An Assessment of the Safety of the Anthrax Vaccine: A Letter Report

Committee on Health Effects Associated with Exposures During the Gulf War, Division of Health Promotion and Disease Prevention, Medical Follow-Up Agency

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the Institute of Medicine in making the published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. The committee wishes to thank the following individuals for their participation in the review of this report:

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While the individuals listed above have provided constructive comments and suggestions, responsibility for the final content of this report rests solely with the authoring committee and the Institute of Medicine.

An Assessment of the Safety of the Anthrax Vaccine A Letter Report

March 30, 2000

Major General Randall L.West, USMC
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Department of Defense
4000 Defense Pentagon Washington, DC 20301–4000

Dear General West:

In February of this year, the Department of Defense (DoD) requested that the Institute of Medicine (IOM) provide a report on the safety and efficacy of the anthrax vaccine that could be used to answer questions raised by Congress. The IOM has agreed to undertake this comprehensive study, which will require approximately 24 months to complete. The questions include the types and severity of adverse reactions, including gender differences; long-term health implications; efficacy of the vaccine against inhalational anthrax; correlation of animal models to safety and effectiveness in humans; validation of the manufacturing process; definition of vaccine components in terms of the protective antigen and other bacterial products and constituents; and identification of gaps in existing research.

Because of immediate concern over anthrax vaccine safety issues, the IOM offered to draw relevant information from an ongoing study of Gulf War exposures funded by the Department of Veterans Affairs. The opportunity to provide limited information relating to the safety of anthrax vaccine is possible due to the ongoing work of the IOM Committee on Health Effects Associated with Exposures During the Gulf War, which was tasked with conducting literature reviews on six Gulf War exposures (including the anthrax vaccine). This committee began its work in January 1999, and it is scheduled to provide its report in August of this year. With the agreement of the Department of Veterans Affairs, the IOM was able to produce this letter report that summarizes the committee's literature review on the safety of the anthrax vaccine. This information, while very narrowly focused, may be helpful now to Congress, the DoD, and others before the IOM begins its comprehensive assessment of the anthrax vaccine. Although DoD requested the IOM's consideration of safety and efficacy, the current IOM committee was not tasked with issues of vaccine efficacy. The report that follows therefore addresses only the limited peer-reviewed literature on the safety of the anthrax vaccine.

The committee evaluated the primary peer-reviewed literature and did not draw conclusions from the secondary literature (e.g., reviews). Publications that were not peer reviewed had no evidentiary value for the committee, and they were not used as a basis for conclusions about the degree of association between an exposure and a health effect. The ability of the IOM to conduct the more comprehensive study of the anthrax vaccine requested by the DoD assumes that the significant body of work that has been conducted by the DoD on this subject will be released for publication in peer-reviewed scientific journals.

INTRODUCTION

Currently there are two types of anthrax vaccine available for human use: a live attenuated spore vaccine that has been tested and used widely in the countries of the former Soviet Union (Shlyakhov and Rubinstein, 1994) and protective-antigen vaccines that were developed in the United States and the United Kingdom in the 1950s using filtrates of attenuated strains of the anthrax bacillus. Protective antigen, one of the three toxin proteins produced by the anthrax bacillus, is the protective component of the British and U.S. vaccines, which differ in their method of production and in the strains of the bacillus used (Ibrahim et al., 1999). The committee decided to base its conclusions solely on studies of the protective-antigen vaccines because the live attenuated spore vaccine differs substantially in terms of composition, reactogenicity, and potential residual virulence.

The U.S. anthrax vaccine, which was used in the Gulf War and is currently still in use, was granted product licensure on November 10, 1970. In 1985, a Food and Drug Administration (FDA) advisory panel reviewing the status of bacterial vaccines and toxoids categorized the anthrax vaccine in Category 1 (safe, effective, and not misbranded) (FDA, 1985). The current dosing schedule is 0.5 ml administered subcutaneously at 0, 2, and 4 weeks and 6, 12, and 18 months, followed by yearly boosters. It is estimated that 68,000 doses of the U.S. anthrax vaccine were distributed from 1974 to 1989; 268,000 doses in 1990; and 1.2 million doses from 1991 to July 1999 (Ellenberg, 1999). The exact number of people who received the vaccine is not known. The following sections provide a synthesis of the available peer-reviewed studies.

