Detailed Safety Review of Anthrax Vaccine Adsorbed
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US Army Medical Command, Falls Church, Virginia

The National Academy of Sciences (NAS) and its Institute of Medicine (IOM) released the most extensive review ever conducted of the science underlying anthrax vaccine on March 6, 2002. The comprehensive 235-page peer-reviewed report, entitled *The Anthrax Vaccine: Is It Safe? Does It Work?*, examined the safety and effectiveness of the vaccine, evaluated the manufacturing processes, and discussed the future needs of the anthrax vaccine. In conducting this review, the IOM invited oral and written testimony from concerned service members and others who have expressed reservations with the vaccine. The committee examined case reports and all available epidemiologic studies, and listened to investigators who had completed or have research underway. The committee concluded that anthrax vaccine is as safe as other vaccines for adults. “The committee found no evidence that people face an increased risk of experiencing life-threatening or permanently disabling adverse events immediately after receiving AVA, when compared with the general population. Nor did it find any convincing evidence that people face elevated risk of developing adverse health effects over the longer term, although data are limited in this regard (as they are for all vaccines)." The full text of the report is available at www.nap.edu/catalog/10310.html.

To date, more than a dozen human studies have assessed the safety of anthrax vaccination. These studies, some stretching back almost 50 years, reported adverse events after vaccination in varying degrees of detail. The following sections report the design characteristics of each study, the number of men and women participating, and their specific findings.

Among the studies described below, one of two vaccine formulations was used. The Brachman study and the early Fort Detrick studies used anthrax vaccine manufactured according to the original 1950s formula developed at Fort Detrick, Maryland (sometimes erroneously called the "Merck vaccine"). Research on this vaccine has been repeatedly accepted by the Food & Drug Administration (FDA) as relevant to the understanding of the safety profile of the current anthrax vaccine, developed in the 1960s.

In the 1960s, the production process for anthrax vaccine was revised to increase the concentration of the active ingredient, known as "protective antigen" (increasing the vaccine’s potency), and to decrease the amount of other bacterial components in the vaccine, thus increasing purity. This purer, more potent vaccine, manufactured in Lansing, Michigan, was licensed by the National Institute of Health (NIH) in 1970. Responsibility for vaccine regulation migrated from NIH to the Food & Drug Administration in 1972. FDA reaffirmed the anthrax vaccine license in 1985). Additional information regarding the transition was published in 1962 (Wright GG, Puziss M, Neely WB. *Journal of Bacteriology* 1962;83:515-22).

The CDC observational study involved people who received either the original vaccine or the revised vaccine, or both. The other studies described below used anthrax vaccine manufactured according to the revised 1960s formula, the same vaccine used in the United States today.

SUMMARY:

Anthrax vaccine prevents anthrax. Anthrax vaccine does not prevent other health problems. This is evident in the similar rates of hospitalization among Service Members vaccinated or unvaccinated against anthrax (section Q).

Like all vaccines, anthrax vaccine can cause soreness, redness, itching, swelling, and lumps at the injection site. About 30% of men and 60% of women report injection-site reactions of 1" or smaller diameter, usually lasting only a few days. Lumps at the injection site can persist a few weeks, but eventually go away. For both genders, between 1% and 5% report moderate reactions of 1 to 5 inches in diameter. Larger reactions occur after about one in a hundred vaccinees.

Beyond the injection site, from 5% to 35% will notice rashes (16%), headaches (14% to 25%), joint aches (12% to 15%), malaise (6% to 17%), muscle aches (3% to 34%), nausea (3% to 9%), chills (2% to 6%), fever (1% to 5%). Again, these symptoms usually go away after a few days.

To monitor rare or unexpected adverse events associated in time to any vaccine, DOD health-care providers have participated in the Vaccine Adverse Event Reporting System (VAERS), since its inception in 1990. In addition, each VAERS report involving anthrax vaccine is reviewed by an independent panel of civilian physicians. Between fall 1998 and the present, this panel has detected no patterns of unexpected adverse events related to anthrax vaccination.

There are no known long-term patterns of side effects from the anthrax vaccine, based on an ongoing series of studies at Fort Detrick, Maryland, and elsewhere. Reports in this series were published in 1958, 1965, 1974, and 2001.

Despite the extensive body of knowledge regarding the safety of anthrax vaccine, safety monitoring continues, as is prudent for all vaccines and medications.

Details of each study appear on following pages. The studies include:

Group I: Studies from 1950s into the Present

A. The Brachman Study (pivotal field trial evaluating safety and efficacy).
Brachman PS, Gold H, Plotkin SA, Fekety FK, Werrin M, Ingram NR. Field evaluation of human anthrax vaccine. *Am J Public Health* 1962;52:632-45.
www.anthrax.mil/media/pdf/field_eval.pdf

B. The CDC Observational Study (the follow-on open-label study between the Brachman study and vaccine licensing in 1970). Food & Drug Administration. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review. *Fed Reg* 1985;50:51002-117. www.anthrax.mil/media/pdf/Fed_Reg.pdf

C. Fort Detrick Multi-Dose, Multi-Vaccine Safety Studies (evaluations of Army laboratory workers vaccinated hundreds of times with dozens of vaccines).

Peeler RN, Cluff LE, Trever RW. Hyper-immunization of man. *Bull Johns Hopkins Hosp* 1958;103:183-98.

Peeler RN, Kadull PJ, Cluff LE. Intensive immunization of man: Evaluation of possible adverse consequences. *Ann Intern Med* 1965;63:44-57. www.anthrax.mil/media/pdf/Intensive.pdf

White CS III, Adler WH, McGann VG. Repeated immunization: Possible adverse effects: Reevaluation of human subjects at 25 years. *Ann Intern Med* 1974;81:594-600. www.anthrax.mil/media/pdf/Repeated.pdf

D. Fort Detrick Special Immunization Program (SIP) Safety Study (continuation of the previous study among more workers into modern times). Pittman PR, Gibbs PH, Cannon TL, Friedlander AM. Anthrax vaccine: Short-term safety experience in humans. *Vaccine* 2001;20:972-8.

Group II: Studies from the 1990s, Data Collection by Survey

E. Fort Bragg Booster Study (evaluation of additional doses of anthrax vaccine among soldiers vaccinated several years earlier during the Persian Gulf War). Pittman PR, Hack D, Mangiafico J, Gibbs P, McKee KT Jr., Eitzen EM, Friedlander AM, Sjogren MH. Antibody response to a delayed booster dose of anthrax vaccine and botulinum toxoid. *Vaccine* 2002;20(May 15): 2107-15.

F. USAMRIID Dose-Reduction / Route-Change Study (study of anthrax vaccine administered by two different injectable routes of administration). Pittman PR, Kim-Ahn G, Pifat DY, Coonan K, Gibbs P, Little S, Pace-Templeton JG, Myers R, Parker GW, Friedlander AM. Anthrax vaccine: Safety and immunogenicity of a dose-reduction, route comparison study in humans. *Vaccine* 2002(Jan 31);20:1412-20.

See also: Pittman PR, Mangiafico JA, Rossi CA, Cannon TL, Gibbs PH, Parker GW, Friedlander AM. Anthrax vaccine: Increasing intervals between the first two doses enhances antibody response in humans. *Vaccine* 2000;18:213-216.

See also: Pittman PR. Aluminum-containing vaccine associated adverse events: Role of route of administration and gender. *Vaccine* 2002;20(May 31):S48-50.

G. Canadian Forces Safety Survey (study of Canadian Service Members). Manuscript in progress.

H. TAMC-601 Survey (study of adverse events after anthrax vaccination of medical personnel at Tripler Army Medical Center). Centers for Disease Control & Prevention. Surveillance for adverse events associated with anthrax vaccination - U.S. Department of Defense, 1998-2000. *Morbidity & Mortality Weekly Report (MMWR)* 2000;49:341-5. www.cdc.gov/epo/mmwr/preview/mmwrhtml/mm4916a1.htm

Wasserman GM, Grabenstein JD, Pittman PR, Rubertone MV, Gibbs PP, Wang LZ, Golder LG. Analysis of adverse events after anthrax vaccination in US Army medical personnel. *Journal of Occupational & Environmental Medicine* 2003;45(Mar):222-33.

I. U.S. Forces Korea Vaccination Series (study of adverse events among personnel there). Centers for Disease Control & Prevention. Surveillance for adverse events associated with anthrax vaccination - U.S. Department of Defense, 1998-2000. *MMWR* 2000;49:341-5. www.cdc.gov/epo/mmwr/preview/mmwrhtml/mm4916a1.htm

Hoffman K, Costello C, Menich M, Grabenstein JD, Engler RJM. Using a structured medical note for determining the safety profile of anthrax vaccine for U.S. Soldiers in Korea. *Vaccine* 2003:21:4399-4409.

J. Reports involving Anthrax Vaccine Submitted to the FDA/CDC Vaccine Adverse Event Reporting System (VAERS) and Evaluated by the Anthrax Vaccine Expert Committee. Sever JL, Brenner AI, Gale AD, Lyle JM, Moulton LH, West DJ. Safety of anthrax vaccine: A review by the Anthrax Vaccine Expert Committee (AVEC) of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS). *Pharmacoepidemiology & Drug Safety* 2002;11:189-202.

Second manuscript in press: Sever JL, Brenner AI, Gale AD, Lyle JM, Moulton LH, Ward BJ, West DJ. Safety of anthrax vaccine: An expanded review and evaluation of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS). *Pharmacoepidemiology & Drug Safety* 2003;12:in press.

