome, seizures, cardiomyopathy, systemic lupus erythematosus, multiple sclerosis, collagen vascular disease, sepsis, angioedema, and transverse myelitis (CDC/FDA, unpublished data, 2000). Analysis of VAERS data documented no pattern of serious adverse events clearly associated with the vaccine, except injection-site reactions. Because of the limitations of spontaneous reporting systems, determining causality for specific types of adverse events, with the exception of injection-site reactions, is often not possible using VAERS data alone.

Published Studies About Adverse Events

Adverse events following anthrax vaccination have been assessed in several studies conducted by the Department of Defense in the context of the routine anthrax vaccination program. At U.S. Forces, Korea, data were collected at the time of anthrax vaccination from 4,348 service personnel regarding adverse events experienced from a previous dose of anthrax vaccine. Most reported events were localized, minor, and self-limited. After the first or second dose, 1.9% reported limitations in work performance or had been placed on limited duty. Only 0.3% reported $\geq$1 day lost from work; 0.5% consulted a clinic for evaluation; and one person (0.02%) required hospitalization for an injection-site reaction. Adverse events were reported more commonly among women than among men. A second study at Tripler Army Medical Center, Hawaii, assessed adverse events among 603 military health-care workers. Rates of events that resulted in seeking medical advice or taking time off work were 7.9% after the first dose; 5.1% after the second dose; 3.0% after the third dose; and 3.1% after the fourth dose. Events most commonly reported included muscle or joint aches, headache, and fatigue (*10)*. However, these studies are subject to several methodological limitations, including sample size, the limited ability to detect adverse events, loss to follow-up, exemption of vaccine recipients with previous adverse events, observational bias, and the absence of unvaccinated control groups (*10*).

No studies have definitively documented occurrence of chronic diseases (e.g., cancer or infertility) following anthrax vaccination. In an assessment of the safety of anthrax vaccine, the Institute of Medicine (IOM) noted that published studies reported no significant adverse effects of the vaccine, but the literature is limited to a few short-term studies (*76*). One published follow-up study of laboratory workers at Fort Detrick, Maryland, concluded that, during the 25-year period following receipt of anthrax vaccine, the workers did not develop any unusual illnesses or unexplained symptoms associated with vaccination (*77,78*). IOM concluded that, in the peer-reviewed literature, evidence is either inadequate or insufficient to determine whether an association exists between anthrax vaccination and long-term adverse health outcomes. IOM noted that few vaccines for any disease have been actively monitored for adverse effects over long periods and encouraged evaluate of active long-term monitoring studies of large populations to further evaluate the relative safety of anthrax vaccine. Such studies are under way by the Department of Defense.

CDC has conducted two epidemiologic investigations of the health concerns of Persian Gulf War (PGW) veterans that examined a possible association with vaccinations, including anthrax vaccination. The first study, conducted among Air Force personnel, evaluated several potential risk factors for chronic multisymptom illnesses, including anthrax vaccination. Occurrence of a chronic multisymptom condition was significantly associated with deployment to the PGW but was not associated with specific PGW exposures and also affected nondeployed veterans (*79*). The ability of this study to detect a significant difference was limited. The second study focused on comparing illness among PGW veterans and controls. The study documented that the self-reported prevalence of medical and psychiatric conditions was higher among deployed PGW veterans than nondeployed veterans. In this study, although a question was asked about the number of vaccinations received, no specific questions were asked about the anthrax vaccine. However, the study concluded that the relation between self-reported exposures and conditions suggests that no single exposure is related to the medical and psychiatric conditions among PGW military personnel (*80*). In summary, current research has not documented any single cause of PGW illnesses, and existing scientific evidence does not support an association between anthrax vaccine and PGW illnesses. No data are available regarding the safety of anthrax vaccine for persons aged <18 years and >65 years.

Management of Adverse Events

Adverse events can occur in persons who must complete the anthrax vaccination series because of high risk of exposure or because of employment requirements. Several protocols have been developed to manage specific local and systemic adverse events (available at www.anthrax.osd.mil). However, these protocols have not been evaluated in randomized trials.

