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Report to Congressional Requesters

September 2002

ANTHRAX VACCINE

GAO's Survey of Guard and Reserve Pilots and Aircrew

GAO-02-445

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Abbreviations

AVIP	Anthrax Vaccine Immunization Program
BW	biological warfare, biological weapon
CDC	Centers for Disease Control and Prevention
DOD	Department of Defense
FDA	Food and Drug Administration
NIH	National Institutes of Health
VAERS	Vaccine Adverse Events Reporting System

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United States General Accounting Office
Washington, DC 20548

September 20, 2002

The Honorable Dan Burton, Chairman
Committee on Government Reform
House of Representatives

The Honorable Benjamin A. Gilman, Chairman
Subcommittee on Middle East and South Asia
Committee on International Relations
House of Representatives

The Honorable Walter B. Jones
House of Representatives

As you requested, we address in this report the views of pilots and other aircrew members of the Air National Guard and Air Force Reserve regarding the Anthrax Vaccine Immunization Program (AVIP) of the Department of Defense (DOD). We received your requests before the terrorist events of September 11, 2001—the destruction of the World Trade Center towers in New York City and the attack on the Pentagon in Washington, D.C. These tragedies were followed in October 2001 by the mailing of anthrax-laced letters that killed five people in the United States. The perpetrator—individual, group, or other entity—responsible for sending the anthrax letters has not yet been identified.

Most of the information in this report was derived from the results and analyses of survey questionnaire responses received from selected pilots and other aircrew members of the Air National Guard and the Air Force Reserve before the events of September and October 2001. If the survey questionnaire on AVIP were administered today, views on some issues discussed in this report could be different, either negatively or positively. However, since most of the questions were, at the time, related to and report views on contemporaneous events (for example, information provided in 1999 and 2000 or information about adverse reactions experienced with inoculations given before 2000), we believe the results of the survey are still valid and useful as a measure of the AVIP program's performance. This information should be of interest to DOD and the Congress as they consider future anthrax vaccine programs.

In December 1997, the Secretary of Defense announced a plan to inoculate U.S. forces against the potential battlefield use of anthrax as a biological

warfare (BW) agent. The mandatory AVIP—using the only available vaccine produced by the BioPort Corporation—was officially launched in August 1998 as a high-priority commander's program. This means that unlike other mandatory vaccines routinely given to the military, AVIP received intense attention from high command levels and was subject to exceptional accountability requirements. It was intended to be compulsory for all 2.4 million DOD military service members—active duty and reserve component members, including certain designated civilian and contractor personnel. DOD still regards the biological agent anthrax, a disease that is usually lethal if inhaled in sufficient quantity, as the single greatest BW threat to U.S. military forces in the battlefield.

AVIP has been the subject of continuing controversy from its inception. Public debate has centered on the vaccine's safety and effectiveness, the extent and severity of adverse reactions experienced by vaccine recipients, and the adequacy and accuracy of the adverse reactions that have been reported. In addition, some Gulf War veterans are suffering from unexplained illnesses that they believe might have been caused by anthrax vaccinations received during the war. We have reported on many of these issues (see the list of related GAO products at the end of the report).

DOD temporarily restricted the mandatory anthrax program in 2000 to a very small group (special mission individuals and researchers) because of limited vaccine supply resulting from the closing of the vaccine manufacturing plant. In January 2001, the Food and Drug Administration (FDA) completed an approval and licensure process, allowing the manufacturing plant to resume production of the anthrax vaccine. In May 2002, DOD announced the resumption of the anthrax immunization program, limiting it to "at risk" troops. However, the identity of the troops receiving the vaccine will not be disclosed for security reasons. DOD also stated that substantial quantities of vaccine would be reserved for civilian uses in homeland security.

Congressional concern continues about the potential effect of this program on the retention of highly trained and experienced personnel in the Air National Guard and Air Force Reserve.

As you requested, we examined

1. the nature and magnitude of the anthrax battlefield threat over time,
2. AVIP's impact on the retention of experienced guard and reserve pilots and aircrew members,
3. the level of support for AVIP among guard and reserve pilots and aircrew members,
4. the level of satisfaction that guard and reserve pilots and aircrew members expressed regarding the information provided to them on AVIP and the anthrax vaccine, and
5. the number and severity of adverse events that vaccinated guard and reserve pilots and aircrew members experienced and reported.

Results in Brief

In the context of the conventional battlefield, the nature and magnitude of the military BW threat has not changed materially since 1990 in terms of the number of countries suspected of developing BW capability, the types of BW agents they possess, or their ability to weaponize and deliver BW agents.[1] This is particularly true regarding the ability to accumulate and deliver sufficient quantities of processed agent to cause mass casualties.

In marked contrast to other mandatory DOD immunization requirements, our sample survey in 2000 showed that AVIP was at that time adversely affecting the retention of trained and experienced guard and reserve pilots and aircrew members. While many factors can and do influence an individual's decision to participate in the military, a significant number of pilot and aircrew members cited the required mandatory anthrax immunization as a key reason for reducing their participation or leaving the military altogether in 2000.

Between September 1998 and September 2000, about 16 percent of the pilots and aircrew members of the guard and reserve had (1) transferred to another unit (primarily to nonflying positions to avoid or delay receiving the anthrax shots), (2) moved to inactive status, or (3) left the military. Additionally, an estimated one in five (18 percent) of those still

[1]U.S. General Accounting Office, *Medical Readiness: Safety and Efficacy of the Anthrax Vaccine*, GAO/T-NSIAD-99-148 (Washington, D.C.: Apr. 29, 1999).

participating in or assigned to a unit in 2000—that is, those who had not already changed their status—indicated their intention to leave in the near future. Both groups, those who had already left and those indicating their intention to leave, ranked AVIP as a key factor in their decision to leave or change their participation. We estimated that about 24 percent of those who had already left did so knowing they were doing so before qualifying for military retirement benefits. A majority of those who had changed status and those intending to do so were experienced pilots who held crew qualifications of flight evaluators, flight instructors, and aircraft commanders, representing the loss of a very seasoned workforce. Both those who had changed status and those intending to change status had accumulated an estimated individual average of more than 3,000 flight hours.

At the time of our survey, two-thirds of the guard and reserve pilots and aircrew members did not support DOD's mandatory AVIP or any future immunization programs planned for other BW agents. However, these negative views did not appear to indicate a general antivaccine bias. To the contrary, most had a positive view—in terms of both effectiveness and safety—toward immunization in general. From our survey, we estimate that 77 percent would not have taken the anthrax vaccine if it had been offered on a voluntary basis. Almost 9 of 10 reported that they would have safety concerns if an additional vaccine for other BW agents were added to the military's required immunization program. Additional analysis showed that officers were statistically more likely than enlisted personnel to report that they would not have taken the anthrax vaccine voluntarily.

Overall, there was general dissatisfaction with the completeness and accuracy of the information DOD provided about AVIP and the anthrax vaccine. We estimated from our survey that only about 4 of 10 guard and reserve pilots and aircrew members were satisfied with the information DOD provided on the military threat from anthrax. Considerably fewer were satisfied with the information DOD provided regarding the anthrax vaccine's effectiveness in battlefield exposures, the history and past usage of the vaccine, the vaccine's short-term safety and long-term safety, and possible side effects caused by reactions to the anthrax vaccine. We also found that officers were statistically more likely than enlisted personnel to question information given to them concerning specific issues such as the vaccine's battlefield effectiveness and its short-term and long-term safety.

On the basis of our survey, we estimated that 37 percent of the guard and reserve pilots and aircrew members had received one or more anthrax shots as of September 2000. Of these recipients, 85 percent reported

experiencing some type of reaction (local or systemic or both).[2] This overall rate reported for adverse reactions following anthrax immunization was more than double the rate published in the vaccine manufacturer's product insert that was in use at the time of our survey (84 percent versus approximately 30 percent). Each shot generated an average of four or more reported reactions. More importantly, almost one-fifth of the reported events were categorized as systemic and about one-fifth of these systemic reactions lasted for more than 7 days. Some of these reactions could have negative implications for an individual's work performance and job safety. The systemic reaction rate reported through the survey represents a level more than a hundred times higher than the 0.2 percent published in the product insert. We were unable to determine why the AVIP reaction rates so exceeded the product insert rates for the vaccine as approved in 1970. However, we found two studies conducted by DOD that looked at the short-term safety of the vaccine—one in Korea and one in Hawaii. Both reported reaction rates similar to those reported in our survey and disclosed a markedly higher rate of reaction for female shot recipients.[3] Since we first reported these results from our survey in September 2000, the manufacturer's product insert has been revised to include the adverse reaction rates reported in post licensure survey studies.[4]

Respondents to our survey indicated that they had not reported most of the reactions they cited to the military chain of command through official or informal channels (such as supervisors) and that they were not reported to FDA's Vaccine Adverse Events Reporting System (VAERS).[5] Reasons survey respondents gave for not reporting to the military chain of command included a lack of awareness of VAERS, a concern about the

[2]A local reaction affects only the general area around the point of injection and may be experienced as redness, itching, or the like. A systemic reaction is more serious because it affects bodily systems after absorption or ingestion and may be experienced as chills, fever, nausea, dizziness, and so on.

[3]The first DOD study of anthrax vaccine reactions was conducted in Korea. A physician collected data for this study in 1997. The second study, in Hawaii, was called the Tripler Army Medical Center Anthrax Survey (Tripler survey). Both reported reaction rates considerably higher than the vaccine product insert rates.

[4]See appendix IV for the revised product insert.

[5]VAERS is a passive surveillance system to alert FDA and the Centers for Disease Control and Prevention (CDC) of adverse events that may be associated with licensed vaccines. Health care providers, patients, or families, who are encouraged to report any adverse events after a person receives a vaccine, report information voluntarily to VAERS.

loss of flight status, a possibly adverse effect on a military or civilian career, and a fear of ridicule.

This report contains recommendations for DOD to direct the establishment of an active surveillance program to identify and monitor adverse events associated with each anthrax vaccine immunization. This program should ensure that appropriate and complete treatment and follow-up is provided to those who have experienced adverse events and to those who may experience them in the future.

Background

Anthrax is an acute infectious disease caused by the spore-forming bacterium *Bacillus anthracis*. It can infect humans; however, it occurs most commonly in warm-blooded animals (herbivores) in the agricultural regions of countries with less standardized and less effective public health programs. Human anthrax occurs only rarely in the United States from natural causes. However, the anthrax attacks in October 2001 through contaminated mail resulted in the death of five persons.

Human infection normally results from an occupational exposure to infected animals or animal products. For example, workers may be exposed to dead animals or to products such as wool, hides, leather, or hair products (especially goat hair). There have been no reports, even now, of the disease spreading from person to person; thus, anthrax is most likely not spread in humans directly.

Anthrax infection can occur in three forms: (1) cutaneous, usually through a cut or an abrasion; (2) gastrointestinal, by ingesting contaminated meat; and (3) inhalation, by breathing anthrax spores into the lungs. Symptoms depend on how the disease is contracted but usually appear within 7 days. The disease can be treated with antibiotics: tetracycline and doxycycline are preferred, but penicillin, erythromycin, chloramphenicol, or ciprofloxacin can also be used. To be effective, treatment should be started early. The symptoms and forms of the disease are presented in table 1.

Table 1: Types of Anthrax Disease, Methods of Contraction, Symptoms, and Outcomes

Disease form	How contracted	Symptoms	Outcome
Cutaneous	By bacteria entering skin cut or abrasion	Begins as a raised itchy bump resembling an insect bite; develops in 1–2 days into a vesicle with black center and then a painless ulcer	Death is rare with appropriate treatment; untreated death rate is about 20%
Gastrointestinal	By consuming contaminated meat	Acute inflammation of the intestinal tract	Death in 20%–60% of cases
Inhalation	By inhaling anthrax spores while handling contaminated animal products; anthrax spores can be sprayed into atmosphere in biological warfare	First resembles a common cold or flu; after several days, acute symptoms develop, such as severe breathing problems and shock	Death 1–2 days after onset of acute symptoms

Source: Arnot Ogden Medical Center, www.aomc.org.

