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MEDICAL READINESS

Issues Concerning the Anthrax Vaccine

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Mr. Chairman and Members of the Subcommittee:

We are pleased to be here today to share the results of our work on the anthrax vaccine. As you know, questions have been raised about the Department of Defense's (DOD) anthrax immunization program because of concerns related to (1) the safety and efficacy of the vaccine and (2) problems found over the past few years by the Food and Drug Administration (FDA) during its inspection of the facility that was manufacturing the vaccine. We reported our findings on these issues to you in previous testimonies.[1]

In December 1997, the Secretary of Defense announced that all U.S. forces would be inoculated against the potential use of anthrax on the battlefield. Although a version of the anthrax vaccine was shown to be effective against cutaneous exposure, the vaccine has not been tested against inhalation anthrax in humans. DOD has recognized that some of the concerns about using the current vaccine might be mitigated in the future through actions such as testing and research and adjustments to the program based on new data.

As requested, we will discuss (1) the extent to which data support the need for six initial shots and an annual booster of the anthrax vaccine, (2) the relative merits and weaknesses of a passive surveillance system in determining adverse events,[2] (3) the available data on differences in adverse reaction rates between men and women receiving the anthrax vaccine, and (4) the disadvantages of the current vaccine and the status of federal efforts to develop an improved anthrax vaccine.

Results in Brief

No studies have been done to determine the optimum number of doses of the anthrax vaccine. A study done during the early 1950s showed that animals could be protected against cutaneous anthrax using a three-dose schedule. However, the number of doses was increased to six when three people who had received three doses of the vaccine were infected after exposure to anthrax. In a study of the vaccine's human efficacy published

[1] Medical Readiness: Safety and Efficacy of the Anthrax Vaccine (GAO/T-NSIAD-99-148, Apr. 29, 1999) and Contract Management : Observations on DOD's Financial Relationship With the Anthrax Vaccine Manufacturer (GAO/T-NSIAD-99-214, June 30, 1999).

[2] Clinical events reported to a passive surveillance system are usually termed adverse events rather than adverse reactions because causally-related events to the vaccine is not usually possible.

in 1962, a six-dose schedule was used, and the researchers concluded that the vaccine provided protection against cutaneous exposure to anthrax. [3] In 1998, the current manufacturer of the vaccine submitted an FDA application (Investigational New Drug) to determine whether the number of shots in the initial schedule could be reduced from six to five. Although annual boosters are given, the need for this frequency and the amount of the booster dose has also not been evaluated.

DOD submits data on adverse events associated with the anthrax vaccine to the Vaccine Adverse Events Reporting System (VAERS).[4] This system has several advantages. It alerts FDA/CDC to previously unreported or unexpected increases in reported adverse events. It is also a relatively affordable way to supplement the data collected on vaccines before they are licensed. However, it is a passive surveillance system, which means that FDA/CDC must rely on vaccine recipients or their health care providers to report any adverse events after receiving the vaccine; studies show that adverse events are reported significantly less than they would be in an active surveillance system. In an active system, which is generally more costly to administer, vaccine recipients are monitored to find out if they had any adverse events after being inoculated.

In addition to reporting data to VAERS, DOD has conducted three efforts to actively collect data on adverse reactions after servicemembers received the anthrax vaccine. Data from these efforts show that women reported twice the rate of adverse reactions than men for both local (e.g., swelling) and systemic (e.g., malaise and chills) reactions. In addition, a higher proportion of women than men reported making an outpatient medical visit after a vaccination, and more than twice the percentage of women reported that they missed one or more duty shifts after their vaccinations than did men.

The anthrax vaccine has several disadvantages. The amount of protective antigen in the vaccine cannot be precisely measured, and it varies from lot to lot. Also, the requirement for a six-dose schedule and annual booster shots, rather than a smaller number of doses, complicates the logistics of inoculating all of DOD's troops and increases the cost of the vaccine program. Knowledge of anthrax infection and studies of experimental

[3]P.S. Brachman et al., "Field evaluation of a human anthrax vaccine," American Journal of Public Health, vol. 52 (1962), pp. 632-645.

[4]The system is an FDA/Centers for Disease Control and Prevention (CDC) system.

anthrax vaccines indicate that a second-generation vaccine with a more precise amount of protective antigen could be developed and that fewer doses of the vaccine would be required. However, a second-generation vaccine has not been fully tested, and the testing required for licensing alone would take about 3 years. FDA approval of the manufacturing of the vaccine would take longer. In 1995, the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID)[5] developed a second-generation recombinant vaccine (that is, a vaccine produced through DNA extraction) against anthrax. The vaccine was tested on animals, but clinical trials were not conducted in humans. DOD currently considers such a vaccine an unfunded requirement. The Department of Health and Human Services recently funded several active research grants to develop a second-generation recombinant vaccine because of a perceived growing bioterrorism concern. In developing a new vaccine, researchers also believe they should consider the impact of new and engineered strains of anthrax.