K. ROTC Cadets at Fort Lewis, Washington. Gunzenhauser JD, Cook JE, Parker ME. Acute side effects of anthrax vaccine in ROTC cadets participating in advanced camp, Fort Lewis, 2000. *Medical Surveillance Monthly Report* 2001;7(5):9-11. amsa.army.mil/1MSMR/2001/v07_n05.pdf

Group III: Studies from the 1990s, Database Analyses

L. USAF Air Combat Command Study, Langley Air Force Base (study of outpatient medical care among Air Force personnel after return from Southwest Asia). Rehme PA, Williams R, Grabenstein JD. Ambulatory medical visits among anthrax vaccinated and unvaccinated personnel after return from southwest Asia. *Military Medicine* 2002;167:205-10.

M. Fort Stewart, Georgia, Reproductive Health Study. Wiesen AR, Littell CT. Relationship between prepregnancy anthrax vaccination and pregnancy and birth

outcomes among US Army women. *JAMA* 2002;287(Mar 27):1556-60. http://jama.ama-assn.org/cgi/reprint/287/12/1556.pdf

N. Reproductive Outcomes of the Wives of Male Soldiers Vaccinated Against Anthrax. Manuscript in progress.

O. USAF Vision Study (a study of visual acuity among vaccinated and unvaccinated air crew members). Manuscript in progress.

P. Army Aviator Flight Physical Examination Study, Aviation Epidemiology Data Register. Manuscript in progress.

Q. Defense Medical Surveillance System (comparison of hospitalization and outpatient visit rates for those vaccinated and unvaccinated against anthrax). Lange JL, Lesikar SE, Brundage JF, Rubertone MV. Comprehensive systematic surveillance for adverse effects of anthrax vaccine adsorbed, US Armed Forces, 1998-2000. *Vaccine* 2003;21:1620-28.

R. Naval Health Research Center, DoD Center for Deployment Health Research. Sato PA, Reed RJ, Smith TC, Wang LZ. DoD-wide medical surveillance for potential long-term adverse events associated with anthrax immunization: Hospitalizations. *Vaccine* 2002;20:2369-75.

Group IV: Other Studies

S. Mycoplasma Study. Hart MK, DelGiudice RA, Korch GW. Absence of Mycoplasma contamination in anthrax vaccine. *Emerging Infectious Diseases* 2002;7:94-96. http://www.cdc.gov/ncidod/eid/vol8no1/01-0091.htm

T. Case Reports

Review by the National Academy of Sciences:

Joellenbeck LM, Zwanziger L, Durch JS, Strom BL, editors. *The Anthrax Vaccine: Is it Safe? Does it Work?* Washington, DC: National Academy Press, March 2002, 235 pages. www.nap.edu/catalog/10310.html.

Group I: Studies from 1950s into the Present

A. The Brachman Study

Citation: Phillip S. Brachman, Herman Gold, Stanley A. Plotkin, F. Robert Fekety, Milton Werrin, Norman R. Ingram. Field evaluation of human anthrax vaccine. *American Journal of Public Health* 1962; volume 52: pages 632-45. <http://www.anthrax.mil/media/pdf/field_eval.pdf>

Investigators: Epidemiologists at the Communicable Disease Center (Atlanta), the Johns Hopkins Hospital (Baltimore), and the Philadelphia Department of Public Health.

Period of Observation: 1955 to 1959

Participants: 1,249 people total, gender unspecified, of whom 379 received anthrax vaccine. At least 3 of the 26 cases of anthrax detected in this study occurred in women. Age range: employed adults, years of age not described.

Vaccine Studied: Fort Detrick formulation

Study Design: Randomized, placebo-controlled trial of anthrax vaccine among mill workers in New Hampshire and Pennsylvania who processed raw imported goat hair.

Findings: "The typical reaction was mild and did not cause any interruption of work."

(a) Injection-site ("local") Reactions:

Mild local reactions, consisting of 1 to 2 cm of redness, plus slight local tenderness, occurred in ~ 30% of recipients within 24 hours after vaccination. Itching was noted less commonly. "In general, all signs and symptoms disappeared within the next 24 to 48 hours. In many of the cases, this minimal degree of local reaction would not have been noticed by the inoculee had not his arm been examined at 24 and 48 hours after inoculation."

Moderate local inflammation (a defensive reaction to irritation) (> 5 cm in diameter), occurred in 4% of recipients.

Large local reactions occurred less frequently and consisted of extensive swelling of the forearm, in addition to local inflammation. "Three individuals experienced edema extending from the deltoid to the mid-forearm and, in one case, to the wrist, with a definite collection of fluid in the bursa of the elbow. This extensive edema disappeared within three to five days."

(b) Events Beyond the Injection Site ("systemic"): Brachman, et al., did not differentiate between nonserious and serious events. Systemic events occurred in fewer than two per thousand (< 0.2%) recipients, including "…two individuals who experienced, along with the edema-producing local reactions, some malaise of 24 hours' duration." Even less frequently, fever and chills were noted.

(c) Events or effects by gender: Brachman, et al., did not differentiate between men and women in describing adverse events.

(d) Length of time to resolution: Brachman reported no adverse events persisting beyond five days, except that "A few inoculees developed small, firm, painless nodules at the site of injections which persisted for several weeks." They also

noted “Half of these edema-producing reactions were maximum at 24 hours, and the remainder at 48 hours."

From the Jan 02 FDA-approved product labeling for anthrax vaccine adsorbed, *BioThrax*:

“A controlled field study using an earlier version of a protective antigen -based anthrax vaccine, developed in the 1950’s, that consisted of an aluminum potassium sulfate-precipitated cell free filtrate from an aerobic culture, was conducted from 1955-1959. This study involved 1,249 eligible workers (379 received vaccine, 414 received placebo and 340 were in an observational group (no treatment) in four mills in the Northeastern United States that processed imported animal hides.[6] As a result of an outbreak of inhalation anthrax that required immunization of all employees, the study in the mill that employed nearly half of the subjects was terminated after the initial series of three injections. At the remaining mills, 480 participants completed the series of six 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. During the trial, 26 cases of anthrax infection were reported across the four mills - five inhalation and 21 cutaneous. Prior to vaccination, the yearly average number of human anthrax infections 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 individuals had received the placebo, three individuals were in an observational group, and three individuals had received less than the 6-dose immunization schedule. Of those three, 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 individual developed disease 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% (lower 95% CI = 65%).”

B. The CDC Observational Study

Citation: FDA Panel on Review of Bacterial Vaccines & Toxoids: Food & Drug Administration. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review. *Federal Register* 1985; volume 50: pages 51002-117. <http://www.anthrax.mil/media/pdf/Fed_Reg.pdf>

Investigators: Data collected under DBS-IND#180 by the Center for Disease Control (CDC), Atlanta. Data submitted to the National Institute of Health (NIH) Division of Biologics Standardization (DBS) to support the license application for anthrax vaccine. NIH granted this license in 1970. In 1972, responsibility for vaccine regulation migrated from NIH to the Food & Drug Administration (FDA).

Period of Observation: 1962 to 1972

Participants: about 7,000 people, gender unspecified, involving about 16,000 doses of anthrax vaccine. At least 227 of these people received 10 or more annual booster doses. Age range: employed adults, years of age not described.

Vaccine Studied: Mixture of people receiving the Fort Detrick formulation and the Lansing formulation

Study Design: Observational study assessing use of vaccine in industrial high-risk settings. Side-effect data was collected on vaccinees, but not on any control subjects. At the same time, CDC collected and analyzed reports of cases of anthrax disease from around the United States (which recorded 24 cases of anthrax in unvaccinated people, but no cases in vaccinated people).

Findings: "Local reactions are typically mild…. Only a few systemic reactions with marked chills and fever have been recorded. All reactions reported have been self-limited." "Severe local reactions and systemic reactions are relatively rare."

(a) Injection-site ("local") Reactions:
Mild local reactions (< 3 cm) were reported after 3% to 20% of doses administered.
Moderate reactions (> 3 cm to < 12 cm) were reported after 1% to 3% of doses.
Large reactions (> 12 cm) were reported after fewer than 1% of doses.

(b) Events Beyond the Injection Site ("systemic"): Report authors did not differentiate between nonserious and serious events. Systemic reactions, reported in four individuals (fewer than 6 per 10,000 doses), consisted of fever, chills, nausea and general body aches, which resolved spontaneously.

(c) Events or effects by gender: Report authors did not differentiate between men and women in describing adverse events.

(d) Length of time to resolution: Authors did not report persistent adverse events.

From the Jan 02 FDA-approved product labeling for anthrax vaccine adsorbed, *BioThrax*:

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%) 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% of

doses administered) of moderate local reactions (edema or induration greater than 30 mm but less than 120 mm in diameter) and 1373 reports (8.63%) of mild local reactions (erythema only or induration measuring less than 30 mm in diameter).
Systemic Reactions- Four cases of systemic reactions were reported during a five-year reporting period (<0.06%). These reactions, which were reported to have been transient, included fever, chills, nausea, and general body aches.

C. Fort Detrick Multi-Dose, Multi-Vaccine Safety Studies

Citation: Richard N. Peeler, Leighton E. Cluff, Robert W. Trever. Hyper-immunization of man. *Bulletin of the Johns Hopkins Hospital* 1958; volume 103: pages 183-98.
Investigators: Scientists at the Johns Hopkins University (Baltimore)
Period of Observation: 1944 to 1956 (mean: 10.4 years)
Participants: 99 men (range: 28 to 65 years old, mean: 40.1 years), 0 women, 99 people total, recipients of multiple immunizations against anthrax, botulism, brucellosis, diphtheria, Eastern equine encephalitis, influenza, plague, poliomyelitis, psittacosis, Q fever, Rift Valley fever, Rocky Mountain spotted fever, smallpox, tetanus, tularemia, typhus, Venezuelan equine encephalitis, Western equine encephalitis, and yellow fever, totaling 36 to 74 milliliters of vaccines, plus multiple skin tests to detect hypersensitivity to microbial antigens. [For comparison, note that the six doses of anthrax vaccine in the primary series total 3 ml.]