The Secretary of the Army is the executive agent for managing AVIP. The dosing regimen or protocol for the anthrax vaccine calls for a series of six shots over 18 months. An initial series of three shots is given at 2-week intervals, followed by a series of three shots at 6-month intervals. Annual boosters are required thereafter. As of early 2001, more than 520,000 service members had received at least one dose of the vaccine. However, since late 2000, DOD has had to significantly reduce the inoculation rate because of a dwindling supply of vaccine from the sole source manufacturer.

The original anthrax vaccine in the United States was developed by George Wright and others in the 1950s and was first produced on a large scale by the pharmaceutical manufacturer Merck Sharp & Dohme.[6] A clinical study in 1962 evaluated the safety and effectiveness of the Merck vaccine in mill workers.[7] This study formed the basis for subsequent licensure of a modified vaccine in 1970. The Division of Biologics of the National Institutes of Health (NIH) issued the original license for anthrax vaccine to the Michigan Department of Public Health.[8] In 1995, the facility changed its name to the Michigan Biologic Products Institute. In 1998, the facility was sold, and its name was changed to BioPort Corporation.

[6]Merck Sharp & Dhome is a subsidiary of Merck & Co., Inc.

[7]Anthrax infection has most commonly occurred in settings like wool mills, where workers may be exposed to infected animal products.

[8]Before FDA was established as the licensing authority for vaccines, NIH performed that function.

Over time, FDA has cited the facility for repeated deviations from applicable manufacturing standards for the vaccine. The facility received warning letters from FDA, including one in March 1997 stating its intent to revoke the facility's license. The facility closed its plant for renovations in 1998 and since then has supported all AVIP requirements with vaccine produced and stockpiled (some from the early to the middle 1990s) before the plant closed. DOD had to restrict the mandatory anthrax program because of the shortage of anthrax vaccine. BioPort has now received FDA's approval to resume production.[9]

Scope and Methodology

To achieve our objectives, we developed, pretested, and validated a questionnaire that we sent to a stratified random probability sample of 1,253 people from DOD's list of Air National Guard and Air Force Reserve personnel. These included pilots, flight engineers, loadmasters, navigators, crew chiefs, and others. Collectively, these individuals represented about 13,000 service members of the total fiscal year 1999 end strength of approximately 176,000, which included about 29,000 officers and 147,000 enlisted personnel. We selected a random sample in four strata, defined by whether a person was currently active or had changed military status as of March 1, 1998, and had been vaccinated or not as of February 2000.

The overall response rate from the sample of 1,253 was 67 percent. Each response was subsequently weighted in the analysis to account statistically for all the members of the population, including those who were not selected. Because our results are based on a sample and different samples could provide different estimates, we express our confidence in the precision of our particular sample's results as a 95 percent confidence interval (for example, plus or minus 5 percentage points). We are 95 percent confident that each of the confidence intervals in this report includes the true values in the study population. Unless we note otherwise, all percentage estimates from the survey have a 95 percent confidence interval of plus or minus 5 percentage points.

The overall survey results can be generalized to all guard and reserve pilots and aircrew personnel. A more complete description of the scope and methodology is in appendix I. We conducted our work between

[9]FDA has revised the adverse reactions section in the product insert to reflect a higher incidence of local and systemic reactions.

May 2000 and July 2002 in accordance with generally accepted government auditing standards.

The Anthrax Threat Has Been Limited and Stable Since 1990

DOD considers inhalation anthrax in an aerosolized form to be the greatest mass destruction BW threat to U.S. military forces, and it bases the scope of AVIP on this threat. According to DOD, this assessment is based on several factors, including (1) the judgment that a few nations, hostile to the United States, consider anthrax to be a potential weapon on the battlefield, and (2) the lethality and relative ease of production and battlefield use.

According to DOD and other, unclassified sources, we found that in terms of conventional battlefield use, the nature and magnitude of the anthrax threat has been stable since 1990 and has not changed materially in terms of the number of countries suspected of developing a BW capability, the types of biological agents they possess, or their ability to weaponize and deliver such agents. We have previously reported that the use of most biological agents would require a relatively high degree of sophistication, in terms of both expertise and equipment, to successfully cause mass casualties.[10] Specialized knowledge would be needed to acquire the right biological agent, process it, improvise a weapon or device, and effectively disseminate it to cause mass casualties. However, as clearly demonstrated in October 2001, the mailing of just a few letters contaminated with refined anthrax spores can cause death and severely disrupt business and government operations.

How the Anthrax Program Affected Aircrew Members' Decisions to Change Military Status

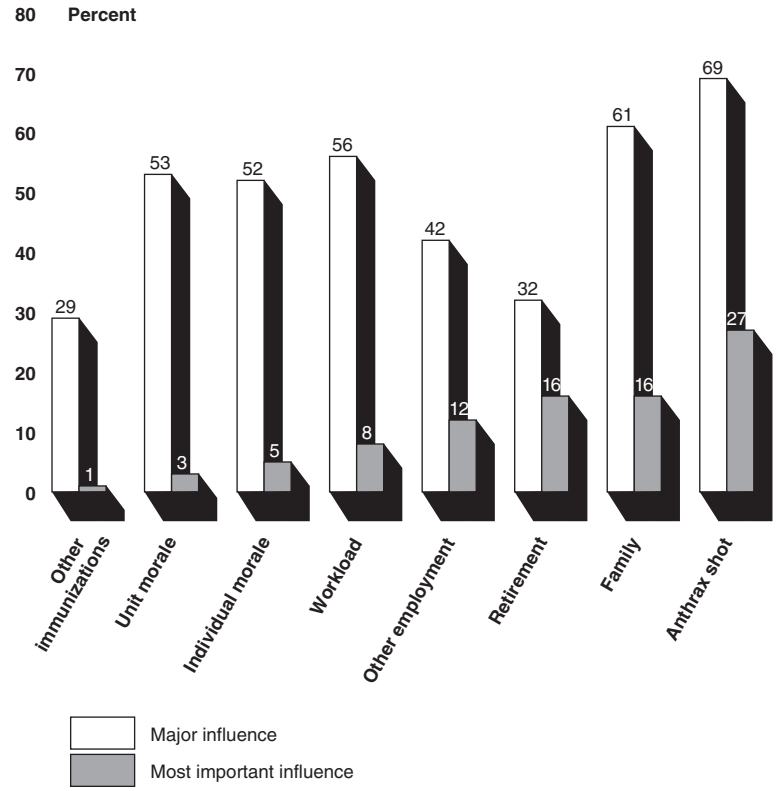
The anthrax program adversely affected the retention of trained and experienced pilots and aircrew members in the guard and reserve. While many factors can and do influence an individual's decision to participate in the military, pilots and other aircrew respondents cited the required anthrax immunization as a key reason for (1) leaving the military altogether, (2) reducing their involvement or participation in the military, and (3) otherwise changing their military status. According to our survey, between September 1998 and September 2000, when AVIP was mandatory, about 16 percent of the guard and reserve pilots and aircrew members had transferred to another unit (primarily to nonflying positions), moved to inactive status, or left the military altogether. In addition, 18 percent of

[10] GAO/T-NSIAD-99-148.

those still participating in units indicated their intention to transfer, move, or leave in the near future. About one-fifth of those who had already left did so knowingly before qualifying for military retirement.

As shown in figure 1, we estimate that more than two-thirds, or 69 percent, of those who changed their status reported that the anthrax shot was the major influence behind their decision to do so—more even than those reporting family reasons as an important factor. Of those who changed their status, 27 percent reported that anthrax immunization was the most important factor influencing their decision to leave or transfer. In addition, the general military immunization program was not an important factor in their decision to change status.

Figure 1: Factors Influencing the Decisions of Pilots and Aircrew to Change Status



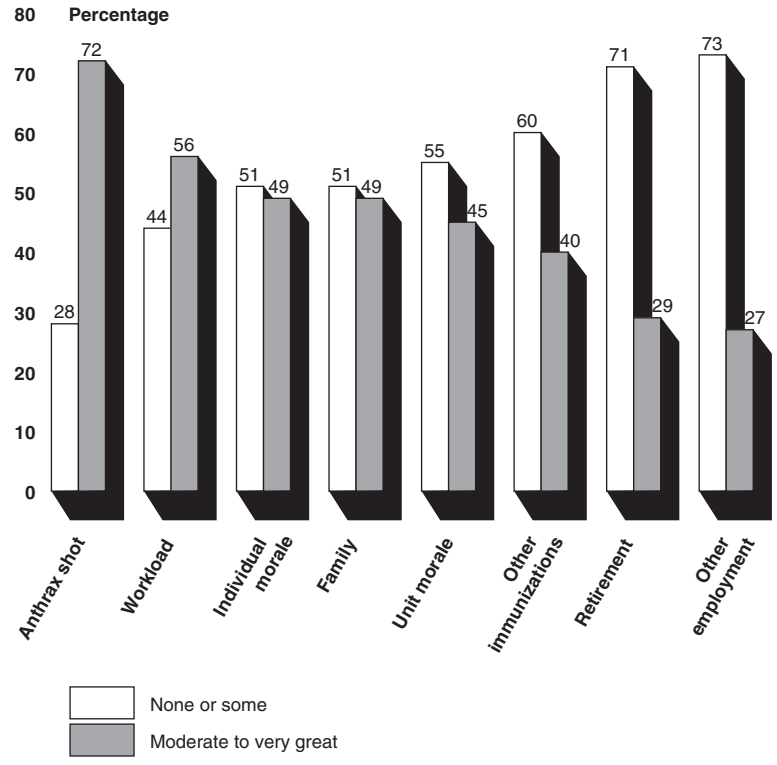
Source: GAO 2000 survey.

Further, according to our survey, an estimated 44 percent of those who had already changed their military status or who were no longer in military

flying status because of AVIP indicated that they probably would consider returning to a unit or to military flying status if AVIP were not mandatory.

Our survey results also indicated that an estimated 18 percent of those who were still participating in guard and reserve units reported that they planned to leave the military or change their military status within 6 months. As shown in figure 2, when asked to indicate the most important factors for their planned decision to leave, an estimated 72 percent reported that anthrax immunizations influenced their decision from a moderate extent to a very great extent, followed by heavy unit workload, individual morale, and family reasons.

Figure 2: Factors Influencing the Decisions of Pilots and Aircrew to Change Status in the Near Future



Source: GAO 2000 survey.

Our survey indicated that the majority of guard and reserve pilots who had already changed their military status or who were intending to do so in the near future were experienced pilots. These were individuals who held

crew qualifications of flight evaluator, flight instructor, or aircraft commander and had each accumulated an average of more than 3,000 flying hours, thus representing a trained and experienced workforce.

Table 2 reflects the composition of the pilots and aircrew members who had already changed status and those indicating plans to do so in the near future. For the same categories—those who had changed status and those indicating plans to do so—table 3 reflects the percentages of pilots with the qualifications of flight evaluator, flight instructor, and aircraft commander that require higher qualifications than the positions of pilot or copilot.

Table 2: Aircrew Who Had Changed Status and Reported Plans to Change Status in the Near Future

Status	Pilot	Nonpilot
Changed: past loss	51%	49%
Intending to change: future loss	69	31

Source: GAO 2000 survey.

