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

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May 4, 2005

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EXECUTIVE SUMMARY

Anthrax is readily weaponized, highly lethal, and poses a clear threat. Anthrax terror attacks along our eastern seaboard in fall 2001 killed five people, infected 17 others, disrupted government operations, and threatened the US Postal Service, US Congress, and US Supreme Court.

Since March 1998, the Department of Defense has protected its personnel against anthrax weapons by means of the Anthrax Vaccine Immunization Program (AVIP). The anthrax vaccine, licensed without interruption since 1970, protects against anthrax with a safety record like that of other vaccines. Seven independent civilian reviews since 1978 unanimously affirmed the value of anthrax vaccination. This includes the comprehensive, peer-reviewed March 2002 report of the National Academy of Sciences' Institute of Medicine reaffirming the vaccine's effectiveness and safety.

More than 5.2 million doses of anthrax vaccine have been given to more than 1.3 million Service Members since March 1998. Twenty human studies involving more than 860,000 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 inhaled exposure to anthrax spores is based on both human and animal studies. A 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 with exposure to inhalational anthrax spores. But results from studies using non-human primates show that the vaccine protected 95% of vaccinated monkeys against inhalational anthrax, whereas all unvaccinated animals died from anthrax infection.

Previous concerns about deficiencies in meeting Good Manufacturing Practices have been resolved by the vaccine manufacturer, to the satisfaction of the Food & Drug Administration (FDA). On January 31, 2002, the FDA granted BioPort Corporation final approval to resume the manufacture and distribution of the US-licensed anthrax vaccine, and released additional vaccine lots for use. As with all vaccines, each lot of anthrax vaccine has passed extensive tests for safety, sterility, purity, and potency before release to immunization clinics.

Balancing the low risk of adverse events after vaccination versus the high risk of disease from failing to vaccinate, the scales decidedly favor immunization. The consequences of unvaccinated Service Members becoming 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. Vaccination protects both the individual and the unit's mission. The Secretary of Defense, after assuring a program of high quality, directed the implementation of the Anthrax Vaccine Immunization Program.

It is very important that DoD be recognized as forthright, honest, and credible. The DoD began with a program to inform people about the scientific basis for anthrax vaccination. We enhanced DoD's education efforts by installing a toll-free information line (877-GET-VACC) and a detailed web site (www.anthrax.mil). Additional educational tools are developed periodically.

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 – such as North Korea and Iran – now possess or are pursuing offensive BW capabilities. Iraq confessed to the United Nations that it loaded anthrax spores into a variety of weapons. The Soviet/Russian biological weapons program is well known. Anthrax is within the reach of not only rogue nations, but also transnational terrorist groups. Anthrax tops the DoD's biological threat list.

Anthrax spores are highly lethal. Small amounts can produce large numbers of casualties. A 1993 report by the U.S. Congressional Office of Technology Assessment estimated that 130,000 to 3 million deaths could follow the aerosolized release of 100 kg of anthrax spores upwind of Washington, DC. 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. An anthrax aerosol would be odorless, invisible, and capable of traveling many miles with the winds.

Anthrax is 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. During the fall 2001 anthrax terror attacks in the eastern United States, delivering weaponized anthrax was as easy as putting it in an envelope and dropping it in a mailbox. While protective clothing and gas masks provide good front-line defense, their effective use requires rapid and early detection of the agent. Detection devices do not issue warnings fast enough to protect against the threat. They may not detect an agent in time to warn personnel to don protective gear before exposure.

AVIP BACKGROUND

On December 15, 1997, Defense Secretary William Cohen announced a plan to immunize military personnel 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.

Immunization of Service Members and Emergency-essential DoD civilians assigned or deployed to Southwest Asia (SWA) began in March 1998. Forces deployed to Korea and surrounding waters were vaccinated starting in August 1998. After a temporary shortage of vaccine, the Department of Defense resumed the Anthrax Vaccine Immunization Program (AVIP) in September 2002.

THE 2000-01 AVIP SLOWDOWNS

Between July 2000 and June 2001, DoD ordered a series of three temporary slowdowns of the AVIP, until additional FDA-approved vaccine became available. The supply was restored in

January 2002, with FDA approval of renovations by BioPort Corporation of its facilities and processes.

Each dose of a vaccine is like climbing a ladder. The first dose of anthrax vaccine begins the process of protection. Anthrax-neutralizing 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. The study found that personnel with an extended amount of time between doses still displayed a vigorous immunologic response.

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.

