Anthrax Vaccine Immunization Program (AVIP)
Questions and Answers

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Regarding Redeployment

1. I've just returned from overseas. Do I have to continue my anthrax vaccinations?

Yes. If you are still in the military, and you've received an anthrax vaccination since the 28 June 2002 policy was implemented, you need to complete the series and maintain annual boosters according to the FDA-licensed schedule.

For information about civilians and Reserve Component personnel, read on.

2. What if I am a Reservist or Guardsman, do I still have to continue my anthrax vaccinations?

Yes. If you received an anthrax vaccination since the 28 June 2002 policy was implemented, and you are still a drilling reservist or guardsman, you need to complete the series and maintain annual boosters according to the FDA licensed schedule.

3. Will I be required to continue the anthrax vaccination series after retirement or transfer to the Individual Ready Reserve (IRR)?

When Active and Reserve Component personnel retire or transfer to the IRR, their obligation to continue anthrax vaccination for military purposes ceases. DoD and the US Coast Guard (USCG) do not provide anthrax vaccine after these types of personnel transitions.

4. Will DoD or USCG civilian employees or contracted workers be allowed or required to continue the anthrax vaccination series upon returning from overseas?

This answer has three parts:

(1) For emergency-essential (EE) civilians and mission-essential (ME) contract workers, anthrax vaccinations continue in their original mandatory fashion so long as these personnel are in EE or ME status. This policy is analogous to that of military personnel.

(2) For other federal employees for whom vaccination is not mandatory, anthrax vaccinations would continue to be made available upon return from overseas to the civilians throughout their federal service. If somebody transitions from an EE slot to a non-EE slot, the current employment status would apply.

(3) For non-ME contract workers, anthrax vaccinations would be made available upon return, so long as these contract workers were performing work for the federal government under an applicable contract.

5. I was on deployment orders, began my anthrax vaccinations, and then never deployed. Do I need to continue the series?

Yes. If you received anthrax vaccinations since the 28 June 2002 policy was implemented, you need to complete the series and maintain annual boosters according to the FDA-licensed schedule and the personnel categories discussed above.

Current Policy

Policy and Management

1. Under this Jun 04 policy update, who will receive the anthrax and smallpox vaccinations?

Military personnel assigned in or deployed to selected units in the U.S. Pacific Command and additional personnel assigned to the U.S. Central Command's area of responsibility (AOR) for 15 or more consecutive days will receive both vaccinations, unless medically exempted. Additionally, we will pursue vaccination, subject to appropriate personnel and contract procedures, for DoD emergency-essential civilian employees assigned to these areas and those DoD contract personnel in these areas who carry out mission-essential services for DoD.

In addition, military personnel vaccinated since 1998, but deferred from further doses during the slowdowns of 2000-01 will resume anthrax vaccinations.

2. Why are we vaccinating these people?

We are concerned that terrorists or governments hostile to the United States may have, or could obtain, bacteria or viruses that could be used as biological weapons. Vaccination will protect our personnel from the diseases caused by these agents.

3. Will the same people receive both vaccinations?

Generally speaking, yes. Individual medical exemptions will be taken into account. In the future, the Secretary of Defense may decide to adjust the scope of both the anthrax and smallpox vaccination programs.

4. Do you intend to vaccinate the Total Force over the long term?

The Department is focused on what we should do **now** to protect our personnel at higher risk whose performance is essential for certain mission critical capabilities. We may further update our immunization policies at a future date.

5. Will vaccinations under your updated program be mandatory?

Yes. It is important that personnel whose duties are essential to mission-critical capabilities are vaccinated—for their personal protection and for success of the military mission. So vaccinations will be mandatory, except as provided under applicable medical and administrative exemption policies, similar to those we've always had in place.

6. Will service members still be deployable if they have not received their vaccinations?

Yes, if they are in one of the groups that should not receive the vaccine for a medical or administrative reason they will still be deployable. In the event of an actual biological attack, their vaccination status will be reevaluated to see if the benefit-risk comparison has changed.

7. Why can't you allow personnel to choose voluntarily to be vaccinated?

We provide many vaccines and medical procedures on a mandatory basis, when it is known that the vaccine or medical measure is safe and effective, and exposure or possible exposure to an agent poses a real risk to individuals and teams. Also, we fight and win as teams—if one or several team members in areas of higher risk are not vaccinated and fall victim to disease, they could jeopardize the lives of other team members and mission success.

In short, military vaccination is one of those cases where individual rights are overshadowed by individual responsibilities to the other members of the unit.

8. Why did you decide to vaccinate only those who will be assigned or deployed for 15 days or more? In those higher threat areas it would seem that everyone there would be at risk.

The choice of a 15-day period in higher threat areas took considered evaluation by our senior leadership. Factors contributing to this decision included the risk to individuals, the numbers of individuals to be in these higher threat areas for more than and less than 15 days, the missions of these individuals, and the fact that it takes six shots at specific intervals over 18 months to assure protection against anthrax.

9. Can personnel deployed 14 days or less volunteer to be vaccinated?

If those individuals have concerns, they should speak with their commanders. We recognize that some of our personnel may be on rotation schedules with duty taking them into higher threat areas multiple times in a given year, bringing cumulative time deployed to 15 or more days in a given year. There are allowances in our policies, by exception, for commanders with personnel with these types of situations.

10. When will these new people begin vaccinations?

Those who fall within the groups defined by this policy will resume as soon as their units begin vaccinations. Some may resume tomorrow, next week or in the weeks and months ahead.

11. Because of the Anthrax Vaccine Immunization Program slowdown in 2000-01, suppose it's been a couple years since the servicemember's last dose of anthrax vaccine; does he or she have to start all over with dose #1?

No. Based on experience with anthrax vaccine and other vaccines, there is no need to restart a multi-dose vaccine series. Civilian medical experts advising the Centers for Disease Control and Prevention recommend resuming where one left off. Each dose is like climbing a set of stairs toward full immunity.

12. What do you mean by "higher threat areas?"

It represents the Department's focus on those personnel whose duties bring them into higher risk of anthrax or smallpox infection, by deployment location and/or occupation, and to preserve mission-critical capabilities in those areas.

13. What countries are included in the "higher threat areas?"

We are not going to comment specifically on that question, but included are areas in the U. S. Central and Pacific Commands' areas of responsibility.

14. Is DoD planning to use all of the anthrax vaccine produced by BioPort?

No. DoD's policy takes into account other national security considerations beyond the needs for military personnel. A certain amount of the produced vaccine will be reserved for contingency use by other federal agencies. The Department of Homeland Security and Department of Health & Human Services head the planning effort among federal agencies for contingency use of the vaccine.

15. Why did you decide to vaccinate these additional groups of people now? Is there a new or greater threat?

The threats to our forces continue and we know that the vaccines will protect our personnel from the diseases caused by these agents.

16. How many service members have been vaccinated for anthrax and for smallpox?

Since the beginning of the Anthrax Vaccine Immunization Program in March 1998, Department of Defense vaccinated over 1.1 million people with more than 4.5 million doses of anthrax vaccine. Since initiating the smallpox vaccination program, we have vaccinated over 630,000 personnel.

20. Does DoD plan to offer the vaccines to dependents or family members living in the selected areas of the U.S. Central and Pacific Commands?

Yes, vaccinations will be offered to adult family members, other DoD civilian employees and their families and non-essential contractor personnel located in these areas on a voluntary basis.

21. Are you prepared to offer anthrax vaccine to US allies and coalition partners?

We are discussing vaccination programs with key allies, coalition partners and friends. During the course of our discussions, we can envision this issue being addressed. We would give serious consideration to any request for vaccine, keeping in mind our own requirements, projected available supply and threat conditions at the time.

Threat

1. What is the threat of anthrax used against our military?

Anthrax is an attractive weapon of mass destruction for our enemies. It is highly lethal, relatively easy to produce in large quantities and to develop as a weapon, easily spread in the air over a large area and it can be stored and remain dangerous for a long time. For this reason, anthrax may be the most important biological warfare threat facing U.S. forces. The Intelligence Community believes several countries currently have or are developing an offensive biological warfare capability using anthrax. Given the ease with which anthrax can be produced, U.S. forces may have little or no warning before an anthrax attack, which could be delivered by unconventional means.

On February 24, 2004, CIA Director George Tenet told the Senate Select Intelligence Committee: "Although gaps in our understanding remain, we see al-Qa'ida's program to produce anthrax as one of the most immediate terrorist CBRN [chemical, biological, radiological, nuclear] threats we are likely to face."

2. How does the threat of a smallpox attack on US forces compare with that of an anthrax attack?

They are both known threats. Many factors go into such determinations including intelligence information, known capabilities and other variables. While we cannot quantify the threat of either one being used as a bioweapon, we know the consequences of their use could be great. Vaccination is a wise, logical step to ensure preparedness for the U.S.

<u>Military Discipline Questions</u>

1. How are refusals to be vaccinated handled?

We know that very few servicemembers refuse to be vaccinated, given present knowledge about the threat of anthrax and also about the validated safety and effectiveness of the vaccine. However, we begin with the assumption that any servicemember covered by this new policy who refuses vaccination may be uninformed about the facts related to the deadly effects of the anthrax agent and the safe protection

afforded by the vaccine. Our first action with those who might refuse the vaccine will be to understand their concern and provide information.

This is a force protection issue. If a servicemember continues to refuse the vaccine, then a commander will manage the situation as he or she would for any failure to obey a lawful order, including educating the member about the AVIP as appropriate.

We expect servicemembers to comply with administration of this vaccine as for any other mandatory vaccination. It is comparable to an order to wear body armor during armed engagement, or to don a protective mask in a suspected chemically or biologically contaminated environment. Any servicemember who does not comply with these measures endangers his/her own health, and places both their unit and mission accomplishment at risk.

In short, military vaccination is one of those cases where individual rights are overshadowed by individual responsibilities to the other members of the unit.

Military and civilian judges uniformly have found orders for members to be vaccinated to be lawful orders. Again, we do not anticipate this issue to be a major problem.

The Threat

1. Why is anthrax vaccination needed?

Anthrax is an attractive weapon of mass destruction for our enemies. It is highly lethal, relatively easy to produce in large quantities and to develop as a weapon, easily spread in the air over a large area and it can be stored and remain dangerous for a long time. For this reason, anthrax may be the most important biological warfare threat facing U.S. forces. The Intelligence Community believes several countries currently have or are developing an offensive biological warfare capability using anthrax. However, given the ease with which anthrax can be produced, the threat could come from anywhere. For that reason, U.S. forces may have little or no warning before an anthrax attack, which could be delivered by unconventional means. As a result, U.S. military forces around the world face a very real threat of a surprise anthrax attack.

2. Has any country ever used anthrax as a weapon?

There is some evidence that the Japanese used anthrax as a biological weapon (BW) on a limited basis in China during World War II (Christopher GW, et al. Biological warfare: A historical perspective. JAMA 1997; 278 (Aug 6): 412-17, http://jama.ama-assn.org/issues/v278n5/fpdf/jsc7044.pdf). Since then, several countries are believed to have incorporated anthrax spores into biological weapons. Intelligence analysts believe that at least seven potential adversaries have an offensive BW capability to deliver anthrax -- twice the number of countries when the 1972 Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Construction (commonly called the Biological Weapons Convention) took effect. The Biological Weapons Convention was designed to prohibit such activity.

Iraq admitted to the United Nations in 1995 that it loaded anthrax spores into warheads during the Gulf War. In the post-cold war era, the former Soviet Union admitted to having enough anthrax on hand to kill every person on the planet several times over. The accidental aerosolized release of anthrax spores from a military microbiology facility in the former Soviet Union city of Sverdlovsk in 1979 resulted in at least 79 cases of anthrax infection and 68 human deaths and demonstrated the lethal potential of anthrax aerosols.

Members of Aum Shinrikyo, the group responsible for the 1995 Tokyo sarin attack, reportedly experimented with biological agents in Japan before resorting to chemical agents. A lengthy article in the May 26, 1998, edition of the New York Times reported that members of Aum Shinrikyo released anthrax spores and botulinum toxin in Tokyo, Yokohama, and Yokosuka in 1990, targeting Japanese government and U.S. Navy facilities. Fortunately, no one was injured in these events.

3. How are biological agents deployed?

Biological agents can be dispersed in many ways, ranging from mailed envelopes, intentional human vectors, spray devices, bombs, to ballistic missiles. Biological agents are often hard to detect. Symptoms are delayed. Without preventive medical efforts, such as vaccination, the results can be devastating and widespread.

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. An anthrax aerosol would be odorless, invisible, and capable of traveling many miles.

4. Has the threat of biological warfare changed?

The threat of biological warfare has been a risk to U.S. forces for many years. The threat of anthrax weapons in the hands of adversarial countries remains. But anthrax was used as a biological weapon in the United States in fall 2001 by unknown terrorists. Delivering anthrax was as simple as putting it in an envelope and dropping it in a mailbox. DoD analysts maintain an updated evaluation of the level of threat, adjusting the information as necessary to reflect the risk to U.S. operations. Assessment of the potential offensive biological threat facing American servicemembers indicate it is necessary to have a robust biological defense program today. The threat is real and the consequences are grave -- former Director of the CIA James Woolsey referred to it as the single most dangerous threat to our national security in the foreseeable future.

5. Who will receive the anthrax vaccination?

Our policy is to immunize military personnel, Emergency-Essential DoD civilians and contractor personnel, assigned to or deployed for 15 or more days in higher threat areas whose performance is essential for certain mission critical capabilities

6. Who is at greater risk from a biological attack? Soldiers? Sailors? Airmen? Marines? Front line? Rear area? Logistical units?

Anthrax weapons have the potential to cover wide areas of a battlefield. It is difficult to determine who would be at a greater risk from a biological threat. All servicemembers meeting the criteria to receive the vaccine need to be protected, regardless of service, specialty, or location within higher threat areas.

7. What preparations have been made to respond to an anthrax release in a higher-threat area?

We are taking necessary steps to develop optimal protection against the threat of anthrax and other potential bioweapon agents, including improved intelligence, detection, and surveillance capabilities, protective clothing and equipment, new generation vaccines, and other medical countermeasures. In addition, we have stockpiled antibiotics in distributed locations and medical personnel are better educated in the treatment of anthrax.

8. Has anthrax vaccine ever been used in the past? How often?

Yes, since licensure in November 1970, anthrax vaccine has been administered to people at risk (both civilian and military) -- veterinarians, laboratory workers, and some people working with livestock) for several decades. The manufacturer and FDA report that about 68,000 doses of anthrax vaccine were distributed between 1974 and 1989.

The Army has purchased anthrax vaccine since its approval by the FDA in 1970, for use by about 1,500 at-risk laboratory workers. Anthrax vaccine was administered during the Gulf War to about 150,000 servicemembers, to protect U.S. forces against the threat of Iraq's biological weapons. Between March 1998 and February 2004, more than 1.1 million people have been vaccinated with more than 4.5 million doses of anthrax vaccine. Under the current DoD AVIP Policy, DoD vaccinates military personnel, Emergency-Essential DoD civilians and contractor personnel, assigned to or deployed for 15 or more days in higher threat areas whose performance is essential for certain mission critical capabilities.

9. If we vaccinate against anthrax, couldn't our adversaries just switch to a different bioweapon?

If the DoD anthrax vaccination program causes adversaries to switch to a different weapon, it can be considered a success. Other bioweapons are less stable, less predictable, or less effective than anthrax weapons.

10. Are vaccines being developed for other biological agents?

Yes. As potential biological warfare threats are identified, DoD is working with the FDA to determine appropriate protection mechanisms. Vaccines are being developed, whenever appropriate, for all validated biological threat agents. More information is provided in the specific Q & A section entitled -- Biological Warfare - Overview.

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Immunization Program Implementation

1. How many DoD and Coast Guard personnel will be vaccinated?

The Department will not focus on a number, but rather those whose performance is essential for certain mission critical capabilities. Over the long term, our goal is to have an easily administered vaccine, which utilizes the latest technology, easily scalable to produce large quantities. We are working together with the Department of Health and Human Services and private industry to produce such a “next-generation vaccine.”

2. How many servicemembers have been vaccinated?

Since the beginning of the Anthrax Vaccine Immunization Program in March 1998, Department of Defense vaccinated over 1.1 million people with more than 4.5 million doses of anthrax vaccine.

3. As a servicemember, am I required to take the anthrax vaccine under this program?

Yes, if you are in one of the designated units. It is important that all personnel whose duties are essential to these mission-critical capabilities are vaccinated against anthrax—for their personal protection and for success of the military mission. So vaccination will be mandatory, except as provided under applicable medical and administrative exemption policies, similar to those we’ve always had in place.

There is a long history of compulsory vaccinations within the Armed Forces, dating back to the Revolutionary War. General Washington required variolation against smallpox. Tetanus, typhoid, and yellow fever vaccinations were required of soldiers in World War II with the following results:

> 0 cases of yellow fever;
>
> 12 cases of tetanus, despite 2.7 million hospital admissions for wounds and injuries;
>
> 5 cases of typhoid fever per 100,000 servicemembers, compared to 42 per 100,000 in World War I.

4. Senior DoD leaders were vaccinated earlier in the AVIP. Will they be vaccinated now?

The current policy is to vaccinate personnel assigned to or deployed to higher risk areas and who perform mission essential jobs. Senior DoD leaders meeting those criteria will be vaccinated.

5. Is the anthrax vaccination program a result of lessons we learned from the 1991 Gulf War?

Yes. Building upon the lessons of past wars and leveraging superior technologies available now and in the future, the AVIP is one of the cornerstones of Force Protection. Additionally, the current world threat environment and the unpredictable nature of terrorism make it prudent to include biological warfare defense in all our force protection planning.

6. Who approved this vaccination program? On what authority?

The final decision to vaccinate was made by the Secretary of Defense in accordance with the procedures prescribed in DoD Directive 6205.3, Immunization Program for Biological Warfare Defense. The Coast Guard Chief of Staff concurred with this action. The vaccine implementation plan was developed with the full cooperation of the Services and the Joint Chiefs of Staff, the Office of the Assistant Secretary of Defense for Health Affairs, and was coordinated with the Armed Forces Epidemiological Board (an independent civilian medical advisory board) and appropriate medical agencies.

8. At what point during the vaccination process will personnel be allowed to deploy to a higher-threat location?

DoD and Coast Guard guidance states that for force protection purposes, a servicemember will be considered deployable if he/she is enrolled in the six-shot protocol, regardless of whether or not he/she has completed theseries. Personnel who are unable to begin the series before deployment may still be deployable based on individual Service policy.

9. Will the anthrax vaccine be a precondition for temporary duty to higher-threat areas by military, DoD civilian, and DoD contract personnel?

The procedure is to vaccinate U.S. military members and Department of Defense (DoD) and Coast Guard civilians and contractors designated as emergency essential rotating to the designated higher threat areas for 15 or more days. Every effort will be made to vaccinate people with the first three vaccinations before they deploy and to complete the 6-dose series in accordance with the FDA-licensed schedule. A minimum of one vaccination is desirable before departure, with the remaining doses administered in theater. However, should extenuating medical or administrative circumstances preclude vaccination of deploying personnel before arrival in a higher threat area, vaccine stocks and operational immunization tracking systems are in place to allow immediate initiation of the primary series upon arrival. Decisions regarding deployability are still a commander's responsibility. We recognize that some of our personnel may be on rotation schedules with duty taking them into higher threat areas multiple times in a given year, bringing cumulative time deployed to 15 or more days in a given year. There are allowances in our policies, by exception, for commanders with personnel with these types of situations.

13. How are DoD and the Coast Guard going to track the immunization process, since it takes 18 months to complete?

The Department of Defense and the Coast Guard track anthrax vaccinations via approved computer software programs. The Army uses the Medical Protection System (MedPROS), a module of the Medical Occupational Database System (MODS). The Navy and Marine Corps uses the Shipboard Automated Medical System (SAMS). The Air Force uses the Air Force Comprehensive Immunization Tracking Application (AFCITA). The Coast Guard uses their Medical Readiness System (MRS). The Services' immunization tracking systems forward anthrax vaccination data to the central repository, the Defense Enrollment Eligibility Reporting System (DEERS).

14. The Secretary of Defense announced his decision to vaccinate the force in December 1997. In his announcement, he noted that four "preconditions" would be met before the program being implemented. What were these four preconditions?