Table 3: Pilots Who Had Changed Status and Reported Plans to Change Status in the Near Future

	Role	
Status	Evaluator, instructor, commander	Pilot or copilot
Changed: past loss	87%	13%
Intending to change: future loss	95	5

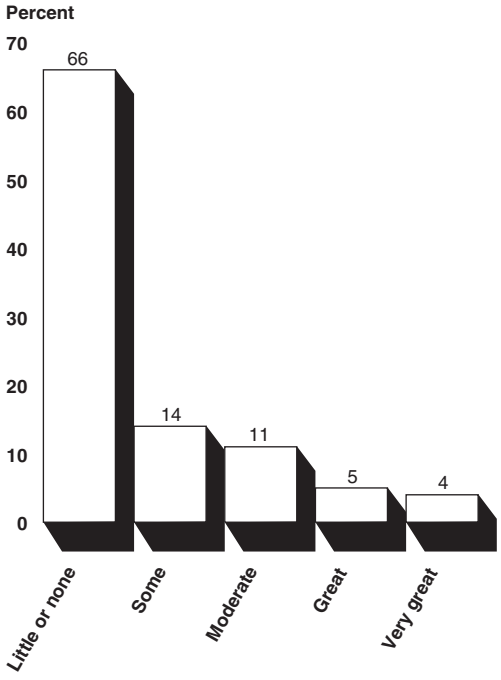
Source: GAO 2000 survey.

Table 2 shows that more than half of the experienced losses, as well as the potential future losses, of aircrew members in the guard and reserve were pilots. Table 3 discloses that the majority of the pilots served or serve in the more experienced positions of flight evaluator, flight instructor, and aircraft commander. In summary, in both groups—those who had left and those intending to leave—most of the pilot losses represented a very seasoned and experienced workforce.

The Anthrax Vaccine Program Was Not Widely Supported

Most survey respondents reported fairly negative views concerning AVIP and any additional biological vaccines DOD planned in the future as well. A substantial majority of all respondents—66 percent—reported supporting AVIP to little or no extent, as shown in figure 3. About 9 percent supported the program to a great or very great extent.

Figure 3: Extent of Support for AVIP Reported by Pilots and Aircrew

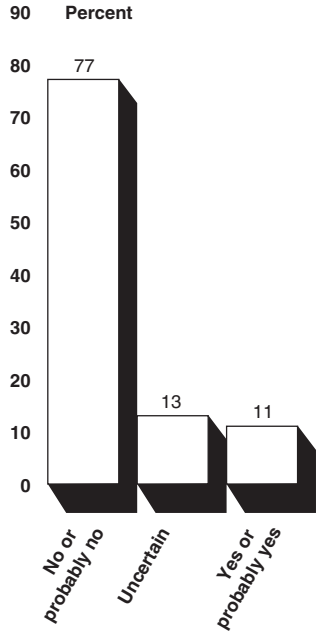


Source: GAO 2000 survey.

We performed additional analyses to determine whether there were statistically significant differences in responses about the extent of AVIP support between Air Force Reserve and Air National Guard members, personnel who had changed their military status and those who had not, and nonrecipients of the vaccination shot versus vaccinated personnel. We found that Air Force Reserve personnel were considerably more likely than Air National Guard personnel to report limited or no support for AVIP. Further, people who had already changed military status were a little more than twice as likely as those who had not changed status to indicate limited support for AVIP. The same ratio held true for a nonshot recipient when compared with an anthrax shot recipient.

Overall, a large majority of the respondents—77 percent—indicated that they would not or probably would not have taken the anthrax vaccine shots if AVIP were a voluntary program. Just 11 percent of the respondents reported that they would have taken or probably would have taken the shot on a voluntary basis; about 13 percent were uncertain. These data are reflected in figure 4.

Figure 4: Aircrew Views on the Likelihood of Their Voluntarily Taking Anthrax Vaccine



Source: GAO 2000 survey.

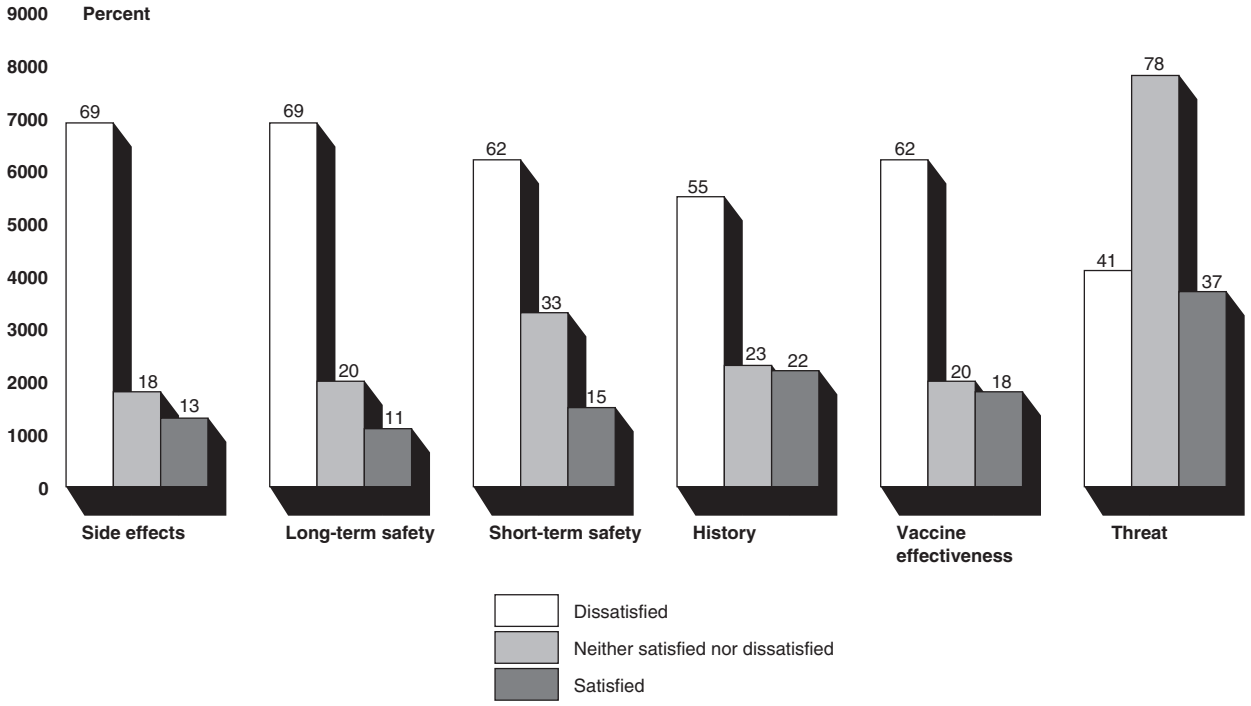
We also found that officers (compared with enlisted personnel), members of the reserve (compared with the guard), those who had changed their military status (compared with those who had not), and nonrecipients of the vaccine (compared with recipients) were statistically more likely to indicate that they probably would not have taken the anthrax shot voluntarily. For example, officers were more than twice as likely as enlisted personnel to indicate they would not or probably would not have taken the anthrax vaccine voluntarily. Similarly, reserve personnel were almost twice as likely as guard personnel to answer "no" or "probably no" to taking the anthrax vaccine voluntarily.

In addition, an estimated 86 percent, or almost 9 of 10, "would have had concerns" or "probably would have had concerns" about safety if additional vaccines for other BW agents were added to military immunization requirements in the future. About three-fourths of guard and reserve personnel reported they had immediate family and co-workers who agreed with their views on the military's AVIP.

Respondents Did Not Deem AVIP Information That DOD Provided Credible

Overall, our survey disclosed a general dissatisfaction with the respondents' perception of the completeness and accuracy of information DOD provided to the guard and reserve about AVIP before 2000. This dissatisfaction appeared to be especially high concerning such key factors as the military threat from anthrax, the anthrax vaccine's battlefield effectiveness, the vaccine's history and past usage, the short-term and long-term safety risks of the vaccine, and the possible side effects from and reactions to the vaccine. Fewer were satisfied with the information provided on other factors, as shown in figure 5.

Figure 5: Aircrew Satisfaction with DOD's Information on Anthrax Issues



Source: GAO 2000 survey.

Our analysis also disclosed that reserve personnel were uniformly less satisfied with the information provided to them about AVIP than were guard personnel. Further, we found that officers were more likely than enlisted personnel to question the information on certain issues, such as the vaccine's battlefield effectiveness and its short-term and long-term safety.

Although DOD employed a high-visibility information campaign on AVIP and took various steps to address the controversy surrounding it, we reported in October 1999—about a year after the official start of AVIP—that service members were not satisfied with the information DOD had provided to them at the time.[11]

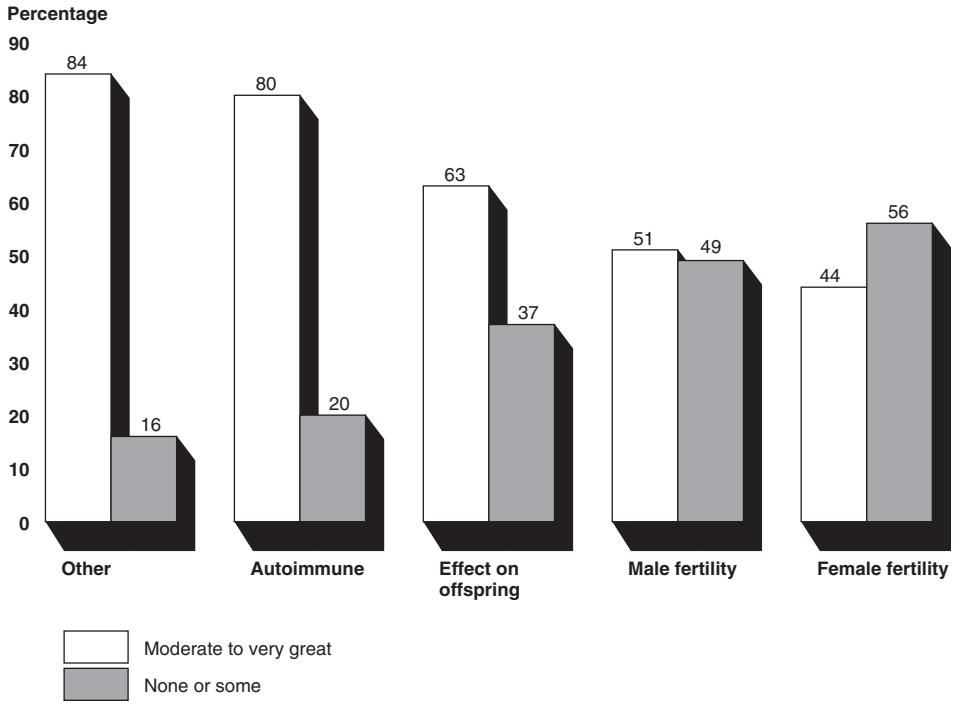
Subsequently, DOD expanded its communications efforts by updating the program's Internet web site, opening a toll-free anthrax information telephone line, and forming a speaker's bureau of anthrax experts. In addition, DOD updated briefings for installation leaders and medical personnel to provide more detailed information on the anthrax threat and vaccine.

Despite DOD's efforts, we found that relatively few survey respondents had visited DOD's Web site at the time of our survey, and few respondents reported being satisfied with the information posted. For example, of those who visited the Web site, 20 percent were moderately to very satisfied with the completeness of the information, 19 percent were moderately to very satisfied with the information's accuracy, and 27 percent were moderately to very satisfied with its timeliness. Just 12 percent were moderately to very satisfied that the information was unbiased.

Concerns were also expressed about the anthrax vaccine and its possible effects on certain health issues such as fertility and the risk of increased autoimmune disease. These issues and respondents' concerns are summarized in figure 6.