ANIMAL STUDIES

Few studies have explicitly looked for adverse health effects of the protective-antigen anthrax vaccine in animals. In a study by Wright and colleagues (1954), 25 rabbits were administered five 0.5-ml intracutaneous injections of anthrax vaccine on alternate days. The rabbits were sacrificed 23 days later. Complete autopsies including gross and microscopic examination of all organs revealed no adverse effects. In studies conducted in nonhuman primates, no remarkable local or systemic reactions were seen (Darlow et al., 1956; Ivins et al., 1998). Few meaningful conclusions regarding adverse effects in humans can be drawn from the animal studies of the vaccine; the primary goal of the majority of those studies has been to determine the vaccine's efficacy.

HUMAN STUDIES

There are only a few published peer-reviewed studies examining the safety of the anthrax vaccine in humans. The studies discussed below, with the exception of the Ft. Detrick studies, administered only the anthrax vaccine and were not intended to examine the effects of multiple vaccinations. The committee notes a recent literature review (Demicheli et al., 1998) on anthrax vaccine studies conducted according to the Cochrane Collaboration guidelines for systematic reviews of health care interventions. Only the Brachman study (described below) met the Cochrane criteria for prospective randomized or quasi-randomized studies of a protective antigen anthrax vaccine.

Short-Term Studies

During the development of the anthrax vaccine, several studies examined adverse reactions in humans. These studies used early versions of the culture filtrate (protective-antigen) vaccine. Wright and colleagues (1954) described the reactions of 660 persons who received a total of 1,936 injections. They found that 0.7% of the vaccinated subjects reported systemic reactions—typically consisting of mild muscle aches, headaches, and mild-to-moderate malaise lasting 1 to 2 days. Significant local reactions—typically swelling (5–10 cm in diameter) and local pruritus (itching)—were reported for 2.4% of the injections. The incidence of local reactions increased with the number of previous injections. Two additional early studies also showed low rates of mild, brief local reactions (Darlow et al., 1956; Puziss and Wright, 1963). There is no long-term follow-up reported on the subjects in these studies.

Brachman Study

Brachman and colleagues (1962) conducted the only randomized clinical trial of vaccination with a protective-antigen anthrax vaccine. Although the vaccine used in this study was similar to the vaccine currently available in the United States in that it was a protective-antigen vaccine, the manufacturing process has since changed and a different strain of anthrax bacillus is now used (GAO, 1999a).

The clinical trial was conducted among 1,249 eligible workers[1] at four goat hair processing mills in which some raw materials were contaminated by the anthrax bacillus. After the initial series of three injections, the study had to be terminated at the largest mill, which employed nearly half of the subjects, because of an outbreak of inhalation anthrax that required the immunization of all employees. At the remaining mills, 480 participants completed the series of injections (230 of whom were randomized to active vaccination and 250 of whom were randomized to receive placebo injections) and 81 participants did not complete the series of injections.[2] The study subjects did not know

[1]Employees who had a previous case of anthrax were not eligible for the study. Of the 1,249 eligible participants, 340 refused to participate in the study.

whether they had received the active vaccine or placebo; the article does not state whether the investigators were also blinded.

The report of the study does not always clearly distinguish the results in the three mills for the 480 subjects who completed the vaccination series from the 81 subjects who did not complete the series. Neither does it clearly distinguish the results for the 480 subjects in the three mills who completed the series from results for the subjects from the largest mill who had been randomized, received the initial injections, and were partially evaluated prior to the mill's withdrawal from the study.

