Detailed Safety Review of Anthrax Vaccine Adsorbed
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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 265-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 is 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, dozens of 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 give a brief synopsis of these studies including 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 (*Fed Reg* 2004;69:255-67; errata 7114-5; 2004;69:78281-93.).

In the 1960s, the production process for anthrax vaccine was revised to increase the concentration of the active ingredient, known as "protective antigen," for increasing the vaccine's potency. Additionally, these process changes decreased 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. The FDA reaffirmed the anthrax vaccine license in December 1985 and again in January 2004. Additional information regarding the transition was published in 1962 (Wright GG, Puziss M, Neely WB. Studies on immunity in anthrax. IX. Effect of variations in cultural conditions on elaboration of protective antigen by strains of *Bacillus anthracis. Journal of Bacteriology* 1962;83:515-22).

The CDC conducted an observational study involving people who received the original vaccine, 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.

In December 2008, based on studies conducted by Pittman et al. in 2002 and the CDC (Marano N, Plikaytis BD, Martin SW, et al.) in 2008, the FDA approved changes in the route of administration and the number of doses in the primary series of the anthrax vaccine. The new route of administration for the anthrax vaccine is intramuscular and the new primary dosing schedule is reduced from six to five doses by eliminating the dose at week two. Together these changes reduced injection site adverse events among those vaccinated with anthrax vaccine.

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 whether vaccinated or

unvaccinated against anthrax.

Like all vaccines, anthrax vaccine can cause soreness, redness, itching, swelling, and lumps at the injection site. Previously when the vaccine regimen included six doses in the primary series and was administered subcutaneously, 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 could persist a few weeks, but eventually went 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 vaccinations. These injection site adverse events are expected to decrease with the new dosing regimen of five doses, which are administered intramuscularly.

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. For anthrax vaccine, each VAERS report involving anthrax vaccine between 1998 and 2001 was reviewed by an independent panel of civilian physicians. This panel detected no patterns of unexpected adverse events related to anthrax vaccination. This VAERS review was updated from 1998 through January 14, 2007, (Niu MT, et al., 2009) to extend the monitoring time for serious unexpected risks and potential rare, serious events. The extended review did not find any definitive links with unexpected serious adverse events to anthrax vaccination, other than injection site and some allergic reactions, which are common with other adult vaccines. Despite the extensive body of knowledge regarding the safety of anthrax vaccine, safety monitoring continues, as is prudent for all vaccines and medications.

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, 2001, and 2004.

Details of the studies appear on the following pages. The studies include:

Historical Studies

A. The Brachman Study was the pivotal field trial evaluating safety and efficacy of the anthrax vaccine.

Brachman PS, Gold H, Plotkin SA, Fekety FK, Werrin M, Ingram NR. Field evaluation of human anthrax vaccine. *American Journal of Public Health* 1962;52:632-45. http://www.vaccines.mil/documents/library/field_eval.pdf

B. The CDC Observational Study was conducted as 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. *Federal Register* 1985;50:51002-117. http://www.vaccines.mil/documents/library/fed_reg.pdf

Multiple Vaccine Administration Studies

C. Fort Detrick conducted several multi-dose, multi-vaccine safety studies evaluating Army laboratory workers vaccinated hundreds of times with dozens of vaccines.

C1. Peeler RN, Cluff LE, Trever RW. Hyper-immunization of man. *Bulletin of the Johns Hopkins Hospital* 1958;103:183-98. http://www.vaccines.mil/documents/library/Peeler1958BJHH183.pdf

C2. Peeler RN, Kadull PJ, Cluff LE. Intensive immunization of man: Evaluation of possible adverse consequences. *Annals of Internal Medicine* 1965;63:44-57. http://www.vaccines.mil/documents/library/Intensive.pdf

C3. White CS III, Adler WH, McGann VG. Repeated immunization: Possible adverse effects: Reevaluation of human subjects at 25 years. *Annals of Internal Medicine* 1974;81:594-600. http://www.vaccines.mil/documents/library/Repeated.pdf

C4. Pittman PR, Coonan KM, Gibbs PH, Scott HM, Cannon TL, McKee KT Jr. Long-term health effects of repeated exposure to multiple vaccines. *Vaccine* 2004;23(Dec 9):525-36. www.vaccines.mil/documents/library/Longtermhealtheffects.pdf

Short Term Health Effects

D. Fort Detrick Special Immunization Program (SIP) Safety Study was a continuation of the previous studies of item C 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(5):972-8. www.vaccines.mil/documents/library/Pittman2002Vaccine972.pdf

E. TAMC-601 Survey is a study of adverse events after anthrax vaccination of medical personnel at Tripler Army Medical Center, HI.