[11]U.S. General Accounting Office, *Medical Readiness: DOD Faces Challenges in Implementing Its Anthrax Vaccine Immunization Program*, GAO/NSIAD-00-36 (Washington, D.C.: Oct. 22, 1999).

Figure 6: Personnel with Moderate to Very Great Concern about the Anthrax Vaccine and Health Issues



Note: Percentages are estimates, based on GAO's 2000 survey.

Although the survey disclosed that the respondents' basic views regarding AVIP and the anthrax vaccine were quite negative, the survey did not indicate a general antivaccine bias. On the contrary, most respondents expressed a positive attitude toward immunization in general in terms of both effectiveness and safety. Overall, 73 percent, or close to three-fourths, believed that immunization is effective, and 59 percent, or about three-fifths, believed it to be safe.

Respondents Reported More Adverse Events than Expected

According to our survey results, the reported rate and severity of adverse events experienced by personnel who had received the anthrax shots were considerably higher than those published in the vaccine manufacturer's product insert in use at the time of the survey or reported by DOD.[12] For example, an estimated 84 percent of the personnel who had had anthrax vaccine shots between September 1998 and September 2000 reported having side effects or reactions. This rate is more than double the level cited in the vaccine product insert. Further, about 24 percent of all events were classified as systemic—a level more than a hundred times higher than that estimated in the product insert. The reaction rates from our survey were also consistent with the results of two earlier DOD studies of the anthrax vaccine. In addition, we found that most events were not being reported to either official or informal DOD channels, partly because most individuals were unaware of the reporting process for documenting any such occurrences.

According to the anthrax vaccine product insert in use at the time of our survey, a number of reactions can be expected from the anthrax vaccine. Table 4 summarizes the type and severity of adverse events reported in the product insert.

Table 4: Adverse Reactions Described in the Anthrax Vaccine Product Insert

Type	Percentage occurrence	Description	Additional Information
Mild local	30	Consists of small erythema, 1–2 cm in diameter; occurs within 24 hours and begins to subside by 48 hours	Erythema may increase to 3–5 cm; severity tends to increase by 5th injection
Moderate local	4	Inflamed reactions greater than 5 cm in diameter; nodules may occur at injection site and may persist for several weeks in a few persons	More severe reactions are less frequent and consist of extensive edema of forearm
Systemic	0.2	Characterized by malaise and lassitude; chills and fever have been reported in only a few cases	Immunization should be discontinued in such instances

Source: Anthrax Vaccine Product Insert, 1999.

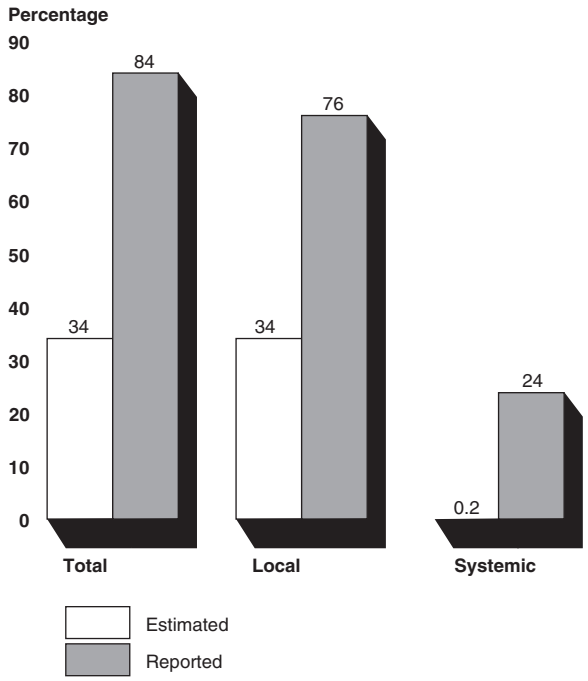
As reflected in the table, at the time of our survey 34.2 percent of all anthrax vaccine recipients were estimated to report experiencing a

[12]While the accuracy of memory may degrade over time, in this case this effect was minimized because of the highly publicized nature of the program, and our survey was administered while respondents were still receiving the shots.

reaction—generally fairly mild and short lived. The vast majority, or 30 percent, of such reactions should consist of an area of redness 1 to 2 centimeters in diameter at the injection site. Moderate local reactions, consisting of increased redness and the possible appearance of persistent nodules, were expected in about 4 percent of shot recipients. A rate of only 0.2 percent for systemic reactions was anticipated. According to the insert, immunization should be discontinued when systemic reactions occur. The duration of most reactions, other than the development of a nodule, was expected to be short and to dissipate in a few days.

According to our survey, 37 percent of guard and reserve personnel received one or more anthrax vaccine shots. Of these, 84 percent reported side effects or adverse events—a rate more than double that expected or cited in the product insert. On the basis of our survey, each anthrax shot generated more than four reported events, and each respondent had received close to four shots of anthrax vaccine. Thus, the average respondent had reported experiencing about 17 reactions or events thought to be attributable to the vaccine. Figure 7 compares the estimated percentages of vaccine reactions in the product insert with the experience reported in our survey.

Figure 7: Estimated and Reported Vaccine Reactions and Events



Source: GAO 2000 survey.

We estimate that almost 44 percent of anthrax shot recipients reported experiencing minor local redness, about 24 percent experienced the enlarged redness associated with a moderate local reaction, and about 69 percent experienced the development of nodules. These data considerably exceed the levels in table 4. The rates, however, are similar and consistent with the Korea and Hawaii studies that DOD conducted after AVIP started. For example, the Hawaii study (the Tripler survey) disclosed a reaction rate for moderate to severe redness ranging from 18 percent to 32 percent for shots one through four. Our survey indicated rates ranging between 21 and 24 percent for the same shots. The Hawaii study also reported that between 64 percent and 66 percent of the vaccine recipients experienced a lump or knot—our survey disclosed a range of 64 to 68 percent for the same shots. Both the Hawaii and Korea studies found that women experienced a reaction rate substantially higher than men did—in some instances double or more. Our survey did not include a sufficient number of women to address this issue.

These two DOD studies found a higher incidence of systemic reactions than estimated in the product insert and also found that women experienced higher rates than men did. Our survey estimated that almost 24 percent of all the events experienced were systemic—a rate more than a hundred times that expected in the product insert in effect at the time of our survey. Almost 19 percent of all reported reactions in our guard and reserve survey exceeded 7 days. The rate for local reactions lasting longer than 7 days was 17 percent and slightly greater than 23 percent for systemic reactions. The rate of event or reaction per shot appeared to be fairly consistent, with some drop-off as the shot series progressed, as shown in table 5.

Table 5: Adverse Events Exceeding 7 Days by Anthrax Vaccination Shot

	Vaccination shot						
Event type	**1**	**2**	**3**	**4**	**5**	**6**	**Average**
Local	19.0%	17.1%	16.6%	14.3%	13.6%	30.0%	17.0%
Systemic	26.5	25.8	23.1	20.6	12.3	5.5	23.4
Total	**20.7%**	**19.1%**	**18.2%**	**15.9%**	**13.4%**	**26.7%**	**18.6%**

Source: GAO 2000 survey.

Some of these reactions could have implications for safety and effective work performance—for example, conditions such as arm pain with limited motion, extreme fatigue, joint pain, and memory loss lasting more than 7 days.

We found that most of the reactions were not reported to the military chain of command through official channels (military medical personnel), informal channels (supervisors), or FDA's VAERS. Since most individuals were not reporting their reactions to military medical personnel, their supervisors, or VAERS, the actual duration, extent, or impact on units and individuals and the ultimate resolution of reactions are unknown.

We estimated that about 67 percent of those who experienced side effects or reactions were unaware of VAERS. As a result, about 6 percent of those who experienced a reaction reported it to this system—altogether 18 individuals reported submitting VAERS reports on their own, and another 6 reported that the military submitted a report for them. Moreover, DOD had initially limited reporting anthrax vaccine events to VAERS to only reactions leading to either hospitalization or the loss of 48 hours or more of duty time. This restriction was subsequently removed. In addition, our survey estimated that about 57 percent of those who

experienced an adverse reaction did not discuss it with anyone in military health care or their individual supervisors. Some 49 percent cited concern about the loss of flight status, possible adverse effects on their military or civilian careers, and the fear of ridicule as reasons for not discussing vaccination shot reactions with others. Another 49 percent indicated that the reactions they experienced were not severe enough to seek medical help or to tell their supervisors about.

DOD continued to use data from VAERS to monitor adverse events or reactions to anthrax vaccination, even though it is a "passive" surveillance system that relies on vaccine recipients or their health care providers to report adverse events after vaccination. Studies show that significantly fewer adverse events are reported under such a system when compared to an active surveillance approach in which vaccine recipients are actively monitored to identify and track any adverse reactions to a vaccine or medication.[13] For example, we estimated that almost three-fourths of vaccinated guard and reserve personnel experienced burning in the vaccinated arm and a knot or lump in the vaccinated arm, compared with DOD's report that 0.007 percent had such reactions. In November 2001, DOD reported that after more than 2 million doses of anthrax vaccine had been administered to more than 522,000 people, only 1,685 VAERS reports were submitted for possible adverse events associated with the vaccine. In contrast, the approximately 380 shot recipients in our survey disclosed more than 6,000 reactions (almost 1,300 of which were systemic) from slightly more than 1,300 shots.

Conclusions

According to DOD, inhalation anthrax is the greatest BW threat to U.S. military forces. To counter this threat, DOD officially established the mandatory AVIP in August 1998 to inoculate all 2.4 million of DOD's service members, including active duty and reserve component personnel, along with some DOD civilian and contractor employees. This major undertaking involved scheduling and administering more than 14 million shots to satisfy the vaccine's initial dosage requirements of six shots per individual over an 18-month period, followed by an annual booster.

[13]S. Rosenthal and R. Chan, "The Reporting Sensitivities of Two Passive Surveillance Systems for Vaccine Adverse Events," *American Journal of Public Health* 85, no. 12 (1995): 1706-09; R. T. Chan and others, "The Vaccine Adverse Event Reporting System (VAERS)," *Vaccine* 12 (1994): 542–50; R. T. Chan, "Special Methodological Issues in Pharmacoepidemiology Studies of Vaccine Safety," in *Pharmacoepidemiology*, ed. B. L. Strom (New York: John Wiley & Sons, 1994).

Accordingly, DOD initiated a large, high-visibility campaign to communicate its views and to inform service members about the anthrax threat and the anthrax vaccine. Among other things, DOD established a Web site, opened a toll-free anthrax information telephone service, formed a speakers' bureau of experts, and provided briefings and other materials for installation leaders and medical personnel to use at unit and base or installation levels.

Our findings suggest that DOD's communications efforts were largely unsuccessful in convincing most guard and reserve pilots and aircrew members that the anthrax threat was as serious as alleged or to support AVIP as an appropriate response. Overall, there was a general and pervasive degree of dissatisfaction among guard and reserve pilots and aircrew members about the completeness and accuracy of most of the information DOD provided on the anthrax vaccine and AVIP. In addition to their response to military threat, surveyed pilots and aircrew members expressed significant dissatisfaction with such key factors as the battlefield effectiveness of the anthrax vaccine, its history and past usage, its short-term and long-term safety risks, and the possible side effects from the vaccine.

In addition, although DOD has maintained from AVIP's outset that the anthrax vaccine is very safe and causes minimally adverse effects, our survey disclosed that a significantly large number of vaccine recipients reported experiencing adverse events. Further, the results of two DOD studies on anthrax vaccine reactions—both of which used active monitoring systems, as opposed to a passive system such as VAERS, for gathering information on adverse events—are consistent with and support the results of our survey. The rates disclosed in the survey and the DOD studies are each significantly higher than those stated in the vaccine product insert until recently. Such marked variances from the product insert data suggest the possibility of change in the composition of the vaccine from the vaccine originally approved in 1970.