The four preconditions are:

(1) Supplemental Testing. Every lot in the 1997 stockpile will be FDA approved and supplementally tested for potency, purity, safety, and sterility. All lots in the original stockpile must pass supplemental testing to reconfirm the same standard required by the FDA when FDA released the lot earlier.

(2) Tracking System. Vaccinations are documented in medical records (Standard Form 601), on the PHS 731 (Yellow Shot Record), and entered into an electronic database, to ensure accurate tracking and record-keeping. The Joint Staff, in conjunction with the AVIP, will conduct worldwide audits of medical records and databases, to ensure accuracy and completeness of documentation.

(3) Service Implementation Plans and Communication Plans. The DoD AVIP and each of the Services (including the Coast Guard) developed detailed implementation plans. Each service also developed communications and education plans to guide program execution. Leader and health-care provider briefings were developed to ensure personnel are educated before beginning anthrax vaccinations. The briefings are required for all personnel. Joint Service work groups update and maintain currency of information within the briefs.

(4) Independent Review. Gerard Burrow, MD, Special Advisor for Health Affairs to the President of Yale University, who previously served as Dean of the Yale University Institute of Medicine, Vice Chancellor for Health Services of the University of California (San Diego), Dean of the School of Medicine of the University of California (San Diego), and Member of the Institute of Medicine, National Academy of Sciences, completed the independent review of the health and medical aspects of the Department of Defense anthrax vaccination program on 19 February 1998.

Summary: All four preconditions were met (with supplemental testing ongoing) and the Secretary of Defense approved implementation of the program on 18 May 1998.

15. What is this Force Protection program you talk about?

DoD's Force Protection program includes a wide array of preventive, surveillance, and clinical efforts to ensure the health and safety of servicemembers against the many threats present in the modern military environment. In the past, military medical services emphasized interventions after casualties had already occurred. Today, we focus on services to prevent casualties. Force Protection includes efforts to prevent infectious diseases, as well as reduce the consequences of risk factors like heat, sand, intense or prolonged work, psychological stress, environmental chemicals, pollutants, dehydration, non-ionizing radiation, and others.

Unit leadership is another important part of Force Protection, because morale and unit cohesion are important contributors to servicemembers' health and well-being. Groups of servicemembers help each other deal with the effects on the body and the mind resulting from both traumatic events and routine life events (e.g., marital, family, and cultural issues).

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ANTHRAX - The Disease

1. What is anthrax?

Anthrax is a rapidly progressing acute infection caused by spore-forming bacteria called Bacillus anthracis. Anthrax most commonly occurs in warm-blooded animals, especially goats, cattle, and sheep, but it can also infect humans. Anthrax spores can be easily produced in a dry form for biological weapons. Spores can survive many years in adverse conditions and still remain capable of causing disease. When inhaled by humans, these spores cause respiratory failure, leading to death within a week.

Anthrax can make an excellent weapon of mass destruction. The spores may be used as a weapon in a variety of delivery systems. They can be produced in large quantities without sophisticated equipment. All it takes is a single breath of aerosolized anthrax to inhale enough spores to cause the disease. Then, if serious symptoms occur, it kills 99% of unprotected people. Even if a person with symptoms receives antibiotics, the death rate is still about 50%. Anthrax spores are odorless, colorless, and tasteless.

2. Who gets infected with anthrax?

Animals and people can get anthrax disease. Anthrax is most commonly found in agricultural regions where goats, sheep, cattle or other plant-eating animals have not been vaccinated. When anthrax infects humans, it is usually due to an occupational exposure to infected animals or their products, especially hides, hair, wool, bones or bone products. Less commonly, ingesting undercooked, contaminated meat can infect humans.

3. Where is anthrax usually found?

Anthrax is found around the globe. It is more often a risk in countries that do not vaccinate their livestock, or that have substandard or ineffective public-health programs.

4. How is anthrax transmitted?

There are three forms of anthrax disease, varying by the route of infection. People can get anthrax through a break in the skin (cutaneous anthrax), by eating inadequately cooked contaminated meat (gastrointestinal anthrax), or by breathing in bacteria or spores (inhalational anthrax). Inhalational anthrax does not typically spread from person to person. Because anthrax spores can live in the soil for many years, animals can get anthrax by grazing or drinking water in contaminated areas. Weaponized anthrax could be used against people in almost any location, and in many different ways. The greatest threat with the most deadly consequences comes from inhaled anthrax.

5. Can people spread anthrax to each other?

Direct person-to-person spread of inhalational anthrax is "very rare," according to the American Public Health Association's *Control of Communicable Diseases Manual*. Presumably, person-to-person spread would require contact with contaminated skin lesions.

6. Can anthrax be transmitted by insects?

One report suggested that black flies may have transmitted anthrax from animals to humans, where there was a large outbreak in the animal population. Insects are not a major factor in the spread of anthrax.

7. How is anthrax diagnosed?

Anthrax is diagnosed by isolating the bacteria, Bacillus anthracis, from the blood, skin, or cerebral spinal fluid, or by measuring specific antibodies in the blood of suspected cases. Generally, diagnosis by antibodies is done weeks or months after the infection occurs, too late to aid in treatment. The best protection is vaccination before exposure, combined with the appropriate Mission-Oriented Protective Posture (MOPP), including protective clothing and detection equipment.

8. Why vaccinate at all? Why not treat with antibiotics after exposure?

There is no better round-the-clock protection against anthrax infection than the anthrax vaccine. Antibiotics are effective when started immediately or very soon after exposure. However, not all exposures can be predicted in advance or even determined in very early stages, particularly in certain military situations. In such situations, the consequences for military personnel and their mission could be very unfavorable. This is not a risk we can afford to take. DoD will therefore vaccinate ahead of time for the best protection.

For More Information:

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General Information

1. What is a vaccine?

A vaccine is a kind of medication intended to prevent an infection.

2. How do vaccines work?

Vaccines work indirectly, not directly. They work indirectly, by stimulating the body's immune system to produce antibodies. The human body responds to different vaccines by making different kinds of antibodies. For example, measles vaccine causes the body to make anti-measles antibodies. Vaccines against tetanus or polio make anti-tetanus or anti-polio antibodies, respectively. These antibodies then circulate throughout the body, on surveillance patrol, on the watch for germ invaders. These antibodies neutralize measles virus or tetanus toxin or other microbes that they encounter in the future. People compare vaccines to shadowboxing or dress rehearsals, to explain how vaccines prepare the body for a later encounter with a dangerous microbe. Vaccines give the body time to prepare defenses against harmful invading germs.

3. How important are vaccines?

Experts at the Centers for Disease Control & Prevention say that only one thing has saved more lives than vaccines: clean water. In 1900, smallpox, diphtheria, measles, and other infections were leading causes of death in the United States. Our grandparents feared them. Today, these diseases are distant memories due to the success of vaccines.

4. What happens if we stop vaccinating?

If we stop vaccinating people, the number of people who are susceptible will gradually increase. When a large enough group is vulnerable to a contagious disease, outbreaks or epidemics can occur. This happened in England, Sweden, and Japan in the 1970s, when many people stopped vaccinating their children against pertussis (whooping cough). Once people started using pertussis vaccine again, the infections came back under control. Remember, infections uncommon in your area are never farther away than an airplane ride.

5. How long have vaccines been around?

In 1796, Edward Jenner developed the first reliable vaccine to prevent smallpox. Louis Pasteur developed an anthrax vaccine for animals in 1880 and a rabies vaccine for humans in 1885. The pace of vaccine research accelerated in the 1950s and 1960s with advances in laboratory methods for growing microbes in cell cultures. The pace is accelerating again now, with recent advances in biotechnology.

6. How are vaccines invented and researched?

Scientists develop a candidate vaccine based on what they know of microbiology and human immunology. The candidate vaccine is tested in animals, then tested in people in three stages or phases. Phase I studies involve a dozen people to see if the vaccine provokes an antibody response, and to begin collecting information about vaccine safety. Phase II studies usually include one or two hundred people, to gather more information about effectiveness and to determine the proper dosage. Phase III studies typically involve a few thousand people, with an unvaccinated (placebo) control group, to definitively measure how good the vaccine is in preventing infection. If the Food & Drug Administration is satisfied that the vaccine has been shown to be safe and to be effective, then it grants a license to the vaccine's manufacturer, permitting the vaccine to be widely distributed.

7. What do safety and efficacy (effectiveness) mean?

FDA defines "safety" as the condition where the benefits of a drug outweigh adverse effects the drug may cause. A safe drug is considered to pose a reasonably low risk of harm, injury, or loss when used in an appropriate manner. Because vaccines are typically given to healthy people, without disease, vaccines are held to the highest standards of safety of all medications. That is, vaccines must cause fewer side effects than other medications. FDA defines "efficacy" as the ability to prevent, treat, diagnose, or otherwise manage a disease or other medical condition. A similar term is effectiveness. An effective vaccine is one that can reduce the risk of infection. Vaccine efficacy of 90% implies that a vaccinated group would have a risk of infection 90% less than the risk of a similar unvaccinated group.

8. How is safety assessed after FDA licenses a vaccine for widespread use?

Manufacturers, government agencies, and academic groups conduct what is called "post-marketing surveillance" of all medications (including vaccines) after licensing. This surveillance identifies uncommon side effects. It may also be used to gather information about groups of people who may not have received the vaccine during initial research studies, such as elderly people, children, pregnant women, or other groups. Initial clinical studies of medications do not usually include more than 5,000 people, nor extend longer than 5 to 8 years. Except for delaying availability of promising medications, post-marketing surveillance is the only way to study larger groups of people for longer periods of time.

9. How are vaccines manufactured?

Vaccines are produced on an industrial scale under rigorous conditions that are approved and audited by the Food & Drug Administration. The FDA must approve each lot (or batch) of vaccine individually before release for public use. Vaccines receive this extra scrutiny, compared to other medications, because vaccines are complex biological mixtures that must be carefully manufactured to assure reproducible potency.

10. How are vaccines tested for potency, safety, sterility, and purity?

The Food & Drug Administration sets the standards for all vaccines used in the United States. Potency is assessed by survival of vaccinated laboratory animals after lethal challenge. Safety is confirmed by testing for weight gain and absence of fever in other animal tests using at least two species. Sterility is tested using two kinds of culture media. Purity is measured by chemical assays.

11. How are vaccines administered to people?

Most vaccines are injected into the body, although a few can be swallowed by mouth. If injections are required, it is because stomach acid would prevent the vaccine from provoking a protective antibody response, or because not enough of the vaccine would get into the blood stream. Typically, vaccines administered by mouth correspond to a microbe that enters the body through the oral route. An influenza vaccine administered as a nasal mist showed promise in recent clinical studies.

12. Do I have to get vaccinated in the buttocks?

No. No vaccine should be administered in the buttocks. Vaccines are injected into the deltoid area (below the shoulder) in adults, adolescents, and older children. Younger children get injected in the front of the thigh. People traveling to places with poor sanitation used to get antibodies administered in the buttocks, because of the large volume of fluid to be injected. But we now have hepatitis A vaccines for international travelers that make this unnecessary.

13. How fast do vaccines work?

After a vaccine is injected or swallowed, the body begins a complex set of steps to process the antigens in the vaccine. Antibodies begin to appear in the blood about 10 to 14 days after the vaccination. Typically, live vaccines protect for many years with just a single dose or two. With inactivated vaccines, a series of several doses is typically needed to develop persistent immunity.

14. What kinds of side effects do vaccines cause?

In general, inactivated vaccines cause side effects that are limited to the injection site, such as redness, tenderness, and swelling. These reactions typically develop in ¼ to ½ of vaccine recipients and persist for a few days before going away on their own. In general, live vaccines cause side effects similar to a mild case of the corresponding natural infection. Thus, measles and varicella vaccines can cause a mild rash or fever in a minority of vaccine recipients. All vaccines can cause allergic reactions, although severe allergic reactions are very rare (about one case per million doses). A few vaccines cause unusual reactions in rare cases (consult Vaccine Information Statements, VISs, for details). But these reactions are either temporary or so rare as to be overshadowed by the consequences of the disease being prevented. If FDA determined that the benefits of a vaccine did not outweigh its side-effect profile, FDA would revoke the manufacturer’s license to distribute the vaccine.

15. Why do shots hurt?

The sensation when a needle pierces the skin is probably best described by the word sting, rather than pain. Nerves are in the surface of the skin. Once a needle passes through the outer layer of the skin, there is no more sensation. After the needle enters the body, one can let a syringe dangle unsupported without causing any pain. After any fluid is pushed through the needle into the tissue or muscle, the body has to adjust to the presence of that fluid. As a result, the injection site may become sore or tender after a few hours. Redness and hardness close to the needle-entry site are not uncommon. The soreness and redness go away after a few days. Vaccines that contain aluminum to increase the antibody response may cause a lump (nodule) at the injection site. These lumps usually go away after a few weeks.

16. What if something serious does occur?

Go get medical care right away. Ask your health-care provider to report the event to VAERS, the Vaccine Adverse Events Reporting System (800-822-7967, http://www.vaers.org/). The FDA and CDC monitor these reports weekly for routine safety purposes.

17. How are vaccines administered to people?

Most vaccines are injected into the body, although a few can be swallowed by mouth. If injections are required, it is because stomach acid would prevent the vaccine from provoking a protective antibody response, or because not enough of the vaccine would get into the blood stream. Typically, vaccines administered by mouth correspond to a microbe that enters the body through the oral route. An influenza vaccine administered as a nasal mist showed promise in recent clinical studies.

18. Why do immunization recommendations change from time to time?

Scientists routinely develop new vaccines or new recipes for existing vaccines. As these improvements are found to be valuable, national policies change to reflect the current state of scientific knowledge.

19. What kind of vaccine records should be kept?

Everyone should have a personal record of vaccinations received during his or her lifetime. People should keep these records readily available and take them to health-care visits. Health-care providers keep records of vaccines they administer. State health departments are developing immunization registries to record this information centrally, a big help with a population as mobile as that of the United States.

20. What is the most used vaccine in America?

Influenza vaccine, with about 70 to 80 million doses distributed each year. Influenza is also the greatest killer among vaccine-preventable diseases. Influenza infection kills an average 36,000 Americans each year.

21. What was the first vaccine used in the United States?

In 1800, Benjamin Waterhouse introduced the new technique of vaccination against smallpox to the U.S., immunizing his 5-year-old son, Daniel. Anti-vaccinationists criticized the practice as sacrilegious and unnatural. On the other hand, President Thomas Jefferson strongly advocated the novel form of medical intervention, helping the practice spread throughout Virginia.

22. When did federal regulation of vaccines begin in the United States?

In 1813, the U.S. Congress empowered President James Madison "to appoint an agent to preserve the genuine vaccine matter [i.e., smallpox vaccine], and to furnish the same to any citizen of the United States," as well as establishing a National Vaccine Agency. The U.S. Post Office was required to carry mail up to one-half ounce containing vaccine material for free. In 1902, the U.S. Congress passed "An act to regulate the sale of viruses, serums, toxins, and analogous products," later called the Biologics Control Act. The first modern federal legislation to control the quality of pharmaceutical products, the Act created the Hygienic Laboratory of the U.S. Public Health Service to control all biological drugs imported, exported, or engaged in interstate commerce. This function later was transferred to the National Institute of Health Division of Biologics Standards, and then to the Food and Drug Administration (FDA) Center for Biologics Evaluation & Research (CBER).

23. What biological medication was closely associated with celebrations of the Fourth of July, Independence Day?

Before the population was routinely vaccinated against tetanus, fireworks explosions would cause burns and wounds that would too often result in tetanus ("lockjaw"). To treat or prevent lockjaw in such casualties, physicians and pharmacies would increase their inventory of tetanus antitoxin (anti-tetanus antibodies).

24. What U.S. president received a dire warning on the dangers of smallpox vaccination to U.S. soldiers and sailors?

Charles M. Higgins (an American citizen) sent a lengthy thesis enumerating alleged hazards of smallpox vaccine to Woodrow Wilson in 1919. Despite his appeal, this vaccine was eventually used to eradicate smallpox from planet Earth. [Higgins CM. Horrors of Vaccination Exposed and Illustrated. New York: DeVinne Press, 1920.]

Independent Scientific Reviews of Anthrax Vaccine

1. Have any independent scientific panels outside the Department of Defense rendered opinions about anthrax vaccine?

Yes, since 1978, seven independent civilian panels affirmed the safety and efficacy of anthrax vaccine. These include (each discussed in detail below):

- Panel on Review of Bacterial Vaccines & Toxoids
- Armed Forces Epidemiological Board (AFEB)
- Advisory Committee on Immunization Practices (ACIP)
- Cochrane Collaboration
- Working Group on Civilian Biodefense
- Anthrax Vaccine Expert Committee (AVEC)
- National Academy of Sciences – Institute of Medicine

2. What is the National Academy of Sciences Institute of Medicine (IOM) Committee on the Safety and Efficacy of Anthrax Vaccine, and what are they doing?

The IOM committee reached two major conclusions: that anthrax vaccine works and that anthrax vaccine is as safe as other vaccines.

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." Pages 7 and 58.

Regarding safety, the committee concluded that "immediate reactions, and the rates at which they occur, are comparable to those observed with other vaccines regularly administered to adults." [Page 2.] "The committee found no evidence that people face an increased risk of experiencing life-threatening or permanently disabling adverse events immediately after receiving AVA, 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)." The scientists also noted, "The committee observes that 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." [Page 150]

The whole report is available at the website of the National Academy Press: 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. http://www.nap.edu/catalog/10310.html

3. Why has anthrax vaccine been subjected to so many independent reviews? Is this normal for a licensed vaccine?

All vaccines used in the United States are subjected to independent scientific review before and after licensing. The same is true for anthrax vaccine.

Because the Anthrax Vaccine Immunization Program (AVIP) is actively opposed by small vocal groups of people, additional scientific panels have evaluated anthrax vaccine. Although anthrax vaccine critics are committed and dedicated, they base their opposition largely on emotion and anecdote. To determine the truth based in science about anthrax vaccine, the Department of Health & Human Services (DHHS) and the Department of Defense (DoD) turn to America's senior vaccine experts for objective findings and advice. The DoD uses facts determined by these scientific bodies for the messages and education material DoD distributes to servicemembers, their families, and the public.

4. What was the Panel on Review of Bacterial Vaccines & Toxoids, and what did they find?

When responsibility for vaccine regulation shifted from the National Institutes of Health (NIH) to the Food & Drug Administration (FDA) in 1972, FDA convened a series of civilian advisory panels. FDA commissioned these panels to determine whether sufficient evidence of safety and effectiveness existed for vaccine licenses to be continued. These panels considered every vaccine used in America at that time, including such "old" vaccines as polio vaccine, tetanus toxoid, measles vaccine, and many others.

The Panel on Review of Bacterial Vaccines & Toxoids met first in 1978 and published their report in 1985 in the Federal Register (1985;50:51002-117; http://www.anthrax.mil/media/pdf/Fed_Reg.pdf). The panel consisted of prominent infectious-disease experts and other physicians and scientists with expertise in pharmaceutical manufacturing quality. The panel recommended that the federal licenses for each bacterial vaccine be continued, but the panel recommended that several other product licenses be terminated.

In the case of anthrax vaccine, this civilian panel concluded: "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."

FDA accepted this recommendation completely. FDA revoked the licenses for the other products, following the recommendations of the civilian panel.

5. What is the Armed Forces Epidemiological Board (AFEB), and what did they find?

The Armed Forces Epidemiological Board (AFEB) has a proud 60-year heritage of protecting the health of America's Armed Forces. The AFEB consists of civilian physicians and scientists selected to advise the Surgeons General of the Armed Services (http://www.tricare.osd.mil/afeb/).

From its first reviews of anthrax vaccine under DoD Directive 6205.3, the AFEB has affirmed the value of this vaccine. In August 1994, the AFEB concluded: "The licensed anthrax vaccine is suitable for use in personnel assigned, pre-designated or scheduled for deployment to areas with a validated high threat under its approved indications."

In November 1996, the Armed Forces Epidemiological Board reported that it "endorses the proposed DoD anthrax vaccine implementation plan under the current vaccine protocol [i.e., dosing schedule]."

The AFEB reaffirmed its recommendations to use anthrax vaccine for biodefense of military personnel in 1999 and 2000. A March 25, 1999, report states "The AFEB continues to strongly endorse the current DoD Anthrax Vaccine Immunization Program."