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Citation: Richard N. Peeler, Paul J. Kadull, Leighton E. Cluff. Intensive immunization of man: Evaluation of possible adverse consequences. *Annals of Internal Medicine* 1965; volume 63: pages 44-57. <http://www.anthrax.mil/media/pdf/Intensive.pdf>.
Investigators: Scientists at the Johns Hopkins University (Baltimore)
Period of Observation: 1944 to 1962 (mean: 15.3 years)
Participants: 76 men (subset of 99 reported above), who received 42 to 102 ml of vaccines (mean: 74 ml)

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Citation: Charles S. White III, William H. Adler, Virginia G. McGann. Repeated immunization: Possible adverse effects: Reevaluation of human subjects at 25 years. *Annals of Internal Medicine* 1974; volume 81: pages 594-600. <http://www.anthrax.mil/media/pdf/Repeated.pdf>.
Investigators: Scientists at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), Fort Detrick, Maryland
Period of Observation: 1944 to 1971
Participants: 97 men (subset of 99 reported above), who received 52 to 134 ml of vaccines (mean: 97 ml), plus 6 to 93 skin tests (mean: 55), compared to 26 age- and gender-matched, unvaccinated control subjects
Vaccine Studied: Mixture of people receiving the Fort Detrick formulation and the Lansing formulation

Study Design: Cohort study, occupational setting. The third study included a small control group.
Findings: While there were some elevations in liver and kidney function tests and white blood cell counts in these men, none of these men developed any unusual diseases or unexplained symptoms that could be attributed to the repeated doses of multiple vaccines.

(a) Injection-site (“local”) Reactions: Not the subject of these studies.
(b) Events Beyond the Injection Site (“systemic”): Several laboratory abnormalities were noted (including elevated white blood cell counts and elevated liver function tests). Many of these abnormalities were transient and not detected in the 1974 study.

“It is of prime significance that long-term follow-up examination of these intensively immunized men failed to demonstrate any evidence of illness attributable to the immunizations. There is no indication that intensive immunization interfered with the ability to produce adequate antibody titers after antigenic challenge.”

The 1974 study concluded, “These data and the accompanying evaluation of an intensively immunized population provide evidence that no obvious adverse effects result from repeated immunization. … Thus, this group provides reassurance that schedules for routine immunization with a diversity of vaccines should not produce untoward effects merely because of frequency of inoculation.”

(c) Events or effects by gender: Not applicable.
(d) Length of time to resolution: Not applicable, long-term health effects sought but no hazard found.

D. Fort Detrick Special Immunization Program (SIP) Safety Study

Citation: Pittman PR, Gibbs PH, Cannon TL, Friedlander AM. Anthrax vaccine: Short-term safety experience in humans. *Vaccine* 2001;20:972-8.
Investigators: Scientists at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), Fort Detrick, Maryland
Period of Observation: 1973 to 1999
Participants: 1,249 men, 334 women, 1,583 people total, who received 10,722 doses of anthrax vaccine from 32 separate vaccine lots, assessed at the USAMRIID Special Immunizations Clinic (its occupational-health clinic). Of this group, 273 people received 10 or more doses of anthrax vaccine, and 46 people received 20 or more doses. Age range: 18 to > 40 years (upper limit not defined).
Vaccine Studied: Lansing formulation

Study Design: Cohort study of repeatedly vaccinated laboratory workers, with data based on visits to an occupational health clinic (the USAMRIID Special Immunizations Clinic).
Findings: All local and systemic events resolved without extended time lost from work, hospitalization or long-term effects. These employees continue to be examined and tested annually for medical conditions since their last visit, yet no diseases or unexplained symptoms have been observed that would not be expected in an unvaccinated group of comparable age and other demographic characteristics.
(a) Injection-site ("local") Reactions: 3.6% of doses resulted in a local reaction consisting of redness, induration (an area of hardened tissue), itching, and soft or puffy swelling (edema) at the injection site. The most common were erythema and/or induration (3.2%). Most people who reacted to a dose of anthrax vaccine received subsequent doses without problems. But people who reported an injection-site reaction were more likely to report a local reaction to a later dose. Injection-site reactions were grouped into three categories: < 5 cm (2"), 5 to 12 cm (2 to 5"), and > 12 cm (5").
(b) Events Beyond the Injection Site ("systemic"): Systemic reactions of headache, fever, chills, malaise (discomfort, uneasiness), muscle or joint aches occurred after 1 per 100 doses. The most common of these were headache (0.4%), malaise (0.4%), and fever (0.1%). One hundred systemic events noted above were classified as nonserious.
One serious systemic event was reported in this study, a woman who developed multiple sclerosis. [Background: About 10,000 people are diagnosed with multiple sclerosis each year in the United States.] Her case resolved in 6 weeks and she returned to duty, without recurrence of her disease. All other systemic events resolved without extensive time lost from work, hospitalization or long-term effects.
(c) Events or effects by gender: Women noted both local (i.e., erythema, induration, edema, swollen lymph nodes, lumps) and systemic events (i.e., headache, fever, dizziness, hives) more commonly than men. Women reported more injection-site reactions for each of the magnitude categories. Adverse events were reported by

0.1% to 2% of men and 0.1% to 6% of women. People < 40 years old reported adverse events more often than those 40 years or older.

(d) Length of time to resolution: All local and nonserious systemic events resolved without extensive time lost from work, hospitalization or long-term effects.

Group II: Studies from the 1990s, Data Collection by Survey

E. Fort Bragg Booster Study

Citation: Pittman PR, Hack D, Mangiafico J, Gibbs P, McKee KT Jr., Eitzen EM, Friedlander AM, Sjogren MH. Antibody response to a delayed booster dose of anthrax vaccine and botulinum toxoid. *Vaccine* 2002;20:2107-15.
Investigators: Scientists at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), Fort Detrick, Maryland
Period of Observation: 1992 to 1994
Participants: 495 men, 0 women, 495 people total, U.S. Army special mission soldiers at Fort Bragg, North Carolina. Age range: 20 to 40 years, mean 33.9 years.
Vaccine Studied: Lansing formulation

Study Design: USAMRIID investigators actively assessed the safety of booster doses of anthrax vaccine, given to soldiers previously vaccinated against anthrax and botulism during the Persian Gulf War of 1990-91. All 495 were assessed for vaccine safety; 279 were assessed for immunogenicity. Some received an anthrax vaccine booster alone, although most received booster doses of both anthrax vaccine and botulinum toxoid.
Findings: No adverse event caused lost time from work or hospitalization and all reactions resolved without lasting consequences.
(a) Injection-site ("local") Reactions:
None: Of these soldiers, 67% to 74% reported no redness or swelling.
Mild: 16% to 28% had local redness and/or swelling in the arm where the booster vaccination was administered, less than 5 cm in diameter.
Moderate: In 4.7% to 9.3%, the redness and/or swelling was > 5 cm.
Large: Three soldiers (0.6%) developed redness or swelling > 12 cm in diameter.
(b) Events Beyond the Injection Site ("systemic"): One or more systemic reactions occurred in 26% to 45% of recipients during the first 30 days after vaccination, most commonly muscle aches (23% to 31%), fever (8% to 20%), malaise (7% to 17%), headache (9% to 17%), rash (0% to 17%), or joint aches (7% to 13%). We should note that these troops were engaged in a field exercise at the time of this study. Therefore, the role of the anthrax vaccination cannot reasonably be separated from the rigorous physical exertion commonly associated with field deployments.
(c) Events or effects by gender: Not evaluable.
(d) Length of time to resolution: No adverse event caused lost time from work or hospitalization and all reactions resolved without lasting consequences.

F. USAMRIID Dose-Reduction / Route-Change Study (the “pilot study”)

Citation: Technical report provided to the Food & Drug Administration.
Pittman PR, Kim-Ahn G, Pifat DY, Coonan K, Gibbs P, Little S, Pace-Templeton JG, Myers R, Parker GW, Friedlander AM. Anthrax vaccine: Safety and immunogenicity of a dose-reduction, route comparison study in humans. *Vaccine* 2002;20(Jan 31):1412-20.
See also: Pittman PR, Mangiafico JA, Rossi CA, Cannon TL, Gibbs PH, Parker GW, Friedlander AM. Anthrax vaccine: Increasing intervals between the first two doses enhances antibody response in humans. *Vaccine* 2000;18:213-216.
See also: Pittman PR. Aluminum-containing vaccine associated adverse events: Role of route of administration and gender. *Vaccine* 2002;20:S48-50.
Investigators: Scientists at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), Fort Detrick, Maryland
Period of Observation: 1998 (enlarged study underway, coordinated by the CDC)
Participants: 109 men, 64 women, 173 people total. Age range: 19 to 64 years. Mean ages per group: 32 to 35 years.
Vaccine Studied: Lansing formulation

Study Design: USAMRIID actively collected safety data during a pilot study to evaluate a reduced schedule for administering the anthrax vaccine. The safety of anthrax vaccination was studied in three cohorts of people: (1) some got the standard schedule of the first three doses (0, 2, 4 weeks) into the subcutaneous layer ½” under the skin, (2) others received two doses given subcutaneously, (3) a third cohort received two injections into the muscle in the upper arm, about 1” below the surface. All these volunteers gave informed consent for the procedure.
Findings: This study provides evidence that local adverse events are less common when the intramuscular route is used to administer anthrax vaccine, compared to the subcutaneous route.
(a) Injection-site (“local”) Reactions: Redness and swelling at the injection site occurred more commonly among those given subcutaneous injections, compared to intramuscular injections. Male vaccine recipients developed injection-site swelling (induration) less frequently after subcutaneous injection (3% to 19%) than female vaccine recipients (38% to 75%), but the rates were comparably low for both genders when the vaccine was given by intramuscular injection (1.4% to 2.2%). Subcutaneous nodules, which resolved spontaneously, were common among recipients of subcutaneous injections (24% of men, 63% of women), but were not observed among recipients of intramuscular injections (0% for both men and women).
(b) Events Beyond the Injection Site (“systemic”): Systemic adverse events were uncommon and their incidence did not differ among the three cohorts. After the first three doses, the side effects noted were headache (7% to 17%); malaise (4% to 10%); loss of appetite (0% to 9%); nausea or vomiting (2% to 6%); muscle ache (2% to 7%); itching (0% to 3%) and low grade fever (0% to 3%). All of these reactions were graded as nonserious; none were serious events.