In summary, AVIP appears to have adversely affected the Air National Guard and Air Force Reserve in terms of retaining needed experienced personnel. Sixteen percent of our survey respondents either left the military or significantly reduced their level of participation, citing the anthrax immunization program as an important factor in their decision to do so. Interestingly, 45 percent of these individuals indicated that they would consider returning if AVIP were made voluntary. Further, at the time of our survey, 18 percent of those still participating indicated their intention to leave in the near future, again citing AVIP as an important

factor in that decision. Unfortunately, the actual losses and expected losses as a result of this program represented some of the most experienced and highly trained individuals in these services and are people not easily replaced. It takes time and a great deal of money and other resources to develop trained, experienced pilots and other aircrew members to support the important missions of these reserve components, particularly in light of the current battle against terrorism.

Recommendations

We recommend that the Secretary of Defense direct the establishment of an active surveillance program (unlike the passive VAERS) to identify and monitor adverse events associated with each anthrax vaccine immunization. This program should ensure that appropriate and complete treatment and follow-up are provided to those who have experienced adverse events and to those who may experience them in the future.

Agency Comments

In comments on a draft of this report (reprinted in app. V), DOD did not concur with our recommendation to establish a surveillance program. In support of its position, DOD cited the following statement from the Institute of Medicine's report: The Institute of Medicine "committee observes that no data that indicate the need for the continuation of special monitoring programs for anthrax vaccine have emerged, but it recognizes the real concerns for service members ordered to take the vaccines."[14] In addition, DOD stated that data from the Defense Manpower Data Center about actual pilot separations did not support the statements in the report in that the center's data show that pilot separations before the beginning of the anthrax program in 1998 were similar to the rates during the time of the survey. DOD further stated that our report did not address the normal or expected rates of turnover known to occur among personnel in the Air National Guard and the Air Force.

DOD's selective use of a conclusion from the Institute of Medicine report that "a separate AVA monitoring program is not necessary" is misleading. This response, while technically correct, ignores the comprehensive recommendations that the institute's report actually made to DOD. Specifically, the institute recommended that DOD (1) use VAERS data to generate hypotheses to study further, using DOD's new unified service

[14]Institute of Medicine, *The Anthrax Vaccine: Is It Safe? Does It Work?* (Washington, D.C.: 2002).

medical reporting system; (2) regularly study those data for new trends; (3) work with the Department of Veterans Affairs to encourage participation in the Millennium Cohort study to better get a handle on all the problems associated with the Gulf War and other actions; and (4) regularly do ad hoc unit-based population monitoring of reactions to all vaccines.[15] In addition, the Institute of Medicine report recommended that anthrax vaccine lots produced after renovations at the BioPort vaccine production facility should continue to be monitored for immunogicity and stability and that individuals receiving these lots should be monitored for possible acute or chronic events of immediate or later onset. Adoption of these recommendations would satisfy our recommendation.

More importantly, DOD did not address two major findings from our survey: (1) some of the adverse reactions that our respondents reported persisted for more than 7 days and (2) given that a large proportion of respondents were not reporting the symptoms to VAERS or their DOD health care practitioners, we do not know whether these reactions were resolved over time. Also, active monitoring would result in a more comprehensive database for conducting specific analysis to test whether the adverse reactions lasting for more than 48 hours are occurring among older recipients, as suggested by a study conducted in the United Kingdom.[16] In that study, older recipients of the anthrax vaccine experienced significant incapacity (inability to lift or drive), which according to the author, would be critical for some military populations, such as aviators. Further, several studies in the United States and the United Kingdom now show a relationship between anthrax vaccine and

[15]The Millennium Cohort Study is a survey sponsored by DOD. It will monitor a total of 140,000 U.S. military personnel during and after their military service for up to 21 years to evaluate the health risks of military deployment, military occupations, and general military service.

[16]M. J. World, "Anthrax Immunization in the Older Warrior," *North Atlantic Treaty Organization: RTO Meeting Proceedings 33, Operational Issues of Aging Crewmembers*, Oct. 11–14, 1999.

Gulf War syndrome.[17] We recommended an active monitoring system not for the sole purpose of identifying adverse reaction rates, since FDA has already recognized much higher local and systematic reaction rates and the recent product insert has been revised accordingly, but also to proactively monitor, identify, and treat individuals experiencing adverse reactions. Our recommendation should lead to better lines of communications in the chain of command and help overcome any fear or mistrust of communicating reactions or symptoms to those responsible for medical care. In addition, since the anthrax vaccine will be offered to civilian first responders or health care workers, civilian doctors would need information on adverse reactions that can be expected to follow.[18] DOD could be instrumental in providing information to civilian and medical doctors about how these symptoms are resolved over time and effective treatment approaches but only if an active monitoring program or the recommendations of the Institute of Medicine are fully implemented.

With regard to our survey's findings on pilot attrition, DOD had not provided data to support its statement that there was no difference between pilot separations before and during the mandatory AVIP program by the time this report was issued. However, DOD's response uses the term "separations" while our report uses the term "change of status," which is a much broader term. We reported on percentages of pilots who changed their status (for example, transferred to another unit, left the military in a "separation," or moved to inactive status) to avoid anthrax vaccine. In any event, although the overall separation rates may be the same before and after the onset of the mandatory anthrax vaccine program, it is clear that the losses among the most experienced pilots (in bases where AVIP was implemented) resulting from change of status were

[17]L. Steele, "Prevalence and Patterns of Gulf War Illness in Kansas Veterans: Association of Symptoms with Characteristics of Person, Place, and Time of Military Service," *American Journal of Epidemiology* 152 (2000): 992–1002; W. R. Schumm and others, "Self-Reported Changes in Subjective Health and Anthrax Vaccination as Reported by Over 900 Persian Gulf War Era Veterans," *Psychological Reports* 90 (2002): 639–53; P. B. Asa and others, "Antibodies to Squalene in Gulf War Syndrome," *Journal of Experimental and Molecular Pathology* 68 (2000): 55–64, and "Antibodies to Squalene in Recipients of Anthrax Vaccine," *Journal of Experimental and Molecular Pathology* 73 (2002): 19–27; N. Cherry and others, "Health and Exposures of United Kingdom Gulf War Veterans, Part II, The Relation of Health to Exposure," *Journal of Occupational and Environmental Medicine* 58 (2001): 299–306; C. Unwin and others, "Health of U.K. Servicemen Who Served in Persian Gulf War,"*Lancet* 353 (1999): 169–78.

[18]D. A. Geier and M. R. Geier, "Anthrax Vaccination and Joint Related Adverse Reactions in Light of Biological Warfare Scenarios," *Journal of Clinical Experimental Rheumatology* 20 (2002): 217–20.

significant at some bases, resulting in the loss of an extremely seasoned workforce.

As we agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution of it until 30 days from its issue date. We will then send copies of the report to other interested congressional members and committees. In addition, the report will be available at no charge on the GAO Web site at http://www.gao.gov.

If you or your staff have any questions about this report or would like additional information, please call me at (202) 512-2700 or Sushil K. Sharma, Assistant Director, at (202) 512-3460. Penny Pickett, Laurel Rabin, and Foy Wicker also made key contributions to this report.

Nancy R. Kingsbury, Managing Director
Applied Research and Methods

Appendix I: Scope and Methodology

The best way to reliably assess the pulse and views of military personnel is by surveying a representative sample. We developed and administered such a survey that was designed to obtain the views of selected Air National Guard and Air Force Reserve personnel regarding issues associated with AVIP. The survey, which was both voluntary and confidential, was mailed in May 2000 to a random sample of 1,253 personnel. As of September 7, 2000, 828 individuals had completed and returned the survey. Follow-up efforts yielded an additional 15 responses. A total of 843 responses were returned, of which 833 provide useful information.

In addition, we performed logistic regression analyses for selected questions in our questionnaire to determine odds ratios to evaluate the responses of certain groups in our survey population. These groups included enlisted personnel and officers, Air National Guard and Air Force Reserve personnel, shot recipients and nonshot recipients, and individuals who had changed their military status and those who had not. We conducted our work in accordance with generally accepted government auditing standards.

Questionnaire Development

We developed the survey with the assistance of discussion groups made up of pilots and other aircrew members of the Air National Guard and Air Force Reserve. It was pretested at Andrews Air Force Base, Maryland, and further pretested and refined at guard and reserve units at March Air Reserve Base, California; Travis Air Force Base, California; Hartford, Connecticut; Battle Creek, Michigan; Newburg, New York; Memphis, Tennessee; and Madison, Wisconsin.

Sample Construction

The sample consisted of 1,253 Air National Guard and Air Force Reserve aircrew personnel who were in the service at any time between September 1998 and February 2000. Our sample was drawn from pilot and aircrew member populations provided by the Air National Guard and Air Force Reserve in early 2000. In addition, the AVIP office provided information as to vaccination status. For the sample design, we categorized personnel in our universe by two factors: military status (left versus onboard) and vaccine status (shot versus no shot). The sample was adjusted for groups with differing expected rates of survey completion and adjusted to provide a level of precision of plus or minus 5 percentage points.

Survey Administration

As of September 6, 2001, we had received 843 responses from eligible respondents, an overall response rate of 67 percent. We used a contractor to key in the data reported in the responses. We validated the data provided to us by the contractor to ensure accuracy.

Weighting Responses and Potential Nonresponse Bias

The survey responses were weighted to reflect the Air National Guard and Air Force Reserve population for the survey. This weighting procedure adjusts for the different proportions of individuals sampled from each cell and the actual response rate for that cell in the sample design. The survey results assumed that nonrespondents would have answered as the respondents did. This assumption involves some unknown risk of nonresponse bias. Weighting can be used to statistically adjust for differing sampling rates and response rates. However, weighting cannot adjust for possible differences between those who do and those who do not respond to a survey.

Appendix II: Estimated Percentages of Vaccination Shot Recipients Experiencing Local and Systemic Adverse Reactions

	Vaccination shot						
Reaction	**1**	**2**	**3**	**4**	**5**	**6**	**Average % experiencing reaction**
Local							
Redness 2.5 inches or less	39.6%	33.5%	32.7%	33.5%	29.2%	42.6%	35.2%
Redness 2.5 inches or more	16.9	19.7	19.4	17.6	16.8	26.2	19.4
Swelling in arm	37.7	37.8	36.3	34.5	29.2	31.5	34.5
Burning in arm	60.7	60.6	58.1	57.8	57.0	63.4	59.6
Arm pain or limited motion	36.1	35.5	36.0	33.2	29.2	26.2	32.7
Itching in arm	27.6	28.3	29.0	27.4	25.6	26.8	27.4
Knot or lump in arm	54.5	55.3	55.3	51.7	52.1	63.4	55.4
Systemic							
Chills	7.7	6.8	8.2	8.4	6.5	5.7	7.2
Fever	9.3	9.6	10.3	9.6	6.6	5.7	8.5
Extreme fatigue	14.5	16.6	16.4	13.8	8.9	0.6	11.8
Dizziness	3.1	2.8	3.3	4.3	2.6	0.6	2.8
Headaches	9.6	8.4	9.8	8.5	5.2	0.6	7.0
Blurred vision	2.3	2.4	2.9	2.5	1.4	0.3	2.0
Numbness in extremities	3.6	3.3	3.4	3.2	1.7	6.3	3.6
Joint pain	16.1	16.3	17.3	18.0	13.0	16.7	16.2
Memory loss	4.0	3.7	4.3	4.3	3.7	0.6	3.4
Blackouts	0.8	0.4	0.4	0.6	1.2	0	0.6
Ringing in ears	5.4	4.5	4.6	3.1	2.7	0.6	3.5
Insomnia	4.3	3.7	3.4	2.5	3.8	0	2.9
Nausea	4.3	4.5	4.7	5.5	6.4	5.7	5.2
Other	4.1	3.5	4.9	5.3	5.0	0	3.8

Source: GAO analysis.