On March 29, 2000, the AFEB reported: "The AFEB was concerned and somewhat surprised at the criticism surrounding the program given the high level of professionalism that had characterized this effort. … Anthrax vaccine is a fully licensed FDA vaccine. The vaccine does cause local side effects, but has an excellent safety profile. The Anthrax Vaccine Immunization Program has carefully tabulated person-specific immunization data and has assiduously investigated reported complications associated with receipt of anthrax vaccine. These data have been regularly reviewed by the board and attest to the safety of the vaccine."
http://www.anthrax.mil/resource/library/afeb.asp

The AFEB continues to receive regular updates regarding implementation of the Anthrax Vaccine Immunization Program and the variety of safety surveillance methods used by the Department of Defense to monitor the vaccine's use.

6. What is the Advisory Committee on Immunization Practices (ACIP), and what did they find?

The Advisory Committee on Immunization Practices (ACIP) consists of America's preeminent vaccine scientists, civilian physicians who advise the Centers for Disease Control & Prevention (CDC) (http://www.cdc.gov/nip/publications/ACIP-list.htm). The ACIP sets national standards for vaccine delivery. ACIP guidelines for the nation are published in the CDC's weekly journal, the Morbidity & Mortality Weekly Report (MMWR).

Between fall 1999 and June 2000, an ACIP working group reviewed published and unpublished information about anthrax vaccine adsorbed (AVA). In June 2000, the ACIP unanimously adopted a report finding anthrax vaccine effective and safe for the prevention of anthrax.

The report notes that: "The efficacy of AVA is based on several studies in animals, one controlled vaccine trial in humans, and immunogenicity data for both humans and lower mammalian species. … 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."

The ACIP recognizes that it is the role of the Armed Forces Epidemiological Board to advise the military Surgeons General on vaccination policies for military personnel. Nonetheless, the ACIP noted that "For the military and other select populations or for groups for which a calculable risk can be assessed, pre-exposure vaccination may be indicated."

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

7. What is the Cochrane Collaboration, and what did they find?

The Cochrane Collaboration is an internationally respected group of scientists who apply principles called evidence-based medicine to discern the most objective use of medications. The Cochrane Collaboration is based in Oxford, England (http://www.cochrane.org).

In 1998, the Cochrane Infectious Diseases Group (http://www.cochrane.org/cochrane/revabstr/g070index.htm) reviewed the evidence for effectiveness and safety of two anthrax vaccines, manufactured in the United States and the former Soviet Union. "Trial quality assessment and data extraction was conducted independently by the six authors."

This international group of scientists found that "Killed anthrax vaccines appear to be effective in reducing the risk of contracting anthrax with a relatively low rate of adverse effects. Further research should be restricted to testing new vaccines only." (http://www.cochrane.org/cochrane/revabstr/ab000975.htm)

This review was later published in the peer-reviewed medical journal Vaccine:

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. http://www.anthrax.mil/media/pdf/EffandSafety.pdf

8. What is the Working Group on Civilian Biodefense, and what did they find?

The Working Group on Civilian Biodefense included 23 representatives from staff of major academic medical centers and research, government, military, public health, and emergency management institutions and agencies. The original consensus statement of 1999 resulted from a synthesis of published information and the revision of three drafts. Members of the working group reviewed anthrax literature again in January 2002, with special attention to articles following the anthrax attacks of 2001. Members commented on a revised document with proposed revisions being incorporated in the final product put out by The Center for Civilian Biodefense Strategies (http://www.hopkins-biodefense.org/).

The working group concurred with the findings of the March 2002 IOM report on the safety and efficacy of AVA, that AVA is effective against inhalational anthrax and concluded that if given with appropriate antibiotic therapy, it may help prevent the development of disease after exposure. The working group also found that: “Pre-exposure vaccination of some persons deemed to be in high-risk groups should be considered when substantial supplies of vaccine become available.”

The working group also addressed the use of anthrax vaccine in children: "The US anthrax vaccine is licensed for use only in persons aged 18 to 65 years because studies to date have been conducted exclusively in this group. No data exist for children, but based on experience with other inactivated vaccines, it is likely that the vaccine would be safe and effective."

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. Journal of the American Medical Association 2002;287:2236-52. http://jama.ama-assn.org/issues/v287n17/ffull/jst20007.html

9. What is the Anthrax Vaccine Expert Committee (AVEC), and what did they find?

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 reports to the Vaccine Adverse Events Reporting System (VAERS) involving 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. In a peer-reviewed publication, the AVEC reported it found no unexpected patterns in the side-effect profile of anthrax vaccine.

10. Besides the seven scientific panels described in detail above, have any other independent scientific individuals or groups rendered opinions about anthrax vaccine?

Gerald R. Burrow, MD, reviewed the health and medical aspects of the Anthrax Vaccine Immunization Program (AVIP) in 1998 before the program began. This is also discussed below.

The Society of Medical Consultants to the Armed Forces (SMCAF) endorsed the anthrax vaccination program in September 1999.

11. Who is Gerald Burrow, MD, and what did he find?

On December 15, 1997, Secretary of Defense William Cohen approved the plan to immunize the Total Force against anthrax, contingent on four conditions: (1) supplemental testing for potency, purity, sterility, and general safety; (2) plans for execution and communication; (3) a system for fully tracking anthrax vaccinations; and (4) review of the health and medical aspects of the program by an independent expert.

To achieve condition (4), Secretary Cohen asked Gerald R. Burrow, MD, to make the review. Dr. Burrow served as dean of medicine at the University of California at San Diego and dean of medicine and special assistant to the president of Yale University. Dr. Burrow was one of a few physicians elected as a member of the prestigious National Academy of Sciences, one of the nation's most prestigious scientific honors.

On February 19, 1998, Dr. Burrow reported: "I have made several visits to the Pentagon, have had a number of telephone conferences and have consulted extensively with experts in allergy, immunology and infectious disease."

Based on his review, Dr. Burrow concluded: "The anthrax vaccine appears to be safe and offers the best available protection against wild-type anthrax as a biological warfare agent. Steps have been taken to ensure the safety and quality of the department's vaccine stockpile."

(http://www.defenselink.mil/other_info/burrows.html)

12. What is the Society of Medical Consultants to the Armed Forces (SMCAF), and what did they say?

The Society of Medical Consultants to the Armed Forces was formed in 1946 to disseminate the knowledge of military medicine gained in both armed conflict and peacetime practice and research, and to respond promptly to the call of the Surgeons

General for advice on issues of professional importance in the Armed Forces (http://www.smcaf.org).

In September 1999, the Society expressed its support of the Anthrax Vaccine Immunization Program of the Department of Defense. In letters to the Secretary of Defense and the Surgeons General, President Nicholas Rock, MD, furnished documentary evidence of the need for and the safety of the Immunization Program, and declared that "The Society of Medical Consultants to the Armed Forces endorses the decision of the Surgeons General to proceed with priority attention, to provide protection against anthrax for our military forces."

Overview

1. What is anthrax vaccine?

Anthrax vaccine is known officially to the FDA as "Anthrax Vaccine Adsorbed." It is abbreviated AVA or ANT. It is also referred to by its trade name “BioThrax.” This vaccine is a sterile product, made from filtrates of microaerophilic cultures of an avirulent nonencapsulated strain of *Bacillus anthracis*. This means that the vaccine is the solution that results after filtration of a culture of anthrax bacteria. If you’ve ever seen percolated coffee, you know that liquid coffee is the filtrate and the coffee grounds are what are left in the filter.

These bacteria are grown with very little oxygen (microaerophilic conditions). The bacteria cannot cause disease themselves (they are avirulent). They are from a strain of anthrax that does not have a capsule around the bacterial cells (they are nonencapsulated). The master seed used for vaccine manufacturing was transferred from Fort Detrick to Lansing in 1970 and is identified as *Bacillus anthracis* strain V-770-NPI-R1.

Adsorbed refers to the fact that the vaccine is deposited on the surface of ("adsorbed to") a chemical called aluminum hydroxide. Aluminum hydroxide is added to the vaccine to increase the amount of antibodies that the body makes in response to vaccination. Aluminum hydroxide is called a vaccine adjuvant. Adjuvant comes from the Latin word meaning "to help."

Anthrax vaccine is a cell-free filtrate vaccine, which means that it contains no whole bacteria, neither live nor dead. The vaccine is manufactured and distributed by BioPort Corporation (formerly the Michigan Biologic Products Institute), in Lansing, Michigan.

2. Isn’t anthrax vaccine based on old (archaic) technology?

Anthrax vaccine was invented using mid-century technology that also led to highly successful vaccines against tetanus, diphtheria, and other infectious diseases. Today’s manufacturing of anthrax vaccine by BioPort meets all current Food and Drug Administration standards of production.

3. Who licensed the availability of anthrax vaccine in the United States?

The vaccine was developed in the United States during the 1950s and 1960s for humans. The vaccine was licensed by the National Institutes of Health’s Division of Biologics Standards for general use on November 4, 1970. In 1972, responsibility for vaccine regulation was transferred from NIH to the Food & Drug Administration (FDA). It is customary to refer to anthrax vaccine as "FDA-licensed."

Since 1970, at-risk veterinarians, laboratory workers, and livestock handlers in the United States have used anthrax vaccine. FDA officials report that about 68,000 doses of anthrax vaccine were distributed in the United States between 1974 and 1989.

4. What is the standard dosing schedule for the anthrax vaccine?

The current FDA-licensed schedule calls for doses to be administered according to the following schedule (the first dose is considered "week 0"): 0, 2 weeks, 4 weeks; 6 months, 12 months, and 18 months. * Recipients receive the first shot, then the second shot two weeks later, and then the third shot another two weeks later. Five months after the third shot, recipients receive the fourth shot. Six months later they receive the fifth shot. Another six months later they receive the sixth shot. The entire primary series takes 18 months to complete. Annual booster doses of the vaccine are required for ongoing protection.

* For computer-programming purposes, a month is typically defined as 30 days (6 months equals 180 days). Annual boosters are based on 365 days.

5. What do I do if I'm late for a dose?

First, let us reemphasize the importance of staying on schedule. This helps you become immune as soon as possible.

The vaccine schedule should be followed as closely as possible. However, if a person is late for a dose, the next dose should simply be given as soon as possible. Then subsequent doses should be given according to the standard dosing intervals from the most recent dose. Recipients receive the first shot, then the second shot two weeks later, and then the third shot another two weeks later. Five months after the third shot, recipients receive the fourth shot. Six months later they receive the fifth shot. Another six months later they receive the sixth shot.

An interrupted vaccination series should not be restarted. This applies to anthrax vaccine, as well as other vaccines, according to the Centers for Disease Control & Prevention. http://www.cdc.gov/mmwr/PDF/rr/rr4915.pdf

If one dose in the primary series has been administered previously, the primary series does not need to be restarted. Resume the primary series with administration of the next dose in the series. Administer subsequent doses of vaccine at intervals based on the date the last dose was given, not when it was originally scheduled.

If an annual booster has not been administered on time, administer the booster dose at the earliest possible date, adjusting the subsequent booster schedule accordingly. Once the primary series of six doses is complete, the primary series is never repeated.

Being late does not reduce the ultimate level of immunity achieved, because of white blood cells called T-memory cells. But being late causes a delay in reaching the state of immunity, so we want you to stay on time.

6. Can I get vaccinated ahead of schedule?

No. If you get vaccinated "too soon," the body's immune system might not have had enough time to prepare for the next dose, and you may not develop as good an antibody response as if you had complied with the standard schedule. Stay on schedule.

7. What does the anthrax vaccine do to make a person immune?

The anthrax vaccine, like other vaccines, stimulates your body to produce protective antibodies. These antibodies help your immune system to prevent the anthrax bacteria from producing toxins that could otherwise kill you, if you became infected with anthrax. Nearly everyone who receives two doses of anthrax vaccine has some antibody response. The full series plus annual booster doses provides maximum and on-going protection.

8. Do pilots who have received the anthrax vaccine have any troubles with FAA flight certification?

No. Being vaccinated against anthrax has no effect on civilian or military aviation status. An excellent independent source for definitive information regarding aviation-related matters and the anthrax vaccine can be found at www.aviationmedicine.com/anthrax.htm.

The Federal Aviation Administration reports that people vaccinated against anthrax are not disqualified from performing civilian airman duties.

9. Can people who have received the anthrax vaccine donate blood?

Yes, the American Association of Blood Banks (AABB) and the Food & Drug Administration allow blood donations following anthrax vaccination without any vaccine-related restrictions. For more information, see the Internet resources of the Armed Services Blood Program Office (http://www.tricare.osd.mil/asbpo), including http://www.tricare.osd.mil/asbpo/asb_immu.html.

Sometimes people are not be allowed to donate blood for other reasons. For example, the Armed Services Blood Program ordered Department of Defense blood banks to defer blood donations from military personnel stationed in Saudi Arabia, Kuwait, Iraq, Bahrain, Qatar, United Arab Emirates, Oman, or Yemen at any time since August 1, 1990. This action was taken after a small number of cases of leishmania infection -- a tropical disease – occurred among military personnel returning from that area.

For more information regarding the temporary donor deferral related to Leishmaniasis http://www.fda.gov/bbs/topics/ANSWERS/ANS00360.html

Data Source: The American Association of Blood Banks (http://www.AABB.org), 1801 Glenbrook Road, Bethesda, MD 20814-2749, 301-907-6977, Standards for Blood Bank and Transfusion Services, 19th ed., Standard B2.600.

10. After anthrax vaccination, is one able to donate a kidney or bone marrow?

Yes. Anthrax vaccine contains no live bacteria and poses no safety risk. There is no bar (contraindication) regarding donating organs or marrow after being vaccinated. In fact, your bone marrow might confer temporary immunity to the diseases to which you are immune to the marrow recipient.

The immune response to anthrax vaccine would have no adverse effect on the internal organs of the kidney or marrow recipient. Anthrax vaccine is a sterile product made from filtrates of inactivated bacterial cultures. Sterile filtration during manufacturing yields a vaccine containing no whole organisms, thereby presenting no possibility of infection to the recipient, whether immunodeficient or not.

11. Has the anthrax vaccine ever been reviewed by any civilian medical review board?

Yes, seven times. See the separate Q&A page on Independent Scientific Reviews of Anthrax Vaccine" for details.

Today, there is a broad consensus that the FDA-licensed anthrax vaccine is safe and effective for people at high risk of exposure. Recent publications of the CDC http://www.cdc.gov/mmwr/PDF/rr/rr4915.pdf and the Johns Hopkins Center for Civilian Biodefense Studies http://jama.ama-assn.org/issues/v287n17/ffull/jst20007.html recognize the anthrax vaccine as part of the national preparedness against biological terrorism.

12. Will military members be asked to sign a consent form before being given anthrax vaccine?

No. This vaccine, like other vaccines, is fully licensed by the FDA and does not require signed consent. Vaccine recipients will be provided with appropriate information on the anthrax vaccine at the time of immunization, or upon their request at any other period.

13. In some DoD documents it states that veterinarians have been "routinely administered" anthrax vaccinations. Why do some people dispute this statement?

Anthrax is not a widespread disease in the United States. Therefore, primarily at-risk veterinarians within the U.S. are vaccinated. "Routinely" was not intended to imply that veterinarians are universally vaccinated (i.e., that they are all vaccinated), but rather that if the person is potentially exposed to anthrax, vaccination is routine, a customary practice.

Also, other at-risk workers such as laboratory personnel and livestock handlers are routinely vaccinated. Other non-military personnel have been vaccinated, including workers at an Alabama sweater factory from 1977-1996. The manufacturer and FDA report that about 68,000 doses of anthrax vaccine were distributed between 1974 and 1989.

Anthrax vaccine is not experimental, not investigational, and does not require special authorization, nor informed consent. Anthrax vaccine was licensed for general use on November 4, 1970. It is a routine, common vaccination for people whose occupation places them at-risk for exposure to anthrax.

For More Information:

Advisory Committee on Immunization Practices. General recommendations on immunization. MMWR-Morbidity & Mortality Weekly Report 2002;51(RR-2):1-35 ftp://ftp.cdc.gov/pub/Publications/mmwr/rr/rr5102.pdf

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

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ANTHRAX VACCINE - Civilian Inquires

1. Can civilians get the anthrax vaccine?

The Department of Homeland Security, working with the Department of Health and Human Services and other federal agencies, is coordinating this policy. The Department of Defense anthrax vaccination policy, and the amount of vaccine needed to implement this policy takes into account other national security considerations outside the Department of Defense. We have worked in close coordination and collaboration with these other federal agencies, and with the Department of Homeland Security.

2. How will I know what to do, if there is a bioweapon attack near me?

If there was an incident, people would be notified by the emergency public announcement system by federal, state, or local authorities about what to do or where to go to obtain treatment.

The closest source of emergency assistance will come from your city, county, or state. Contact your state or local Health Department to find out procedures for handling possible bioterrorist incidents in your area.

3. How can bioterrorist attacks be detected?

The investigative skills, diagnostic techniques, and physical resources required to detect and diagnose a disease outbreak are the same ones required to identify and respond to a silent bioterrorist attack. A key component to success will continue to be the sharing of information among all components of the public health system so that early diagnosis and response [can happen] as quickly as possible.

4. How would one respond to a bioterrorist attack involving anthrax?

The course of action for preventing anthrax after exposure in the civilian population would be with antibiotics, or a combination of anthrax vaccine and antibiotics. Anthrax vaccine is not available to health care providers or the general public for routine use.

5. What other reliable information is available from health authorities?

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- CDC Bioterrorism Preparedness and Response: http://www.bt.cdc.gov/
- CDC Public Inquiry line: 1-800-311-3435
- CDC National Immunization HOTLINE 1-800-232-2522

Civilian Panel on Review of Bacterial Vaccines & Toxoids, advising the FDA from 1978 to 1985. Federal Register 1985;50:51002-117. http://www.anthrax.mil/media/pdf/Fed_Reg.pdf

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ANTHRAX VACCINE -- Eligibility Criteria

1. Who should not take the anthrax vaccine?

Those with a true hypersensitivity reaction (serious allergic reaction) to a previous dose of the anthrax vaccine, people infected with HIV, people who have other kinds of immune suppression, pregnant women, and people under 18 and over 65 years of age. Other temporary reasons for deferring anthrax vaccination include an acute respiratory disease or active infection, and a temporary course of immune-suppressing drugs such as steroids (e.g., prednisone). Vaccinations should be resumed when these issues are resolved. If a person has an active infection or is taking a prescription medication that suppresses the immune system, a decision to give the anthrax vaccine will be made on a case-by-case basis.

2. Why doesn't DoD policy include giving anthrax vaccine to people younger than 18 years or older than 65 years?

The FDA has only licensed the anthrax vaccine for use in people between ages 18 and 65. FDA does not perform its own clinical research; it reviews the quality of research performed by others. FDA can only determine the effectiveness of a vaccine in the same kind of population as the vaccine was tested in. No formal studies of children, adolescents, or the elderly have been performed to date. Once such studies are performed, FDA can determine if sufficient evidence is available.

Individual physicians can treat individual people in ways that are outside the limitations of a package insert (these are called "off-label" uses of drugs). Indeed, DoD knows of no example of a vaccine that is effective among adults that is not also effective in the elderly or in adolescents. DoD policy is to abide by the age ranges in the FDA-approved labeling for its anthrax vaccine immunization program.

3. Why aren't HIV-positive or immunodeficient people included in DoD's anthrax vaccine immunization program?

Anthrax vaccine's package insert says "anyone that is immunodeficient should not receive the vaccination." This precaution refers to the fact that the recipient, being immunodeficient, would be less likely to mount a full immune response to the vaccine, thus reducing the vaccine's intended benefit. Inactivated vaccines are not considered to be harmful to immunodeficient people. HIV-positive and other immunodeficient people should receive the anthrax vaccine if exposure occurs or is imminent. These personnel should be counseled that the vaccine is not expected to harm them, but they may not mount as complete an immune response to protect against anthrax as other people do. Under these conditions, the adage "some protection is better than none" would apply.

4. Should people with lupus (SLE) get vaccinated?

People who have been diagnosed with lupus should talk with their physician about whether or not they should be vaccinated, considering the state of their disease, the medications they take, and their personal risk for specific infections. Several medical studies have shown that people with lupus can be safely and effectively vaccinated against influenza, hepatitis B, pneumococcal disease and other diseases that would pose a significant risk if they were infected. For military personnel with lupus, providers are authorized to grant medical exemptions according to the patient's specific situation. Medical specialists can advise how to get the best benefit from vaccination in such circumstances.