Background

DOD currently plans to vaccinate all 2.4 million servicemembers against anthrax using the vaccine licensed in 1970 by the Division of Biologics Standards, National Institutes of Health (NIH). As of July 14, 1999, more than 300,000 servicemembers had received at least one dose of the vaccine. Initial immunization consists of three shots given at 0, 2, and 4 weeks followed by three additional shots given at 6, 12, and 18 months.

Some studies have been done on the short-term effects of the licensed vaccine. We previously testified that the number of adverse reactions reported in these studies partly depended on whether an active or passive surveillance system was used to monitor adverse reactions.[6] Also, we reported that the long-term safety of the vaccine has not been investigated but that DOD is considering a study to examine long-term effects of the vaccine.

[5]USAMRIID, an organization of the U.S. Army Medical Research and Materiel Command, conducts research to develop strategies, products, information, procedures, and training programs for medical defense against biological warfare threats and naturally occurring infectious diseases that require special containment. It is located at Fort Detrick, Maryland.

[6]Medical Readiness (GAO/T-NSIAD-99-148, Apr. 29, 1999).

Data on the Need for Six Shots Are Not Available

The original inoculation schedule of three doses was based on a regimen developed using animals in the early 1950s. However, three people (two in Fort Detrick and one in a private wool mill) who received three doses of the vaccine became infected after exposure to anthrax. The number of doses was then increased to six for the human efficacy study published in 1962. The study did not provide enough information to determine whether the vaccine was effective against inhalation anthrax. There were no studies done to determine the optimum number of doses of the vaccine. Also, according to DOD researchers, the choice of six doses was arbitrary. The license for the vaccine, which was granted to the Michigan Department of Public Health (MDPH),[7] calls for the six-dose schedule and annual boosters used in the human efficacy study, and DOD has followed this regimen. In September 1998, BioPort submitted to FDA an application (Investigational New Drug) to determine whether the number of shots in the initial schedule could be reduced from six to five.

In November 1971, the Division of Biologics Standards, NIH, noted an apparent increase in reports of adverse reactions after individuals received booster shots. The Division considered it advisable to reevaluate the need for annual boosters and possibly the amount of the booster dose. Although the record is unclear as to whether or not NIH requested a reevaluation, to date, no such reevaluation has been done.

The Relative Merits and Weaknesses of Passive Surveillance Systems in Determining Adverse Events

DOD submits data on adverse events associated with the anthrax vaccine to VAERS. VAERS is a passive surveillance system to alert FDA and CDC of adverse events that may be associated with licensed vaccines. Information is voluntarily reported to VAERS by health care providers, patients, or families, who are encouraged to report any adverse events after a person receives a vaccine.

VAERS has several advantages. It is a relatively affordable way to supplement data on short-term adverse events that are collected using active means during the clinical trials before a vaccine is licensed. Most important, however, VAERS serves as a signal for the detection of previously unreported adverse events and/or unexpected increases in

[7]MDPH was granted the original license to produce the anthrax vaccine. 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.

reported events. Prelicensing clinical trials are limited in detecting the range of adverse reactions because of the small samples, short durations, and the homogeneous population used as subjects. In addition, both the general public and doctors can report adverse events to the system, and the data is open to public scrutiny.

VAERS also has several disadvantages. Studies show that adverse events are often underreported in a passive surveillance system.[8] A former FDA commissioner acknowledged the underreporting of adverse events in passive surveillance systems and cited one study showing that "only about 1 percent of serious events" attributable to drug reactions are reported to FDA.[9] Reporting of adverse events appears to depend on several factors, such as the clinical seriousness of the event, the length of time between the shots and the event, and health care workers' awareness of and obligation to report particular adverse events. Also, outcomes with delayed onset after vaccination or outcomes not generally recognized to be associated with vaccination are often underreported. According to the National Vaccine Information Center, there is no mechanism within VAERS for a 1-, 3-, or 10-year follow-up to evaluate vaccine reactions that have a long latency period. According to CDC, the limitations of VAERS data suggest it is not a valid source for assessing the rate of adverse events.

In an active surveillance system, health care workers monitor people that have been vaccinated to find out if they have had adverse reactions. Such systems are generally used during clinical trials and are more costly to administer than passive systems because of the additional infrastructure and personnel required. However, such systems are sometimes used to obtain information when questions arise about the safety of a vaccine after licensing.