(c) Events or effects by gender: Male vaccine recipients developed injection-site swelling (induration) less frequently after subcutaneous injection (3% to 19%) than female vaccine recipients (38% to 75%), but the rates were comparably low for both genders when the vaccine was given by intramuscular injection (1.4% to 2.2%). Subcutaneous nodules, which resolved spontaneously, were common among recipients of subcutaneous injections (24% of men, 63% of women), but were not observed among recipients of intramuscular injections (0% for both men and women).

(d) Length of time to resolution: Not specifically described, but temporary duration was common, as in other studies.

From the Jan 02 FDA-approved product labeling for anthrax vaccine adsorbed, *BioThrax*:

"Recently (1996-1999), 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 (7) 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 (100.7oF).

Local Reactions- The most common local reactions reported after the first dose (n=28) in this study were tenderness (71%), erythema (43%), subcutaneous nodule (36%), induration (21%), warmth (11%) and local pruritus (7%). The most frequently reported local reactions after the second dose (n=28) were tenderness (61%), subcutaneous nodule (39%), erythema (32%), induration (18%), local pruritus (14%), warmth (11%), and arm motion limitation (7%). After the third dose (n=26), the most frequently reported local reactions were tenderness (58%), warmth (19%), local pruritis (19%), erythema (12%), arm motion limitation (12%), induration (8%), edema (8%), and subcutaneous nodule (4%). 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%), respiratory difficulty (4%) and fever (4%). After the second dose (n=28), the most frequently reported systemic reactions were malaise (11%), myalgia (7%), fever (7%), headache (4%), anorexia (4%) and nausea or vomiting (4%). After the third dose (n=26), the most frequently reported systemic reactions were headache (4%), malaise (4%), myalgia (4%) and fever (4%). 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.

G. Canadian Forces Safety Survey

Citation: Canadian Forces Medical Group. Letter from Assistant Chief of Staff Operations to Canadian Clinical Trials and Special Access Programme, 15 October 1999.
Investigators: Canadian military physicians, Canadian Forces Medical Group, Ottawa
Period of Observation: February to May 1998
Participants: 576 people total, gender unspecified, members of three Canadian Forces units deployed to the Persian Gulf during Operation Determination who received 1,676 doses of anthrax vaccine (1, 2, or 3 doses per person). Age range: adult military personnel, years of age not described.
Vaccine Studied: Lansing formulation

Study Design: Actively monitored study of adverse events after anthrax vaccination.
Findings:
(a) Injection-site ("local") Reactions:
Mild (1 to 5 cm): after 4.4% of doses, reported by 12.7% of recipients
Moderate (> 5 to 12 cm): after 0.2% of doses, reported by 0.5% of recipients
Large: none reported
(b) Events Beyond the Injection Site ("systemic"): Systemic reactions occurred after 2.2% of doses, reported by 5.7% of recipients. Reported systemic events included headache (13 reports), flu-like gastrointestinal symptoms (9), fever with or without chills (5), foul taste in mouth (3), and neurologic symptom (1, temporary, not considered serious). Two individuals reported heartburn after each of three vaccine doses. . One individual reported a persistent lump (nodule) at the injection site and multiple nodules at several distant sites, but it is unknown whether those lumps existed unnoticed before the vaccination. One medical officer noted several cases of fever and chills, with or without malaise; in all cases these events resolved within 2 to 5 days.
(c) Events or effects by gender: Not described
(d) Length of time to resolution: In all cases except the persistent nodule, these events resolved within 2 to 5 days.

H. TAMC-601 Survey

Citation: Centers for Disease Control & Prevention. Surveillance for adverse events associated with anthrax vaccination - U.S. Department of Defense, 1998-2000. *Morbidity & Mortality Weekly Report* (*MMWR*) 2000;49(Apr 28):341-5. Reprinted in *JAMA* 2000;283:2648-9. <http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/mm4916a1.htm>.

Wasserman GM, Grabenstein JD, Pittman PR, Rubertone MV, Gibbs PP, Wang LZ, Golder LG. Analysis of adverse events after anthrax vaccination in US Army medical personnel. *Journal of Occupational & Environmental Medicine* 2003;45:222-33.

Investigators: Preventive Medicine Division, Tripler Army Medical Center (TAMC), Honolulu, Hawaii

Period of Observation: 1998 to 2000

Participants: 416 men, 185 women, 601 people total; physicians, nurses, medics and other medical-support personnel who augment U.S. medical forces in Korea in military contingencies. Age range: 17 to 61 years, mean: 29.9 years, standard deviation 7.5 years.

Vaccine Studied: Lansing formulation

Study Design: Prospective, population-based, self-reported survey. The people surveyed are a highly educated, medically experienced population, more able than the norm to describe adverse events and with more ready access to care than other populations.

Findings: Regardless of gender, most adverse events after vaccination were mild and self-limited. The results for all systemic complaints did not substantially vary between dose #1, dose #2, dose #3, and dose #4.

(a) Injection-site ("local") Reactions:

Mild, redness < 5 cm (35% to 40%). Women reported more localized itching (39% to 63%), compared to men (25% to 28%). Women developed more subcutaneous nodules (73% to 90%), compared to men (61% to 66%).

Moderate, redness 5 to 10 cm (20% to 25%).

Large, redness > 10 cm (5% to 10%). Moderate to large injection-site reactions were more common among women (40% to 51%) than among men (17% to 32%). Women reported more swelling of the lower arm (8% to 14%), compared to men (7% to 10%)

(b) Events Beyond the Injection Site ("systemic"): Women reported muscle soreness more often (62% to 80%), compared to men (60% to 67%). About 20% of men and women reported symptoms that they personally judged could be ignored; 15% reported symptoms that affected their activity for a short time but did not limit their ability to perform duties; 8% reported symptoms that affected their activity for a short time that was relieved by self-treatment with nonprescription medication; and fewer than 2% reported that their symptoms were unrelieved by medication and that their ability to perform their duties was limited for a short time. From 1.5%

to 2.7% of women and 1.2% to 2.1% of men reported systemic events leading to limitation of performing duties.

(c) Events or effects by gender: Individual injection-site and systemic events occurred more frequently among women than men, but events in both genders were similar in resolving on their own over the course of a few days without residual consequences. Between 4% and 14% of women had an outpatient medical visit, compared to 2% to 5% of men. From 4% to 12% of women and 2% to 6% of men reported they could not perform a duty for a short period after vaccination.

(d) Length of time to resolution: Muscle aches typically lasted between 7 hours and 3 days.

I. U.S. Forces Korea Vaccination Series

Citation: Centers for Disease Control & Prevention. Surveillance for adverse events associated with anthrax vaccination - U.S. Department of Defense, 1998-2000. *Morbidity & Mortality Weekly Report (MMWR)* 2000;49(Apr 28):341-5. Reprinted in *JAMA* 2000;283:2648-9. <http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/mm4916a1.htm>.

Hoffman K, Costello C, Menich M, Grabenstein JD, Engler RJM. Using a structured medical note for determining the safety profile of anthrax vaccine for U.S. Soldiers in Korea. *Vaccine* 2003:21:4399-4409.

Investigators: Department of Preventive Medicine, 121st General Hospital, Seoul, Republic of Korea

Period of Observation: 1998 to 1999

Participants: 2,214 men, 610 women, 2,824 people total at Camp Casey. Age range: adult military personnel, years of age not described.

Vaccine Studied: Lansing formulation

Study Design: Systematic recording of self-reported surveys when personnel returned for subsequent doses of anthrax vaccine.

Findings: Regardless of gender, almost all reported events were localized or minor, self-limited, and did not lead to impairment of work performance.

(a) Injection-site ("local") Reactions: Women reported lumps more frequently (50% to 62%) than did men (21% to 29%).

Mild (redness < 5 cm): Women (12% to 14%), men (7% to 8%)

Moderate (redness 5 to 12 cm): Women (11% to 13%), men (4% to 5%)

Large (redness > 12 cm): Women (2% to 4%), men (0.4% to 1%)

(b) Events Beyond the Injection Site ("systemic"): Itching was reported by 20% to 37% of women and 6% to 8% of men. Fever was reported by 2% to 4% of women and 1% of men. Chills were reported by 3% to 6% of women and 1% to 2% of men. Malaise was reported by 8% to 15% of women and 4% to 7% of men. Overall, 0% to 1.9% reported that their work activity had been limited to some extent or were placed on limited duty. From 0% to 1.1% reported losing one or more days of duty; 0.4% to 1.7% consulted a clinic for the reaction. One individual was treated in an emergency room (analyzed under VAERS, below).

(c) Events or effects by gender: Overall, 60% to 68% of women and 32% to 40% of men reported at least one adverse event after the first or second doses of anthrax vaccine.

(d) Length of time to resolution: Almost all reported events were localized or minor, self-limited, and did not lead to impairment of work performance.