For More Information:

Advisory Committee on Immunization Practices. General recommendations on immunization. MMWR-Morbidity & Mortality Weekly Report 2002;51(RR-2):1-35. ftp://ftp.cdc.gov/pub/Publications/mmwr/rr/rr5102.pdf

ANTHRAX VACCINE - Effectiveness

1. Why would anthrax vaccine protect people if anthrax inhalation occurs? What scientific evidence do we have?

This vaccine prevents anthrax regardless of route of exposure. Based on human and animal data, the National Academy of Sciences' Institute of Medicine concluded in March 2002 that anthrax vaccine is "an effective vaccine for the protection of humans against anthrax, including inhalational anthrax, caused by all known or plausible engineered strains of *Bacillus anthracis*."

The original Brachman and CDC studies of anthrax vaccine in textile workers proved that the vaccine protected against anthrax. The calculations performed in that study combined the cutaneous (skin) and inhalational forms of anthrax infection that occurred. No inhalational anthrax occurred among the vaccinated workers, while five cases of inhalational anthrax occurred among workers who had not been vaccinated. The total number of cases was judged too few to show statistically conclusive proof of protection.

However, results from several animal studies provide additional evidence that the vaccine protects against anthrax challenge with more than 500 times the lethal dose of anthrax by inhalation. This information coupled with the encouraging results of the effectiveness and immune response in humans assures us that the vaccine will greatly increase the chances of soldiers surviving exposure to inhalational anthrax. When full immunization is combined with proper use of protective masks, detection devices, surveillance and post-exposure treatment with antibiotics, the threat is even further reduced.

2. I heard that the vaccine used in the 1962 Brachman study isn't the same as the vaccine used today. Is that true?

Yes, it is true that the current vaccine has more protective antigen (PA) in it than Brachman's vaccine formula, and also that the current vaccine is more highly purified than the vaccine used in the Brachman study. Between the time of the Brachman study and the licensing of the vaccine produced in Lansing, the conditions under which the anthrax bacteria were cultured were changed. These changes resulted in a purer, more potent vaccine. Government authorities were aware of and approved the changes at that time the license application was considered in 1970. The independent, civilian review panel advising the FDA was aware of the changes, and described them in its 1985 report. Both vaccine formulas are based on protective antigen (PA), the key protein common to all strains of anthrax.

3. What will happen if personnel are exposed to anthrax before they gain immunity through vaccination?

Personnel will be treated with antibiotics if there is a known exposure to anthrax before gaining immunity through vaccination. Antibiotics are effective in treating animals,

including primates, exposed to inhalational anthrax, but only if started before symptoms develop. This would usually mean starting antibiotics in the first 24 hours after exposure. Unfortunately, servicemembers may not know they have been exposed until symptoms develop; by then, the infection is nearly always fatal within a few days, whether antibiotics are given or not. The best protection to counter inhalational anthrax is the use of the anthrax vaccine combined with the appropriate Mission Oriented Protective Posture (MOPP), including protective clothing and detection equipment.

4. If you receive all the shots, are you 100% protected?

No medication, no vaccine is 100% effective. The antibodies that result from any vaccine theoretically could be overwhelmed if one is exposed to extremely large doses of any pathogen. Even if vaccinated, one may not be completely safe if one is close to the point of release of the biologic agent. Antibiotics for such people will offer additional protection. That's why vaccination is only one part of force protection efforts, which also includes protective gear and detection equipment. For continued protection, annual booster doses are required.

5. Does anthrax vaccine protect against disease if someone inhales anthrax spores?

The original studies of anthrax vaccine showed 93% fewer anthrax infections (combining both cutaneous and inhalational cases of anthrax) among vaccinated people, compared to unvaccinated people.

In those original studies, no cases of inhaled (inhalation) anthrax occurred among vaccine recipients, while five cases of anthrax occurred among unvaccinated or incompletely vaccinated people. This difference involved too few people to be statistically conclusive, although the trend is obvious.

It is unethical to intentionally expose human beings to inhaled anthrax to test the vaccine. Instead, anthrax vaccine was tested on rhesus monkeys. After 65 animals received one or two doses of vaccine, 62 of 65(95%) survived aerosol challenge in full health. One animal died from anthrax exposure two years after the second dose of vaccine. This illustrates the importance of annual booster doses of anthrax vaccine.

These data lead us to expect that anthrax vaccine would be quite effective in preventing inhaled anthrax.

6. How long does it take after the first shot before protection begins?

Antibodies begin to develop within a week or two after the first dose of vaccine. Protection levels increase as shots in the series are given, like walking up a set of stairs. The entire six-shot series is needed for full protection as licensed by the Food & Drug Administration.

7. Will this anthrax vaccine protect soldiers from all forms of anthrax, including the ones reportedly developed in Russia?

Every disease-causing strain of *Bacillus anthracis* causes anthrax disease via the same protein. The vaccine produces antibodies that neutralize that protein. The National Academy of Sciences' Institute of Medicine concluded in March 2002 that "it is unlikely that either naturally occurring or anthrax strains with bioengineered protective antigen could both evade AVA [the U.S. anthrax vaccine] and cause the toxicity associated with anthrax."

DoD is aware of the Russian research effort recently reported in a British scientific journal. Russian scientists reported using technology to introduce two foreign genes into anthrax. The potential for a genetically altered virulent organism is of concern to us and we are anxious to learn more about this organism. Hamsters, vaccinated with the Russian live attenuated anthrax vaccine were not resistant to challenge with their engineered strain.

There are substantive scientific questions about this report. First, the validity of the animal model that the Russians used needs to be addressed, because hamsters may not be predictive of results in other animals (including humans). Second, the strain produced may not be stable, a fact the Russians admit. An unstable organism would not be a candidate for weaponization. There have been ongoing efforts by OSD Cooperative Threat Reduction Program, the National Academy of Sciences, and the International Science and Technology Center to evaluate the possibility of a potential threat from genetically modified strains, and to ensure that our vaccine is effective against them. We believe that the current anthrax vaccine would be effective against altered genetic strains based on the biologic principles of the U.S. vaccine, which is different from the Russian vaccine.

8. Is the anthrax vaccine licensed for use against biological agents?

The anthrax vaccine is licensed for people at risk for exposure to anthrax spores. Biological weapons are designed to deliver aerosolized anthrax spores that will result in inhalational anthrax. The FDA concurs that the use of the anthrax vaccine to protect against inhalational anthrax is consistent with indications for use of the vaccine.

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Anthrax Vaccine – Ingredients

1. What are the ingredients of the anthrax vaccine?

Anthrax vaccine is a sterile product made from filtrates of microaerophilic cultures of an avirulent nonencapsulated strain of Bacillus anthracis. These bacteria are grown with very little oxygen (microaerophilic conditions). The bacteria cannot cause disease themselves (they are avirulent). They are from a strain of anthrax that does not have a capsule around the bacterial cells (they are nonencapsulated).

This means that the vaccine is the solution that results after filtration of a culture of anthrax bacteria. If you've ever seen percolated coffee, you know that liquid coffee is the filtrate and the coffee grounds are what are left in the filter. In this example, the vaccine is like the cup of coffee.

Anthrax vaccine is known officially to the Food & Drug Administration (FDA) as "Anthrax Vaccine Adsorbed," generating its abbreviation "AVA." Adsorbed refers to the fact that the vaccine is deposited on the surface of ("adsorbed to") a chemical called aluminum hydroxide. Aluminum hydroxide is added as an adjuvant to the vaccine to increase the amount of antibodies that the body makes in response to vaccination.

Anthrax vaccine is a cell-free filtrate vaccine, which means that it contains no whole bacteria, neither live nor dead. The bacteria used to make the vaccine cannot cause disease themselves. For these two reasons, it is impossible to contract the anthrax disease from the anthrax vaccine.

The final product is formulated to contain 1.2 mg/mL aluminum, added as aluminum hydroxide in 0.85% sodium chloride. The product is formulated to contain 25 mg/mL benzethonium chloride and 100 mg/mL formaldehyde, added as preservatives.

2. Why is aluminum in anthrax and other vaccines?

Aluminum is an adjuvant. The word adjuvant comes from the Latin, meaning "to help." Adjuvants are added to vaccines to increase antibody responses to vaccination. Aluminum salts are the only kind of adjuvant so far licensed by the FDA and the only kind of adjuvant used in anthrax vaccines for humans in the United States.

Anthrax vaccine contains aluminum hydroxide, as do FDA-licensed diphtheria, *Haemophilus influenzae* type b, hepatitis A, hepatitis B, pertussis, and tetanus vaccines.

3. What is benzethonium chloride?

Benzethonium chloride is used as a preservative in the anthrax vaccine. It is also a common component in other injectable and nasal medications (such as thrombin,

ketamine, orphenadrine [Norflex], and butorphanol [Stadol]). Benzethonium chloride is sometimes also called Phemerol, a trade name.

4. Does anthrax vaccine contain mercury?

No. The preservative of anthrax vaccine is benzethonium chloride.

5. Formaldehyde is not approved for human consumption. Why is it used in the anthrax and other vaccines?

Material Safety Data Sheets correctly warn people not to swallow formaldehyde. Small amounts of formaldehyde are approved by the FDA for use in manufacturing several vaccines, including vaccines against anthrax, diphtheria, hepatitis A, influenza, Japanese encephalitis, and tetanus.

A small amount of formaldehyde, less than 2 parts per 10,000 (0.02%), is permitted by FDA to remain in the anthrax vaccine. Formaldehyde has been used in vaccine manufacturing since the 1960s, if not earlier. Literally billions of people around the world have been given tetanus toxoid processed with formaldehyde (as anthrax vaccine is), which is recognized as safe. FDA closely monitors all the ingredients and processing steps of all vaccines and other medications before they can be distributed for widespread use.

Material Safety Data Sheets (MSDS) are a method to explain chemical hazards, according to OSHA standards (see http://www.osha-slc.gov/SLTC/smallbusiness/sec16.html). For any given chemical, health hazards vary by amount of chemical (concentration), duration of exposure (time), and route of exposure (skin, stomach, lungs, etc.).

FDA's decision to permit formaldehyde to be present as residues in vaccines is based, in part, on the low concentrations and infrequent exposures involved. While it might not be prudent to have formaldehyde contact the skin every day at work, or to inhale formaldehyde fumes repeatedly, a few minute doses of formaldehyde in vaccines are recognized as safe.

6. Does the anthrax vaccine contain pork or egg products?

Anthrax vaccine adsorbed is a sterile, cell-free (filtered) bacterial vaccine that contains no live or dead organisms. It is not made from or with pork or egg products.

7. Does the anthrax vaccine contain any fetal tissue?

No human tissues of any kind are used in the process of making the anthrax vaccine.

8. Does the anthrax vaccine use squalene as an adjuvant?

No, the adjuvant in the anthrax vaccine is aluminum hydroxide.

9. Does the anthrax vaccine contain squalene?

In September 2000, DoD became aware of FDA test results finding trace amounts of squalene in three out of three US vaccines tested: anthrax, diphtheria, and tetanus. The level of squalene identified by the FDA test is so minute that it likely the result of squalene in the oil of a fingerprint not cleaned from lab glassware.

Before the FDA test results, Stanford Research International (SRI), under a DoD contract, looked for squalene in anthrax vaccine. At the limit of detectability of its test, 140 parts per billion, SRI found no squalene in anthrax vaccine. The FDA's test is more sensitive, able to detect as little as 10 parts per billion. The FDA found squalene at 10 to 83 parts per billion in various lots of anthrax vaccine.

The trace level of squalene found by the FDA in anthrax vaccine is less than the concentration normally present in human blood (250 parts per billion).

10. Is the Food & Drug Administration concerned about the quantity of squalene found in these vaccines?

No. In Congressional testimony on 3 October 2000, FDA's Mark Elengold said that the trace quantities of squalene detected were "within the realm of both naturally occurring and safe."

For more information on squalene, click here.

For More Information:

Food & Drug Administration. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review. Federal Register 1985;50:51002-117. http://www.anthrax.mil/media/pdf/Fed_Reg.pdf

Safety

1. Is the anthrax vaccine safe?

Yes, this vaccine has been safely administered in the U.S. to at-risk veterinary and laboratory workers, livestock handlers, and servicemembers since licensure by the Food & Drug Administration (FDA) in 1970. The FDA certifies the safety and efficacy of all pharmaceuticals (medications) used in the U.S. One of FDA's primary missions is to ensure that pharmaceuticals released for use by the American public are tested for both safety and efficacy.

Like all vaccines, anthrax vaccine may cause soreness, redness, itching, swelling, and lumps at the injection site. About 30% of men and 60% of women report these local reactions, but they usually last only a short while. Lumps can persist a few weeks, but eventually disappear. Injection-site problems occur about twice as often among women. For both genders, between 1% and 5% report reactions of 1 to 5 inches in diameter. Larger reactions occur in about one in a hundred vaccine recipients.

Beyond the injection site, from 5% up to 35% will notice muscle aches, joint aches, headaches, rash, chills, fever, nausea, loss of appetite, malaise, or related symptoms. Again, these symptoms usually go away after a few days. Over-the-counter medications before or after the anthrax vaccine may help reduce bothersome symptoms.

Like all vaccines, most adverse events are minor and temporary. Serious events, such as those requiring hospitalization, are rare. They happen about once per 200,000 doses. Severe allergic reactions can occur after any vaccination, less than once per 100,000 doses.

Anthrax vaccine is as safe as other vaccines. Like other vaccines, deaths have been reported rarely after anthrax vaccination. Each of these cases is carefully reviewed by CDC, FDA, and DoD, to make vaccinations as safe as possible.

For independent information about vaccines and vaccine safety see:

Centers for Disease Control & Prevention's National Immunization Program:
http://www.cdc.gov/nip

2. What about long-term side effects?

There are no known long-term side effects to anthrax vaccine. At Fort Detrick, more than 1,500 laboratory workers followed for up to 10 to 20 or more years after receiving anthrax vaccine. Most of these workers received 150 to 200 vaccinations and skin tests; some received more than 300 such injections during their tenure at Fort Detrick. The first report of this group of 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. An updated manuscript is currently being finalized. These employees have been followed annually. 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.

An extension of this long-term study is underway to determine, in even greater detail, whether people who received multiple vaccines, including anthrax vaccine, during their past 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. All volunteers signed an informed-consent document. The study methods include 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 complex of symptoms reported by veterans of the Persian Gulf War), diseases, and abnormal laboratory and urine tests. Study subjects will be compared to two to three 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.

3. Is there a requirement for long-term follow-up after the anthrax vaccine is administered?

No. Like other FDA-licensed products, the anthrax vaccine does not require follow-up monitoring of healthy vaccine recipients. Nonetheless, the DoD has already conducted such studies and is conducting more. No data collected to date shows any patterns of adverse events developing years after people have been vaccinated with anthrax vaccine or any other vaccine.

4. Is this an experimental vaccine?

No, the anthrax vaccine has been FDA licensed since 1970. License No. 99 was issued on November 4, 1970. It is neither "experimental" nor "investigational."

Since 1970, this vaccine has been administered to people at risk for anthrax exposures including certain veterinary and laboratory workers and civilians who work with animal products. FDA officials reported that about 68,000 doses of anthrax vaccine were distributed in the United States between 1974 and 1989. Since licensure in 1970, the U.S. Army purchased this vaccine for use by at-risk laboratory workers, and it was used during the Gulf War (approximately 150,000 recipients) to vaccinate U.S. forces against Iraq’s production of biological weapons. The military currently vaccinates people working in at-risk jobs and some 3,000 personnel assigned to special operations units, the Army Technical Escort Unit and the Marine Corps Chemical-Biological Incident Response Force (C-BIRF).

The Centers for Disease Control and Prevention offer of anthrax vaccine for Congressional and U.S. Postal Service workers used anthrax vaccine for “post-exposure treatment” in three doses. This is not a Food and Drug Administration-licensed use of the vaccine, although the vaccine itself was, and is, licensed. Therefore, in that case (postexposure), the vaccine was administered under an “investigational new drug” protocol, with informed consent. The Department of Defense’s use of anthrax vaccine in the Anthrax Vaccine Immunization Program for pre-exposure prevention using six doses over 18 months is consistent with the Food and Drug Administration-licensed use of the vaccine.

When BioPort bought the facilities of the Michigan Biologic Products Institute, License No. 1260 was substituted for License No. 99.

5. What about sterility or impairment of fertility?

In 30 years of licensed use, there is no evidence of any sterility or fertility impairment from anthrax vaccine. Regarding reproductive health, the Center for Disease Control and Prevention Advisory Committee on Immunization Practices states, "there is no convincing risk from vaccinating pregnant women with inactivated virus or bacterial toxoids."

In the March 27, 2002, issue of the *Journal of American Medical Association*, two Army physicians published their peer-reviewed findings that women get pregnant at the same rate, whether anthrax-vaccinated or unvaccinated. These physicians from Fort Stewart, Georgia, also showed that women deliver offspring at the same rate, whether anthrax-vaccinated or unvaccinated. The Fort Stewart found no difference in birth defect rates, either, but the study may have been too small to detect small differences. [Wiesen AR, Littell CT. Relationship between prepregnancy anthrax vaccination and pregnancy and birth outcomes among US Army women. *Journal of the American Medical Association* (JAMA) 2002;287:1556-60. http://jama.ama-assn.org/issues/v287n12/fpdf/joc20240.pdf

Preliminary data from the Naval Health Research Center raised a tentative signal that there may be an association with an increased rate of birth defects. This signal is being investigated thoroughly, to determine which of several explanations for the signal is most likely.

Long-standing Defense policy is to defer routine vaccinations in women until after pregnancy. This policy has always applied to anthrax vaccine. Women are asked if they are pregnant before vaccination. Women who are not sure are offered pregnancy tests.

6. Is there any risk of cancer or mutagenesis (genetic mutations)?

In 30 years of use, there is no evidence that the anthrax vaccine causes cancer or mutagenesis. As with most other vaccines or other pharmaceuticals, studies regarding carcinogenesis or mutagenesis have not been performed with anthrax vaccine. Such studies have not been performed, in large part, because in over 200 years of

administering vaccines to humans, no vaccine has ever been shown to cause cancer or genetic mutations.

7. I don't have a spleen. Can I still get vaccinated?

Yes, you may receive the anthrax vaccine if your spleen was removed in surgery or if your spleen no longer works properly. Several vaccines are specifically recommended for people without a spleen (asplenic people), to improve the body's defense against infections. In general, inactivated or killed vaccines (including anthrax vaccine) are recommended for people without spleens. In many cases, such vaccines may be life-saving by preventing overwhelming infection. The American College of Physicians (ACP) specifically names anthrax vaccine in its 1994 guidelines for people at risk of exposure to this bacterium. People without a spleen should get some live vaccines and avoid others.

Spleens help people fight infections. People who do not have a spleen have a hard time protecting themselves against bacteria. Without a spleen, people are at risk of severe bacteremia (infection in the blood) from many types of bacteria. Some people lose their spleens during surgery to repair abdominal injuries suffered during accidents or their spleen is removed to help them respond to certain kinds of cancer. Certain diseases, especially sickle cell disease, destroy the spleen, while other people may be born without a spleen. According to the American College of Physicians (ACP), people without spleens or people whose spleens don't work properly should be vaccinated against the following diseases, if they are susceptible to them: Tetanus, diphtheria, pneumococcal, *Haemophilus influenzae* type b (Hib), meningococcal, and influenza. These people should be vaccinated against anthrax, cholera, hepatitis B, measles, mumps, plague, poliovirus (injectable vaccine), rabies, rubella, and typhoid fever (injectable vaccine), if these vaccines are needed. The ACP concludes by saying “In addition, the importance of antimalarial prophylaxis must be emphasized for those planning foreign travel to areas where malaria occurs." (Guide for Adult Immunization, 3rd ed. Philadelphia: 1994) The American Academy of Pediatrics and the CDC’s Advisory Committee on Immunization Practices provide similar recommendations on vaccines for persons with surgical or functional asplenia.

8. Should people with lupus (SLE) get vaccinated?

People who have been diagnosed with lupus should talk with their physician about whether or not they should be vaccinated, considering the state of their disease, the medications they take, and their personal risk for specific infections. Several medical studies have shown that people with lupus can be safely and effectively vaccinated against influenza, hepatitis B, pneumococcal disease and other diseases that would pose a significant risk if they were infected. For military personnel with lupus, providers are authorized to grant medical exemptions according to the patient's specific situation. Medical specialists can advise how to get the best benefit from vaccination in such circumstances.