Reporting of Adverse Events

Adverse events occurring after administration of anthrax vaccine --- especially events that are serious, clinically significant, or unusual --- should be reported to VAERS, regardless of the provider's opinion of the causality of the association. VAERS forms can be obtained by calling (800) 822-7967. Information about VAERS and how to report vaccine adverse events is available from http://www.vaers.org >, <http://www.fda.gov/cber/vaers/vaers.htm> or <http://www.cdc.gov/nip/>.

PRECAUTIONS AND CONTRAINDICATIONS

Vaccination During Pregnancy

No studies have been published regarding use of anthrax vaccine among pregnant women. Pregnant women should be vaccinated against anthrax only if the potential benefits of vaccination outweigh the potential risks to the fetus.

Vaccination During Lactation

No data suggest increased risk for side effects or temporally related adverse events associated with receipt of anthrax vaccine by breast-feeding women or breast-fed children. Administration of nonlive vaccines (e.g., anthrax vaccine) during breast-feeding is not medically contraindicated.

Allergies

Although anaphylaxis following anthrax vaccination is extremely rare and no anaphylaxis deaths associated with AVA have been reported, this adverse event can be life threatening. AVA is contraindicated for persons who have experienced an anaphylactic reaction following a previous dose of AVA or any of the vaccine components.

Previous History of Anthrax Infection

Anthrax vaccine is contraindicated in persons who have recovered from anthrax because of previous observations of more severe adverse events among recipients with a vaccine history of anthrax than among nonrecipients. The vaccine is also contraindicated in persons with a history of an anaphylactic reaction to the vaccine.

Illness

In the context of the routine preexposure program, vaccination of persons with moderate or severe acute illness should be postponed until recovery. This prevents superimposing the adverse effects of the vaccine on the underlying illness or mistakenly attributing a manifestation of the underlying illness to the vaccine. Vaccine can be administered to persons who have mild illnesses with or without low-grade fever.

RECOMMENDATIONS FOR USE OF AVA

Preexposure Vaccination

Occupational and Laboratory Exposures

Routine vaccination with AVA is indicated for persons engaged a) in work involving production quantities or concentrations of *B. anthracis* cultures and b) in activities with a high potential for aerosol production (*81*). Laboratorians using standard Biosafety Level 2 practices in the routine processing of clinical samples are not at increased risk for exposure to *B. anthracis* spores.

The risk for persons who come in contact in the workplace with imported animal hides, furs, bone meal, wool, animal hair, or bristles has been reduced by changes in industry standards and import restrictions (*82*). Routine preexposure vaccination is recommended only for persons in this group for whom these standards and restrictions are insufficient to prevent exposure to anthrax spores.

Routine vaccination of veterinarians in the United States is not recommended because of the low incidence of animal cases. However, vaccination might be indicated for veterinarians and other high-risk persons handling potentially infected animals in areas with a high incidence of anthrax cases.

Bioterrorism Preparedness

Although groups initially considered for preexposure vaccination for bioterrorism preparedness included emergency first responders, federal responders, medical practitioners, and private citizens, vaccination of these groups is not recommended. Recommendations regarding preexposure vaccination should be based on a calculable risk assessment. At present, the target

population for a bioterrorist release of *B. anthracis* cannot be predetermined, and the risk of exposure cannot be calculated. In addition, studies suggest an extremely low risk for exposure related to secondary aerosolization of previously settled *B. anthracis* spores (*28,83*). Because of these factors, preexposure vaccination for the above groups is not recommended. For the military and other select populations or for groups for which a calculable risk can be assessed, preexposure vaccination may be indicated.

Options other than preexposure vaccination are available to protect personnel working in an area of a known previous release of *B. anthracis*. If concern exists that persons entering an area of a previous release might be at risk for exposure from a re-release of a primary aerosol of the organism or exposure from a high concentration of settled spores in a specific area, initiation of prophylaxis should be considered with antibiotics alone or in combination with vaccine as is outlined in the section on postexposure prophylaxis.