J. Reports involving Anthrax Vaccine Submitted to the FDA/CDC Vaccine Adverse Event Reporting System (VAERS) and Evaluated by the Anthrax Vaccine Expert Committee

Citation: Centers for Disease Control & Prevention. Surveillance for adverse events associated with anthrax vaccination - U.S. Department of Defense, 1998-2000. *Morbidity & Mortality Weekly Report (MMWR)* 2000;49(Apr 28):341-5. Reprinted in *JAMA* 2000;283:2648-9. <http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/mm4916a1.htm>.

Sever JL, Brenner AI, Gale AD, Lyle JM, Moulton LH, West DJ. Safety of anthrax vaccine: A review by the Anthrax Vaccine Expert Committee (AVEC) of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS). *Pharmacoepidemiology & Drug Safety* 2002; 11:189-202.

Second manuscript under review: Sever JL, Brenner AI, Gale AD, Lyle JM, Moulton LH, Ward BJ, West DJ. Safety of anthrax vaccine: An expanded review and evaluation of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS).

See also: Brenner AI, Gale AD, Lyle JM, Moulton LH, Sever JL, Ward BJ, West DJ. Articular complaints following anthrax vaccine (AVA): an analysis of data from the Vaccine Adverse Event Reporting System (VAERS). *Arthritis Rheum* 2002;46:3417.

Investigators: Civilian medical experts convened by US Department of Health & Human Services (DHHS). Health Resources & Services Administration

Period of Observation: 1990 to present. Data collection and analysis ongoing

Participants: 1,793 vaccine recipients reflected in 1,893 VAERS reports (1,857 when duplicates are omitted), as of February 21, 2002. Vaccinee age range: 18 to 61 years.

Vaccine Studied: Lansing formulation

Note: The most detailed information on VAERS reports is maintained by the Food & Drug Administration (FDA) *and the Centers for Disease Control & Prevention (CDC). The following analysis is based on VAERS information made available to the DoD. Questions involving more detailed analyses should be referred to DHHS.*

Study Design: DoD relays all reports (whether initiated by vaccinee, guardian, health-care provider, or any other source) of adverse events after any vaccination to VAERS. The VAERS staff seeks additional medical records, if needed, and follows subjects of these reports to gather information about symptom resolution.

At the request of DoD, the Department of Health and Human Services (DHHS) established an Anthrax Vaccine Expert Committee (AVEC) in October 1998 to review VAERS forms related to anthrax vaccine. The AVEC independently reviews all anthrax vaccine-related reports received by VAERS. The AVEC meets every 3 to 6 weeks, along with representatives of DoD, CDC, FDA, and DHHS, to review all the new anthrax adverse events reports submitted in the

interim. The AVEC reviews the quality of the submitted information, evaluates the reported event in the context of expected and unexpected adverse events to vaccines, and assesses the cause-and-effect relationship of the event with the anthrax vaccine. The AVEC also looks for any clinically significant patterns in the aggregate data.

Findings: To date, the AVEC reports that it has found nothing unexpected in the side-effect profile of anthrax vaccine. The chairman of the AVEC stated, "Based on the review of these adverse events, it is apparent that it is safe to continue the anthrax vaccine immunization program of the Department of Defense and it is appropriate to continue to monitor the vaccine adverse events reports and review the safety of the vaccine on an ongoing basis."

As of February 21, 2002, the independent AVEC reviewed 1,857 unique VAERS reports related to anthrax vaccination. The 1,857 reports were grouped into three main categories, based on effect on the vaccine recipient's functional status: hospitalization, loss of duty $\geq$ 24 hours, and other (reports involving neither hospitalization nor loss of duty $\geq$ 24 hours).

Sixty-four of the 1,857 reports involved hospitalization. The civilian panel found that 11 of the 64 "very likely/certainly" or "probably" were caused by anthrax vaccine. All 11 involved allergic or inflammation reactions at the injection site.

For background, the other 53 hospitalizations (those not categorized as "very likely/certainly" or "probably" caused by anthrax) vaccine involved the following diagnoses:

Abdominal pain (1-"unclassifiable" according to AVEC)
Acute encephalitis (1-"unrelated")
Angioedema (1-"unrelated")
Aplastic Anemia (1- "unclassifiable")
Atrial fibrillation (1-"unlikely," 1-"unclassifiable")
B-cell lymphoma involving CNS (1-"unrelated")
Bipolar psychiatric disorder (1--"unclassifiable," 1-"unrelated")
Blackout episode (1-"unrelated")
Breast cancer (1-"unrelated")
Cardiac arrest (1-"unrelated")
Cardiomyopathy with atrial fibrillation (1-"unlikely," 1-"unrelated")
Diabetes mellitus, insulin-requiring (1-"unclassifiable")
Diabetes mellitus, non-insulin-requiring (1-"unrelated")
Dysethesias (T1 and below) (1-"unclassifiable")
Dyspnea (2-"unclassifiable")
Endocarditis with perirectal abscess (1-"unrelated")
Fatigue and injection-site inflammation (1-"possible")
Febrile illness (1-"unrelated")
Gastrointestinal symptoms (1-"unrelated")
Guillain-Barré syndrome (GBS, 3-"unclassifiable," 2-"unrelated")
Idiopathic thrombocytopenic purpura (ITP, 1-"unclassifiable")
Inflammation over olecranon process (1-"unrelated")
Liver abscess with *E. coli* septicemia (1-"unrelated")

Intestinal surgery (appendectomy) (1-“unrelated”)
Meningitis, aseptic (1-”unrelated”)
Meningitis, viral (1-“unclassifiable”)
Meningitis, unspecified (1-”unrelated”)
Migratory arthralgia (1-”unrelated”)
Multiple sclerosis (1-“unlikely”)
Neurological symptoms (facial weakness, slurred speech) (1-“unlikely”)
Neutropenia, fever (2-“unclassifiable”)
Optic neuritis (1-”unclassifiable”)
Pemphigus vulgaris (1-“unlikely”)
Pericarditis (1-“unlikely”)
Progressive paralytic neurologic disease (1-“unlikely”)
Rash (1-“possible”)
Scleritis bilaterally (1-“unrelated”)
Seizure (1-“unrelated”)
Syncope (1-“unrelated”)
Systemic lupus erythematosus (1-“unlikely”)
Tension-migraine headaches (1-”unrelated”)
Thrombotic thrombocytopenic purpura (1-”unrelated”)
Toxic epidermal necrolysis syndrome (1-“unrelated”)
Viral-like syndrome (2-”unrelated”)

Six forms reported the death of a vaccine recipient (cardiovascular-3, aplastic anemia-1, suicide-1, B-cell lymphoma-1; mean age = 50 years old). The AVEC categorized none of the deaths as related to anthrax vaccination.

Another 172 reports involved loss of duty $\geq$ 24 hours (but did not involve hospitalization); the civilian panel found that 94 of the 172 certainly or probably were caused by anthrax vaccine. These 94 reports described injection-site reactions (54 reports), various rashes (10), acute allergic reactions (9), viral-like symptoms (10), itching (2), gastroenteritis (2), muscle aches (2), bronchiolitis obliterans (1), tingling sensation (1), photophobia (1), ulnar nerve neuropathy (1), and other symptoms. Some reports described multiple symptoms.

The balance of the 1,857 reports, 1,621, involved neither hospitalization nor loss of duty $\geq$ 24 hours. All were reviewed by the AVEC, which found no patterns of unexpected adverse events.

* * *

No VAERS reports have been submitted regarding microbial contamination of vaccine vials.

(c) Events or effects by gender: Women represented 27% of VAERS reports submitted during an interval when women received 9.8% of anthrax vaccine doses.

(d) Length of time to resolution: Based on information available to the Anthrax Vaccine Immunization Program (AVIP) Agency (some of which includes records with information redacted by the FDA), all personnel described by VAERS reports

judged by the AVEC to be “very likely/certainly” or “probably” caused by anthrax vaccine have recovered or are recovering.

From the Jan 02 FDA-approved product labeling for anthrax vaccine adsorbed, *BioThrax*:

Postlicensure Adverse Event Surveillance

Data regarding potential adverse events following anthrax vaccination are available from the Vaccine Adverse Event Reporting System (VAERS).[7] 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 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 1850 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% 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 body systems and defined as 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 erythematosis, 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 fibrilation, syncopy, 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 out-of-hospital arrest (2), myocardial infarction with chronic patchy vasculitis (1), aplastic anemia (1), suicide (1) and central nervous system (CNS) lymphoma (1).

K. ROTC Cadets at Fort Lewis, Washington

Citation: Gunzenhauser JD, Cook JE, Parker ME. Acute side effects of anthrax vaccine in ROTC cadets participating in advanced camp, Fort Lewis, 2000. *Medical Surveillance Monthly Report* 2001;7(5):9-11. http://amsa.army.mil/1MSMR/2001/v07_n05.pdf.

Investigators: Preventive Medicine Service, Madigan Army Medical Center, Fort Lewis, Washington

Period of Study: Summer 2000

Participants: 73 cadets attending Advance Camp for the Reserve Officer Training Corps (ROTC) with orders for follow-on training in Korea. Age range: not described, typically in their early 20s.

Vaccine Studied: Lansing formulation

Study Design: 25 cadets who inadvertently received a 1-ml dose of anthrax vaccine for their first dose were contrasted with 48 cadets who received the proper 0.5-ml volume.

Findings:

(a) Injection-site ("local") Reactions: The most common symptom was sore arm, reported by 67% of cadets, regardless of first dose received. The next three most common symptoms occurred more commonly in the double-dose group: redness-39% vs. 19%, lump-44% vs. 29%, swelling-50% vs. 19%.