Appendix III: The Weighted Numbers of Local and Systemic Adverse Reactions by Vaccination Shot Number

Reaction type and duration	Estimated number receiving each vaccination shot						Total number of reactions
	1	2	3	4	5	6	
	4,678	**4,492**	**4,316**	**2,933**	**1,389**	**336**	
Local							
Redness 2.5 inches or less							
Less than 24 hours	663	605	570	376	142	38	2,394
1–3 days	680	538	502	356	173	52	2,301
4–7 days	290	250	195	159	35	17	946
7 days or more	217	112	146	91	55	36	657
Total weighted number	**1,850**	**1,505**	**1,413**	**982**	**405**	**143**	**6,298**
% 7 days or more	**11.7%**	**7.4%**	**10.3%**	**9.3%**	**13.6%**	**25.2%**	
Redness 2.5 inches or more							
Less than 24 hours	112	158	112	91	38	2	513
1–days	282	334	350	228	140	69	1,403
4–7 days	220	200	181	126	54	17	798
7 days or more	176	192	194	71	2	0	635
Total weighted number	**790**	**884**	**837**	**516**	**234**	**88**	**3,349**
% 7 days or more	**22.3%**	**21.7%**	**23.2%**	**13.8%**	**0.9%**	**0%**	
Swelling in arm							
Less than 24 hours	463	446	477	301	157	35	1,879
1–3 days	537	617	513	334	104	0	2,105
4–7 days	349	294	291	181	55	0	1,170
7 days or more	413	339	288	197	90	71	1,398
Total weighted number	**1,762**	**1,696**	**1,568**	**1,013**	**406**	**106**	**6,551**
% 7 days or more	**23.4%**	**20.0%**	**18.4%**	**19.4%**	**22.2%**	**67.0%**	
Burning sensation in arm							
Less than 24 hours	2,211	2,099	1,995	1,304	702	194	8,505
1–3 days	498	498	406	301	90	19	1,812
4–7 days	41	58	55	55	0	0	209
7 days or more	90	69	52	35	0	0	246
Total weighted number	**2,840**	**2,724**	**2,508**	**1,695**	**792**	**213**	**10,772**
% 7 days or more	**3.2%**	**2.5%**	**2.1%**	**2.1%**	**0%**	**0%**	
Arm pain or limited motion							
Less than 24 hours	524	455	573	334	142	35	2,063
1–3 days	564	592	491	359	157	36	2,199
4–7 days	356	337	332	194	87	0	1,306
7 days or more	247	209	156	87	19	17	735
Total weighted number	**1,691**	**1,593**	**1,552**	**974**	**405**	**88**	**6,303**
% 7 days or more	**14.6%**	**13.1%**	**10.1%**	**8.9%**	**4.7%**	**19.3%**	

Reaction type and duration	Estimated number receiving each vaccination shot						Total number of reactions
	1	2	3	4	5	6	
	4,678	**4,492**	**4,316**	**2,933**	**1,389**	**336**	
Local							
Itching in arm							
Less than 24 hours	567	572	554	340	145	19	2,197
1–3 days	324	307	375	211	69	17	1,303
4–7 days	231	247	178	145	71	19	891
7 days or more	167	145	145	109	71	35	672
Total weighted number	**1,289**	**1,271**	**1,252**	**805**	**356**	**90**	**5,063**
% 7 days or more	**13.0%**	**11.4%**	**11.6%**	**13.5%**	**19.9%**	**38.9%**	
Knot or lump in arm							
Less than 24 hours	548	465	461	249	157	35	1,915
1–3 days	337	381	345	282	192	19	1,556
4–7 days	553	624	653	499	159	36	2,524
7 days or more	1,110	1,013	929	485	216	123	3,876
Total weighted number	**2,548**	**2,483**	**2,388**	**1,515**	**724**	**213**	**9,871**
% 7 days or more	**43.6%**	**40.8%**	**38.9%**	**32.0%**	**29.8%**	**57.7%**	
Systemic							
Chills							
Less than 24 hours	167	77	159	140	54	17	614
1–3 days	107	124	106	71	19	2	429
4–7 days	71	71	71	36	0	0	249
7 days or more	17	35	17	0	17	0	86
Total weighted number	**362**	**307**	**353**	**247**	**90**	**19**	**1,378**
% 7 days or more	**4.7%**	**11.4%**	**4.8%**	**0%**	**18.9%**	**0%**	
Fever							
Less than 24 hours	203	167	197	157	54	0	778
1–3 days	180	178	176	72	38	19	663
4–7 days	19	36	19	36	0	0	110
7 days or more	35	52	52	17	0	0	156
Total weighted number	**437**	**433**	**444**	**282**	**92**	**19**	**1,707**
% 7 days or more	**8.0%**	**12.0%**	**11.7%**	**6.0%**	**0%**	**0%**	
Extreme fatigue							
Less than 24 hours	159	213	211	139	36	2	760
1–3 days	233	213	211	71	35	0	763
4–7 days	72	88	54	54	36	0	304
7 days or more	214	231	231	140	17	0	833
Total weighted number	**678**	**745**	**707**	**404**	**124**	**2**	**2,660**
% 7 days or more	**31.6%**	**31.0%**	**32.7%**	**34.7%**	**13.7%**	**0%**	

	Estimated number receiving each vaccination shot						
Reaction type and duration	**1**	**2**	**3**	**4**	**5**	**6**	**Total number of reactions**
	4,678	**4,492**	**4,316**	**2,933**	**1,389**	**336**	
Local							
Dizziness							
Less than 24 hours	57	39	38	38	36	0	208
1–3 days	36	54	88	52	0	2	232
4–7 days	17	17	0	0	0	0	34
7 days or more	35	17	17	35	0	0	104
Total weighted number	**145**	**127**	**143**	**125**	**36**	**2**	**578**
% 7 days or more	**24.1%**	**13.4%**	**11.9%**	**28.0%**	**0%**	**0%**	
Headaches							
Less than 24 hours	184	146	178	123	52	0	683
1–3 days	124	106	175	71	19	0	495
4–7 days	71	54	36	19	2	0	182
7 days or more	71	71	36	36	2	2	218
Total weighted number	**450**	**377**	**425**	**249**	**75**	**2**	**1,578**
% 7 days or more	**15.8%**	**18.8%**	**8.5%**	**14.5%**	**2.7%**	**0%**	
Blurred vision							
Less than 24 hours	55	55	55	36	17	0	218
1–3 days	0	0	35	0	0	0	35
4–7 days	19	19	19	19	2	1	79
7 days or more	35	35	17	17	0	0	104
Total weighted number	**109**	**109**	**126**	**72**	**19**	**1**	**436**
% 7 days or more	**32.1%**	**32.1%**	**13.5%**	**23.6%**	**0%**	**0%**	
Numbness in extremities							
Less than 24 hours	60	41	39	54	17	17	228
1–3 days	2	2	19	3	2	2	30
4–7 days	35	35	36	36	2	0	144
7 days or more	71	71	52	0	2	2	198
Total weighted number	**168**	**149**	**146**	**93**	**23**	**21**	**600**
% 7 days or more	**42.3%**	**47.7%**	**35.6%**	**0%**	**8.7%**	**9.5%**	
Joint pain							
Less than 24 hours	180	164	180	175	71	54	824
1–3 days	178	140	175	106	17	0	616
4–7 days	128	161	161	126	38	0	614
7 days or more	268	265	230	121	54	2	940
Total weighted number	**754**	**730**	**746**	**528**	**180**	**56**	**2,994**
% 7 days or more	**35.5%**	**36.3%**	**30.8%**	**22.9%**	**30.0%**	**3.6%**	

Reaction type and duration	Estimated number receiving each vaccination shot						Total number of reactions
	1	2	3	4	5	6	
	4,678	**4,492**	**4,316**	**2,933**	**1,389**	**336**	
Local							
Memory loss							
Less 24 hours	55	38	55	54	17	0	219
1–3 days	2	19	2	0	17	0	40
4–7 days	35	35	35	17	0	0	122
7 days or more	93	76	93	54	17	2	335
Total weighted number	**185**	**168**	**185**	**125**	**51**	**2**	**716**
% 7 days or more	**50.3%**	**45.2%**	**50.3%**	**43.2%**	**33.3%**	**0%**	
Blackouts							
Less 24 hours	19	19	19	19	17	0	93
1–3 days	0	0	0	0	0	0	0
4–7 days	0	0	0	0	0	0	0
7 days or more	17	0	0	0	0	0	17
Total weighted number	**36**	**19**	**19**	**19**	**17**	**0**	**110**
% 7 days or more	**47.2%**	**0%**	**0%**	**0%**	**0%**	**0%**	
Ringing in ears							
Less 24 hours	107	107	55	38	19	2	328
1–3 days	36	36	54	0	17	0	143
4–7 days	19	19	19	2	2	0	61
7 days or more	91	38	71	52	0	0	252
Total weighted number	**253**	**200**	**199**	**92**	**38**	**2**	**784**
% 7 days or more	**36.0%**	**19.0%**	**35.7%**	**56.5%**	**0%**	**0%**	
Insomnia							
Less 24 hours	39	38	38	19	17	0	151
1–3 days	19	3	3	0	17	0	42
4–7 days	55	55	38	19	19	0	186
7 days or more	87	69	69	35	0	0	260
Total weighted number	**200**	**165**	**148**	**73**	**53**	**0**	**639**
% 7 days or more	**43.5%**	**41.8%**	**46.6%**	**47.9%**	**0%**	**0%**	
Nausea							
Less 24 hours	90	106	106	87	69	17	475
1–3 days	39	57	76	54	3	2	231
4–7 days	52	36	17	19	17	0	141
7 days or more	19	2	2	2	0	0	25
Total weighted number	**200**	**201**	**201**	**162**	**89**	**19**	**872**
% 7 days or more	**9.5%**	**1.0%**	**1.0%**	**1.2%**	**0%**	**0%**	

	Estimated number receiving each vaccination shot						
Reaction type and duration	**1**	**2**	**3**	**4**	**5**	**6**	**Total number of reactions**
	4,678	**4,492**	**4,316**	**2,933**	**1,389**	**336**	
Local							
Other							
Less 24 hours	19	20	36	17	0	0	92
1–3 days	35	35	35	17	35	0	157
4–7 days	69	69	88	52	0	0	278
7 days or more	69	35	54	69	34	0	261
Total weighted number	**192**	**159**	**213**	**155**	**69**	**0**	**788**
% 7 days or more	**35.9%**	**22.0%**	**25.4%**	**44.5%**	**49.3%**	**0%**	

Source: GAO analysis.

Appendix IV: Anthrax Vaccine Adsorbed Revised Product Insert (Jan. 31, 2002)

Description

Anthrax Vaccine Adsorbed (BioThrax™) is a sterile, milky-white suspension (when mixed) made from cell-free filtrates of microaerophilic cultures of an avirulent, nonencapsulated strain of *Bacillus anthracis*. The production cultures are grown in a chemically defined protein-free medium consisting of a mixture of amino acids, vitamins, inorganic salts and sugars. The final product, prepared from the sterile filtrate culture fluid, contains proteins, including the 83kDa protective antigen protein, released during the growth period. The final product contains no dead or live bacteria. The final product is formulated to contain 1.2 mg/mL aluminum, added as aluminum hydroxide in 0.85% sodium chloride. The product is formulated to contain 25 mg/mL benzethonium chloride and 100 mg/mL formaldehyde, added as preservatives.