9. Are there any other groups or agencies besides DoD that advocate the use of the anthrax vaccine?

In addition to the Department of Defense, other agencies and groups advocate or support the use of the anthrax vaccine. The Food & Drug Administration licensed the anthrax vaccine in 1970. The Centers for Disease Control & Prevention, the World Health Organization, the Armed Forces Epidemiological Board, and many other respected public health organizations support use for people at risk or exposed to Bacillus anthracis. Information about the AVIP is available on the Internet (a variety of DoD web sites as well as the Centers for Disease Control & Prevention and the Food & Drug Administration web sites), which includes facts about the anthrax vaccine, history, side effects, purpose for immunizations and more. [See the Q&A page on independent scientific reviews.] Evidence for the efficacy of the anthrax vaccine is sufficient for it to be included in standard medical reference books in the United States and around the world. These references include:

Control of Communicable Diseases Manual, 17th ed. James Chin, ed. "An official report of the American Public Health Association," Washington, DC, 2000. http://www.anthrax.mil/media/pdf/ccd_manual.pdf

Guide for Adult Immunization, 3rd ed, Philadelphia: American College of Physicians, 1994.

Immunisation Against Infectious Disease. Her Majesty's Stationery Office, London: British Joint Committee on Vaccination and Immunisation, 1996.

Report of the Committee on Infectious Diseases, 26th edition, Elk Grove Village, IL: American Academy of Pediatrics, 2003.

ImmunoFacts: Vaccines & Immunologic Drugs. Saint Louis: Facts and Comparisons, Inc., 2004.

Merck Manual on Drugs & Therapeutics. West Point, PA: Merck and Company, 1999.

Anthrax vaccine is a prominent part of the World Health Organization's 1998 Guidelines for the Surveillance and Control of Anthrax in Humans and Animals. http://www.who.int/emc-documents/zoonoses/whoemczdi986c.html

Similarly, anthrax vaccination is specifically endorsed in the Working Group on Civilian Biodefense position paper on preparedness against anthrax (Inglesby, et al. Anthrax as a Biological Weapon, 2002. Journal of the American Medical Association (JAMA) 2002;287:2236-52). http://jama.ama-assn.org/issues/v287n17/fpdf/jst20007.pdf

The U.S. Department of Agriculture lists anthrax vaccine as a condition of employment for personnel of the Animal & Plant Health Inspection Service (APHIS), if potentially exposed on the job.

10. Is the Department of Defense continuing to research safety aspects of the anthrax vaccine?

The 30 years of experience with anthrax vaccine in the United States suggests it has a similar side-effect profile compared to other commonly used vaccines. Nonetheless, the Department of Defense continues to monitor the safety of the anthrax vaccine during program execution. As the National Academy of Sciences pointed out, the most scientifically powerful way of assessing vaccine safety is by comparing and contrasting people vaccinated and unvaccinated against anthrax. To see the National Academy of Sciences report on the safety of anthrax vaccine, click here: http://www.nap.edu/catalog/10310.html

In addition, DoD scientists are currently conducting more long-term research and designing yet more studies. In designing these studies, we will draw from the accumulated experience of some of the nation's best vaccine researchers at CDC and FDA. One of the methods used is a surveillance technique used by CDC in post-marketing studies: large, linked databases. DoD uses the large, linked database approach in its long-term research efforts through access to its immunization tracking programs database and though the medical databases maintained by the Defense Medical Surveillance System (DMSS).

For More Information:

Advisory Committee on Immunization Practices. General recommendations on immunization. MMWR-Morbidity & Mortality Weekly Report 2002;51(RR-2):1-35. ftp://ftp.cdc.gov/pub/Publications/mmwr/rr/rr5102.pdf

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Food & Drug Administration. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review. Federal Register 1985;50:51002-117. http://www.anthrax.mil/media/pdf/Fed_Reg.pdf

Hambleton P, Carman JA, Melling J. Anthrax: The disease in relation to vaccines. Vaccine 1984;2:125-32.

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Peeler RN, Kadull PJ, Cluff LE. Intensive immunization of man: Evaluation of possible adverse consequences. Annals of Internal Medicine 1965;63:44-57.

Singleton JA, Lloyd JC, Mootrey GT, Salive ME, Chen RT, VAERS Working Group. An overview of the vaccine adverse event reported system (VAERS) as a surveillance system. Vaccine 1999;17:2908-17.

Turnbull PCB. Guidelines for the Surveillance and Control of Anthrax in Humans and Animals, 3rd ed., WHO Report WHO/EMC/ZDI/98.6. http://www.who.int/emc-documents/zoonoses/whoemczdi986c.html

White CS III, Adler WH, McGann VG. Repeated immunization: Possible adverse effects: Reevaluation of human subjects at 25 years. Annals of Internal Medicine 1974;81:594-600. http://www.anthrax.mil/media/pdf/repeated.pdf

Long Term Safety

1. What do we know about the long-term safety of anthrax vaccine?

Based on multiple objective sources of data, there are no known long-term side effects to anthrax vaccine.

2. When people talk about "long term," what do they mean?

There is no universal definition for "long term." When applied to vaccines, scientists may consider "long term" to be 6 months to 1 year or longer.

3. I have heard people say that "no data has been collected more than 48 hours after anthrax vaccination." Is that statement true?

No. Eighteen safety studies of various types have been performed to assess anthrax vaccine. Several of these studies actively collected data for weeks or months after each vaccination:

Brachman study 24 and 48 hours after each dose

Fort Bragg study 1, 2, 3, 7, and 30 days after each dose

Fort Detrick route-change study 1, 2, 3, 7, and 30 days after each dose

Tripler Army Medical Center study 7 days or more after each dose

Korea study 2 weeks to 5 months after each dose

4. I have heard people say "there are no long-term safety studies of anthrax vaccine." Is that statement true?

No. Unlike the safety studies of single-dose vaccines, the 6-dose vaccination schedule for anthrax vaccine requires that individual vaccine recipients be observed for multiple months or years. Numerous studies have assessed the health of anthrax vaccine recipients over extended periods of time. The following list shows how much time elapsed after individual anthrax vaccine recipients received their first dose of anthrax vaccine:

Vaccine Adverse Event Reporting System (VAERS) minutes to years

Fort Detrick route-change study 6 months

Korea study 6 months

USAF vision study at least 6 months

Langley AFB study at least 6 months

Tripler Army Medical Center study at least 1 year

Brachman study at least 1.5 years

Inpatient/outpatient cohort study at least 6 to 18 months

Fort Detrick and US Army Medical Research Institute of Infectious Diseases (USAMRIID) 10 years or more

5. Laboratory workers at Fort Detrick, Maryland, have been vaccinated against anthrax since the 1940s. What do we know about the long-term health of those workers?

At Fort Detrick, Maryland, 99 laboratory workers were evaluated 10 to 20 years after receiving anthrax vaccine. Most of these workers received 150 to 200 doses of various vaccines (including anthrax vaccine); some received more than 300 such injections during their tenure at Fort Detrick. This study "failed to produce evidence that development of neoplasms, amyloidosis, or autoimmune diseases was associated with the vaccine dosages and frequencies used at Fort Detrick. The authors concluded "These data and the accompanying evaluation of an intensively immunized population provide evidence that no obvious adverse effects result from repeated immunization." The first report of this group of vaccine recipients was published in the Bulletin of the Johns Hopkins Hospital in 1958. Two follow-up reports were published in the Annals of Internal Medicine in 1965 and 1974.

An extension of this long-term study is underway at the US Army Medical Research Institute for Infectious Diseases (USAMRIID) to determine, in even greater detail, whether people who received multiple vaccines, including anthrax vaccine, during their past employment at Fort Detrick demonstrated any adverse health effects over the long term. More than 1,500 employees have been followed annually there. In a case-control study begun in 1996, vaccinated and unvaccinated volunteers have been enrolled. All volunteers signed an informed-consent document. The study methods include a 9-page health history questionnaire, extensive blood tests, and urinalysis. The questionnaire queries mental and physical conditions of the volunteers, as well as the health of their offspring. Study end points include symptoms, symptom complexes (including symptoms reported by veterans of the Persian Gulf War), diseases, and abnormal laboratory and urine tests. Study subjects will be compared to two to three 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. No unexplained symptoms due to repeated doses of anthrax or other vaccines have been found.

From this and other monitoring, no patterns of delayed side effects to anthrax vaccine have been found. Monitoring continues.

White CS III, Adler WH, McGann VG. Repeated immunization: Possible adverse effects: Reevaluation of human subjects at 25 years. Annals of Internal Medicine 1974;81:594-600. http://www.anthrax.mil/media/pdf/repeated.pdf

Legal Status

1. Is the anthrax vaccine licensed for use by the Food and Drug Administration (FDA)? Is it an investigational new drug (IND) under FDA rules? Or is DoD using it under terms that subject it to IND rules?

Anthrax vaccine is licensed by the FDA. According to the FDA, DoD is not using anthrax vaccine as an IND. The FDA is the agency authorized to make determinations on whether a drug is being used under terms that make it subject to IND regulations. The FDA determined that the anthrax vaccine as used by DoD in the Anthrax Vaccine Immunization Program (AVIP) is not an investigational new drug, but is an approved drug being used in accordance with its approved label. This is based on the judgment that the protective effect of the anthrax vaccine against the often-fatal disease is not dependent on the route of exposure (cutaneous or inhalation) and recognition that the vaccine is being used in accordance with its approved label.

The Department of Defense's use of anthrax vaccine in the Anthrax Vaccine Immunization Program for pre-exposure prevention using six doses over 18 months is consistent with the Food and Drug Administration-licensed use of the vaccine. The Centers for Disease Control and Prevention offer of anthrax vaccine for Congressional and U.S. Postal Service workers used anthrax vaccine for "post-exposure prophylaxis" in three doses. This is not a Food and Drug Administration-licensed use of the vaccine. Therefore, in that case (post exposure), the vaccine was administered under an "investigational new drug" protocol, which required informed consent.

2. Do DoD and FDA interpretations of the approved anthrax vaccine label encompass use for both inhalational and cutaneous exposures?

Yes. The approved anthrax vaccine labeling is nonspecific as to the route of exposure. The label states that Anthrax Vaccine Adsorbed is recommended for animal product workers, persons engaged in certain medical activities, persons handling potentially infected animals, and other high risk persons involved in activities that may bring them into contact with B. anthracis spores. The label does not distinguish among these individuals becoming infected by spores entering the body through the skin, being breathed (such as in dust from animal hides or medical equipment), or being ingested. DoD has long interpreted the label as encompassing inhalational exposure, including that which would occur in a biological warfare context, and the FDA agrees.

DoD medical experts have also been aware that because inhalational exposure is not specifically listed on the label, there was a lack of clarity. During the Gulf War, where threat of exposure to anthrax by aerosol was high, DoD used the anthrax vaccine consistent with its interpretation of the label, and did not file an IND application for its use. This use was with the full knowledge of the FDA.

After the Gulf War, as part of the effort to improve refine medical countermeasures to chemical and biological weapons, DoD began a research initiative to determine whether

the same level of protection against anthrax can be achieved with a shorter shot schedule – specifically, two shots with annual boosters, instead of the current requirement of six shots over 18 months -- and by administering the vaccine through intramuscular, rather than subcutaneous, shots (to reduce inflammation at the shot site). This led to the 1996 IND application filed by Michigan Biological Products Institute (MBPI, the predecessor to BioPort as the vaccine manufacturer) to develop research data to support possible amendments to the label. The IND application included a proposed study of the effectiveness of the vaccine against inhalational exposure (using an animal model) under the investigational, two intramuscular shot schedule. The IND was designed to support possible amendments to the label to reduce the shot schedule, provide for intramuscular injections and specifically list inhalational exposure as a labeled indication. This IND application in no way suggests that DoD believed the approved label did not already encompass inhalational exposure under the normal, six subcutaneous shot schedule.

In 1997, DoD moved ahead with AVIP plans. At that time, the IND application had not progressed to the point of allowing a proposed amendment to the label. Thus, AVIP incorporated all current label specifications, including the six-shot regimen and subcutaneous route of administration. Recognizing that the label was still nonspecific as to route of exposure, on March 4, 1997, the Assistant Secretary of Defense (Health Affairs) wrote to the Lead Deputy Commissioner of the FDA (the Commissioner's position was then vacant) restating that "DoD has long interpreted the scope of the license to include inhalational exposure, including that which would occur in a biological warfare context," and asking "whether the FDA has any objection to our interpretation of the scope of the licensure for the anthrax vaccine." The Lead Deputy Commissioner (exercising the authorities of the Commissioner) responded March 13, 1997: "I believe your interpretation is not inconsistent with the current label." This determination eliminated any remaining doubt on the interpretation of the label.

3. Have arguments that the Anthrax Vaccine Immunization Program should be considered an IND use been specifically presented to the FDA?

Yes, and the FDA reaffirmed that the AVIP is NOT subject to IND rules.

Opponents of the AVIP and some counsel for servicemembers involved in disciplinary actions for failure to obey the lawful order to receive anthrax shots have argued that AVIP should be considered an IND use of the vaccine. On November 3, 1999, four Members of Congress asked the FDA Commissioner to rule that the AVIP must be carried out under an IND protocol with informed consent of persons receiving the shots. The FDA responded November 26, 1999 (signed by Associate Commissioner Melinda K. Plaisier):

> "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."

This determination is vested by law in the FDA Commissioner. The FDA Commissioner has determined that the anthrax vaccine is safe and effective for the prevention of anthrax disease, an often-fatal disease, for persons at risk of exposure to anthrax spores, whether by cutaneous or inhalational exposure, when used in accordance with the FDA approved label.

An assertion has been made that various letters from the most senior officials of the FDA to senior DoD officials and to Members of Congress should be disregarded because they did not purport to be official "advisory opinions" issued under a specific provision of the FDA regulations. Although such a distinction might be relevant in an FDA-initiated legal enforcement action, it is nonsense to suggest that the FDA has not made its decision. The cited letters clearly show FDA's determination that the AVIP is not subject to IND regulations. If the FDA changes its position and decides otherwise in the future, the Department of Defense has stated its policy to comply.

In December 2003, the FDA issued a final rule and order confirmed that anthrax vaccine is effective in preventing anthrax, regardless of the route of exposure. [FDA. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review. Fed Reg 2004;69:255-67; errata 7114-5; 2004 Jan 05; Feb 13. www.access.gpo.gov/su_docs/fedreg/a040105c.html

4. Is there a basis to challenge the legality of an order to a military member to receive anthrax immunizations?

No. Medical treatment and immunizations determined reasonably necessary to accomplish a military mission or safeguard military members may be required of military personnel. The decision of the Secretary of Defense to approve the unanimous recommendation of the Chairman and members of the Joint Chiefs of Staff to vaccinate all military personnel authorizes military commanders to issue orders to receive shots. Such an order is not in conflict with any law, including any requirement of the Food and Drug Administration. It is a lawful order that a military member has a duty to obey.

Vaccination and Reproductive Health

1. Can the anthrax vaccine be taken by military members who are pregnant?

It is DoD policy not to give anthrax vaccine to women who are pregnant or who think they may be pregnant. This is consistent with the general practice of withholding most medications from women who are pregnant. Most vaccinations are routinely deferred until after pregnancy, unless immunity is needed during pregnancy. Tetanus, meningococcal, hepatitis B, and influenza vaccines, for example, are specifically recommended for susceptible women during their pregnancy. As with other vaccines in the U.S., studies on possible reproductive side effects by intentionally giving anthrax vaccine to pregnant women have not been performed. However, there has been no confirmed evidence of infertility, miscarriages, or other reproductive problems with the use of inactivated vaccines.

Because the anthrax vaccine is a sterile, cell-free (filtered) bacterial vaccine, it is non-infectious and is not expected to cause any harm to the fetus. If a pregnant woman is known to have been exposed to anthrax, she could be offered the vaccine as a potential life-saving measure.

Women who believe that 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. Once a woman is no longer pregnant, deferred anthrax vaccination will resume. A woman can safely become pregnant any time after vaccination that she wishes.

Preliminary data from the Naval Health Research Center raised a tentative signal that there may be an association with an increased rate of birth defects. This signal is being investigated thoroughly, to determine which of several explanations for the signal is most likely.

2. What happens to vaccinated women who later get pregnant?

In the March 27, 2002, issue of the Journal of American Medical Associations, two Army physicians published their peer-reviewed findings that women get pregnant at the same rate, whether anthrax-vaccinated or unvaccinated. These physicians from Fort Stewart, Georgia, also showed that women deliver offspring at the same rate, whether anthrax-vaccinated or unvaccinated. The Fort Stewart found no difference in birth defect rates, either, but the study may have been too small to detect small differences.
http://jama.ama-assn.org/issues/v287n12/fpdf/joc20240.pdf

Long-standing Defense policy is to defer routine vaccinations in women until after pregnancy. This policy has always applied to anthrax vaccine. Women are asked if they are pregnant before vaccination. Women who are not sure are offered pregnancy tests.

3. What about men who get vaccinated? Should they delay child-bearing?

No. For all the same reasons mentioned above, there is no reason for a man to delay fathering a child after vaccination. A man can safely father a child any time after vaccination that he wishes.

4. What about a woman who is taking fertility-enhancing drugs in an effort to become pregnant?

No drug interactions are known between fertility medications (such as clomiphene, Clomid) and any vaccination. Women on fertility-enhancing drugs receive all DoD vaccinations on schedule until they have a positive pregnancy test. At this point, further vaccinations are deferred as described above.

5. Why is anthrax vaccine not contraindicated with breast-feeding?

Women who are breast-feeding may safely receive any vaccine. As an inactivated vaccine, anthrax vaccine contains no living or dead organisms and is non-infectious. No ill effects to the infant are anticipated through breast-feeding. As recommended by the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC), there is no need to interrupt breast-feeding (lactation) for inactivated vaccines.

For More Information:

Advisory Committee on Immunization Practices. General recommendations on immunization. MMWR-Morbidity & Mortality Weekly Report 2002;51(RR-2):1-35. ftp://ftp.cdc.gov/pub/Publications/mmwr/rr/rr5102.pdf

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Anthrax and the Persian Gulf War

1. Is the anthrax vaccination program a result of lessons we learned from the 1990-91 Persian Gulf War?

Yes. Building upon the lessons of past wars and leveraging superior technologies available today and in the future, the AVIP is one of the cornerstones of Force Protection. Additionally, the current world threat environment and the unpredictable nature of terrorism make it prudent to include biological warfare defense in all our force protection planning.

We also learned that we need to put more effort into documentation of vaccinations in servicemembers' medical records. This is the reason for the new immunization tracking systems operated by each of the military services.

2. Anthrax vaccine was administered to personnel deployed in the Persian Gulf War. How many servicemembers received vaccines against biological weapons during the Gulf War?

During the Persian Gulf War approximately 150,000 servicemembers (about 1 in 5 of the people who served in the operation) received at least one dose of anthrax vaccine to vaccinate U.S. forces against Iraq’s weaponization of Bacillus anthracis. Approximately 8,000 doses of botulism vaccine were also administered during the Gulf War.

3. Was the anthrax vaccine FDA-licensed at the time it was given to Gulf War veterans?

Yes. The FDA licensed the anthrax vaccine in 1970. All of the anthrax vaccine administered during the Persian Gulf War was produced at the Lansing facility and release according to the lot-release test criteria for potency, purity, safety, and sterility.

4. Has the anthrax vaccine been linked to illnesses among Persian Gulf War veterans?

No. Several independent nationally renowned scientific groups have addressed this issue and have found no evidence to link anthrax vaccine with illnesses among Gulf War veterans. Symptoms have been reported both by Gulf War veterans who were vaccinated and those who were not. The Institute of Medicine, the Presidential Advisory Committee on Gulf War Veterans' Illnesses, National Institute of Health, and the Defense Science Board have reviewed the correlation and concluded that the anthrax vaccine does not explain the reported chronic effects associated with illnesses among Gulf War veterans.

There have been several unsubstantiated allegations in the media and elsewhere about experimental vaccines that may have contained non-FDA-licensed substances. Only the FDA-licensed anthrax vaccine was used then or now.