(b) Events Beyond the Injection Site ("systemic"): Of nine specific symptoms queried, similar proportions of double- and standard-dose cadets reported one or more symptoms. However, 44% of double-dose and 26% of standard-dose cadets reported three or more symptoms. Seventeen percent of double-dose cadets and 7% of standard-dose cadets reported decreased performance after the second anthrax vaccination. One cadet who received a doubled first dose attended sick call with a chief complaint of feeling feverish and was returned to duty. There were no hospitalizations, ER visits, or missed training related to vaccination.

(c) Events or effects by gender: Not analyzed by gender.

(d) Length of time to resolution: All reactions to the vaccine were mild and self-limited. None affected cadet training.

Group III: Studies from the 1990s, Database Analyses

L. USAF Air Combat Command Study, Langley Air Force Base

Citation: Rehme PA, Williams R, Grabenstein JD. Ambulatory medical visits among anthrax-vaccinated and unvaccinated personnel after return from southwest Asia. *Military Medicine* 2002; 167:205-10.

Investigators: USAF Air Combat Command, 1st Aerospace Medicine Squadron, Langley AFB, Virginia

Period of Observation: 1998 to 1999

Participants: 3,390 vaccinated men, 655 vaccinated women, 4,045 total vaccinated personnel; compared to 962 unvaccinated men, 170 unvaccinated women, 1,132 total unvaccinated personnel, 5,177 people total, USAF personnel deployed to Southwest Asia between January and September 1998. Age range: 19 to 43 years.

Vaccine Studied: Lansing formulation

Study Design: Electronic records of anthrax vaccination were linked with electronic records of ambulatory medical visits among vaccinated and unvaccinated personnel who had returned from Southwest Asia in the previous 6 months.

Findings: No statistically significant associations between anthrax vaccination and any ambulatory diagnosis were found. These diagnoses included allergy, arthropathy, circulatory, dermatological, digestive, endocrine, headache/neurological, hearing, infectious/parasitic, injuries, mental health, musculoskeletal, nasal, neoplastic, ocular, reproductive, respiratory, sleep disorders, urinary, unexplained illness, or more than one diagnosis. In addition, vaccination status did not cause any statistically significant elevation in ambulatory visits for 16 specific diagnoses (e.g., autoimmune disease, thyroid disorder, infertility, dizziness/syncope, tinnitus).

(a) Injection-site ("local") Reactions: Not applicable.

(b) Events Beyond the Injection Site ("systemic"): No effects observed.

(c) Events or effects by gender: No difference in findings when men and women are considered separately. No gender effects observed.

(d) Length of time to resolution: Not applicable, no hazard found.

M. Fort Stewart, Georgia, Reproductive Health Study

Citation: Wiesen AR, Littell CT. Relationship between prepregnancy anthrax vaccination and pregnancy and birth outcomes among US Army women. *Journal of the American Medical Association (JAMA)* 2002;287:1556-60. http://jama.ama-assn.org/cgi/reprint/287/12/1556.pdf

Investigators: Department of Preventive Medicine, Winn Army/Community Hospital, 3rd Infantry Division, Fort Stewart and Hunter Army Air Field, Georgia

Period of Study: January 1999 to March 2000

Participants: All 4,092 active-duty women assigned to either Fort Stewart or Hunter Army Air Field, Georgia. Age range: 17 to 44 years (mean 25.7 years).

Vaccine Studied: Lansing formulation

Study Design: Cohort study of all active-duty women, 17 to 44 years old, assigned to either Fort Stewart and Hunter Army Air Field, evaluating likelihood and outcomes of pregnancy, contrasting 3,135 women vaccinated against anthrax and 957 unvaccinated women, with 39,549 person-months of follow-up.

Findings:

(a) Conception: 385 of the 3,136 vaccinated women (12%) became pregnant, compared to 128 of 956 unvaccinated women (13%), statistically equivalent proportions. After adjustment for marital status, race and age, the rate ratio was 0.94.

(b) Giving Birth: Women who received anthrax vaccine were 1.2 times as likely to give birth as unvaccinated women (95% CI: 0.8 to 1.8), before and after adjustment for marital status, race and age. 276 births resulted among the 385 vaccinated women followed to term (78%), compared to 77 births among 103 unvaccinated women who became pregnant (75%), statistically equivalent proportions, with an adjusted odds ratio of 0.9.

(c) Birth Defects: Data for 327 births were available for birth outcome analysis. Eleven (3.3%) of the births were of low birth weight (< 2,500 grams). The odds ratio for anthrax vaccination and low birth weight, after adjusting for age, was 1.3 (95% confidence interval (CI): 0.2 to 6.4). There were 15 structural abnormalities of cosmetic and/or medical significance (ICD-9 codes 740-759). No unusual patterns or clusters were noted. The only abnormality with multiple occurrences was polydactyly of the fingers (3 cases, 2 in the anthrax immunized group and 1 in the non-immunized group). The odds ratio for anthrax vaccination and structural abnormality, after adjusting for age, was 0.7 (95% CI: 0.2 to 2.3). The odds ratio for anthrax vaccination and any adverse birth outcome, after adjusting for age, was 0.9 (95% CI: 0.4 to 2.4). However, the study did not have adequate statistical power to rule out a small effect of vaccination on adverse birth outcome, given the low number of adverse outcomes.

(d) Length of time to resolution: Not applicable, long-term health effects sought but no hazard found.

N. Reproductive Outcomes of the Wives of Male Soldiers Vaccinated Against Anthrax (Preliminary Report)

Citation: None yet, report in progress. Wojcik B, Abbott CA. Reproductive health outcomes in spouses and neonates of anthrax-vaccinated male soldiers.

Investigators: Center for Health Education & Studies, Army Medical Department Center & School

Period of Study: January 1998 to August 2000

Participants: 237,022 active-duty Army male soldiers married to civilian women, contrasting 68,267 wives of anthrax-vaccinated men and 168,755 wives of anthrax-unvaccinated men. Pregnancy-related hospitalizations occurred as follows: 5,153 women hospitalized with 17,909 diagnoses in the vaccinated group and 28,117 women hospitalized with 89,108 diagnoses in the unvaccinated group. Further analysis evaluated 4,425 deliveries to wives of anthrax-vaccinated men and 22,802 deliveries to wives of anthrax-unvaccinated men. Age range not described.

Vaccine Studied: Lansing formulation

Study Design: Electronic records of anthrax vaccination were linked with electronic personnel records and electronic medical records of obstetric and gynecologic outpatient visits and hospitalizations. First, cohorts of anthrax-vaccinated and unvaccinated men were defined. From these cohorts, a smaller secondary set of cohorts of their wives was defined. Paternity of the husband for the offspring was assumed.

Findings:

(a) Rates of various hospitalizations did not differ significantly between the wives of anthrax-vaccinated men and the wives of anthrax-unvaccinated men.

Condition (ICD-9 code)	Fraction of Wives, Vaccinated Group	Fraction of Wives, Unvaccinated Group	Statistical Finding
Menstrual disorders (626)	0.8%	0.6%	p=0.09
Infertility (628)	0.2%	0.2%	p=0.55
Ectopic pregnancy (630-633)	0.7%	0.6%	p=0.16
Complications of labor (660-69)	28.5%	28.2%	p=0.50
Normal pregnancy (V22)	0.2%	0.2%	p=0.13
High-risk pregnancy (V23)	0.8%	0.9%	p=0.37

(b) Outcomes of delivery did not differ significantly between the wives of anthrax-vaccinated men and the wives of anthrax-unvaccinated men.

Birth Outcome	Deliveries Among Vaccinated Group	Deliveries Among Unvaccinated Grp	Statistical Finding

Single live born	98.8%	98.4%	p=0.21
Single stillborn	0.3%	0.5%	
Twins, both live born	0.9%	1.1%	
Twins, both stillborn	0.0% (n=0)	0.0% (n=5)	
Length of stay $\geq$ 4 d	8.0%	8.4%	

(c) Length of time to resolution: Not applicable, long-term health effects sought but no hazard found.

O. USAF Vision Study

Citation: Gibson RL, Hinten SR. Study of the effects of anthrax immunization on vision. Institute for Environment, Safety, & Occupational Health Risk Analysis, Brooks Air Force Base, Texas. Full manuscript for publication in final draft.

Investigators: Force Health Protection and Surveillance Division, Institute for Environment, Safety, & Occupational Health Risk Analysis (IERA/RSRH). Personnel were seen by Aeromedical Consult Service, United States Air Force School of Aerospace Medicine.

PHASE I

Period of Observation: 1998 to 1999

Participants: 178 case subjects with vision change (161 men and 17 women) and 1,803 control subjects without vision change (1,744 men and 59 women), 1,981 people total, USAF aircrew members, deployed worldwide. Mean age: 35.5 years for cases and 34.4 years for controls.

Vaccine Studied: Lansing formulation

Study Design: Aviators who suffered a change in vision sufficient to jeopardize flying status were enrolled as cases, with ten age-matched controls identified from automated records of physical examinations. Next, the vaccination status of cases and controls were determined from the anthrax vaccination database.

Findings: Seventeen of 95 cases (18%) had received at least one dose of anthrax vaccine, compared to 451 of 1,060 control aviators (43%). The resulting odds ratio of 0.30 (95% confidence interval: 0.18 to 0.52) provides evidence that vaccination is not associated with vision change. Technically, the value less than one (with a confidence interval that excludes one) implies that vaccination is protective against vision change, but such a phenomenon is not biologically plausible.

(a) Injection-site (“local”) Reactions: Not applicable.

(b) Events Beyond the Injection Site (“systemic”): Vaccination is not associated with vision change.

(c) Events or effects by gender: Not applicable, no effect observed.

(d) Length of time to resolution: Not applicable, long-term health effects sought but no hazard found.

PHASE II

Period of Observation: 1998 to 1999

Participants: 448 case subjects with vision change and 510 control subjects without vision change, 958 people total, USAF aircrew members, deployed worldwide. Mean age: 34.8 years for cases and 33.9 years for controls.