Emergency Use Authorization

On October 27, 2004, the U.S. District Court for the District of Columbia (the Court) issued an opinion overturning FDA's finding in December 2003 that AVA is effective to prevent anthrax regardless of the route of exposure. The court did not suspend or revoke the license of AVA for the prevention of anthrax disease and the vaccine remains licensed. To address the Court's order, FDA published a proposed rule and proposed order on December 29, 2004, which allows a notice and comment period of 90 days. In the meantime, however DOD has sought an Emergency Use Authorization (EUA) to address the threat to military personnel.

Pending reanalysis of the evidence and new public comments concerning use of the vaccine to protect against inhalational anthrax, FDA issued an Emergency Use Authorization for this use. The purpose of the EUA is to ensure that people at risk, including members of the Armed Forces, have the benefit of available medical countermeasures to protect them against biological, chemical, and radiological threats.

On January 27, 2005, the Food & Drug Administration (FDA) granted an EUA for anthrax vaccine to prevent inhalational anthrax. U.S. anthrax vaccine has been FDA-licensed to prevent anthrax since 1970. Anthrax vaccine is 92.5% effective, against both cutaneous and inhalational anthrax. DoD will continue to educate, track and monitor service member vaccinations and adverse events.

Mandatory vaccination will be reconsidered after FDA completes its administrative review, which DoD expects to occur later in 2005.

HISTORY OF ANTHRAX VACCINE

The Federal Government licensed the anthrax vaccine given to U.S. forces on November 4, 1970. For 35 years, anthrax vaccine has been recommended for some 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 to 300,000 doses of anthrax vaccine in 1991 during Operation Desert Storm.

The FDA-licensed anthrax vaccine is effective and has an excellent safety record. It is a 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 booster doses are administered thereafter to maintain immunity. Although protection levels increase as shots in the series are given, the entire six-shot series is needed. Research into simpler dosing schedules is underway, coordinated by the Centers for Disease Control & Prevention.

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 inhalational 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 inhalational anthrax was 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 combined human and animal evidence of effectiveness are 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 intentionally 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, 20 human studies among more than 860,000 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 35 years of experience with anthrax vaccine, we expected up to 30% of men and 60% of women would 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 experience 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, a recommended vaccine for every American over the age of 65, has a 71% rate for localized soreness. 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 spontaneous or 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 24 hours or longer; (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 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 chaired this review committee of civilian physicians with expertise in immunology, internal medicine, neurology, rheumatology, and microbiology. The AVEC independently reviewed 1,857 anthrax vaccine-related reports. The Committee met every 3 to 6 weeks, along with nonvoting representatives of DoD, CDC, FDA, and DHHS. The AVEC reviewed the quality of the submitted information, evaluated the reported event in the context of expected and unexpected adverse events to vaccines, and assessed the cause-and-effect relationship of the event with anthrax vaccine. The Committee also looked for any significant patterns in the aggregate data. The review performed by the AVEC is unprecedented for a licensed vaccine.

The AVEC reported in 2 articles in medical journals that it found nothing unexpected in the side-effect profile of anthrax vaccine. The AVEC reviewed 1,857 VAERS reports, corresponding to more than 2.1 million doses of anthrax vaccine administered to over 525,000 people. Sixty-four of the 1,857 reports involved hospitalization; the civilian panel found that 11 of the 64 certainly or probably were caused by anthrax vaccine. All 11 involved allergic, inflammation reactions at the injection site. Another 174 of the 1,857 reports involved loss of duty of 24 hours or more without hospitalization; the civilian panel found that 93 of the 174 certainly or probably were caused by anthrax vaccine. These 93 reports described injection-site reactions (53 reports), various rashes (10), viral-like symptoms (10), acute allergic reactions (9), or other symptoms.

The FDA-licensed anthrax vaccine was used during the Persian Gulf War to protect 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.

Long-Term Safety

Our leaders respect the concerns expressed by Service Members about the possibility of long-term health effects and acted to address these concerns using the best 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, 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.

An October 2004 review of over 716,000 active-duty service members discharge rates shows anthrax vaccination does not increase the risk of disability. Overall, the disability evaluation rate in the Army was very low for the 4.25 years covered in this study, and there appeared to be no effect of exposure to anthrax vaccine on the risk of disability evaluation.

Reproductive Health

DoD policy defers most vaccinations until after pregnancy. 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 other adverse reproductive effects, including infertility or miscarriage. 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.

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 January 1999 to March 2000. 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.

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. Because 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.

A study published in *Fertility and Sterility* in 2005 shows no difference in male fertility between anthrax-vaccinated and unvaccinated men. The study was conducted at Walter Reed Army Medical Center from October 1999 to December 2004. A diagnosis of male infertility was less common in anthrax-vaccinated men than in their unvaccinated peers.