5. What did the Centers for Disease Control and Prevention find in their study?

Scientists at the CDC coordinated one study of the health of Gulf War veterans. The clinical evaluation portion of their study assesses 158 Gulf War veterans from one Air Force unit, regardless of health status. Portions of their research report is reprinted verbatim here:

METHODS: "...To screen for exposure (either by vaccination or in combat) to 2 widely discussed putative biologic warfare agents, we tested serum samples for antibodies to toxin produced by Clostridium botulinum and Bacillus anthracis. Serum samples were screened at the Division of Bacterial and Mycotic Diseases, CDC, for antibodies to type A botulinum toxin. Serum samples were assayed at the US Army Medical Research Institute of Infectious Diseases, Washington, DC [sic], for antibodies against anthrax protective antigen and lethal factor...."

RESULTS: "...There was no association between seropositivity to various infectious agents and chronic multisymptom cases. ... Ten subjects reacted to botulina [sic] toxin and 14 to anthrax protective antigen, but there were no differences between cases and noncases...."

COMMENT: "We tested participants for exposure to several infectious agents that are important health problems in the Gulf region, that may have been used in vaccines, and that might be associated with a chronic illness. ... Similarly, we found no association between illness and antibody against the other viruses, rickettsiae, parasites or bacteria for which we assayed...."

CITATION: Fukuda K, Nisenbaum R, Stewart G. Thompson WW, Robin L, Washko RM, Noah DL, Barrett DH, Randall B, Herwaldt BL, Mawle AC, Reeves WC. Chronic multisystem illness affecting Air Force veterans of the Gulf War. Journal of the American Medical Association (JAMA) 1998;280:981-8.

6. Where can I get more information about reputable studies of Gulf War illnesses?

The Special Assistant for Gulf War Illnesses, Dr. Bernard Rosker, published an info paper entitled "Vaccine Use During the Gulf War" (http://www.gulflink.osd.mil/va/).

When Persian Gulf War veterans returned and started reporting symptoms, some people asked if vaccines administered during the Gulf War might have caused the symptoms.

Several independent expert panels addressed this and related questions head-on. These panels consisted of veterans, civilian academic experts, scientists, health-care professionals, and policy specialists. Each of these panels included some of the nation's best scientists, who spent months or even years listening to veterans, reviewing the evidence, and deliberating the issues.

In each case, the independent expert panels found that there was no evidence of any link between any vaccine and any illness common to Gulf War veterans. These reports include:

Presidential Advisory Committee on Gulf War Veterans' Illnesses: Final Report, December 1996. (http://www.gwvi.ncr.gov/toc-f.html) Pages of Interest: second page, Executive Summary, plus pages 112-114 of the original document (Chapter 4 in the web version).

Institute of Medicine, Health Consequences of Service During the Persian Gulf War: Recommendations for Research & Information Systems, 1996. (http://books.nap.edu/books/0309055369/html/1.html)Pages of Interest: 49-52, 55, 100.

National Institutes of Health, Technology Assessment Workshop: The Persian Gulf Experience and Health, 29 April 1994. [no longer available by Internet]

Defense Science Board Task Force on Persian Gulf War Health Effects, June 1994. (http://www.gulflink.osd.mil/dsbrpt/index.html) See chapter VIII, section E.2.

Three specific studies looking into the health of Gulf War veterans and their families were published in the New England Journal of Medicine.

The postwar hospitalization experience of U.S. veterans of the Persian Gulf war. New England Journal of Medicine 1996;335:1505-13. This study concluded that "During the two years after the Persian Gulf War, there was no excess of unexplained hospitalization among Americans who remained on active duty after serving in that conflict."

The risk of birth defects among children of Persian Gulf war veterans. New England Journal of Medicine 1997;336:1650-6. The authors concluded that "This analysis found no evidence of an increase in the risk of birth defects among the children of Gulf War veterans."

Mortality among U.S. veterans of the Persian Gulf war. New England Journal of Medicine 1996;335:1498-1504. The authors concluded: "Among veterans of the Persian Gulf War, there was a significantly higher mortality [death] rate than among veterans deployed elsewhere, but most of the increase was due to accidents rather than disease, a finding consistent with patterns of postwar mortality among veterans of previous wars."

A DoD-funded British team at King's College, London, reported in the 20 May 00 issue of British Medical Journal that multiple vaccinations given in a theater of war, but not before deployment, were associated with multisymptom illness, fatigue, psychological distress, health perception, and physical functioning. The analysis was limited to veterans who kept vaccination records. Exposures other than vaccination were not controlled for, except pesticide use. Anthrax vaccine was not analyzed independently. The lead author was Matthew Hotopf; the research team included Catherine Unwin. The authors recommend that Armed Forces be vaccinated before deployment: "It would be folly to allow service personnel to be committed to a modern battlefield without all necessary means of protection against endemic infection and biological weapons."

The accompanying editorial calls Hotopf's evidence "inconclusive," citing design limitations and contradictory findings.

Next Generation Anthrax Vaccine (NGAV)

1. Is the Department of Defense (DoD) pursuing an improved anthrax vaccine?

Yes. DoD is actively pursuing a next-generation anthrax vaccine (NGAV) in cooperation with the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).

2. Why is DoD pursuing another anthrax vaccine? Doesn't the one you have now work?

The National Academy of Sciences and its Institute of Medicine (IOM) stated in no uncertain terms that "AVA [the current FDA-licensed anthrax vaccine], as licensed, is an effective vaccine to protect humans against anthrax, including inhalational anthrax." This was in its March 2002 report, which can be found at: http://www.nap.edu/catalog/10310.html.

3. Then why are you pursuing a next-generation anthrax vaccine?

We want to explore whether a newer anthrax vaccine would be easier to produce and require fewer doses to achieve immunity. The IOM study also recognized the advantages of developing a next-generation anthrax vaccine when it said, "the production, testing, and licensure of a new vaccine requiring fewer doses and producing fewer local reactions are needed."

Aviators consistently seek better airplanes. Similarly, we seek better vaccines.

4. What efforts does DoD have underway? Who are DoD's partners?

DoD and the National Institutes of Health (NIH) have been working on a next-generation anthrax vaccine (NGAV). Specifically, the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) and the Joint Vaccine Acquisition Program (JVAP) collaborated to develop an NGAV that uses state-of-the-art recombinant technology. The NIAID collaborates with this effort by preparing the NGAV product and sponsoring human clinical phase-1 trials.

The NIAID is independently pursuing multiple "recombinant protective antigen" (rPA) candidate vaccines, to identify and develop the most promising next-generation vaccine as quickly as possible. This is a parallel effort from the DoD/NIAID cooperative effort on the DoD NGAV candidate.

5. How will this new anthrax vaccine be produced?

The next-generation anthrax vaccine (NGAV) is based on a protein called "recombinant protective antigen" (rPA). rPA is a single purified protein that protects animals against

aerosol exposure to deadly *Bacillus anthracis* spores. rPA can be produced in several genetically-engineered bacteria.

6. What advantages could an NGAV offer?

NGAV is a more highly defined product (a single highly purified protein). As a result, there should be more consistency from production lot to production lot, making release testing more predictable. Additionally, it might be possible to achieve immunity with fewer doses, because higher and more consistent doses of the protective-antigen protein may be administered. It might also be possible to use an intramuscular injection route, which may cause fewer adverse events after vaccination (i.e., be less reactogenic). However, this possibility won't be known until human clinical trials of the vaccine are completed. Finally, the rPA is produced in non-spore-forming bacteria that permit the vaccine to be made in the same production facility as other vaccines, unlike anthrax vaccine adsorbed (AVA).

7. When will human clinical trials of next-generation anthrax vaccines (NGAV) begin?

These clinical trials began in fall 2002.

8. Will a next-generation anthrax vaccine protect as well as the current anthrax vaccine?

That is our goal, yes. Until completion of human clinical trials, we do not know how much protective antibody human volunteers will produce. Preliminary data from non-human primates (rhesus monkeys) seems to indicate similar protection profiles compared to anthrax vaccine adsorbed (AVA).

9. What has to be done before we can use an NGAV?

We are in the beginning stages of clinical testing of an NGAV. Phase I tests in a few dozen people will study this new vaccine's safety. Next, a preliminary Phase II test in a few hundred people will test antibody responses to the new vaccine. Expanded Phase III testing among thousands of volunteers will produce pivotal information about both safety and immune responsiveness required for product licensing.

Advanced studies (post-clinical trials) will be conducted in animals to define the protective immune response induced by the NGAV candidate. Additionally, studies will be performed to optimize the vaccine's formula and immunization schedule.

In addition, results from the study of the current FDA-licensed anthrax vaccine, being conducted by the Centers for Disease Control & Prevention (CDC), will provide critical information on immune responses that will be required to license an NGAV.

Finally, the FDA will study all of the data and eventually determine if the NGAV will become a licensed product.

10. When do you project that a next-generation anthrax vaccine could be licensed by the Food & Drug Administration (FDA)?

DoD cannot speak for the NIH effort to license a NGAV. For the DoD effort, it is difficult to predict until all clinical data has been collected and reviewed by the FDA, but current estimates for FDA licensing are around 2010-2011.

Educational Materials

1. Will anthrax vaccine recipients receive any educational information about the anthrax vaccine? How will this information be presented?

Commanders and health care professionals will provide anthrax vaccine recipients information about the vaccine. Information has been provided to military personnel and DoD civilians through command channels and internal and external public affairs programs to include web sites, commanders' calls, military newspapers, television, radio and messages.

2. Anthrax vaccine information is also available through:

DoD and Service Web Sites

Information brochures

- Anthrax Vaccine Trifold Brochure
- Information Pamphlet

The AVIP Leaders briefing

The AVIP Health-Care Providers briefing

The AVIP toll-free information line (877-GET-VACC)

The AVIP question-and-answer service (mailto:avip@otsg.amedd.army.mil)

Other agencies, including:

Centers for Disease Control & Prevention (http://www.cdc.gov/nip)

Food & Drug Administration (http://www.fda.gov)

World Health Organization (http://www.who.int)

Reserve Components

1. Will Reserve component personnel be required to take a full series of shots?

Yes, if their unit is designated for vaccination. Full immunization with anthrax vaccine adsorbed requires six doses administered over 18 months to complete the primary series. This is the schedule licensed by the Food & Drug Administration (FDA). It is DoD and Coast Guard policy to adhere to this vaccination schedule. Guardsmen and Reservists with less than 18 months until separation or retirement from military service will be treated as in any other vaccination program that is required to prepare them for deployment. They will be required to begin the vaccination series unless medically deferred. The Services will not require completion of the six-shot vaccination series for Reserve Component members once they leave military service.

2. Will getting the anthrax vaccine make me ineligible to work for the airlines?

No. For a more complete discussion of this question, see independent information posted by "The Virtual Flight Surgeons," at http://www.aviationmedicine.com/anthrax.htm.

3. Does the government have a program to care for Reserve Component personnel who develop possible medical conditions or complications after anthrax vaccination?

Yes, the Guard and Reserve cover the cost of health care for Reserve Component members who experience illness or injury as a result of performing duty. Complications that develop after anthrax or any vaccination are considered to be line-of-duty illnesses.

Therefore, a member of the Reserve Component may present themselves for treatment at any medical treatment facility (MTF), for initial evaluation and treatment of possible reactions after vaccination during duty. The member must be examined and provided necessary medical care. Once treatment is rendered or the individual’s emergent condition is stabilized, a Line of Duty and/or Notice of Eligibility status will be determined by the member’s unit, as required.

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.

Some RC members may seek medical care from their private physicians while others may seek medical care at a local MTF. This will vary by individual and circumstances. Regardless of the source of the care, each Reserve Component should ensure that procedures are in place that facilitates prompt evaluation and treatment of its members in the event of an adverse event. Members must be advised of these procedures and provided information related to pay status or compensation issues.

Information for Civilian Healthcare Providers: If a Reservist or Active Duty Military Member presents to you for a condition that may be an adverse event caused by a military vaccination, please provide the appropriate care and contact the following for authorization and payment:

The Military Treatment Facility (MTF) where the member is enrolled, OR contact

The Military Medical Support Office (MMSO) 888-647-6676 if the member is not enrolled to an MTF.

4. Will DoD and USCG provide the opportunity for Reserve Component personnel to receive the full series of shots after separation from the military?

When Reserve Component personnel separate from the military before completion of the anthrax vaccine primary series there will be no need to complete the series, because the individual would not be subject to deployment to a higher-threat area. DoD and USCG will not provide the anthrax vaccine to these people to complete the series.

5. Will DoD and USCG provide the anthrax vaccine for Reserve Component personnel to receive the full series of shots after retirement or transfer to the Individual Ready Reserve (IRR)?

When Active and Reserve Component personnel retire or transfer to the IRR before completion of the anthrax vaccine primary series there will be no need to complete the series, because the individual would not be subject to deployment to a higher-threat area. DoD and USCG will not provide the anthrax vaccine for these people to complete the series.

If recalled to military service, Reserve Component members who have not completed the primary vaccination series will continue the series where they left off.

6. What plans are in place to provide the anthrax vaccine to Reserve Component personnel?

Reserve Component personnel who will be deploying to a higher-threat area for a period of 15 or more days will receive the anthrax vaccination. Active-duty personnel and most Reserve Component members can be supported with existing medical resources as they have since the program's inception. Designated military personnel may receive any dose at any DoD or Coast Guard medical treatment facility (MTF). Reserve Component members must be in a duty status. Mass vaccinations require prior coordination with the MTF. The DoD is collaborating with several organizations, such as the Department of Veterans Affairs, the Federal Occupational Health division of the Department of Health & Human Services, and a private contractor to create a nationwide provider network to improve accessibility for administration of anthrax vaccinations for the Reserve Component and other remotely assigned personnel.

Unit commanders are responsible for ensuring that their members are vaccinated and ready for deployment. It is also necessary for Reserve Component commanders to advise their members that they may seek medical care if they have an adverse reaction to any vaccination. Our Reserve Component members trust that they will be cared for, if injured in the line of duty. The leadership has a duty to ensure that this trust is fulfilled.

Other Categories

1. Will DoD or Coast Guard civilians and government contractors be vaccinated?

DoD or USCG civilians and contract workers in designated Emergency Essential (EE) or Mission Essential (ME) positions are required to be vaccinated. The procedure is to vaccinate U.S. military members and emergency-essential civilians and contract workers in or rotating to designated higher-threat areas for 15 days or more. The DoD Directive 6205.3, DoD Immunization Program for Biological Warfare Defense, dated 26 November 1993, applies to EE DoD civilian personnel, and personnel of other Federal Departments, when assigned as part of the U.S. Armed Forces. DoD Instruction 3020.37, Continuation of Essential DoD Contractor Services During Crises, dated 6 November 1990, with Change 1 dated 26 January 1996, states that employees designated as mission essential in the contract statement of work (SOW) must be identified. DoD civilians and contractors are subject to the same vaccination requirements as active-duty personnel upon deployment.

2. How are Emergency Essential Employees notified about their requirement to receive anthrax vaccine?

Notification of requirements for emergency-essential positions is performed on DD Form 2365, DoD Civilian Employee Overseas Emergency-Essential Position Agreement. Regulations to ensure notification of civilian employees of medical standards established for emergency-essential positions are codified in DoD Directive 1404.10, "Emergency-Essential (E-E) DoD U.S. Citizen Civilian Employees," April 10, 1992. For more information please see policy letter and sample form at this link: http://www.anthrax.mil/media/pdf/EECpolicy.pdf

2. How will the Attaché personnel who work for the Defense Intelligence Agency, personnel who work for the CINC, Marine Security Personnel who work for the Ambassador, and Special Category People receive the anthrax vaccine?

DoD included estimated numbers of DoD personnel attached, assigned, or associated with U.S. embassy duty within the higher-threat area (HTA) countries when it calculated total vaccine requirements. There is sufficient vaccine to accommodate these personnel. Anthrax vaccine is given only to those personnel assigned, attached, or deploying to the designated HTAs for 15 days or more per Secretary of Defense guidance.

According to the DoD directive, each Service AVIP Plan and the DoD Travel Guide, personnel deploying for assignment, attachment, or association with these duty assignments in the HTA countries will start their anthrax vaccinations before arriving on the job, whether for Temporary Duty or Permanent Change of Station. In some countries, the medical sections of U.S. Embassies either give the vaccinations or facilitate getting them with contract medical support using U.S.-provided vaccine. In

other countries, DoD personnel get their anthrax vaccinations from the nearest supporting DoD Medical Treatment Facility.

4. Why is the anthrax vaccination program voluntary for personnel at the Department of State?

All vaccinations for Department of State (DoS) personnel are voluntary. The conditions under which DoS personnel work differ significantly from the roles of military personnel. Because of the benefits of the anthrax vaccine, the Department of State instituted a worldwide anthrax vaccination program for eligible U.S. government employees and their families serving abroad. The program will be phased in over several years. [Link to Department of State: http://travel.state.gov/cbw.html]

While State Department personnel are often evacuated during military contingencies, Department of Defense and Coast Guard personnel must remain in theater to fight and win America's wars.

Refusals

1. How will refusals to be vaccinated be handled?

We know that few servicemembers refuse to be vaccinated, given current understanding about the lethal threat of anthrax and also about the validated safety and effectiveness of the vaccine. However, we begin with the assumption that any servicemember covered by DoD policy who refuses vaccination may be uninformed about the facts related to the deadly effects of the anthrax agent and the significant protection afforded by the anthrax vaccine. Our first action with those who might refuse the vaccine will be to understand their concern and provide information.

This is a force protection issue and management of refusals will be in accordance with policies of the respective Services. If a servicemember continues to refuse the vaccine, then a commander will manage the situation as he or she would for any failure to obey a lawful order, including educating the member about the AVIP as appropriate.

We expect servicemembers to comply with administration of this vaccine as for any other mandatory vaccination. It is comparable to an order to wear body armor during armed engagement, or to don a protective mask in a suspected chemically or biologically contaminated environment. Any servicemember who does not comply with these measures endangers his/her own health, and places both their unit and mission accomplishment at risk.

In short, military vaccination is one of those cases where individual rights are overshadowed by individual responsibilities to the other members of the unit.

Military and civilian judges uniformly have found orders for members to be vaccinated to be lawful orders. Again, we do not anticipate this issue to be a major problem.

Vaccine Religious Waivers

1. Does the DOD grant waivers to their immunization policy for religious reasons?

Religious waivers are granted in the case of legitimate religious objections to immunization and are revoked if necessary to ensure the accomplishment of the military mission. Waivers from private physicians based on personal or philosophical beliefs or attitudes are not authorized.

2. What regulations govern this practice?

DOD guidance for granting immunization waivers to military and DoD civilian personnel for religious reasons are covered by the following directive - AFJI 48-110/AR 40-562/BUMEDINST 6230.15/CG COMDTINST M6230.4E.

3. Who has the authority to grant a religious waiver?

The authority to grant temporary waivers is delegated as follows:

Army—Medical authority at major commands;

Air Force—Major command surgeons;

Navy and Marine Corps—The Chief, Bureau of Medicine and Surgery.

4. What information is required to support an application for a religious waiver?

Applicants forward the following information through the appropriate authority: full name, rank, and SSN; name of recognized religious group and the date of the applicants affiliation; supporting certification signed by an authorized personal religious counselor. The counselor must attest that the applicant is "an active member in good standing of the espoused religious group, adheres to tenets consistent with the espoused religious beliefs, and the religious group has a tenet or belief opposing immunizations".

5. Am I still deployable after receiving this waiver?

Commanders ensure a medical officer counsels the applicant that noncompliance with immunization requirements may adversely impact deployability and that administrative action may be taken; with this noncompliance come additional health risks upon exposure to disease against which he/she is not protected. The medical officer will also advise applicant that he/she may be detained during travel across international borders in accordance with international health regulations.

6. Is this waiver irrevocable?

A waiver can be revoked if the individual is at imminent risk of exposure to a disease for which an immunization is available. This is in keeping with the tenets concerning involuntary therapeutic care when military mission accomplishment may be compromised.

Production Issues

1. The production facility for the anthrax vaccine, located in Lansing, Michigan, changed ownership in 1998. Who are the current owners?

The State of Michigan opened its first laboratory to manufacture vaccines and antibodies in Lansing in 1925, over 75 years ago, receiving license #99 to manufacture biological medications. On 7 July 1998, the State of Michigan approved the sale of the United States' only licensed manufacturer of anthrax vaccine to a for-profit company. The state-owned entity known as the Michigan Biologic Products Institute (MBPI) was sold effective 5 September 1998 to become BioPort Corporation. The facility's license is now listed as license #1260, with the sale of MBPI to BioPort Corporation - http://www.bioport.com

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 U.S. 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.