E1. 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(16):341-5. www.cdc.gov/mmwr/PDF/wk/mm4916.pdf

E2. 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. www.anthrax.mil/documents/library/AnthraxVaccineEvaluation.pdf

F. U.S. Forces Korea Vaccination Series is a study of adverse events among personnel stationed in Korea.

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(Oct 1):4399-409. www.vaccines.mil/documents/library/Hoffman2003Vaccine4399.pdf

G. 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 (MSMR)* 2001;7(5):9-11. http://amsa.army.mil/1MSMR/2001/v07_n05.pdf#page=9

H. Defense Medical Surveillance System performed a 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(Apr 2):1620-8. www.anthrax.mil/documents/library/science.pdf

I. Naval Health Research Center, DoD Center for Deployment Health Research.

Wells TS, Sato PA, Smith TC, Wang LZ, Reed RJ, Ryan MAK. Military hospitalizations among deployed US service members following anthrax vaccination, 1998-2001. *Human Vaccines* 2006;2:2,e1-e6. http://www.landesbioscience.com/journals/vaccines/article/wellsHV2-2.pdf

J. A comparison of optical neuritis in US Military Personnel based on whether or not they received the anthrax vaccine.

Payne DC, Rose CE, Kerrison J, Aranas A, Duderstadt S, McNeil MM. Anthrax Vaccination and Risk of Optic Neuritis in the United States Military, 1998-2003. *Archives of Neurology*. 2006;63:871-875. http://www.anthrax.mil/documents/library/AnthraxVaccAndRiskofOpticNeuritis-ArchNeurol-June12-2006.pdf

Comments & Opinions to Payne, et al. (2006):

Nass M. Data vs. conclusions in the optic neuritis vaccination investigation. *Archives of Neurology* 2006;63:1809. Author's (Payne, et al.) reply, page 1810.

Schumm WR. Adverse reactions to anthrax vaccine (eg, optic neuritis) may be more complex or delayed than reported initially by Payne et al (2006). *Archives of Neurology* 2007;64(3):457-8. Author's (Payne, et al.) reply, page 458.

Engler RJM, Klote M, Nelson MR. Optic Neuritis and Vaccination Investigation: Failure to Consider Significant Sex Differences and Multiple Vaccine Combinations. *Archives of Neurology* 2007;64:1673. Author's (Payne, et al.) reply, page 1674.

Long-Term Health Effects

K. USAF Air Combat Command Study, Langley Air Force Base study of outpatient medical care among Air Force personnel after they returned 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(Mar):205-10. www.anthrax.mil/documents/library/SWasia.pdf

L. Naval Health Research Center, DoD Center for Deployment Health Research.

L1. Sato PA, Reed RJ, Smith TC, Wang LZ. Monitoring anthrax vaccine safety in US military service members on active duty: surveillance of 1998 hospitalizations in temporal association with anthrax immunization. *Vaccine* 2002;20:2369-74.

L2. Smith B, Leard CA, Smith TC, Reed RJ, Ryan MA. Anthrax vaccination in the Millennium Cohort: validation and measures of health. *Am J Prev Med* 2007;32(4):347-53.

M. Army Disability Discharge Study.

Sulsky SI, Grabenstein JD, Delbos RG. Disability among U.S. Army personnel vaccinated against anthrax. *Journal of Occupational & Environmental Medicine* 2004;46(Oct):1065-75. www.anthrax.mil/documents/library/Anthrax2004.pdf

N. US Army Aircrew Physical Examination Study.

Downing J, Greig TW, Quattlebaum MD, Valentin M, Heeren, T, Grabenstein JD. Assessing the Safety of Anthrax Immunization in US Army Aircrew Members via Physical Examination. *Journal of Occupational & Environmental Medicine* 2007;49(Oct):1079-85.

VAERS

O. Reports involving anthrax vaccine submitted to the FDA/CDC Vaccine Adverse Event Reporting System (VAERS) and evaluated by the Anthrax Vaccine Expert Committee.

O1. 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/mmwr/PDF/wk/mm4916.pdf

O2. 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 (Apr-May):189-202. www.vaccines.mil/documents/library/AVEC_ms.pdf

O3. 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* 2004;13(Dec):825-40. www.vaccines.mil/documents/library/SeverArticle.pdf

O4. 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 Rheumatology* 2002;46:3417.