[8]S. Rosenthal and R. Chen, "The Reporting Sensitivities of Two Passive Surveillance Systems for Vaccine Adverse Events," American Journal of Public Health, vol. 85 (1995), pp. 1706-1709; R.T. Chen et al., "The Vaccine Adverse Event Reporting System (VAERS)," Vaccine, vol. 12 (1994), pp. 542-550; and R.T. Chen, "Special Methodological Issues in Pharmacoepidemiology Studies of Vaccine Safety," Ed. B.L. Strom, Pharmacoepidemiology (Chicester: John Wiley and Sons, 1994).

[9]D.A. Kessler, "Introducing MEDWatch: A New Approach to Reporting Medication and Devise Adverse Effects and Product Problems," Journal of the American Medical Association, vol. 269 (1993), pp. 2765-2768, and H.D. Scott, et al., "Rhode Island Physicians' Recognition and Reporting of Adverse Drug Reactions," Rhode Island Medical Journal, vol. 70 (1987), pp. 311-316.

Women Report More Adverse Reactions Than Men

In addition to DOD's reporting of adverse events to VAERS, DOD has conducted three efforts to actively collect data that can be used to examine gender differences in adverse reactions after servicemembers have received the anthrax vaccine. The first effort, conducted by USAMRIID, included data on shots given at Fort Detrick during 1977-96. The second effort, conducted in 1999 by a DOD physician stationed in Korea, was a survey given to servicemembers when they reported for their initial six-dose schedule of shots; it asked questions about their reactions to the previous shot. Results from this effort reflect the researcher's preliminary analysis of the data. The third effort, conducted in 1998-99 at Tripler Army Medical Center, Hawaii, included a survey on adverse reactions to the first three shots when individuals reported for their fourth shot and later included a follow-up survey on adverse reactions to the fourth shot. None of the efforts used a control group. Also, all three relied on self-reported data and were not adjusted for factors such as occupation, physical activity level, and age. Because of differences in the way data were collected, reaction rates are not strictly comparable among the different efforts.

According to the data gathered in all three efforts, a higher proportion of females reported reactions to the anthrax vaccine than did their male counterparts. Tables 1 and 2 summarize the rates of reported reactions to the vaccine during the two efforts at Fort Detrick and in Korea. The researchers at Fort Detrick determined that the statistical difference was significant[10] in the reported reaction rates of males and females after their second and subsequent shots. The researchers for the other two efforts did not report whether the difference in reported reaction rates was statistically significant.

[10]Tests of significance deal with the question of whether a difference is real or just a chance variation. It does not deal with the question of how important the difference is or what caused the difference. The test does not check the design of the study. If a test is significant at the 99-percent level, the results could be due to chance 1 percent of the time.

Table 1: Gender Differences in the Reported Rate of Reactions to the Anthrax Vaccine, From Fort Detrick Data (1977-96)

Dose number	Males percent (number of doses)	Females percent (number of doses)
First	3.75 (1,013)	3.86 (259)
Second	3.06[a] (979)	7.29[a] (247)
Third	1.71[a] (938)	5.06[a] (237)
Fourth and subsequent	3.40[b] (5062)	7.06[b] (737)

Note: As a result of GAO's recalculation, the percentages reflect minor differences from those reported by the researcher.

[a] The gender difference in reported reaction rates is statistically significant at the 99-percent confidence level.

[b] The gender difference in reported reaction rates is statistically significant at the 99.99-percent confidence level.

Source: DOD.

Table 2: Preliminary Data on Gender Differences in the Reported Rate of Reactions to the Anthrax Vaccine, From Korea Survey (1999)

Dose number	Males percent (number of doses)	Females percent (number of doses)
First	42.1 (2036)	71.6 (495)
Second	44.4 (1953)	74.0 (474)

Note: This represents a preliminary analysis of the data by the researcher, and at the time of our review, data on reactions to the third shot were not available.

Source: DOD.

The data gathered in Korea shows that after the first two shots, more than twice the proportion of women reported the systemic reactions of fever, malaise, or chills than men (see table 3).

Table 3: Preliminary Data on Gender Differences in Systemic Reactions, From Korea Survey (1999)

Numbers in percent

	Fever		Malaise		Chills	
Dose number	Male	Female	Male	Female	Male	Female
First	0.9	2.8	6.0	15.6	1.5	5.5
Second	1.7	4.8	7.1	15.4	1.9	4.0

Note: This represents a preliminary analysis of the data by the researcher, and at the time of our review, data on reactions to the third dose were not available.

Source: DOD.

The Tripler effort also demonstrates gender differences in reported reactions (see table 4). These data show that a higher proportion of women reported making an outpatient visit after a vaccination than their male counterparts. In addition, more than twice the proportion of women reported that they missed one or more duty shifts after their vaccinations than did males.