2. Did the Food and Drug Administration revoke BioPort's license to manufacture anthrax vaccine?

No. BioPort's predecessor, the Michigan Biological Products Institute (MBPI), owned by the State of Michigan, approved renovations in 1995 for the Lansing facility. In 1997, the Food and Drug Administration (FDA) issued a notice of intent to revoke licenses issued to MBPI. MBPI responded within 30 days with a strategic plan for compliance to FDA standards. The manufacturer voluntarily closed the anthrax vaccine production line in January 1998 for renovation. BioPort submitted a highly detailed set of quality control documents to FDA in fall 2001. FDA approved BioPort's facilities and processes, as they relate to the manufacture of anthrax vaccine, on January 31, 2002.

3. The manufacturing facility owned by BioPort was recently renovated. Is this due to any findings made by the inspections by the Food & Drug Administration?

The planning for renovations to the physical plant began in 1996. Construction began in early 1998 and was completed in May 1999. The Food and Drug Administration approved the renovations to BioPort's anthrax vaccine manufacturing facilities and processes January 31, 2002. FDA has steadily approved release of anthrax vaccine lots manufactured by BioPort ever since.

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 as part of a routine program inspected the anthrax vaccine manufacturing facility at BioPort. To improve its operations, a renovation to the Lansing facility was approved by the State of Michigan in July 1993 with funding coming in later years. The manufacturer closed the anthrax vaccine production line in January 1998 for planned renovation. Although the decision to close the facility for planned renovation was part of the manufacturer's facility improvement strategy, it was, in part, also based on a 1996 DoD assessment that concluded that the facility was inadequate to meet future production requirements. This 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.

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. After a November 1996 inspection, findings 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."

The FDA conducted a pre-approval inspection of the newly renovated production facility at BioPort in November 1999. The FDA inspection reported 30 observations to BioPort management that needed to be corrected as well as identified process validation steps that needed to be addressed for FDA to approve the new facility. FDA completed its approval of BioPort's physical renovations, as well as its extensive process-validation documentation in December 2001.

4. Is there a connection between deficiencies found in the 20 February 1998 FDA Inspection Report and the fact that MBPI suspended anthrax vaccine production?

There is no connection between the deficiencies found on the 20 February 1998 FDA inspection report and the fact that MBPI ceased production of anthrax vaccine in its original production suite. FDA did not order MBPI to suspend production. DoD in coordination with MBPI determined several years ago that the current production line would require scheduled renovation. The start of the renovation was contingent upon MBPI completing the production requirements needed to meet the terms of the production contract (DAMD 17-97-D1139). MBPI fulfilled the contract in December 1997, and the planned renovations began shortly thereafter.

5. Given the nature of the problems identified by the FDA in their inspection of the Michigan Biological Products Institute (now BioPort) in 1996, what safeguards did DoD take to assure that the anthrax vaccine is safe and effective?

DoD directed that supplemental testing be done on all lots in the stockpile at MBPI produced under contract DAMD 17-97-D0003. Of these lots, only lots of vaccine that passed supplemental testing were approved for shipment and use by DoD and Coast Guard personnel.

6. There have been questions raised about the anthrax vaccine due to the results of the FDA inspections over the past few years. Are there reasons to be concerned about the inspection results?

No, once you separate the facts from the misunderstandings. All lots of anthrax vaccine that have ever been released, including those used in the DoD's immunization program, met all FDA release criteria: general safety, purity, sterility, and potency. All stockpiled lots that have been used in the DoD immunization program have met DoD-mandated supplemental testing criteria and oversight of that testing has been provided by an independent DoD-contractor, Mitretek Systems, Inc.

Over the last few years the FDA acknowledged that the manufacturer made progress in achieving compliance with FDA standards and regulations. FDA found no deficiencies serious enough to warrant recall of the anthrax vaccine, which is within FDA's authority. Link to FDA Enforcement Reports: http://www.fda.gov/opacom/enforce.html.

Results of the FDA inspections of BioPort in Nov 1999 and Oct 2000, indicated BioPort's progress toward licensure in an environment of increasingly stringent FDA standards for process validation and demonstrating consistency of manufacturing.

FDA's actions in December 2001 and January 2002, approving all aspects of anthrax vaccine manufacture, reflect the FDA's satisfaction with BioPort's renovations and quality controls. FDA officials have visited BioPort several times since. FDA officials visit all vaccine manufacturers periodically.

7. Since 1970, how many times has FDA inspected the anthrax vaccine production facility in Lansing?

The FDA or the National Institute of Health (NIH) has inspected MBPI's (now BioPort's) Lansing facilities at least 50 times since 1969. Each inspection focused on one or more of three manufacturing activities: bacterial vaccines and toxoids, viral vaccines, or plasma derivatives. Examined during each of these inspections were elements common to the manufacturing of all products at the Lansing site, including the manufacture of anthrax vaccine.

The anthrax vaccine manufacturing facilities specifically have been inspected 12 times in the years following licensure. Further, the FDA did not force BioPort to close its facility and rebuild. The decision to renovate the anthrax vaccine manufacturing facilities was made in an effort to meet the demand for vaccine from the Department of Defense.

8. Since 1970, has anthrax vaccine been subject to additional FDA evaluation or testing?

Some lots of the anthrax vaccine have been tested and evaluated in accordance with procedures approved by the Food & Drug Administration (FDA) for extending the shelf life of vaccines. The approved procedure used to extend the usable life of the anthrax vaccine is the same procedure applied to any other vaccine. This was funded under a DoD stability-testing contract.

9. What is required before releasing the anthrax vaccine into interstate commerce?

Each lot of vaccine is approved and released by the Food & Drug Administration, after specific tests for potency, purity, safety, and sterility.

General Safety: 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. Each animal must survive the test period, gain weight, and show no adverse reaction. Three vials per lot will be tested for safety. General safety tests are required for lot release. Other safety studies have been performed that establish that anthrax vaccine adsorbed has a side-effect profile similar to that of other vaccines.

Potency: Potency is determined in the following manner: guinea pigs are vaccinated with one of several serial dilutions of vaccine or no vaccine (control group). All guinea pigs are injected with known amounts of virulent anthrax 14 days after vaccination, and average time to death is calculated for each group. The test vaccine must be no less potent than the FDA's reference vaccine.

Sterility: Sterility testing is performed on sub-lots and on final product to detect the presence of bacterial contamination. Twenty vials per lot will be tested for sterility.

Purity: Requirements exist calibration and controls. Purity testing consists of four individual tests for aluminum, benzethonium chloride, sodium chloride, and formaldehyde. One vial per lot will be tested for purity.

10. Is it unusual for a vaccine to be manufactured by only one company in the United States?

No. About half of FDA-licensed vaccines are produced by only one manufacturer. These include: Japanese encephalitis vaccine, measles vaccine, meningococcal vaccine, mumps vaccine, pneumococcal 7-valent vaccine, pneumococcal 23-valent vaccine, injectable poliovirus vaccine, rubella vaccine, live typhoid vaccine, injectable typhoid vaccine, varicella vaccine, and yellow fever vaccine.

Vaccines available from multiple manufacturers include: diphtheria toxoid, tetanus toxoid, pertussis vaccine, Haemophilus influenzae type b (Hib) vaccine, hepatitis A vaccine, hepatitis B vaccine, influenza vaccine, and rabies vaccine.

11. Why was supplemental testing ordered for some lots of the anthrax vaccine by the Department of Defense? What tests are involved?

The Secretary of Defense ordered supplemental testing of all lots of anthrax vaccine in the Lansing stockpile when he authorized the Anthrax Vaccine Immunization Program in December 1997. DoD requested the supplemental testing because of FDA concerns, raised during routine inspections, about the facility's quality control procedures. Supplemental testing repeats the original FDA required tests for sterility, purity, potency, and general safety. Supplemental tests were performed by the manufacturer and overseen by an independent contractor (Mitretek, McLean, Virginia).

Supplemental tests are not performed on lots 040 or higher, because these lots underwent the same tests for sterility, purity, potency, and general safety more recently and the data were independently reviewed by the FDA to determine whether the lots meet approval criteria for FDA release.

Lot-release tests performed by the manufacturer include: general safety, purity, potency and sterility (see question 8 for a description of each). Supplemental testing reports may be accessed at the AVIP web site.

12. Is the anthrax vaccine available outside of DoD?

BioPort of Lansing, Michigan, is the only manufacturer licensed by the FDA to produce anthrax vaccine at present. The Joint Program Office for Biological Defense contracted for several million doses of anthrax vaccine, more than BioPort's current inventory. BioPort cannot release vaccine purchased by DoD to non-DoD activities without express permission from DoD. The anthrax vaccine has been, and is currently being, used to protect a limited number of civilian government and university laboratory

technicians involved in research, and certain at-risk non-government civilians such as veterinarians and laboratory workers.

13. BioPort recently received a full go-ahead from FDA. What did it take for BioPort to earn this FDA approval?

BioPort ceased manufacturing to renovate its vaccine production facility in February 1998. When the manufacturing process or equipment in a renovated facility or establishment differs materially from that in the former facility or establishment (CFR 21.314.70), a Biologics License Application (BLA) Supplement must be submitted for Agency approval before production can be resumed. BioPort's BLA Supplement consisted of many parts. Included in the BLA supplement were data validating an updated potency test, process validation test results, information concerning the qualification and testing of three fermentation systems, raw material quality and acceptance criteria, and updated procedures for operating the new facility. In addition, BioPort submitted test data to demonstrate that the potency, safety, sterility and composition of the vaccine were maintained when Hollister-Stier LLC, BioPort's contract filling facility in Spokane, WA, filled AVA into vials for distribution. BioPort produced three separate lots of vaccine in the renovated facility. These were analyzed to assure consistency of production. The results were submitted to the FDA for approval.

After the FDA received BioPort's BLA Supplement, a review committee was established consisting of personnel from the following Offices: Vaccines Research & Review (OVRR), Biostatistics & Epidemiology, and Compliance & Biologics Quality. This committee completed an in-depth review of the submission. An integral part of the review included an on-site inspection by the FDA of production activities at both BioPort and Hollister-Stier. The inspectors reviewed hundreds of documents and physically inspected areas and processes associated with the manufacture and packaging of anthrax vaccine. Following these inspections, BioPort was granted approval for the renovations to the AVA manufacturing suite on December 21, 2001. Hollister-Stier was approved as a contract manufacturer for the packaging of AVA on January 31, 2002.

FDA Inspections

1. September 9, 1969	27. July 8-9, 1985
2. August 3-4, 1970	28. November 18-20, 1985
3. April 11-12, 1972	29. August 6-8, 1986
4. September 18-19, 1972	30. June 4-5, 1987
5. July 24-25, 1973	31. August 26-28, 1987
6. July 26, 1973	32. April 26-27, 1988
7. October 15-16, 1974	33. September 26-27, 1988
8. April 16, 1975	34. May 30- June 1, 1989
9. October 21, 1975	35. July 10-12, 1989
10. April 5, 1976	36. September 12-13, 1990
11. October 28-29, 1976	37. September 9-10, 1991
12. March 14, 1977	38. June 30- July 1, 1992
13. April 13-14, 1978	39. July 29-31, 1992
14. May, 3,5,8,10,12,15,1978	40. August 31- September 2, 1992
15. June 6-8, 1979	41. January 14-15, 1993
16. October 18, 19, 25, 26, Nov 6, 1979	42. May 4-7, 1993
17. April 20, May 1, 1980	43. May 31- June 3, 1994

18. May 21, 1980	44. July 25-26, 1994
19. March 25, 1981	45. April 24- May 5, 1995
20. June 28-29, 1982	46. November 18-27, 1996
21. July 11, August 11, 1982	47. February 4-20, 1998
22. October 26-28, 1982	48. October 19-23, 1998
23. May 2-4, 1983	49. November 15-23, 1999
24. September 21-22, 1983	50. October 10 - 26, 2000
25. June 25-27, 1984	51. December 11-14, 2001
26. August 15-16, 1984	52. September 4-13, 2002
	53. May 11-20, 2004

The Facts on Squalene

1. What is squalene?

Squalene is a naturally occurring substance found in plants, animals, and humans. Squalene is manufactured in the liver of every human body and circulates in our bloodstreams. Humans cannot live without squalene, because we use squalene as a building block to make hormones and other substances in our bodies.

Squalene is also found in a variety of foods (for example, eggs, olive oil, cookies), cosmetics, over-the-counter medications, and health supplements. In fact, people can purchase squalene at health food stores. It is more commonly known as shark oil. Click here to view some commercial squalene resources.

2. Does the anthrax vaccine use squalene as an adjuvant?

An adjuvant is a substance to improve the body's immune response to a vaccine.

No, the adjuvant in the anthrax vaccine is aluminum hydroxide.

3. Does the anthrax vaccine contain squalene?

Maybe. There are conflicting test results.

In September 2000, DoD became aware of Food & Drug Administration (FDA) test results finding trace amounts of squalene in three out of three US vaccines tested: tetanus, diphtheria, and anthrax. The level of squalene identified by the FDA test is so minute that it is likely the result of squalene in the oil of a fingerprint not completely cleaned from lab glassware.

It is hard to completely remove fingerprint oils from glassware. Lab workers have to use a chemical solvent such as hexane to completely remove fingerprint oils from lab glassware. When SRI workers intentionally tested an extract of fingerprint oil, the squalene reading went off the chart.

Before the FDA test results became known, Stanford Research International (SRI), under DoD contract, looked for squalene in anthrax vaccine. At the limit of detection of its test, 140 parts per billion, SRI found no squalene in several lots of anthrax vaccine. The FDA's test, which was developed later, is more sensitive. It is able to detect as little as 10 parts per billion. The FDA found squalene at 10 to 83 parts per billion in five lots of anthrax vaccine. The trace level of squalene found by the FDA in anthrax vaccine is less than the concentration naturally present in human blood (250 parts per billion).

After the FDA reported its results, DoD asked SRI to refine its assay. Using an improved method that could detect as little as 2 parts per billion, SRI found no squalene in 32 out

of 33 lots of anthrax vaccine tested (including lots in which FDA found low levels of squalene). In one lot, they found up to 9 parts per billion. The details appear below.

4. Should we be concerned about the presence of trace quantities of squalene in tetanus, diphtheria, and anthrax vaccines?

No. The trace level of squalene found by the FDA and SRI in anthrax vaccine is well below the concentration naturally present in human blood (250 parts per billion). So injecting trace amounts of squalene are unlikely to have any biological effect, given that it is already present in the body. In fact, without squalene in the body to manufacture hormones and other substances in our bodies, we would die.

In Congressional testimony on 3 October 2000, FDA official Mark Elengold said that the trace quantities of squalene detected were “both naturally occurring and safe."

5. Is it possible that extremely low doses of squalene might trigger the immune system?

It is not unusual for proteins to be recognized by the immune system at very low concentrations. Platelet activating factor (PAF) is the name of a phospholipid (but not an oil) that has biological activity at very low concentrations. But PAF is present in the body at only very low concentrations. Squalene, on the other hand, is normally present in the body at higher concentrations than what squalene in a dose of vaccine might contribute.

The appropriate scientific expertise for this question comes from scientists who specialize in the biological effects of adjuvants, oils, emulsions, and antibodies that bind to lipids or oils. Specialists of this sort do not find that a molecule normally present at a certain level has any effects at substantially lower levels. Such is the case with squalene.

When squalene was intentionally added to an influenza vaccine licensed in Europe (Fluad), researchers needed a squalene concentration of 4.3% (4 parts per hundred or 40 million parts per billion) to increase the immune response. This squalene had to be in the form of an emulsion (a mixture of tiny droplets) to be recognized by the immune system. Squalene in its oily state is naturally present inside the human body.

6. If you wanted to use squalene as an adjuvant, what form would it take?

If you wanted to use squalene as an adjuvant (to boost immune responses) you would have to multiply the amount of squalene found by the FDA about 1 million times, as well as changing it from a simple liquid (its natural state) to an emulsion. An emulsion is a stable suspension of tiny droplets, like an oil-and-vinegar mixture that doesn’t separate. This double difference is like the difference between a teaspoon of oil and 2,000 pounds of mayonnaise. [If you emulsify oil with eggs, you get mayonnaise.]

Squalene in the form of an emulsion (emulsified squalene, such as an adjuvant called MF59) has been added as an adjuvant to some investigational vaccines in the U.S.

In 1997, European health agencies approved emulsified squalene (with influenza virus in the center of each droplet) for use as an adjuvant in an influenza vaccine (Fluad, Chiron Corporation, Marburg, Germany, and Siena, Italy, www.forum-impfen.de/impfnavigator/packungsbeilage/5205fluad.pdf). This European influenza vaccine has been administered safely to hundreds of thousands of people, perhaps millions by now.

There is no squalene adjuvant in any US-licensed vaccine.

Whatever the arguments for or against squalene as a vaccine adjuvant, the fact is that none of the anthrax vaccines administered to U.S. troops contained squalene as an adjuvant. Based on manufacturing records, FDA verifies that no squalene was added to any vaccine formulation used during the Gulf War. This includes the anthrax vaccine. To date, the FDA has licensed, and US manufacturers have used, only aluminum salts (for example, aluminum hydroxide, aluminum phosphate, aluminum potassium sulfate) as adjuvants.

7. Did DoD initially report that anthrax vaccine contained no squalene?

Yes. DoD's declarations were based on tests from a reputable independent laboratory, Stanford Research International (SRI). At the initial limit of detection of its test, 140 parts per billion, SRI found no squalene in anthrax vaccine. It was scientifically proper to say 'no squalene was found to the limit of detection of the assay,' which DoD speakers sometimes oversimplified to say 'there is no squalene.'

Later tests conducted by the FDA were more sensitive than the independent laboratory's tests, able to detect as little as 10 parts per billion. The FDA test found squalene that the independent lab was unable to find. The FDA found squalene at 10 to 83 parts per billion in various lots of anthrax vaccine. The level of squalene identified by the FDA test is so minute that it is likely the result of squalene in the oil of a fingerprint not cleaned from lab glassware.

The trace level of squalene found by the FDA in anthrax vaccine is less than the concentration naturally present in human blood (250 parts per billion). When SRI improved its test, it found no squalene in the lots where FDA found squalene.

8. What did SRI find the first time?

To determine whether squalene was present in anthrax vaccine, the DoD contracted with an independent civilian laboratory, Stanford Research Institute (SRI) International of Menlo Park, California (www.sri.com), to test for the presence of squalene in anthrax vaccine. SRI developed a laboratory method to detect squalene as dilute as 140 parts per billion (ppb). At this level of detection, extraordinary measures must be taken to

avoid contaminating samples, glassware, and equipment with squalene from the skin, because squalene is a natural component of the oils in our skin. The SRI test used a technique called high-pressure liquid chromatography (HPLC) with ultraviolet detection at a wavelength of 203 nanometers. Testing 17 consecutive lots of anthrax vaccine, SRI reported "based on triplicate analysis, no squalene was detected in the sample. The limit of detection is 70 nanograms per 0.5 milliliter dose (140 ppb)." (Spanggord et al., 2002)

9. What did the FDA find?

Using a more sensitive test, developed after the initial SRI test, FDA found trace amounts of squalene in three out of three US vaccines tested: diphtheria toxoid, tetanus toxoid, and anthrax vaccine (<>see letter<>). The FDA test used a technique called gas chromatography with flame-ionization detection. The FDA method could detect squalene as dilute as 10 parts per billion (ppb). Testing five lots of anthrax vaccine and two lots each of diphtheria and tetanus vaccines, FDA concluded, "there were only trace amounts of squalene in the lots tested." Based on manufacturing records, FDA verified that no squalene was added to any vaccine formulation used during the Gulf War.

The amounts of squalene identified in specific lots of anthrax vaccine were:

Lot FAV020 11 ppb
Lot FAV030 10 ppb
Lot FAV038 27 ppb
Lot FAV043 40 ppb
Lot FAV047 83 ppb

Squalene is constantly present in the human blood stream at 250 ppb (250 nanograms per milliliter), a concentration 3 to 25 times higher than the level detected in the FDA test. The amount of squalene added as an adjuvant to a European-approved influenza vaccine is 4 grams per 100 ml (4 parts per hundred), which is about 1,000,000 times more than the concentration of squalene detected in the FDA test. This European influenza vaccine has been administered safely to hundreds of thousands of people.