O5. Niu MT, Ball R, Woo EJ, Burwen DR, Knippen M, Braun MM, and the VAERS Working Group. Adverse events after anthrax vaccination reported to the vaccine Adverse Event Reporting System (VAERS), 1990-2007. *Vaccine* 2009; 27:290-297. http://www.vaccines.mil/documents/library/adverse_events_Vaccine_27_2009.pdf

Reproductive Health

P. Female Reproductive Study.

P1. Ryan MA, Smith TC, Sevick CJ, Honner WK, Loach RA, Moore CA, Erickson JD. Birth defects among infants born to women who received anthrax vaccine in pregnancy. *Am J Epidemiol* 2008;168(4):434-42. http://www.ncbi.nlm.nih.gov/pubmed/18599489?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

P2. 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(Mar 27):1556-60. *www.*jama.ama-assn.org/cgi/reprint/287/12/1556.pdf

Q. Male Fertility Study.

Catherino WH, Levi A, Kao T-C, Leondires MP, McKeeby J, Segars JH. Anthrax vaccine does not affect semen parameters, embryo quality, or pregnancy outcome in couples with a vaccinated male military service member. *Fertility & Sterility* 2005;83:480-3. www.vaccines.mil/documents/library/Catherino_Anthrax_Vaccine_2005.pdf

R. Dosing Change Studies

R1. 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. www.vaccines.mil/documents/library/Antibody_resp.pdf

R2. Marano N, Plikaytis BD, Martin SW, Rose C, Semenova VA, Martin SK, et al. Effects of a reduced dose schedule and intramuscular administration of Anthrax Vaccine Adsorbed on immunogenicity and safety at 7 months. *JAMA* 2008;300(13):1532-1543. http://jama.ama-assn.org/cgi/reprint/300/13/1532

S. USAMRIID Dose-Reduction / Route-Change Study of anthrax vaccine administered by two different injectable routes of administration and dosing schedules.

S1. Pittman PR, Kim-Ahn G, Pifat DY, Coonan K, Gibbs P, Little S, Pace-Templeton JG, Myers R, Parker GW, Friedlander AM. Anthrax vaccine: Immunogenicity and safety of a dose-reduction, route-change comparison study in humans. *Vaccine* 2002;20(Jan 31):1412-20. www.vaccines.mil/documents/library/Immunogenicity.pdf

S2. 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* 2001;19:213-6. http://www.vaccines.mil/documents/library/Vaccine19(2-3)213-6.pdf

S3. Pittman PR. Aluminum-containing vaccine associated adverse events: Role of route of administration and gender. *Vaccine* 2002;20(May 31):S48-50. www.vaccines.mil/documents/library/VaccineS48-50.pdf

T. Naval Institute for Dental and Biomedical Research.

Lininger LA, Cullum ME, Lyles MB, Bienek DR. The impact of incomplete vaccination schedules on the magnitude and duration of protective antigen-specific IgG responses in recipients of the US licensed anthrax vaccine. *Vaccine* 2007;25(9):1619-25.

U. Army Medical Surveillance Activity.

Singer DE, Schneerson R, Bautista CT, Rubertone MV, Robbins JB, Taylor DN. Serum IgG antibody response to the protective antigen (PA) of Bacillus anthracis induced by anthrax vaccine adsorbed (AVA) among U.S. military personnel. *Vaccine* Feb 2008(26);869-873

International Studies

V. Canadian Forces Safety

Hunter D, Zoutman D, Whitehead J, Hutchings J, MacDonald K. Health effects of anthrax vaccination in the Canadian Forces. *Military Medicine* 2004;169:833-8. www.anthrax.mil/documents/library/anthraxvaccinestudy.pdf

W. United Kingdom Armed Forces Safety

Murphy D, Hull L, Horn O, Jones M, Marteau T, Hotopf M, Rona RJ, Wessely S. Anthrax vaccination in a military population before the war in Iraq: side effects and informed choice. *Vaccine* 2007; 25(44): 7641-8.