Clinical Pharmacology

Epidemiology

Anthrax occurs globally and is most common in agricultural regions with inadequate control programs for anthrax in livestock. Anthrax is a zoonotic disease caused by the Gram-positive, spore-forming bacterium *Bacillus anthracis*. The spore form of Bacillus anthracis is the predominant phase of the bacterium in the environment and it is largely through the uptake of spores that anthrax disease is contracted. Spore forms are markedly resistant to heat, cold, pH, desiccation, chemicals and irradiation. Following germination at the site of infection, the bacilli can also enter the blood and lead to septicemia. Antibiotics are effective against the germinated form of *Bacillus anthracis*, but are not effective against the spore form of the organism.

The disease occurs most commonly in wild and domestic animals, primarily cattle, sheep, goats and other herbivores. In humans, anthrax disease can result from contact with animal hides, leather or hair products from contaminated animals, or from other exposures to *Bacillus anthracis* spores. It occurs in three forms depending upon the route of infection: cutaneous anthrax, gastrointestinal anthrax and inhalation anthrax.

Cutaneous anthrax is the most commonly reported form in humans (> 95% of all anthrax cases). It can occur when the bacterium enters a cut or abrasion on the skin, such as when handling contaminated meat, wool, hides, leather or hair products from infected animals or other

contaminated materials. The symptoms of cutaneous anthrax begin with an itchy reddish-brown papule on exposed skin surfaces and may appear approximately 1–12 days after contact. The lesion soon develops a small vesicle. Secondary vesicles are sometimes seen. Later the vesicle ruptures and leaves a painless ulcer that typically develops a blackened eschar with surrounding swollen tissue. There are often associated systemic symptoms such as swollen glands, fever, myalgia, malaise, vomiting and headache. The case fatality rate for cutaneous anthrax is estimated to be 20 percent without antibiotic treatment.

Gastrointestinal anthrax usually begins 1–7 days after ingestion of meat contaminated with anthrax spores. There is acute inflammation of the intestinal tract with nausea, loss of appetite, vomiting and fever followed by abdominal pain, vomiting of blood and bloody diarrhea. There can also be involvement of the pharynx with sore throat, dysphagia, fever, lesions at the base of the tongue or tonsils and regional lymphadenopathy. The case fatality rate is unknown but estimated to be 25 percent to 60 percent.

Inhalation (pulmonary) anthrax has been reported to occur from 1 to 43 days after exposure to aerosolized spores.1 Studies in rhesus monkeys indicate that a small number of inhaled spores may remain viable for at least 100 days following exposure.2 However, information on how long spores remain viable in the lungs of humans is unavailable and the incubation period for inhalation anthrax is unknown. Initial symptoms are non-specific and may include sore throat, mild fever, myalgia, coughing and chest discomfort lasting up to a few days. The second stage develops abruptly with findings such as sudden onset of fever, acute respiratory distress with pulmonary edema and pleural effusion followed by cyanosis, shock and coma. Meningitis is common. The fatality rate for inhalation anthrax in the United States is estimated to be approximately 45 percent to 90 percent. From 1900 to October 2001, there were 18 identified cases of inhalation anthrax in the United States, the latest of which was reported in 1976, with an 89 percent (16/18) mortality rate. Most of these exposures occurred in industrial settings—i.e., textile mills.3 From October 4, 2001 to December 5, 2001, a total of 11 cases of inhalation anthrax linked to intentional dissemination of Bacillus anthracis spores were identified in the United States. Five of these cases were fatal.4

Mechanism of Action

Virulence components of *Bacillus anthracis* include an antiphagocytic polypeptide capsule and three proteins known as protective antigen (PA), lethal factor (LF) and edema factor (EF). Individually these proteins are not cytotoxic but the combination of PA with LF or EF results in the

formation of the cytotoxic lethal toxin and edema toxin, respectively. Although an immune correlate of protection is unknown, antibodies raised against PA may contribute to protection by neutralizing the activities of these toxins.5 The contribution of *Bacillus anthracis* proteins other than PA, that may be present in BioThrax, to the protection against anthrax has not been determined.

Clinical Studies

A controlled field study using an earlier version of a protective antigen-based anthrax vaccine, developed in the 1950s, that consisted of an aluminum potassium sulfate-precipitated cell free filtrate from an aerobic culture, was conducted from 1955 to 1959. This study included 1,249 workers (379 received anthrax vaccine, 414 received placebo, 116 received incomplete inoculations [with either vaccine or placebo] and 340 were in the observational group [no treatment]) in four mills in the northeastern United States that processed imported animal hides.6 During the trial, 26 cases of anthrax were reported across the four mills—five inhalation and 21 cutaneous. Prior to vaccination, the yearly average number of human anthrax cases was 1.2 cases per 100 employees in these mills. Of the five inhalation cases (four of which were fatal), two received placebo and three were in the observational group. Of the 21 cutaneous cases, 15 received placebo, three were in the observational group, and three received anthrax vaccine. Of those three cases in the vaccine group, one case occurred just prior to administration of the scheduled third dose, one case occurred 13 months after an individual received the third of the scheduled 6 doses (but no subsequent doses), and one case occurred prior to receiving the scheduled fourth dose of vaccine. In a comparison of anthrax cases between the placebo and vaccine groups, including only those who were completely vaccinated, the calculated vaccine efficacy level against all reported cases of anthrax combined was 92.5 percent (lower 95 percent CI = 65 percent).

From 1962 to 1974, based on information reported to Centers for Disease Control and Prevention (CDC), 27 cases of anthrax occurred in mill workers or those living near mills in the United States. Of those, 24 cases occurred in unvaccinated individuals, one case occurred after the person had been given one dose of anthrax vaccine and two cases occurred after individuals had been given two doses of anthrax vaccine. No documented cases of anthrax were reported for individuals who had received the recommended six doses of anthrax vaccine. These individuals received either an earlier version of a protective antigen-based anthrax vaccine or BioThrax.

In an open-label safety study conducted by the CDC, BioThrax was administered in 0.5 mL doses according to a 0, 2, 4 week initial dose schedule followed by additional doses at 6, 12 and 18 months to complete the 6 dose vaccination series. Annual boosters were administered thereafter. In this study, 15,907 doses of BioThrax were administered to approximately 7,000 textile employees, laboratory workers and other at-risk individuals and the incidence rates of local and systemic adverse reactions were recorded. (See ADVERSE REACTIONS)

A randomized clinical study was conducted by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) from 1996 to 1999 in 173 volunteers to evaluate changes to the vaccination schedule and route of vaccine administration. Of those, 28 were enrolled into the study arm to receive the licensed schedule (initial injections at 0, 2 and 4 weeks followed by additional doses at 6, 12 and 18 months) and were subsequently monitored for the occurrence of local and systemic adverse events. (See ADVERSE REACTIONS)

Indications and Usage

BioThrax is indicated for the active immunization against *Bacillus anthracis* of individuals between 18 and 65 years of age who come in contact with animal products such as hides, hair or bones that come from anthrax endemic areas, and that may be contaminated *with Bacillus anthracis* spores. BioThrax is also indicated for individuals at high risk of exposure to *Bacillus anthracis* spores such as veterinarians, laboratory workers and others whose occupation may involve handling potentially infected animals or other contaminated materials.

Since the risk of anthrax infection in the general population is low, routine immunization is not recommended.

The safety and efficacy of BioThrax in a post-exposure setting has not been established.

Contraindications

The use of BioThrax is contraindicated in subjects with a history of anaphylactic or anaphylactic-like reaction following a previous dose of BioThrax, or any of the vaccine components.

Warnings

Preliminary results of a recent unpublished retrospective study of infants born to women in the U.S. military service worldwide in 1998 and 1999 suggest that the vaccine may be linked with an increase in the number of

birth defects when given during pregnancy (unpublished data, Department of Defense). Although these data are unconfirmed, pregnant women should not be vaccinated against anthrax unless the potential benefits of vaccination have been determined to outweigh the potential risk to the fetus.

Animal reproduction studies have not been conducted with BioThrax.

Precautions

Before administration, the patient's medical immunization history should be reviewed for possible vaccine sensitivities and/or previous vaccination-related adverse events, in order to determine the existence of any contraindications to immunization.

Pregnant women should not be vaccinated against anthrax unless the potential benefits of vaccination clearly outweigh the potential risks to the fetus.

BioThrax should not be administered to individuals with a history of Guillain-Barré Syndrome (GBS) unless there is a clear benefit that outweighs the potential risk of a recurrence.

History of anthrax disease may increase the potential for severe local adverse reactions.

Patients with impaired immune responsiveness due to congenital or acquired immunodeficiency, or immunosuppressive therapy may not be adequately immunized following administration of BioThrax. Vaccination during chemotherapy, high-dose corticosteroid therapy of greater than 2-week duration, or radiation therapy may result in a suboptimal response. Deferral of vaccination for 3 months after completion of such therapy may be considered.7

The administration of BioThrax to persons with concurrent moderate or severe illness should be postponed until recovery. Vaccination is not contraindicated in subjects with mild illnesses with or without low-grade fever.7

This product should be administered with caution to patients with a possible history of latex sensitivity since the vial stopper contains dry natural rubber.

Epinephrine solution, 1:1000, should always be available for immediate use in case an anaphylactic reaction should occur.

Pregnancy

PREGNANCY CATEGORY D.

See Warnings.

Nursing Mothers

It is not known whether exposure of the mother to BioThrax poses a risk of harm to the breast-feeding child. However, administration of non-live vaccines (e.g., anthrax vaccine) during breast-feeding is not medically contraindicated.7

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No data regarding the safety of BioThrax are available for persons aged > 65 years.

Adverse Reactions

Pre-Licensure

Local Reactions

In an open-label safety study, 15,907 doses of BioThrax were administered to approximately 7,000 textile employees, laboratory workers and other at-risk individuals (see *Clinical Studies*). Over the course of the 5-year study, there were 24 reports (0.15 percent of doses administered) of severe local reactions (defined as edema or induration measuring greater than 120 mm in diameter or accompanied by marked limitation of arm motion or marked axillary node tenderness). There were 150 reports (0.94 percent of doses administered) of moderate local reactions (edema or induration greater than 30 mm but less than 120 mm in diameter) and 1,373 reports (8.63 percent of doses administered) of mild local reactions (erythema only or induration measuring less than 30 mm in diameter).

Systemic Reactions

In the same open label study, four cases of systemic reactions were reported during a 5-year reporting period (< 0.06 percent of doses administered). These reactions, which were reported to have been transient, included fever, chills, nausea and general body aches.

Post-Licensure

Recently (1996-99), an assessment of safety was conducted as part of a randomized clinical study conducted by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) (see *Clinical Studies*). A total of 28 volunteers were enrolled to receive subcutaneous doses of BioThrax according to the licensed schedule. Each volunteer was observed for approximately 30 minutes after administration of AVA and scheduled for follow-up evaluations at 1-3 days, 1 week and 1 month after vaccination. Four volunteers reported seven acute adverse events within 30 minutes after the subcutaneous administration of BioThrax. These included erythema (3), headache (2), fever (1) and elevated temperature (1). Of these events, a single patient reported the simultaneous occurrence of headache, fever and elevated temperature (100°F).

Local Reactions

The most common local reactions reported after the first dose (n = 28) in this study were tenderness (71 percent), erythema (43 percent), subcutaneous nodule (36 percent), induration (21 percent), warmth (11 percent) and local pruritus (7 percent). The most frequently reported local reactions after the second dose (n = 28) were tenderness (61 percent), subcutaneous nodule (39 percent), erythema (32 percent), induration (18 percent), local pruritus (14 percent), warmth (11 percent) and arm motion limitation (7 percent). After the third dose (n = 26), the most frequently reported local reactions were tenderness (58 percent), warmth (19 percent), local pruritis (19 percent), erythema (12 percent), arm motion limitation (12 percent), induration (8 percent), edema (8 percent) and subcutaneous nodule (4 percent). Local reactions were found to occur more often in women. No abscess or necrosis was observed at the injection site.