The participants were examined 24 and 48 hours following each vaccination to assess both local and systemic reactions to the vaccine. There was no report of subsequent active or passive surveillance for possible adverse effects beyond 48 hours after each vaccination (there was further monitoring for the vaccine's efficacy, however). The typical reaction is described as a ring of erythema (1–2 cm in diameter) at the injection site, with local tenderness that lasted 24–48 hours. Some subjects (a number was not given) reported more extensive edema, erythema (>5 cm in diameter), pruritus, induration, or small painless nodules at the injection site (lasting up to several weeks). Twenty-one persons had moderate local edema that lasted up to 48 hours. Three individuals had edema extending from the deltoid to the mid-forearm (in one case, to the wrist) that dissipated within 5 days. The only systemic reactions were reported in two individuals (0.9% of the actively vaccinated subjects), who experienced "malaise" lasting 24 hours following vaccination. The study notes that three individuals who received the placebo (0.1% alum) had mild reactions.

Long-Term Studies

The committee located only one published series of studies that discussed long-term follow-up of individuals who received multiple vaccinations, including the anthrax vaccine, due to the nature of their employment. A group of employees at Fort Detrick, Maryland, were followed for an average of 25 years to investigate the potential subclinical effects of intensive vaccination.[3] The participants underwent physical examinations and/or laboratory testing in 1956 (n=93), 1962 (n=76), and 1971 (n=77) (Peeler et al., 1958, 1965; White et al., 1974).

No clinical sequelae attributable to intense long-term immunization could be identified in this cohort. None of the subjects suffered unexplained clinical symptoms requiring them to take sick leave that could be attributed to the vaccination program. There was some evidence of a chronic inflammatory response, as characterized by certain laboratory test abnormalities: elevated levels of hexosamine, an acute-phase reactant, and polyclonal

[2]The authors state that there was a gradual decline in participation in the study, partly because of changes in the nature of the textile business and partly because some of the employees withdrew from the program.

[3]Prior to 1956, all 99 persons had been vaccinated against botulism, tularemia, Rocky Mountain spotted fever, Q fever, plague, typhus, psittacosis, and Eastern, Western, and Venezuelan equine encephalitis; in addition, 95 of the subjects were also immunized against smallpox, 37 against brucellosis, 28 against anthrax, and 25 against diphtheria. By 1962, 72 of the 76 study subjects had been vaccinated against anthrax (in addition to other vaccinations) (Peeler et al., 1958, 1965).

elevations in levels of gamma globulins. These changes cannot necessarily be attributed to the vaccinations, as the workers studied were occupationally exposed to a number of virulent microbes. However, the studies did not report any clear adverse clinical consequences, such as neoplasms, amyloidosis, or autoimmune diseases.

This series of longitudinal clinical studies had several shortcomings. There was no comparison cohort and no random sampling of the employees. Therefore, the results may not be applicable to a broader population. Further, the outcomes may be due in part to the healthy worker effect, since the subjects were selected for the intensity and length of their immunization history, and individuals who left employment were not considered. Thus, the studies may have inadvertently focused on the most resilient individuals. Moreover, it would be difficult, if not impossible, to attribute adverse effects to any one vaccine, since the study subjects received multiple vaccines.

Non-Peer-Reviewed, Unpublished Information

The committee reviewed summaries of data from the Vaccine Adverse Event Reporting System (VAERS).[4] We did not, however, review the individual VAERS forms submitted by health care providers, people receiving the vaccination, family members, or others. VAERS data are useful as a sentinel for adverse events but are limited in their usefulness for assessing the rate or causality of adverse events since the information may be underreported, incomplete, or duplicative and may not always have been confirmed by medical personnel (IOM, 1994). From its inception in 1990 through July 1, 1999, there have been 215 VAERS reports regarding anthrax vaccination (Ellenberg, 1999). The majority of the reports describe local or systemic symptoms including injection site edema, injection site hypersensitivity, rash, headache, and fever. Twenty-two of the VAERS reports are considered serious events and were described as occurring (or being diagnosed) from 45 minutes to 41/2 months after the vaccination. The reports of serious events include severe injection site reactions, a widespread allergic reaction, a case of aseptic meningitis, an onset of lupus, an onset of inflammatory demyelinating disease, a diagnosis of bipolar disease, and two cases of Guillain-Barré syndrome (Ellenberg, 1999). FDA and CDC are responsible for monitoring the VAERS data to detect unusual trends and occurrences of adverse health effects. That monitoring assists the FDA and CDC in responding appropriately to adverse events. In recent congressional testimony, FDA stated that "the reports on the anthrax vaccine received thus far do not raise any specific concerns about the safety of the vaccine" (Ellenberg, 1999).