Miscellaneous

X. Mycoplasma Contamination Study.

Hart MK, DelGiudice RA, Korch GW. Absence of mycoplasma contamination in anthrax vaccine. *Emerging Infectious Diseases* 2002;8:94-96. www.cdc.gov/ncidod/eid/vol8no1/01-0091.htm

Y. Vaccine Analytic Unit

Payne DC, Franzke LH, Stehr-Green PA, Schwartz B, McNeil MM. Development of the Vaccine Analytic Unit's research agenda for investigating potential adverse events associated with anthrax vaccine adsorbed. *Pharmacoepidemiol Drug Saf* 2007;16(1):46-54.

Z. Anthrax Vaccine and Immunogenicity

Grabenstein JD. Countering Anthrax: Vaccines and Immunoglobulins. *Vaccine* 2008;46:129-136.

AA. Case Reports

See attached for specifics

Institute of Medicine Summaries

Summary for General Public: www.iom.edu/Object.File/Master/4/149/0.pdf
Summary for Policy Makers: www.iom.edu/Object.File/Master/4/150/0.pdf

AB. Books

Joellenbeck LM, Zwanziger L, Durch JS, Strom BL, editors. *The Anthrax Vaccine: Is it Safe? Does it Work?* Washington, DC: National Academy Press, April 2002, xxi + 265 pages. www.nap.edu/catalog/10310.html

Historical Studies
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.vaccines.mil/documents/library/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 (Dec 13): pages 51002-117.
http://www.vaccines.mil/documents/library/fed_reg.pdf

See further consideration at: FDA. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review. *Federal Register* 2004;69 (Jan 5):255-67; errata 2004;69 (Feb 13):7114-7115. And Federal Register 2004;69(Dec 29):78281-93.
http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/2004/pdf/03-32255.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.

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

C1. *Citation:* Richard N. Peeler, Leighton E. Cluff, Robert W. Trever. Hyper-immunization of man. *Bulletin of the Johns Hopkins Hospital* 1958;103:183-98.
http://www.anthrax.mil/documents/library/Peeler1958BJHH183.pdf

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.]

C2. *Citation*: Richard N. Peeler, Paul J. Kadull, Leighton E. Cluff. Intensive immunization of man: Evaluation of possible adverse consequences. *Annals of Internal Medicine* 1965;63:44-57.
http://www.vaccines.mil/documents/library/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)

C3. *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;81:594-600. http://www.vaccines.mil/documents/library/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.

C4. *Citation:* Pittman PR, Coonan KM, Gibbs PH, Scott HM, Cannon TL, McKee KT Jr. Long-term health effects of repeated exposure to multiple vaccines. *Vaccine* 2004;23(Dec 9):525-36. www.vaccines.mil/documents/library/Longtermhealtheffects.pdf

Investigators: Scientists at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), Fort Detrick, Maryland

Period of Observation: 1943 to 1996. Interval for each worker from first vaccination to survey completion was 15 to 55 years (mean 43.1 years). Mean age of participants was 69 years.

Participants: 155 former workers (including 21 women) at Fort Detrick laboratories between 1943 and 1969 (who received a median of 154 vaccinations or skin tests) over a median of 17.3 years.

Of the 155 lab workers, 142 (92%) received anthrax vaccination. They were compared to 265 community controls (including 50 women) from central Maryland matched on age, ethnicity and gender.

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

Study Design: Cohort study, occupational setting, compared to matched community control subjects.

Findings: Laboratory workers characterized themselves as healthy slightly less often than controls (p=0.057). Fatigue, but no other symptoms, was reported more frequently in the multiply immunized group, but was not associated with number of injections, number of vaccines, or time in program. No differences were seen for self-reported medical conditions. Several laboratory abnormalities were more common in the MIP group, but none appeared to be clinically significant. A significant increase in frequency of monoclonal spikes or paraprotein peaks appeared (12.5% vs. 4.5%), but no association with lifestyle, vaccine exposure, or medical conditions were found. Intensive vaccination was not associated with an elevated risk of any disease or medical condition.

Short Term Health Effects
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. www.vaccines.mil/documents/library/Pittman2002Vaccine972.pdf

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 a condition suggesting 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.

E. TAMC-601 Survey

Citations:

E1. 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.
www.cdc.gov/epo/mmwr/preview/mmwrhtml/mm4916a1.htm

E2. 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.
www.anthrax.mil/documents/library/AnthraxVaccineEvaluation.pdf

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 yrs, mean: 29.9 yrs, standard deviation 7.5 yrs.

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.

F. U.S. Forces Korea Vaccination Series

Citation: 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(Oct 1):4399-409. www.vaccines.mil/documents/library/Hoffman2003Vaccine4399.pdf

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.