Vaccine Studied: Lansing formulation

Study Design: Medical records with pairs of physical examination data were collected that recorded changes in visual acuity. Next, the vaccination status of cases and controls were determined from the anthrax vaccination database.

Findings: 109 of 448 aviators (24.4%) with visual acuity change had been vaccinated against anthrax, compared to 134 of 510 (26.3%) of aviators without visual acuity change. The resulting odds ratio of 0.90 (95% confidence interval: 0.68 to 1.20) provides evidence that there is no association between anthrax vaccination and changes in visual acuity.

(a) Injection-site (“local”) Reactions: Not applicable.

(b) Events Beyond the Injection Site (“systemic”): Vaccination is not associated with vision change.

(c) Events or effects by gender: Not applicable, no effect observed.

(d) Length of time to resolution: Not applicable, long-term health effects sought but no hazard found.

P. Army Aviator Flight Physical Examination Study

Citation: Mason KT, Grabenstein JD, McCracken LR. Hearing loss after anthrax vaccination among US Army aircrew members. Manuscript in progress.
Mason KT, Grabenstein JD, McCracken LR. US Army Aviation Epidemiology Data Register: Physical findings after anthrax vaccination among US Army aircrew members. Technical report, October 2001.

Investigators: Aviation Epidemiology Data Register, US Army Aeromedical Activity, US Army Aeromedical Center, Fort Rucker, Alabama (<www.rucker.amedd.army.mil>)

Period of Study: 1998 to 2000

Participants: 3,356 matched pairs of anthrax vaccinated and unvaccinated aircrew members (6,712 personnel), matched by gender, race, age, class of flying duties and service component. Age range: 20 to 64 years.

Vaccine Studied: Lansing formulation

Study Design: Matched pairs were contrasted for the presence of hearing loss, defined as a > 15 decibel hearing loss in any frequency in any ear when comparing the audiology examination before and after the first anthrax vaccination date of vaccinated personnel

Findings:

(a) Among the 3,356 matched pairs, 83 pairs had a hearing loss in both the vaccinated and unvaccinated individual, whereas 2,439 pairs had no hearing loss in either the vaccinated and unvaccinated individual. In 429 pairs, the unvaccinated individual had a hearing loss, but the vaccinated person did not. In 405 pairs the converse was true: the vaccinated individual had a hearing loss, but the unvaccinated person did not. Thus, the odds ratio for hearing loss due to vaccination is 0.94 (95% confidence interval: 0.82, 1.09), meaning that anthrax vaccination is unrelated to hearing loss.

(b) Similarly, no significant elevations in the rates of the following conditions were detected in matched-pairs analysis:

weight loss or gain of 20 pounds or more
hypertension $\geq$ 140/90 or began taking antihypertensive medication
abnormal change in blood pressure
abnormal hematocrit
intraocular hypertension $\geq$ 21 or began taking medication for glaucoma
stereopsis greater than 40-second arc
abnormal stereopsis
loss of vision of 1 or more Snellen lines
loss of vision of 2 or more Snellen lines
loss of vision of 3 or more Snellen lines
development of proteinuria, glycosuria, or hematuria
fasting blood sugar > 115 or diagnosis of diabetes mellitus

(d) Length of time to resolution: Not applicable, long-term health effects sought but no hazard found.

Q. Defense Medical Surveillance System (comparison of hospitalization rates for selected diagnoses before and after introduction of Anthrax Vaccine Immunization Program)

Citation: Lange JL, Lesikar SE, Brundage JF, Rubertone MV. Comprehensive systematic surveillance for adverse effects of anthrax vaccine adsorbed, US Armed Forces, 1998-2000. *Vaccine* 2003;21:1620-28.

Investigators & Design: The Defense Medical Surveillance System (DMSS) is a longitudinal, relational database of personnel and demographic data, augmented with military experience and medical event data for active-duty personnel in each of the military services. The DMSS is coordinated by the Army Medical Surveillance Activity (AMSA, <http://amsa.army.mil/AMSA/amsa_home.htm>), a component of the US Army Center for Health Promotion & Preventive Medicine (USACHPPM, <http://chppm-www.apgea.army.mil>).

Period of Study: 1998 to 2001

Vaccine Studied: Lansing formulation

I. *TRENDS OVER TIME*

The rate of hospitalization for any cause among Service Members assigned to US Forces Korea shows a steady decline since 1993, despite introduction of the hepatitis A vaccination program in 1996 and the anthrax vaccination program in 1998. These data are especially meaningful, given that all military personnel in Korea received anthrax vaccine between August 1998 and November 2000. The evidence shows that there has not been an increase in hospitalizations in a theater where all Service members were vaccinated against anthrax and all hospitalizations are recorded electronically.

The rate of death due to illness for any cause at any location among active-duty Service Members has stayed steady or declined slightly, despite introduction of a hepatitis A vaccination program in 1996 and the anthrax vaccination program in 1998.

The rates of hospitalization for diagnoses alleged to be related to anthrax vaccination (including leukemia, Guillain-Barré syndrome, erythema multiforme, thyroid disorders, multiple sclerosis, lupus erythematosus, and aortic aneurysm) are essentially unchanged since 1993, despite introduction of a hepatitis A vaccination program in 1996 and the anthrax vaccination program in 1998.

Analysis of trends over time is helpful, but not as meaningful a comparison as when the health experiences of vaccinated and unvaccinated Service Members are contrasted directly. Such analyses appear in the next section.

II. *DIRECT COMPARISONS OF VACCINATED & UNVACCINATED PEOPLE*

The most scientifically powerful evidence for the safety of this vaccine comes from the Defense Medical Surveillance System, which establishes that anthrax-vaccinated and -unvaccinated personnel are hospitalized and visit outpatient clinics at basically the same rates, both overall and for each organ system of the body. For example, one per 35 anthrax-vaccinated people is hospitalized each year, compared to one per 28 unvaccinated people hospitalized per year. Anthrax-vaccinated personnel are as healthy (and as sick) as unvaccinated personnel.

Automated records of immunization and hospitalization were linked electronically. This analysis consisted of 757,540 person-years of experience in the anthrax-vaccinated group and 3,430,459 person-years experience in the anthrax-unvaccinated group. A person-year is analogous to a man-hour. Effectively, it is the experience of one person followed for one year of time. Two people followed for 6 months each also constitutes a person-year.

Rates of hospitalization for each of 14 major diagnostic categories among anthrax vaccine recipients were contrasted with Service Members (SMs) who have not received anthrax vaccine. The rate of hospitalization for each of the 14 major diagnostic categories was the same for SMs vaccinated or unvaccinated against anthrax. These categories include Blood and Blood Formation, Circulatory, Digestive, Endocrine / Immunology / Metabolic, Genitourinary-Female, Genitourinary-Male, Infectious Disease, Mental Health, Musculoskeletal / Connective Tissue, Neoplasms, Nervous System, Respiratory, Skin, Injury or Poisoning, and Ill-Defined Conditions.

The accompanying table shows the rate of hospitalization for each category per 100,000 Service Members per year, differentiating people vaccinated or unvaccinated against anthrax. The next column shows the ratio (the unadjusted ratio) of these two rates. If the rates between two groups are the same, the ratio is one.

The column labeled “adjusted ratio” uses the standard statistical method known as regression to remove the effects of age, gender, rank, deployment, service, ethnicity, previous hospitalization, calendar year, and occupation. Statistical adjustment simplifies the comparison to just the effect of the vaccine, holding other effects constant, providing an apples-to-apples comparison. The adjusted ratio is a more specific measure of the relationship between anthrax vaccination and hospitalization.

To account for the inherent variability in measures such as these, the 95% confidence interval is provided. The 95% confidence intervals (CIs) are the range of values within which the true value would lie 95% of the time, if you repeated the analysis multiple times. The 95% CIs shown are for the adjusted rate ratios. For a rate ratio to find a “statistically significant elevation,” the confidence interval would have to be entirely above 1.00.

* Finding: Assessing 14 broad categories of hospitalization, rate ratios for vaccinated active-duty Service Members are comparable to SMs unvaccinated against anthrax. None of the rate ratios is elevated. The rates of hospitalization are essentially the same for vaccinated and unvaccinated Service Members. [Details appear in the graphic.]

Within these 14 broad categories of hospitalization, specific diagnoses are of interest. Another accompanying table shows the rates of hospitalization for various disorders alleged to be associated with anthrax vaccination. The accompanying table shows data for lymphatic cancers (such as leukemia), thyroid disorders, multiple sclerosis, Guillain-Barré syndrome, disorders of the ear, asthma, ulcers or gastritis, joint problems (arthropathies), diffuse disorders of connective tissue (e.g., lupus erythematosus), heart rhythm, or complications of surgery or medical care not elsewhere classified. As with the major categories above, no rate ratio is elevated for vaccinated active-duty Service Members, compared to SMs unvaccinated against anthrax.

* Finding: Again, none of the rate ratios is elevated for vaccinated active-duty Service Members, compared to SMs unvaccinated against anthrax. The rates of hospitalization are essentially the same for SMs vaccinated or unvaccinated against anthrax. [Details appear in the graphic.]

Similarly, rates of outpatient medical visits (ambulatory visits) for each major diagnostic category among anthrax vaccine recipients was contrasted with Service Members (SMs) who have not received anthrax vaccine.

* Finding: None of the rate ratios is elevated for vaccinated active-duty Service Members, compared to SMs unvaccinated against anthrax. The rate of outpatient visits for each major diagnostic category was comparable for SMs vaccinated or unvaccinated against anthrax. [Details appear in the graphic.]