Additionally, there are a number of unpublished studies with data on the safety of the anthrax vaccine (Table 1). However, these studies are either ongoing or have not been published in the peer-reviewed literature, and they were therefore not considered in the committee's conclusions regarding the strength of the evidence for associations with adverse health outcomes. In its full report, the committee uses these studies in determining its recommendations for future research directions. The studies are currently described

[4]VAERS is a passive surveillance system that is overseen jointly by the Centers for Disease Control and Prevention (CDC) and the FDA. Reports may be sent in to VAERS at any time following vaccination.

only in secondary sources (e.g., reviews, congressional testimony, and reports from the General Accounting Office). The publication of these studies would substantially increase the available body of information on which conclusions regarding health effects can be made.

TABLE 1. Unpublished and Ongoing Studies of the Anthrax Vaccine

Study	Brief Description
Licensure Safety Study	Data submitted in support of the application for licensure describes approximately 7,000 persons who received approximately 16,000 doses
Special Immunization Program Safety Study	Follow-up study on 1,590 workers at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) who received 10,451 doses since 1973
Ft. Bragg Booster Study	An assessment of the safety of booster shots given to 486 male military personnel who had received initial anthrax vaccinations during the Gulf War
Canadian Forces Safety Survey	Active monitoring of 576 persons in the Canadian military who received the anthrax vaccine in 1998
USAMRIID Reduced Dose and Route Change Study	Pilot study involving 173 persons who received a reduced dose schedule or vaccination via a different route (intramuscular)
Tripler Army Medical Center Survey	Survey of 603 health care personnel who were vaccinated at Tripler Army Medical Center in 1998–1999
U.S. Air Force Vision Study	A comparison of visual acuity in 354 vaccinated aircrew members with 363 unvaccinated aircrew personnel
Korea Survey	Survey of military personnel at the time they received subsequent doses of the vaccine

SOURCES: Claypool, 1999; GAO, 1999b.

Conclusions on Human Studies

There is a paucity of published peer-reviewed literature on the safety of the anthrax vaccine. The committee located only one randomized peer-reviewed study of the type of anthrax vaccine used in the United States (Brachman et al., 1962). However, the formulation of the vaccine used in that study differs from the vaccine currently in use. The series of Ft. Detrick studies shows no clinical sequelae from multiple vaccinations, including the anthrax vaccination, over 25 years of intermittent observation in a highly selected cohort. However, there was no active surveillance for chronic symptoms in these studies, which raises the possibility of underreporting of symptoms.

The published studies have found transient local and systemic effects (primarily erythema, edema, or induration) of the anthrax vaccine. There have been no studies of the anthrax vaccine in which the long-term health outcomes have been systematically evaluated with active surveillance. That is not unusual, however, as few vaccines for any disease have been actively monitored for adverse effects over long periods of time. The commit

tee strongly encourages the development of active monitoring studies that evaluate long-term safety in recipients of the anthrax vaccine.

The committee concludes that in the peer-reviewed literature there is inadequate/ insufficient evidence to determine whether an association does or does not exist between anthrax vaccination and long-term adverse health outcomes. This finding means that the evidence reviewed by the committee is of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association between the vaccine and a health outcome in humans. Reviewing the large body of results that have not yet been published would enable more definitive conclusions about the vaccine's safety. The committee strongly urges the investigators conducting studies on the safety of the anthrax vaccine to submit their results to peer-reviewed scientific journals for publication. The proposed IOM study to evaluate the safety and efficacy of the anthrax vaccine will be able to examine a more extensive literature, as the DoD has agreed to make its studies of the vaccine available.