G. 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 (MSMR)* 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.

H. 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(Apr 2):1620-8. www.anthrax.mil/documents/library/science.pdf

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, 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 does not increase through the 1990s, despite introduction of the hepatitis A vaccination program in 1996 and the anthrax vaccination program in August 1998. These data are especially meaningful, given that all military personnel in Korea received anthrax vaccine between August 1998 and November 2000. Systematic automated records show 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, 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 through the 1990s, 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 following 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, for the interval 1998 to 2000, one per 35 anthrax-vaccinated people was 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. The two groups have similar health expectations.

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. This reflected 20,765 hospitalizations among the vaccinated group and 115,549 hospitalizations among the unvaccinated group.

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.

Findings:

(a) 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. 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.

(b) 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.

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.

(c) 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.

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.

(d) 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.

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, each major diagnostic category among anthrax vaccine recipients was contrasted with Service Members (SMs) who have not received anthrax vaccine.

(e) 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.

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

(f) 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.

(g) Gender-Specific Effects: When these analytic approaches are repeated looking at men and women separately, the authors found 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.

I. Naval Health Research Center, DoD Center for Deployment Health Research

Citation:

Wells TS, Sato PA, Smith TC, Wang LZ, Reed RJ, Ryan MAK. Military hospitalizations among deployed US service members following anthrax vaccination, 1998-2001. *Human Vaccines* 2006;2:2,e1-e6. http://www.landesbioscience.com/journals/vaccines/article/wellsHV2-2.pdf

Investigators: Department of Defense Center for Deployment Health, Naval Health Research Center, San Diego, CA

Period of Observation: 1998 to 2001

Participants: 170,723 adult military personnel who received the anthrax vaccine and deployed between 01 Jan 98 to 31 Dec 2001 ages 17-45 years of age. 148,502 male and 22,221 female participants.

Vaccine Studied: Lansing formulation

Study Design: A retrospective cohort study examining medical records for vaccination status and

hospitalizations.

Findings:

(a) There are significantly decreased hazard ratios for hospitalizations from all causes regardless of gender, for those who were vaccinated with the anthrax vaccine.

(b) There were no significant increased hazards for outcomes investigated.

J. A comparison of optic neuritis in US Military Personnel based on whether they received the anthrax vaccine

Citation: Payne DC, Rose CE, Kerrison J, Aranas A, Duderstadt S, McNeil MM. Anthrax Vaccination and Risk of Optic Neuritis in the United States Military, 1998-2003. *Archives of Neurology*. 2006;63. 871-875. http://www.anthrax.mil/documents/library/AnthraxVaccAndRiskofOpticNeuritis-ArchNeurol-June12-2006.pdf

Investigators: Centers for Disease Control, Atlanta, GA.

Period of Study: 1998-2003.

Participants: Matched case control study of 1131 cases of AD service members with at least 18 weeks of military service who developed optic neuritis after receiving anthrax vaccine compared to 3393 matched service members who did not develop optical neuritis after receiving the anthrax vaccine.

Vaccine Studied: Lansing formulation

Study Design: A matched case control study analyzing ICD-9 codes within the Department of Defense Medical Surveillance Database.

Findings:

(a) This study found no evidence that the anthrax vaccine causes an increase in optical neuritis in vaccine recipients.

(b) There was no association with giving smallpox, influenza and/or hepatitis B vaccines in conjunction with the anthrax vaccine and cases of optical neuritis.

Long Term Health Effects

K. 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(Mar):205-10. www.anthrax.mil/documents/library/SWasia.pdf

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.

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

L1. *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

Study Design: 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 than the unvaccinated group.

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.

Findings: 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.

L2. *Citation*: Smith B, Leard CA, Smith TC, Reed RJ, Ryan MA. Anthrax vaccination in the Millennium Cohort: validation and measures of health. *Am J Prev Med* 2007;32(4):347-53.

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; thus, called the Millennium Cohort Study. The NHRC coordinates the DoD Center for Deployment Health Research, Naval Health Research Center, San Diego.

Period of Study: September 2005 to February 2006

Participants: 67,018 military service members enrolled in the Millennium Cohort Study. Individuals who served in the first Gulf War were excluded because immunization tracking databases were not launched until 1998.

Vaccine Studied: Lansing formulation

Study Design: The Millennium Cohort Study was launched in 2001 to evaluate risk factors related to military service that may be associated with long-term adverse health outcomes. Analysis to compare the concordance of self-reported anthrax vaccination from a large, population-based cohort study with electronic vaccination records. The analysis used multivariable modeling investigated vaccination concordance as it pertains to subjective and objective health metrics.