Systemic Reactions

All systemic adverse events reported in this study were transient in nature. The systemic reactions most frequently reported after the first dose (n = 28) were headache (7 percent), respiratory difficulty (4 percent) and fever (4 percent). After the second dose (n = 28), the most frequently reported systemic reactions were malaise (11 percent), myalgia (7 percent), fever (7 percent), headache (4 percent), anorexia (4 percent) and nausea or vomiting (4 percent). After the third dose (n = 26), the most frequently reported systemic reactions were headache (4 percent), malaise (4 percent), myalgia (4 percent) and fever (4 percent). There was one report of delayed hypersensitivity reaction beginning with lesions 3 days after the first dose. The subject was reported to have diffuse hives by day 17, 3 days after the second dose, and had swollen hands, face and feet by day 18 and discomfort swallowing. The subject did not receive any subsequent scheduled doses.

Post-Licensure Adverse Event Surveillance

Data regarding potential adverse events following anthrax vaccination are available from the Vaccine Adverse Event Reporting System (VAERS).8 The report of an adverse event to VAERS is not proof that a vaccine caused the event. Because of the limitations of spontaneous reporting systems, determining causality for specific types of adverse events, with the exception of injection-site reactions, is often not possible using VAERS data alone. The following four paragraphs describe spontaneous reports of adverse events, without regard to causality.

From 1990 to October 2001, over 2 million doses of BioThrax have been administered in the United States. Through October 2001, VAERS received approximately 1,850 spontaneous reports of adverse events. The most frequently reported adverse events were erythema, headache, arthralgia, fatigue, fever, peripheral swelling, pruritus, nausea, injection site edema, pain/tenderness and dizziness.

Approximately 6 percent of the reported events were listed as serious. Serious adverse events include those that result in death, hospitalization, permanent disability or are life-threatening. The serious adverse events most frequently reported were in the following body system categories: general disorders and administration site conditions, nervous system disorders, skin and subcutaneous tissue disorders, and musculoskeletal, connective tissue and bone disorders. Anaphylaxis and/or other generalized hypersensitivity reactions, as well as serious local reactions, were reported to occur occasionally following administration of BioThrax. None of these hypersensitivity reactions have been fatal.

Other infrequently reported serious adverse events that have occurred in persons who have received BioThrax have included: cellulitis, cysts, pemphigus vulgaris, endocarditis, sepsis, angioedema and other hypersensitivity reactions, asthma, aplastic anemia, neutropenia, idiopathic thrombocytopenia purpura, lymphoma, leukemia, collagen vascular disease, systemic lupus erythematosus, multiple sclerosis, polyarteritis nodosa, inflammatory arthritis, transverse myelitis, Guillain-Barré Syndrome, immune deficiency, seizure, mental status changes, psychiatric disorders, tremors, cerebrovascular accident (CVA), facial palsy, hearing and visual disorders, aseptic meningitis, encephalitis, myocarditis, cardiomyopathy, atrial fibrillation, syncope, glomerulonephritis, renal failure, spontaneous abortion and liver abscess. Infrequent reports were also received of multisystem disorders defined as chronic symptoms involving at least two of the following three categories: fatigue, mood-cognition, musculoskeletal system.

Reports of fatalities included sudden cardiac arrest (2), myocardial infarction with polyarteritis nodosa (1), aplastic anemia (1), suicide (1) and central nervous system (CNS) lymphoma (1).

Post-Licensure Survey Studies

In addition to the VAERS data, adverse events following anthrax vaccination have been assessed in survey studies conducted by the Department of Defense in the context of their anthrax vaccination program. These survey studies are subject to several methodological limitations—e.g., sample size, the limited ability to detect adverse events, observational bias, loss to follow-up, exemption of vaccine recipients with previous adverse events and the absence of unvaccinated control groups. Overall, the most reported events were localized, minor and self-limited and included muscle or joint aches, headache and fatigue. Across these studies, systemic reactions were reported in 5 to 35 percent of vaccine recipients and included reports of malaise, chills, rashes, headaches and low-grade fever. Women reported these symptoms more often than men.

Reporting Adverse Events

Adverse events following immunization with BioThrax should be reported to the Medical Affairs Division of BioPort Corporation (517) 327-1675 during regular working hours and (517) 327-7200 during off hours. Adverse events may also be reported to the U. S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System. Report forms and reporting requirement information can be obtained from VAERS through a toll free number 1-800-822-7967.

Dosage and Administration

Dosage

Immunization consists of three subcutaneous injections, 0.5 mL each, given 2 weeks apart followed by three additional subcutaneous injections, 0.5 mL each, given at 6, 12, and 18 months. Subsequent booster injections of 0.5 mL of BioThrax at 1-year intervals are recommended.

Administration

Use a separate 5/8-inch, 25- to 27-gauge sterile needle and syringe for each patient to avoid transmission of viral hepatitis and other infectious agents. Use a different site for each sequential injection of this vaccine and do not mix with any other product in the syringe.

1. Shake the bottle thoroughly to ensure that the suspension is homogeneous during withdrawal and visually inspect the product for particulate matter and discoloration. If the product appears discolored or has visible particulate matter, DISCARD THE VIAL.

2. Wipe the rubber stopper with an alcohol swab and allow to dry before inserting the needle.

3. Clean the area to be injected with an alcohol swab or other suitable antiseptic.

4. Holding the needle at a 45° angle to the skin, inject the vaccine subcutaneously.

5. DO NOT inject the product intravenously. Follow the usual precautions to ensure that you have not entered a vein before injecting the vaccine.

6. After injecting, withdraw the needle and briefly and gently massage the injection site to promote dispersal of the vaccine.

How Supplied/Storage

Anthrax Vaccine Adsorbed (BioThrax TM) is supplied in 5 mL multidose vials.

THIS PRODUCT IS TO BE STORED AT 2.2°C TO –15°C (36° TO 4°F). Do not freeze. Do not use after the expiration date given on the package.

Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been performed to ascertain whether BioThrax has carcinogenic action, or any effect on fertility.

References

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Revision: January 31, 2002.

Rx Only—Federal (U.S.A.) law prohibits dispensing without a prescription.

Manufactured by

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50483-04

Appendix V: Comments from the Department of the Army

DEPARTMENT OF THE ARMY
OFFICE OF THE ASSISTANT SECRETARY
MANPOWER AND RESERVE AFFAIRS
111 ARMY PENTAGON
WASHINGTON, DC 20310-0111

July 15, 2002

REPLY TO
ATTENTION OF

Ms. Nancy Kingsbury
Managing Director
Applied Research and Methods
U.S. General Accounting Office
Washington, D.C. 20548

Dear Ms. Kingsbury:

This is the Department of Defense (DoD) response to the General Accounting Office (GAO) draft report, GAO-02-445, dated 11 June 2002, "ANTHRAX VACCINE: GAO's Survey of Guard and Reserve Pilots and Aircrew" (GAO Code 460501).

The Department of Defense is committed to giving the best possible care to servicemembers who develop a problem after receiving this or any vaccine. The Department agrees with the GAO that those who have experienced adverse events to the anthrax vaccine and those who may experience them in the future should have appropriate and complete treatment and follow-up.

The Department recognizes the importance of our need to continually improve our education efforts among our servicemembers and their families to increase understanding of the anthrax threat, anthrax vaccine and the Anthrax Vaccine Immunization Program.

The Department nonconcurs with the report's primary recommendation. After performing a comprehensive analysis and review of data, the National Academy of Sciences reported in March 2002, "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 for service members ordered to take the vaccines."

Data from the Defense Manpower Data Center (DMDC) regarding actual pilot separations do not support the GAO report. The DMDC data shows pilot separations before beginning the AVIP in 1998 are similar to the rates during the time of the survey. The GAO report does not address these normal or expected rates of turnover known to occur among personnel in the Air National Guard and the Air Force Reserve.

Reginald J. Brown
Assistant Secretary of the Army
(Manpower and Reserve Affairs)

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GAO ANTHRAX VACCINE
GAO's SURVEY OF GUARD/RESERVE PILOTS AND AIRCREW MEMBERS
GAO-02-445

DEPARTMENT OF DEFENSE COMMENTS ON THE GAO RECOMMENDATION

RECOMMENDATION 1: The GAO recommended that the Secretary of Defense direct the establishment of an active surveillance program (unlike the passive VAERS) to identify and monitor adverse events associated with each anthrax vaccine immunization. (p.42/GAO-02-445)

DOD RESPONSE: Nonconcur. After performing comprehensive analysis and review of data, the National Academy of Sciences reported in March 2002, "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 for service members ordered to take the vaccines."

Further, DoD has assembled 18 safety studies using both active and passive surveillance. Active data collection has already occurred at Tripler Army Medical Center, Camp Casey in Korea, and elsewhere. A comprehensive and automatic review of every inpatient and outpatient medical visit, both anthrax vaccinated and unvaccinated servicemembers, around the globe is included in one of the 18 studies using the Defense Medical Surveillance System. These and other studies were reported in detail to the National Academy of Sciences. The Centers for Disease Control and Prevention (CDC) is currently coordinating a 5-site, active surveillance human safety, reactogenicity and immunogenicity trial to address changes in route of administration and dose reduction. The current FDA-licensed 6-dose vaccination series will be administered to one of the subgroups.

DoD takes its responsibility seriously to provide for an open assessment of the safety of anthrax vaccine. Safety studies in addition to the first 18 are in progress and will be published in the peer-reviewed literature when completed. To enhance the care delivered to service members in the interval after any vaccination, DoD and the Centers for Disease Control and Prevention (CDC) collaborated to create a center for excellence in vaccine care at the Walter Reed Army Medical Center. This center of excellence is known as the Vaccine Healthcare Center, the first of what may become a triservice network of similar centers. It is the combination of additional research and enhanced care that will provide the best possible prevention programs and care delivery.

Related GAO Products

Anthrax Vaccine: Changes to the Manufacturing Process. GAO-02-181T. Washington, D.C.: Oct. 23, 2001.

Anthrax Vaccine: Preliminary Results of GAO's Survey of Guard/Reserve Pilots and Aircrew Members. GAO-01-92T. Washington, D.C.: Oct. 11, 2000.

Medical Readiness: DOD Continues to Face Challenges in Implementing Its Anthrax Vaccine Immunization Program. GAO/T-NSIAD-00-157. Washington, D.C.: Apr. 13, 2000.

Medical Readiness: DOD Faces Challenges in Implementing Its Anthrax Vaccine Immunization Program. GAO/NSIAD-00-36. Washington, D.C.: Oct. 22, 1999.

Anthrax Vaccine: Safety and Efficacy Issues. GAO/T-NSIAD-00-48. Washington, D.C.: Oct. 12, 1999.

Medical Readiness: Issues Concerning the Anthrax Vaccine. GAO/T-NSIAD-99-226. Washington, D.C.: July 21, 1999..

Contract Management: Observations on DOD's Financial Relationship with the Anthrax Vaccine Manufacturer. GAO/T-NSIAD-99-214. Washington, D.C.: June 30, 1999.

Medical Readiness: Safety and Efficacy of the Anthrax Vaccine. GAO/T-NSIAD-99-148. Washington, D.C.: Apr. 29, 1999.

Gulf War Illnesses: Questions about the Presence of Squalene Antibodies in Veterans Can Be Resolved. GAO/NSIAD-99-5. Washington, D.C.: Mar. 29, 1999.

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