Table 4: Gender Differences in Reported Local Reactions, Outpatient Medical Visits, and Missed Duty, From Tripler Army Medical Center Survey (1998-99)

Numbers in percent

Reaction	Dose 1	Dose 2	Dose 3	Dose 4
Moderate to severe redness				
Male	17.5	20.4	17.2	31.6
Female	49.1	46.9	51.4	39.8
Swelling of lower arm				
Male	9.7	9.5	9.2	7.1
Female	13.4	13.5	13.0	8.4
Pain limiting motion of elbow				
Male	9.7	8.7	7.6	7.9
Female	17.1	13.5	11.7	8.6
Localized itching				
Male	25.2	25.7	24.5	27.7
Female	62.6	60.4	57.9	39.2
Lump or knot				
Male	63.9	64.4	60.5	65.5
Female	89.9	87.8	83.6	73.2
Muscle soreness				
Male	66.6	64.7	61.8	60.4
Female	79.7	76.4	70.8	61.6
Outpatient medical visit				
Male	5.3	2.0	2.7	
Female	10.0	13.8	3.9	[a]
Missed one or more shifts of duty				
Male	2.2	2.0	0.9	
Female	5.0	5.1	3.9	[a]

Note: Between 421 and 471 men and between 74 and 83 women responded to each question on the survey.

[a]Data were not available.

Source: DOD.

Status of Federal Efforts to Develop a Second-Generation Anthrax Vaccine

According to researchers and the Institute of Medicine of the National Academy of Sciences, the current anthrax vaccine has several disadvantages.[11] The amount of protective antigen in the vaccine is variable from lot to lot because the manufacturing process cannot precisely quantify the antigen.[12] Also, there is some evidence that the current anthrax vaccine may have diminished efficacy against certain virulent strains of anthrax (*Bacillus anthracis*). And the required six-dose schedule and annual boosters complicate the logistics of inoculating all of DOD's troops and increase the cost of the vaccine program.

According to DOD research, a second-generation recombinant vaccine created with a process that is fully defined, quantified, and controlled in terms of protective antigen, can be developed and that fewer doses could be required.[13] DOD research also shows that a recombinant vaccine could be created using modern techniques to produce highly purified protective antigen. This process not only would remove unwanted bacterial proteins but also would enable precise amounts of the purified protective antigen to be incorporated into the vaccine. A further potential benefit is that, compared to the current vaccine, the protective antigen could be produced in a nonspore-forming organism. As a result, according to DOD officials, manufacturers could use their buildings and equipment to produce the anthrax vaccine as well as other vaccines.

In 1995, USAMRIID developed a new recombinant protective antigen vaccine against anthrax. This vaccine was successfully tested in experiments using animals but has not been tested on humans. USAMRIID officials stated that this testing would take about 3 years, and FDA approval of the manufacturing of the vaccine could take years longer. DOD considers further development of this vaccine candidate an unfunded requirement. In response to the perceived threat of bioterrorism, the

[11]P.S. Brachman and A. Friedlander, "Anthrax," Vaccines, ed. S.A. Plotkin and E.A. Mortimer, Jr., (Philadelphia: W.B. Saunders Company, 1994), p. 737, and Chemical and Biological Terrorism: Research and Development to Improve Civilian Medical Response, Institute of Medicine (Washington, D.C.: National Academy Press, 1999), p. 135.

[12]Chemical and Biological Terrorism: Research and Development to Improve Civilian Medical Response, Institute of Medicine (Washington, D.C.: National Academy Press, 1999), p. 135.

[13]B. Ivins et al., "Immunization Studies with attenuated strains of *Bacillius anthracis,*" Journal of Infection and Immunity, vol. 52 (1986), pp. 454-458; B.E. Ivins, "The Search for a New-Generation Human Anthrax Vaccine," Clinical Immunology Newsletter, vol. 9 (1988), pp. 30-32; and Y. Singh et al., "Study of Immunization Against Anthrax with the Purified Recombinant Protective Antigen of *Bacillus anthracis,*" Journal of Infection and Immunity, vol. 66 (1998), pp. 3447-3448.

Department of Health and Human Services' National Institute of Allergy and Infectious Diseases formed a working group to develop and test a second-generation anthrax vaccine. The Institute recently funded several active research grants in this regard.

In developing a second-generation recombinant anthrax vaccine, researchers believe they will need to address the additional problem of whether strains of deliberately engineered or naturally occurring anthrax can overcome the protective immunity of such a vaccine. A variation in virulence among anthrax strains and a variation in relative resistance to vaccine-induced immunity has been observed in experiments on animals. However, the reasons for the variation have not been scientifically proven.

Mr. Chairman, this concludes my formal statement. If you or other members of the Subcommittee have any questions, we will be pleased to answer them.

Contacts and Acknowledgments

For future contacts regarding this testimony, please contact Kwai-Cheung Chan at 512-3652. Individuals making key contributions to this testimony included Sushil Sharma, Howard Deshong, and Nancy Ragsdale.

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