Postexposure Prophylaxis --- Chemoprophylaxis and Vaccination

Penicillin and doxycycline are approved by FDA for the treatment of anthrax and are considered the drugs of choice for the treatment of naturally occurring anthrax (*14,83,84*). In addition, ciprofloxacin and ofloxacin have also demonstrated in vitro activity activity against *B. anthracis* (*14,85*). On the basis of studies that demonstrated the effectiveness of ciprofloxacin in reducing the incidence and progression of inhalation anthrax in animal models, FDA recently approved the use of ciprofloxacin following aerosol exposure to *B. anthracis* spores to prevent development or progression of inhalation anthrax in humans. Although naturally occurring *B. anthracis* resistance to penicillin is rare, such resistance has been reported (*86*). As of November 2000, no naturally occurring resistance to tetracyclines or ciprofloxacin had been reported.

Antibiotics are effective against the germinated form of *B. anthracis* but are not effective against the spore form of the organism. Following inhalation exposure, spores can survive in tissues for months without germination in nonhuman primates (*30,87*). This phenomenon of delayed vegetation of spores resulting in prolonged incubation periods has not been observed for routes of infection other than inhalation. In one study, macaques were exposed to four times the LD50 dose* of anthrax spores, and the pro portion of spores that survived in the lung tissue was estimated to be 15%--20% at 42 days, 2% at 50 days, and <1% at 75 days (*8*). Although the LD50 dose for humans is believed to be similar to that for nonhuman primates, the length of persistence of *B. anthracis* spores in human lung tissue is not known. The prolonged incubation period reported in the Soviet Union outbreak of inhalation anthrax suggests that lethal amounts of spores might have persisted up to 43 days after initial exposure. Although postexposure chemoprophylaxis with tetracycline was reportedly initiated during this outbreak, the duration of therapy was not reported.

Currently, ciprofloxacin is the only antibiotic approved by FDA for use in reducing the incidence or progression of disease after exposure to aerosolized *B. anthracis*. Although postexposure chemoprophylaxis using antibiotics alone has been effective in animal models, the definitive length of treatment is unclear. Several studies have demonstrated that short courses (5--10 days) of postexposure antibiotic therapy are not effective at preventing disease when large numbers of spores are inhaled (*7,30*). Longer courses of antibiotics may be effective (*87*). The study findings indicate that seven of 10, nine of 10 and eight of nine macaques exposed to 240,000--560,000 anthrax spores (8 times the LD50) survived when treated for 30 days with penicillin, doxycycline, or ciprofloxacin, respectively. All animals survived while undergoing antibiotic prophylaxis. Three animals treated with penicillin died on days 9, 12, and 20 after antibiotics were discontinued (days 39, 42, and 50 after exposure). A single animal in the doxycycline group died of inhalation anthrax 28 days after discontinuing treatment (day 58), and one animal in the ciprofloxacin group died 6 days after discontinuation of therapy (day 36).

In addition, studies have demonstrated that antibiotics in combination with postexposure vaccination are effective at preventing disease in nonhuman primates after exposure to *B. anthracis* spores (*30,87*). Vaccination alone after exposure was not protective. Because the current vaccine is labeled for use in specifically defined preexposure situations only, no FDA-approved labeling addresses the optimal number of vaccinations for postexposure prophylaxis use of the vaccine. An estimated 83% of human vaccinees develop a vaccine-induced immune response after two doses of the vaccine and >95% develop a fourfold rise in antibody titer after three doses (*57,65*). Although the precise correlation between antibody titer and protection against disease is not clear, these studies of postexposure vaccine regimens used in combination with antibiotics in nonhuman primates have consistently documented that two to three doses of vaccine were sufficient to prevent development of disease once antibiotics were discontinued.

Only one study has directly compared antibiotics plus vaccine with a longer course of antibiotics following aerosol exposure (*87*). This study documented no significant difference in survival for animals treated with doxycycline alone for 30 days or animals treated with 30 days of doxycycline plus two doses of anthrax vaccine postexposure (nine of 10 versus nine of nine, $p = 0.4$). However, the study suggests a possible benefit of postexposure combination of antibiotics with vaccination.