To date, published studies have reported no significant adverse effects of the vaccine, but the literature is limited to a few short-term studies. The committee's findings are best regarded as an early step in the complex process of understanding the vaccine's safety, which began with the vaccine's licensure in 1970 and the 1985 FDA advisory panel finding that categorized the anthrax vaccine as safe and effective. Active long-term monitoring of large populations will provide further information for documenting the relative safety of the anthrax vaccine.

Sincerely,
Institute of Medicine Committee on Health Effects Associated with Exposures During the Gulf War

REFERENCES

Brachman PS, Gold H, Plotkin S, Fekety FR, Werrin M, Ingraham NR. Field evaluation of a human anthrax vaccine. *American Journal of Public Health.* 1962; 52:632–645.

Claypool GR, Deputy Assistant Secretary for Health Operations Policy, U.S. Army Medical Corps. *The Anthrax Vaccine Immunization Program.* Statement at the July 21, 1999 Hearing of the Subcommittee on National Security, Veterans Affairs, and International Relations, Committee on Government Reform, U.S. House of Representatives, 1999.

Darlow HM, Belton FC, Henderson DW. The use of anthrax antigen to immunise man and monkey. *Lancet.* 1956; 2:476–479.

Demicheli V, Rivetti D, Deeks JJ, Jefferson T, Pratt M. The effectiveness and safety of vaccines against human anthrax: A systematic review. *Vaccine.* 1998; 16:880–884.

Ellenberg SS, Center for Biologics Evaluation and Research, Food and Drug Administration. Statement at the July 21, 1999, Hearing of the Subcommittee on National Security, Veterans Affairs, and International Relations, Committee on Government Reform, U.S. House of Representatives, 1999.

FDA (Food and Drug Administration). Biological products: Bacterial vaccines and toxoids; implementation of efficacy review. *Federal Register.* 1985; 50(240):51002–51117.

GAO (General Accounting Office). *Medical Readiness: Safety and Efficacy of the Anthrax Vac cine. Testimony.* GAO/T-NSAID-99–148. Washington, DC: GAO. 1999a.

GAO. *Medical Readiness: Issues Concerning the Anthrax Vaccine. Testimony.* GAO/T-NSAID-99–226. Washington, DC: GAO. 1999b.

Ibrahim KH, Brown G, Wright DH, Rotschafer JC. *Bacillus anthracis:* Medical issues of biologic warfare. *Pharmacotherapy.* 1999; 19 (6):690–701.

IOM (Institute of Medicine). *Adverse Effects of Pertussis and Rubella Vaccines.* Washington, DC: National Academy Press, 1994.

Ivins BE, Pitt ML, Fellows PF, Farchaus JW, Benner GE, Waag DM, Little SF, Anderson GW Jr, Gibbs PH, Friedlander AM. Comparative efficacy of experimental anthrax vaccine candidates against inhalation anthrax in rhesus macaques. *Vaccine.* 1998; 16:1141–1148.

Peeler RN, Cluff LE, Trever RW. Hyper-immunization of man. *Bulletin of the Johns Hopkins Hospital.* 1958; 103:183–198.

Peeler RN, Kadull PJ, Cluff LE. Intensive immunization of man: Evaluation of possible adverse consequences. *Annals of Internal Medicine.* 1965; 63(1):44–57.

Puziss M, Wright GC. Studies on immunity in anthrax. X. Gel-adsorbed protective antigen for immunization of man. *Journal of Bacteriology.* 1963; 85:230–236.

Shlyakhov EN, Rubinstein E. Human live anthrax vaccine in the former USSR. *Vaccine.* 1994; 12:727–730.

White CS, Adler WH, McGann VG. Repeated immunization: Possible adverse effects. *Annals of Internal Medicine.* 1974; 81(5):594–600.

Wright GG, Green TW, Kanode RG Jr. Studies on immunity in anthrax. V. Immunizing activity of alum-precipitated protective antigen. *Journal of Immunology.* 1954; 73:387–391.