10. What did SRI find after it revised its test procedures?

After the FDA released its findings, SRI revised its squalene test, lowering its limit of detection of 1.8 ppb or 0.9 nanograms per 0.5 ml. With this more sensitive test, SRI found no squalene in 32 out of 33 lots tested. SRI found squalene in each of three vials of lot FAV008, at 1, 7, and 9 ppb.

SRI found no squalene in lots 12, 13, 18, FAV001, FAV002, FAV003, FAV004, FAV005, FAV006, FAV007, FAV009, FAV012, FAV016, FAV017, FAV018, FAV019, FAV020, FAV022, FAV024, FAV030, FAV031, FAV032, FAV033, FAV034, FAV036, FAV037, FAV038, FAV041, FAV043, FAV044, FAV047, and FAV048B.

SRI also tested some non-vaccine injectable pharmaceuticals. SRI found no squalene in human insulin regular U-100, human insulin isophane (NPH) U-100, lidocaine 2% solution, sodium chloride 0.9% solution, or potassium chloride 2 mEq/ml solution.

11. Did DoD mislead or lie to anybody about the squalene tests conducted by SRI?

No. DoD truthfully and fully reported its findings at each step since May 1999, when SRI first developed its squalene test. DoD did not know of FDA's findings until they were publicly released.

12. Where did the squalene FDA found in its anthrax vaccine tests come from?

The most likely source of the trace squalene in the FDA tests is the result of squalene in the oil of a fingerprint not cleaned from lab glassware. Squalene is not added to anthrax vaccine or any US-licensed vaccine. It is hard to completely remove fingerprint oils from glassware. Lab workers have to use a chemical solvent such as hexane to completely remove fingerprint oils from lab glassware.

13. Has anyone, anywhere found squalene added as an adjuvant to any US-licensed vaccine?

No.

14. What are the claims about anti-squalene antibodies?

In an effort to explain the health problems of some Gulf War veterans, a few people have theorized that a vaccine adjuvant may have caused an autoimmune disease in veterans. A *Vanity Fair* article by Gary Matsumoto, "The Pentagon's Toxic Secret" (May 1999), alleges that the DoD possibly used "an illicit and secret anthrax vaccine" on its own soldiers. The writer's interpretation and presentation of the facts regarding the Department's use of anthrax vaccine are speculative, inflammatory, and wrong. His allegations and the reported "clinical evidence" are not new. Since 1997, reports in the *Washington Times*, its magazine *Insight on the News*, and the (Wilmington) *Delaware News Journal*, have made similar allegations regarding "secret medical experiments" and the like.

Investigators cited in these articles (Pamela Asa, Ph.D., Memphis, TN, and Robert Garry, Ph.D., Tulane University School of Medicine, New Orleans, LA) report they developed and patented a test for anti-squalene antibodies (ASA). Autoimmune Technologies, LLC, of New Orleans, has an exclusive license on the use of this test. The investigators report that they detected anti-squalene antibodies in the blood of ill Gulf War veterans. Their methods were published in the February 2000 and August 2002 issues of the journal *Experimental and Molecular Pathology*.

In the February 2000 article, the authors themselves conclude: "It is important to note that our laboratory-based investigations do not establish that squalene was added as adjuvant to any vaccine used in military or other personnel who served in the Persian Gulf War era."

Asa and colleagues published a second article in the August 2002 issue of *Experimental and Molecular Pathology*, but it also provides no validation of the original assay. As a result, the findings of the second article are also in question. The authors' comment that the Matyas article of 2000 supports their findings is mistaken.

15. Have any independent panels evaluated the claims of researchers to find anti-squalene antibodies in the blood of ill Gulf War veterans?

Yes, four independent civilian panels considered the February 2000 article by Asa and colleagues and other allegations related to squalene and anti-squalene antibodies.

When the Institute of Medicine (part of the National Academy of Sciences) Committee on Gulf War and Health evaluated the 2000 Asa claims of anti-squalene antibodies in the blood of ill Gulf War veterans, it concluded that the paper contains shortcomings, some serious, that combine to invalidate the authors' conclusions. The report says: "The committee does not regard this study as providing evidence that the investigators have successfully measured antibodies to squalene." See www.nap.edu/books/030907178X/html pages 311-312.

The civilian experts on the Armed Forces Epidemiological Board (AFEB) said, "the research reported in this paper does not support this claim; … it remains unclear if the assay actually measures antibodies to squalene, as the authors assert…"

Regarding assertations that Service Members who received anthrax vaccination from the five lots cited in the FDA squalene tests experienced more or more severe adverse events after vaccination, the civilian physicians on the Anthrax Vaccine Expert Committee (AVEC) evaluated adverse events by lot and geographic location. They found no meaningful differences based on lot or on geographic location. (Sever, et al. 2002; Sever, et al, 2004)

Of note, the five lots cited in the FDA squalene tests were shipped to multiple DoD installations. In addition, Dover AFB received lots other than the five lots mentioned above.

After the comprehensive review of anthrax vaccine safety by the National Academy of Sciences (March 2002, www.nap.edu/catalog/10310.html), which included hearing from personnel from Dover AFB and elsewhere concerned that they suffered adverse events after anthrax vaccination, the civilian physicians and scientists concluded that "The [SRI] study report, dated August 14, 2001, found that 1 lot of over 30 lots tested contained measurable levels of squalene. Three samples from that lot [FAV008] contained squalene at 7, 9, and approximately 1 parts per billion, respectively. Use of

vaccine from that lot has not been associated with elevated rates of adverse events. … Because the available data ... demonstrate that the presence of trace amounts of squalene is not associated with an increase in the rates of adverse events following vaccination with AVA, the committee concludes that further investigation of possible AVA contamination is not warranted at this time."

16. Are these panels really independent?

The IOM committee members were selected by the National Academy of Sciences to be fully independent of both the Department of Defense and the Department of Veterans Affairs.

The AVEC committee members were selected by the Department of Health & Human Services to be fully independent of the Department of Defense.

The AFEB is appointed by the Secretary of the Army to advise the Surgeons General of the military services. These civilians constitute a highly accomplished and widely respected scientific advisory board. These civilians are free to render whatever opinions they wish, and their candidness is important to ensuring that DoD is using the best possible medical information.

17. What did the GAO say about squalene testing and what are DoD researchers doing?

In 1999, the U.S. General Accounting Office (GAO, now the Government Accountability Office) released a report "Gulf War Illnesses: Questions about the Presence of Squalene Antibodies in Veterans Can be Resolved" (GAO/NSIAD-99-5). The Department of Defense disagreed with the GAO's opinion that "the first step is to determine the extent to which they [antibodies to squalene] are present in a larger group of sick Gulf War-era veterans." The proper first step is to show that the test for squalene antibodies measures what it claims to measure. Further, the medical significance and the origin of antibodies to squalene, even if their existence is corroborated, remain unknown. Without such information, Gulf War veterans get only speculation about the meaning of the test result and its implication for their health. Gulf War veterans deserve objective evidence and recommendations based on sound science.

To investigate the anti-squalene antibody theory, a scientifically proven test for squalene antibodies is needed to assess whether Gulf War veterans have antibodies to squalene. In response to a DoD solicitation for research on illnesses among Gulf War veterans, a DoD investigator and nationally recognized expert on antibodies to cholesterol and other lipids submitted a research proposal to determine the feasibility of developing a test for antibodies to squalene. The competitively funded research project to determine whether antibodies to squalene exist has five main objectives: 1) Development and validation of an enzyme-linked immunosorbant assay (ELISA) for antibodies against squalene. 2) Evaluation and potential development of other assays for antibodies to squalene. 3) Development of a positive control antibody to squalene. 4)

Production of the positive control antibody to squalene for use in the assays. 5) Testing of normal human serum for antibodies to squalene by ELISA and other methods.

18. What did the competitively funded research project find regarding squalene antibodies?

In April 2000, the research project published its first peer-reviewed report, describing an enzyme-linked immunosorbent assay (ELISA) that could detect antibodies to squalene induced in mice. Use of squalene alone did not produce a significant amount of anti-squalene antibodies. A special chemical was needed to induce the antibodies against squalene in mice. After injecting mice with liposomes (fat globules) containing 71% squalene (710 million parts per billion), plus a second chemical called lipid A, antibodies to squalene were readily induced in mice. The validity of the method was established using positive and negative controls to preclude false-positive and false-negative test results. The investigators concluded that squalene is a weak antigen (a weak inducer of antibodies). (Matyas et al., 2000).

By December 2001, researchers reported improving the assay and ensuring these tests were reproducible and sensitive enough to detect 80 ng/ml of anti-squalene antibody. The test was also reproducible from experiment to experiment. (Matyas et al., 2001).

The third study from this research effort, published in 2004, adapts the test described above so that it could detect anti-squalene antibodies if present in human serum. Serum from three groups of people were tested: retired employees of the US Army Medical Research Institute of Infectious Diseases (average 68 years of age, 88% of whom received anthrax vaccine, mean = 26 doses per person) , civilian volunteers of similar age from Frederick, Maryland (none of whom received anthrax vaccine), and random blood donors from Fort Knox, Kentucky (vaccination status unknown), This next study indicates that anti-squalene antibodies are found in 7.5% of the vaccinated USAMRIID alumni, 15% of the unvaccinated Frederick civilians, and in 0% of the Fort Knox blood donors. The antibodies described in the previous sentence were a type of antibody called IgG. Researchers found another type of anti-squalene antibody called IgM in all three groups (37%, 32%, 19%). The researchers found that anti-squalene antibodies are more common with increasing age (a characteristic also found in mice). The presence of anti-squalene antibodies was unrelated to anthrax vaccination status. They concluded that antisqualene antibodies occur naturally in human, (Matyas et al., 2004).

19. What did the U.S. Senate say about squalene?

In its investigations of illnesses among Gulf War veterans, the Senate Special Investigations Unit (SIU) found no credible information indicating that vaccines used during the Gulf War contained squalene (1998, page 123). In its report, the SIU stated that according to the Food and Drug Administration (FDA), squalene can be contained in a vaccine due to two different processes: 1) as an adjuvant, which is an agent to enhance the immune response; or 2) in minute quantities in certain vaccines manufactured using eggs, since eggs are rich in squalene and cholesterol. The FDA

verified that none of the vaccines used during the Gulf War contained squalene as an adjuvant.

20. Has DoD ever tested squalene-adjuvanted vaccines against malaria or HIV?

Yes. The DoD conducted several human clinical trials using investigational vaccines containing squalene (investigational vaccines for the prevention of malaria and HIV infection) in FDA-approved vaccine studies. The Department of Defense (DoD) has never exposed any military member or civilian to any squalene-adjuvanted investigational product without the person's informed consent, abiding by FDA regulations.

21. Bottom line, is there any reason for alarm here?

No. Squalene is not added to any US-licensed vaccine, including anthrax vaccine. The background level of squalene found by the FDA is less than the concentration normally present in human blood. The FDA confirms that these trace levels are "naturally occurring and safe." Improved tests found no squalene in the lots where FDA found it.

Nonetheless, DoD continues its pursuit of additional knowledge about squalene and anti-squalene antibodies.

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Joint Program Executive Office for Chemical-Biological Defense

1. What mechanism exists to ensure supply of the anthrax vaccine for a complete series of shots for all personnel?

The Joint Program Executive Officer for Chemical and Biological Defense (JPEO-CBD) - http://www.jpeocbd.osd.mil/ , through the Joint Vaccine Acquisition Program (JVAP), Chemical and Biological Medical Systems (CBMS), Frederick, Maryland, is responsible to the Secretary of Defense for maintaining an adequate stockpile of biological warfare defensive vaccines and defined production capabilities, as determined by the Joint Staff and Services' demands. The JPEO-CBD has developed an anthrax vaccine production model to use as a tool to balance the total annual requirement for production with vaccination and inventory requirements to support total force vaccination.

BioPort received FDA approval for the newly renovated manufacturing suite and its contract filler, Hollister-Stier LLC in January 2002 and production of licensed Anthrax Vaccine Adsorbed, BioThrax™, continues today. To be used by DoD, each vial of anthrax vaccine must meet all FDA requirements. Additionally, a stockpile exists that could be used in an emergency situation. This stockpile has undergone supplemental testing under the oversight of an independent quality-assurance organization.

2. What is the mission of the Anthrax Vaccine Adsorbed Production Program, Joint Program Executive Office for Chemical-Biological Defense (JPEO-CBD)?

The mission of the Anthrax Vaccine Adsorbed Production Program (AVAPP) is to provide an assured supply of Food and Drug Administration (FDA) licensed Anthrax Vaccine Adsorbed (AVA), BioThrax™, to meet the requirements of the Department of Defense's Anthrax Vaccine Immunization Program (AVIP). The AVAPP provides technical, managerial, financial, scientific, regulatory, program management, and quality oversight of the production of AVA and serves as a liaison between the AVIP and the manufacturer, BioPort Corporation. This mission is accomplished by both an on-site presence at the manufacturing site and a program management office.

3. Is the AVAPP part of the Joint Vaccine Acquisition Program (JVAP)?

Yes, the AVAPP is part of the JVAP, a component of the Chemical and Biological Medical Systems management office, Frederick, Maryland. The JVAP manages the production of licensed vaccines and the advanced development, testing and licensing of vaccines and therapeutic blood products against other biological warfare agents

A "next-generation" anthrax vaccine, a new smallpox vaccine, and vaccinia immune globulin is one of several products in development by the JVAP. For more information on the JVAP, please click here - http://www.jpeocbd.osd.mil/

4. Is biological agent detection a part of the JPEO-CBD mission?

Yes. Please see the JPO-BD website for more information -http://www.jpeocbd.osd.mil/.

Myths and Facts About Anthrax Vaccine

- MYTH: Anthrax vaccine is dangerous.
  FACT: Anthrax vaccine is as safe as any other vaccine. Like other vaccines, deaths have been reported rarely after anthrax vaccination. Each of these cases is carefully reviewed by Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), and DoD, to make vaccinations as safe as possible. An independent panel of civilian physicians reviews complex cases. These groups all agree that anthrax vaccine is not associated with any unexpected patterns of adverse events. The National Academy of Sciences' Institute of Medicine reported in March 2002, "There is no evidence that life-threatening or permanently disabling immediate-onset adverse events occur at higher rates in individuals who have received AVA [U.S. anthrax vaccine] than in the general population." In rare cases, patients experience serious adverse effects; these are treated and followed appropriately.

- MYTH: Anthrax vaccine causes terrible side effects.
  FACT: Based on over 30 years of anthrax vaccine use, we know that severe, albeit transient, injection site reactions do occur. It is known that from 30 to 60 percent of people who receive anthrax vaccine will develop an injection site reaction (less than one inch). About 1 in 100 develops a reaction five inches in diameter or larger. The rate of side effects away from the injection site is about the same as other vaccines: from 5 to 35 percent, with these events going away within a few days. The National Academy of Sciences' Institute of Medicine reported in March 2002, "Local events, especially redness, swelling, or nodules at the injection site, are associated with receipt of AVA [U.S. anthrax vaccine], are similar to the events observed following receipt of other vaccines currently in use by adults, and are fairly common" and "There is no evidence that life-threatening or permanently disabling immediate-onset adverse events occur at higher rates in individuals who have received AVA than in the general population."

- MYTH: Women have long-term side effects from anthrax vaccine more than men.
  FACT: Women experience more small injection site reactions than men. For skin reactions smaller than one inch in diameter, the likelihood is 60 percent for women and 30 percent for men. For side effects away from the injection site, the rates for men and women are about the same.

- MYTH: Antibiotics are more effective than anthrax vaccine.
  FACT: There is no better round-the-clock protection against anthrax infection than the anthrax vaccine. Antibiotics are effective when started immediately or very soon after exposure. However, not all exposures can be predicted in advance or even determined in very early stages, particularly in certain military situations. In such situations, the consequences for military personnel and their mission could be dire. This is not a risk DoD can afford to take. DoD will therefore vaccinate ahead of time for the best protection.

- MYTH: Anthrax vaccine only protects against cutaneous anthrax.
  FACT: While no vaccine is 100% effective, this vaccine will greatly reduce the risk of contracting anthrax regardless of route of exposure. Based on human and animal data, the National Academy of Sciences' Institute of Medicine concluded in March 2002 that anthrax vaccine is "an effective vaccine for the protection of humans against anthrax, including inhalational anthrax, caused by all known or plausible engineered strains of Bacillus anthracis." FDA agrees.

- MYTH: Anthrax vaccine won't protect against all strains of anthrax.
  FACT: Every disease-causing strain of Bacillus anthracis produces the same protein, a protein that is required to cause disease. The vaccine induces the production of antibodies that neutralize that protein. The National Academy of Sciences' Institute of Medicine concluded in March 2002 that "it is unlikely that either naturally-occurring or anthrax strains with bioengineered protective antigen could both evade AVA [the U.S. anthrax vaccine] and cause the toxicity associated with anthrax."

- MYTH: Some lots of anthrax vaccine cause more problems than other lots.
  FACT: Based on self-administered surveys and spontaneous reports, lot-to-lot comparisons in the various human safety studies performed to date found no meaningful differences based on lot. No vial of anthrax vaccine was distributed by the manufacturer without lot-specific manufacturing and testing data, explicitly reviewed and approved by the Food and Drug Administration (FDA). The Department of Defense uses only vaccine lots that the FDA released as meeting all applicable standards.

- MYTH: The anthrax vaccine is based on old technology.
  FACT: Anthrax vaccine was invented using mid-century technology that also led to highly successful vaccines against tetanus, diphtheria, and other infectious diseases. Today's manufacturing of anthrax vaccine by BioPort meets all current Food and Drug Administration standards of production.

- MYTH: The Department of Defense added squalene, an oil naturally produced in the human body and by bacteria, to the vaccine in 1990-91 to stretch the supply.
  FACT: No one added squalene to anthrax vaccine. Food and Drug Administration (FDA) scientists found trace quantities of squalene in anthrax, diphtheria, and tetanus vaccines (less than the natural level of squalene in the human bloodstream). The FDA notes that these minute quantities could have come from the bacteria involved or from processing during FDA tests (squalene is present in the oil in fingerprints). The FDA called the squalene in vaccines "naturally occurring and safe."

- MYTH: The Food and Drug Administration revoked the license of BioPort, the Department of Defense's vaccine supplier, because of manufacturing problems.

FACT: BioPort's predecessor, the Michigan Biological Products Institute (MBPI), owned by the State of Michigan, approved renovations in 1995 for the Lansing facility. In 1997, the Food and Drug Administration (FDA) issued a notice of intent to revoke licenses issued to MBPI. MBPI responded within 30 days with a strategic plan for compliance to FDA standards. The manufacturer voluntarily closed the anthrax vaccine production line in January 1998 for renovation. BioPort submitted a highly detailed set of quality control documents to FDA in fall 2001. FDA approved BioPort's facilities and processes, as they relate to the manufacture of anthrax vaccine, on January 31, 2002.

- MYTH: The Centers for Disease Control and Prevention use of anthrax vaccine to Congressional staff and U.S. Postal Service workers was "experimental" and "investigational," requiring informed consent, so the Department of Defense's use of anthrax vaccine requires consent from servicemembers as well.
  FACT: The Department of Defense's use of anthrax vaccine in the Anthrax Vaccine Immunization Program for pre-exposure prevention using six doses over eighteen months is consistent with the Food and Drug Administration-licensed use of the vaccine. The Centers for Disease Control and Prevention offer of anthrax vaccine for Congressional and U.S. Postal Service workers used anthrax vaccine for "post-exposure prophylaxis" in three doses. This is not a Food and Drug Administration-licensed use of the vaccine, therefore, in that case (post-exposure), the vaccine was administered under an "investigational new drug" protocol, with informed consent.

- MYTH: The anthrax vaccine can cause miscarriages.
  FACT: There is no study to support this claim. Consistent with the national standard and the Centers for Disease Control and Prevention recommendation, the Department of Defense policy does not vaccinate pregnant woman. Women who receive the vaccine get pregnant and deliver children at the same rates as unvaccinated women. A preliminary report (not yet published, not reviewed by peer scientists) suggested that women vaccinated during pregnancy might have an elevated rate of birth defects. However, medical scientists and study experts who have reviewed this preliminary information expressed concerns about the study's methods, and recommended further analysis. The Department of Defense is working with the Centers for Disease Control and Prevention to see if these preliminary data are accurate, or if they are not.