Following Inhalation Exposure

Postexposure prophylaxis against *B. anthracis* is recommended following an aerosol exposure to *B. anthracis* spores. Such exposure might occur following an inadvertent exposure in the laboratory setting or a biological terrorist incident. Aerosol exposure is unlikely in settings outside a laboratory working with large volumes of *B. anthracis*, textile mills working with heavily contaminated animal products, or following a biological terrorism or warfare attack. Following naturally occurring anthrax among

livestock, cutaneous and rare gastrointestinal exposures among humans are possible, but inhalation anthrax has not been reported. Because of the potential persistence of spores following a possible aerosol exposure, antibiotic therapy should be continued for at least 30 days if used alone, and although supporting data are less definitive, longer antibiotic therapy (up to 42--60 days) might be indicated. If vaccine is available, antibiotics can be discontinued after three doses of vaccine have been administered according to the standard schedule (0, 2, and 4 weeks) (Table 3). Because of concern about the possible antibiotic resistance of *B. anthracis* used in a bioterrorist attack, doxycycline or ciprofloxacin can be chosen initially for antibiotic chemoprophylaxis until organism susceptibilities are known. Antibiotic chemoprophylaxis can be switched to penicillin VK or amoxicillin once antibiotic susceptibilities are known and the organism is found to be penicillin susceptible with minimum inhibitory concentrations (MICs) attainable with oral therapy.

Although the shortened vaccine regimen has been effective when used in a postexposure regimen that includes antibiotics, the duration of protection from vaccination is not known. Therefore, if subsequent exposures occur, additional vaccinations might be required.

Following Cutaneous or Gastrointestinal Exposure

No controlled studies have been conducted in animals or humans to evaluate the use of antibiotics alone or in combination with vaccination following cutaneous or gastrointestinal exposure to *B. anthracis*. Cutaneous and rare gastrointestinal exposures of humans are possible following outbreaks of anthrax in livestock. In these situations, on the basis of pathophysiology, reported incubation periods, current expert clinical judgment, and lack of data, postexposure prophylaxis might consist of antibiotic therapy for 7--14 days. Antibiotics could include any of those previously mentioned in this report and in Table 3.

RESEARCH AGENDA

The following research priorities should be considered regarding anthrax vaccine: immunogenicity, evaluation of changes in use of the current vaccine, human safety studies, postexposure prophylaxis, antibiotic susceptibility and treatment studies, and safety of anthrax vaccine in clinical toxicology studies among pregnant animals.

Immunogenicity

Regarding the immunogenicity of AVA, priority research topics include a) identifying a quantitative immune correlate(s) of protection in relevant animal species (especially rabbits and nonhuman primates) and b)defining the quantitative relation between the vaccine-elicited immune response in these animal species and humans. Specifically, such information could help to provide scientific justification for changing the schedule and route of administration of the existing vaccine.

Evaluating Changes in the Current Vaccine Schedule and Route

Studies evaluating the effects of variations in use of the current anthrax vaccine should include a definitive clinical evaluation comparing the intramuscular and subcutaneous routes of administration and an assessment of the effects of reducing the number of inoculations required for protection. Both immunogenicity and safety of these changes should be evaluated. Information about the efficacy and safety of AVA use in children and elderly persons is needed. Information about safety of the vaccine during pregnancy is also needed. In addition, research to develop the next generation of anthrax vaccines should continue.

Human Safety Studies

To assess the safe use of anthrax vaccine in humans, the Advisory Committee on Immunization Practices (ACIP) recommends several areas of research. Adverse event surveillance through VAERS should be enhanced, which could include development of electronic reporting capability and implementation of strategies to facilitate reporting. In addition, the influence of lot-to-lot variations in the vaccine on rates of adverse events should be evaluated. Other safety issues related to use of anthrax vaccine that should be addressed include development and evaluation of pretreatment strategies to decrease short-term adverse events; assessment of risk factors for adverse events, including sex and preexisting antibody levels; and analysis of differences in rates of occurrence of adverse events by route of anthrax transmission and method of vaccine administration (intramuscular, subcutaneous, or jet injector). Because the role of repeated inoculations in local and systemic reactions remains unclear, further research is needed regarding this subject. In addition, the feasibility of studies to evaluate longer term and systemic adverse events should be determined.