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 Michigan organization, known as the Michigan Biologic Products Institute (MBPI), was sold effective September 5, 1998, to the BioPort Corporation. The facility's license is now listed as license #1260.

Multiple shareholders own BioPort, whose headquarters remain in Lansing, Michigan. The two main companies that make up BioPort are Intervac, headed by William Crowe and Fuad 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 200+ 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 Michigan authorities had approved the renovation schedule, 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.

The manufacturer voluntarily 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, including upgrades of the manufacturing space. FDA conducted a preliminary on-site inspection of the new facility in November 1999, identifying additional needs for documentation of manufacturing processes. BioPort submitted these documents to FDA in the second half of 2001. FDA approved all aspects of BioPort's facilities and processes on January 31, 2002.

All lots of anthrax vaccine are fully tested to FDA standards. No lot of anthrax vaccine has ever left Lansing that has not been current and fully FDA approved.

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.

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 www.anthrax.mil/ (in place since September 1999).
- A customized email question-and-answer service, at vaccines@amedd.army.mil (in operation since August 1999).
- A speakers' bureau to conduct AVIP open-house forums, staff-assistance visits, briefings, conferences, exhibits, and coordinate 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 higher-threat areas. Unlike physical protective devices (e.g., 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 higher-threat areas on short notice. The risk-versus-risk balance clearly requires 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 1950s and 1960s 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 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. Seven 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. www.anthrax.mil/media/pdf/Fed_Reg.pdf
- Armed Forces Epidemiological Board (AFEB), civilian scientists advising the Surgeons General, from 1990 to present. www.anthrax.mil/resource/library/afeb.asp
- Cochrane Collaboration, the international evidence-based medicine group from Oxford. Demicheli V, Rivetti D, Deeks JJ, Jefferson T, Pratt M. The effectiveness and safety of vaccines against human anthrax: A systematic review. *Vaccine* 1998;16:880-4. www.anthrax.mil/media/pdf/EffandSafety.pdf
- Working Group on Civilian Biodefense, based at Johns Hopkins University. Inglesby TV, O'Toole T, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Friedlander AM, Gerberding J, Hauer J, Hughes J, McDade J, Osterholm MT, Parker G, Perl TM, Russell PK, Tonat K, Working Group on Civilian Biodefense. Anthrax as a biological weapon, 2002: Updated recommendations for management. JAMA 2002;287:2236-52. http://jama.ama-assn.org/issues/v287n17/fpdf/jst20007.pdf
- Anthrax Vaccine Expert Committee (AVEC), civilian physicians selected by the Department of Health & Human Services, who independently evaluate VAERS reports, 1998 to present. *Pharmacoepidemiology & Drug Safety* 2002;11 (Apr-May):189-202. www.anthrax.mil/media/pdf/AVEC_ms.pdf
  Pharmacoepidemiology & Drug Safety 2004;13(Dec):825-840. www.anthrax.mil/media/pdf/SeverArticle.pdf
- 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. www.cdc.gov/mmwr/pdf/rr/rr4915.pdf>
- Joellenbeck LM, Zwanziger L, Durch JS, Strom BL, editors. *The Anthrax Vaccine: Is it Safe? Does it Work?* Washington, DC: National Academy Press, March 2002, 235 pages. www.nap.edu/catalog/10310.html
  Summary for General Public: www.iom.edu/Object.File/Master/4/149/0.pdf
  Summary for Policy Makers: www.iom.edu/Object.File/Master/4/150/0.pdf

The seventh, 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 summer 2000). This expert IOM committee heard details on the safety studies of anthrax vaccine, as well as hearing from people who dissent from the use of anthrax vaccine. The Institute of Medicine reported: "The committee found no evidence that people face an increased risk of experiencing life-threatening or permanently disabling adverse events immediately after receiving AVA [anthrax vaccine adsorbed], when compared with the general population. Nor did it find any convincing evidence that people face elevated risk of developing adverse health effects over the longer term, although data are limited in this regard (as they are for all vaccines)." They found "…no data that indicate the need for the continuation of special monitoring programs for AVA have emerged, but it recognizes the real concerns of Service Members ordered to take the vaccine." Regarding effectiveness, "The committee finds that the available evidence from studies with humans and animals, coupled with reasonable assumptions of analogy, shows that AVA as licensed is an effective vaccine for the protection of humans against anthrax, including inhalational anthrax, caused by all known or plausible engineered strains of *B. anthracis*."

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 35 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. The number of vaccinations given to date

exceeds 5.2 million doses, with few serious adverse events. Reports of adverse events are consistent with expectations based on previous 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,. 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.