Again, within these broad categories of outpatient medical visits, specific diagnoses are of interest. Another accompanying table shows the rates of outpatient visits for various disorders alleged to be associated with anthrax vaccination. The accompanying table shows data for thyroiditis, hypothyroidism, multiple sclerosis, Guillain-Barré syndrome, visual disturbances, vertigo, asthma, migraine, rheumatoid arthritis, lupus erythematosus, heart rhythm, atherosclerosis, diabetes mellitus, testicular dysfunction, ulcerative colitis, erythema multiforme. As with the major categories above, none of these rate ratios is elevated for vaccinated active-duty Service Members, compared to SMs unvaccinated against anthrax.

* Finding: None of the rate ratios is elevated for vaccinated active-duty Service Members, compared to SMs unvaccinated against anthrax. The rates of outpatient medical visits are essentially the same for SMs vaccinated or unvaccinated against anthrax. [Details appear in the graphic.]

For a third analysis, only incident hospitalizations and outpatient medical visits were considered. Incident visits are defined here as the first visit for a given diagnosis, regardless of inpatient or outpatient setting. This approach removes some practice-pattern differences that exist across the wide range of military treatment facilities around the globe, as well as removing the effect of repeat visits for the same diagnosis. Incident analysis emphasizes the number of people with a diagnosis, with less focus on the number of visits they experienced. Again, for each major diagnostic category among anthrax vaccine recipients was contrasted with Service Members (SMs) who have not received anthrax vaccine.

* Finding: None of the rate ratios is elevated for vaccinated active-duty Service Members, compared to SMs unvaccinated against anthrax. The rate of incident visits for each major diagnostic category was comparable for SMs vaccinated or unvaccinated against anthrax. [Details appear in the graphic.]

Once again, within the broad categories, we analyzed the same specific diagnoses.

* Finding: As with the major categories above, none of these rate ratios is elevated for vaccinated active-duty Service Members, compared to SMs unvaccinated against anthrax. The rates of outpatient medical visits are essentially the same for SMs vaccinated or unvaccinated against anthrax.

Rate Ratios for Specific Medical Visits & Anthrax Vaccination

(Incident Hospitalization & Outpatient Visit Rate Among Anthrax Vaccine Recipients Divided by Rate Among Nonrecipients, for Active-Duty Personnel)

Recipients = 757,540 person-years of experience
Nonrecipients = 3,430,459 person-years of experience

Category	Rate per 100,000 per Year: Vaccinated	Unvaccinated	Rate Ratios: Unadjust.	Adjusted	95% Confidence Interval (Adjusted)	Significant Elevation?
Aplastic anemia	2.1	4.8	0.44	0.56	0.33 --- 0.94	no
Conn tiss dis (lupus)	23.9	45.8	0.52	0.71	0.61 — 0.83	no
Diabetes mellitus	157	271	0.58	0.74	0.69 — 0.79	no
Erythema multiforme	99	160	0.62	0.89	0.83 --- 0.97	no
Fainting,malaise,sleep	1557	2439	0.64	0.78	0.76 — 0.79	no
Guillain-Barré syndrome	20.5	26.6	0.77	0.86	0.72 --- 1.02	no
Hypotension	15.0	18.6	0.81	0.85	0.69 --- 1.05	no
Hypothyroidism	138	272	0.51	0.72	0.67 --- 0.77	no
Lymphoma, leukemia	35.8	60.5	0.59	0.72	0.60 — 0.87	no
Migraine	613	1091	0.56	0.74	0.72 — 0.77	no
Multiple sclerosis	16.0	25.9	0.62	0.84	0.69 — 1.02	no
Myocardial infarction	12.3	21.1	0.58	0.72	0.58 --- 0.90	no
Polyarteritis nodosa	3.8	6.0	0.63	0.74	0.50 --- 1.10	no
Rheumatoid arthritis	66.1	79.5	0.83	1.02	0.92 — 1.13	no
Testicular dysfunction	32.7	31.8	1.03	0.88	0.77 — 1.02	no
Thyroiditis	15.3	28.2	0.54	0.77	0.63 — 0.94	no
Vertigo	136	179	0.76	0.81	0.76 --- 0.87	no
Visual disturbances	520	726	0.72	0.78	0.75 --- 0.81	no

Source:
Defense Medical Surveillance System
20 Aug 01
Data for Jan 98 to Dec 00

Rate ratios adjusted by standard manner (regression) to control independent effects of age, gender, rank, deployment, service, ethnicity, previous hospitalization, year, and occupation.
If confidence interval includes 1.00, then difference between vaccinated and unvaccinated group is not statistically significant, although adjustment for multiple comparisons needed.

Gender-Specific Effects: When these analytic approaches are repeated looking at men and women separately, we again find that

a. anthrax-vaccinated women are hospitalized and have outpatient medical visits at the same rates as unvaccinated women.

b. anthrax-vaccinated men are hospitalized and have outpatient medical visits at the same rates as unvaccinated men.

R. Naval Health Research Center -- Center for Deployment Health Research

Citation: Sato PA, Reed RJ, Smith TC, Wang LZ. DoD-wide medical surveillance for potential long-term adverse events associated with anthrax immunization: Hospitalizations. *Vaccine* 2002;20:2369-75.
Investigators & Design: The Naval Health Research Center developed a longitudinal, relational database of personnel and demographic data, augmented with military experience and medical event data for active-duty personnel in each of the military services. The NHRC coordinates the DoD Center for Deployment Health Research, Naval Health Research Center, San Diego.
Period of Study: January 1998 to March 2000
Vaccine Studied: Lansing formulation

NHRC monitors hospitalizations among Service Members on active duty for potential associations with anthrax. Their Oct 01 provisional report analyzes hospitalizations in both military and civilian medical treatment facilities between 1 January 1998 and 31 March 2000. Approximately 20% of Service Members on active duty had received at least one dose of anthrax vaccine by the end of March 2000. Demographic differences between vaccinated and unvaccinated Service Members were slight, but the vaccinated group had a greater proportion of males and were slightly younger.

Person-years of observation among anthrax-vaccinated personnel were counted, within a 42-day window, from the date of vaccination until whichever of the following came first: (a) the date of first hospital admission, (b) the date of next anthrax vaccination, (c) the date of separation from the military, or (d) 31 March 2000. Person-years for unvaccinated Service Members were calculated from 1 January 1998 until whichever of the following came first: (a) the date of first hospital admission, (b) the date of separation from military service, or (c) 31 March 2000. Hospitalization discharge diagnoses in each of 14 diagnostic categories of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) were analyzed.

Lower hospitalization rates were observed in anthrax-vaccinated Service Members, compared to unvaccinated Service Members, across all doses and diagnostic categories. Point estimates of adjusted risk ratios by diagnostic category were significantly less than 1.0. None included 1.0 in the 95% confidence interval. These provisional findings continue to suggest that anthrax-vaccinated active-duty Service Members were at equal or lesser risk of hospitalization than their nonimmunized counterparts.

Group IV: Other Studies

S. Mycoplasma Study

Citation: Hart MK, DelGiudice RA, Korch GW. Absence of Mycoplasma contamination in anthrax vaccine. *Emerging Infectious Diseases*, 2002;7:94-96. www.cdc.gov/ncidod/EID/vol8no1/01-0091.htm.

Investigators: US Army Medical Research Institute of Infectious Diseases and National Cancer Institute.

Period of Study: 2000

Participants: Laboratory study. No human subjects. Twenty vials of anthrax vaccine from four lots retrieved from eight military clinics across the United States. The vials were divided into two matched sets and sent to both the National Cancer Institute for live mycoplasma organisms by culture in anaerobic SP-4, anaerobic DM-1, and aerobic M-CMRL media. Charles River Tektagen (Malvern, PA) tested the second set for mycoplasma DNA by polymerase chain reaction (PCR) assay.

Vaccine Studied: Lansing formulation

Study Design: Laboratory analysis of the presence of mycoplasma in anthrax vaccine, and the ability of containers of anthrax vaccine to support the growth of mycoplasma bacteria [a putative cause of illness among Gulf War veterans].

Findings:

(a) Contents of vials of anthrax vaccine were cultured in three media at several dilutions, but mycoplasma did not grow.

(b) To test the ability of mycoplasma to survive in the vaccine, 154 million colony-forming units of live *Mycoplasma fermentans* were intentionally placed into vaccine vials, mixed, incubated, and sampled 24, 48, and 72 hours later. Inactivation of mycoplasma by the preservatives in the vaccine was rapid, as no growth was detected from any of the samples taken at any time point.

(c) Testing for the presence of mycoplasma DNA produced negative results for all 10 lots evaluated.

T. **Case Reports**

1. Swanson-Biearman B, Krenzelok EP. Delayed life-threatening reaction to anthrax vaccine. *Journal of Toxicology & Clinical Toxicology* 2001;39:81-4.

2. Kerrison JB,Lounsbury D, Thirkill CE, Lane RG, Schatz MP, Engler RM. Optic neuritis after anthrax vaccination. *Ophthalmology* 2002;109:99-104.

3. Greidanus TG, Honl BA. Delayed-type hypersensitivity reaction to anthrax vaccine. *Military Medicine* 2002;167:74-75.

4. Timmer SJ, Amundson DE, Malone JE. Hypersensitivity pneumonitis following anthrax vaccination. *Chest* 2002;122:741-45.

Commentary: Schuyler M. Amundson DE, Malone JD. Link between anthrax immunization and hypersensitivity pneumonitis. *Chest*; 2003;123:1769-70.

Comprehensive Review by the National Academy of Sciences:

Joellenbeck LM, Zwanziger L, Durch JS, Strom BL, editors. *The Anthrax Vaccine: Is it Safe? Does it Work?* Washington, DC: National Academy Press, March 2002, 235 pages. www.nap.edu/catalog/10310.html.