Postexposure Prophylaxis

Although a substantial benefit of postexposure antibiotics in preventing development of inhalation anthrax has been demonstrated in macaques, further research is needed to determine the optimal number of days of administration of those antibiotics and any additional benefit of receiving the anthrax vaccine in combination with antibiotics. This is a high priority for the current federal initiative regarding bioterrorism preparedness. Determining alternative antibiotics for children and pregnant women should be an

important part of this research.

Antibiotic Susceptibility and Treatment Studies

Studies are needed that assess in vitro susceptibility of *B. anthracis* strains to azithromycin, erythromycin, and other antibiotics that are practical for children and elderly persons. In addition, treatment trials in animals for antibiotic alternatives to penicillin and doxycycline are recommended.

Safety of Anthrax Vaccine in Clinical Toxicology Studies Among Pregnant Animals

To assess the safety of anthrax vaccine use during human pregnancy, ACIP recommends that regulatory toxicology studies be conducted in pregnant animals. The study findings could provide baseline data for further studies of the safety of AVA use in pregnant women.

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*LD50=a lethal dose of 50%; defined as the dose of a product that will result in the death of 50% of a population exposed to that product.

Table 1

TABLE 1. Recommended vaccination schedule and contraindications for Anthrax V
Adsorbed (AVA)

Recommended vaccination schedule	Subcutaneous injections at 0, 2, and 4 wks, then 6 mos, 12 mos, and 18 m Annual booster injection if immunity be maintained.
Contraindications	a) Previous history of anthrax infecti or b) Experiencing an anaphylactic reaction following a previous dose o or any of the vaccine components.
Postponement of vaccination	Moderate or severe acute illness.

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Table 2

TABLE 2. Summary of efficacy studies of acellular filtrate vaccines against inhalati

Vaccine*	No. doses	Route of vaccine administration	Challenge dose†	Challenge strain§
Alum[52]	3	Subcutaneous	50 x LD50	Vollum
Alum[51]	2	Subcutaneous	100 x LD50	Vollum
Alum[68]	2	Subcutaneous	10 x LD50	M36 (Vollum)
AVA[70]	2	Intramuscular	200 x LD50	Ames
AVA[71]	2	Intramuscular	200 x LD50	Ames

* Alum=aluminum potassium sulfate; AVA=Anthrax Vaccine Adsorbed.

† In multiples of macaque LD50. LD50=a lethal dose of 50% (defined as the dose of a product that will result

§ Route of challenge was inhalation.

¶ Duration of challenge following vaccination.

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Table 3

TABLE 3. Suggested postexposure antibiotic prophylaxis following confirmed or suspected

Drug	Adults	
One of the following		
Oral fluoroquinolones		
Ciprofloxacin	500 mg orally twice daily	†
Ofloxacin	400 mg orally twice daily	N
Oral tetracyclines		
Doxycycline	100 mg orally twice daily	5
Oral penicillins		
Penicillin VK	7.5 mg/kg orally four times daily	5
Amoxicillin	500 mg orally three times daily	8 t

\# Prophylaxis should continue until exposure to *B. anthracis* has been excluded. If exposure is confirmed and vaccine 4 weeks and until three doses of vaccine have been administered or for 30–60 days if vaccine is not available.

† Use of tetracyclines and fluoroquinolones in children have potential adverse effects including staining of teeth and c risks must be weighed carefully against the risk for developing anthrax. If a release of *B. anthracis* is confirmed, chil kg of body mass per day divided every 8 or 12 hours (not to exceed 500 mg three times daily) or oral penicillin VK 50 m as penicillin susceptibility of the organism has been confirmed.

§ Data are limited regarding the use of ofloxacin or other fluoroquinolones in children (except for ciprofloxacin).

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