Findings: Results indicate that military members accurately recall their anthrax vaccinations. Vaccination status is not associated with self-reported health problems or broad measures of health problems severe enough to require hospitalization.

M. Army Disability Discharge Study

Citation: Sulsky SI, Grabenstein JD, Delbos RG. Disability among U.S. Army personnel vaccinated against anthrax. *Journal of Occupational & Environmental Medicine* 2004;46(Oct):1065-75. www.anthrax.mil/documents/library/Anthrax2004.pdf

Investigators: ENVIRON Health Sciences Institute, Amherst, Massachusetts; analyzing the Total Army Injury & Health Outcomes Database (TAIHOD), maintained by the US Army Research Institute of Environmental Medicine (USARIEM)

Period of Study: Vaccinations between March 1998 to February 2002

Participants: 716,833 active-duty Army Soldiers, contrasting 154,456 anthrax-vaccinated Soldiers (22%) and 562,377 anthrax-unvaccinated Soldiers (78%) over 4.25 years. Of the 716,833 Soldiers, 29,332 (4%) were evaluated for disability discharge. Of those evaluated, 15% had received at least one dose of anthrax vaccine.

Vaccine Studied: Lansing formulation

Study Design: Electronic records of anthrax vaccination were linked with electronic personnel records and electronic disability evaluation records.

Findings:

(a) Rates of disability evaluations did not differ significantly between the anthrax-vaccinated Soldiers and the anthrax-unvaccinated Soldiers, with an adjusted hazard ratio of 0.96 (95% confidence interval: 0.92 to 0.99). The unadjusted rates of disability evaluations evaluated were 140 per 100,000 person-months for unvaccinated Soldiers and 68 per 100,000 person-months for anthrax-vaccinated Soldiers. The unadjusted hazard ratio was 0.77.

(b) Subset analyses that calculated separate adjusted hazard ratios similarly found no differences for men alone, women alone, permanent disability, temporary disability, musculoskeletal disability, or neurologic disability.

(c) Adjusting the analysis to insert a lag time between vaccination and disability evaluation did not change the conclusion that anthrax vaccination is unrelated to disability evaluation.

(d) Segmenting the anthrax-vaccine exposures into 18 subcategories, no substantial variations by lot were seen. For lot FAV030, the hazard ratio was slightly elevated at 1.13 (95% confidence interval: 1.00 to 1.27), a finding that could be influenced by multiple comparisons and the lengthy interval since that lot was used (compared to other lots).

(e) Soldiers who received one or two doses of anthrax vaccine had higher hazard ratios than both those unvaccinated and those who received 3 or more doses of vaccine. This observation is attributed to influences of the "healthy warrior effect" and a need for an adequate administrative latency interval to elapse between vaccination and disability evaluation.

N. US Army Aircrew Physical Examination Study

Citation: Downing J, Greig TW, Quattlebaum MD, Valentin M, Heeren, T, Grabenstein JD. Assessing the Safety of Anthrax Immunization in US Army Aircrew Members via Physical Examination. *Journal of Occupational & Environmental Medicine* 2007;49(Oct):1079-85.

Investigators: Boston University School of Public Health, Boston, MA; US Army Aeromedical Center, Fort Rucker, AL; Military Vaccine Agency, US Army Medical Command, Falls Church, VA; analyzing data from the US Army Aviation Epidemiology Data Register (AEDR) and Medical Protection System (MEDPROS) immunization tracking database.

Period of Study: Vaccinations between 1998 and 2005

Participants: 10,965 Army aircrew members, contrasting 6,820 immunized AVA-immunized aircrew members (62%) and 4,145 AVA-unimmunized aircrew members (38%) over eight years. Those who participated were required to have at least two physical examinations in the database during the study period.

Vaccine Studied: Lansing formulation

Study Design: Retrospective cohort study. Electronic records of anthrax vaccination were linked with electronic flight duty medical examination records.

Findings:

(a) No significant evidence was found that suggests immunization with AVA leads to an increase in abnormal examination findings.

(b) No association between anthrax immunization and a clinically relevant change in a tested physiologic parameter was detected.

(c) No attributable risk of anthrax immunization was observed in this group of Army aircrew members.

VAERS

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

Citations:

O1. 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. www.cdc.gov/epo/mmwr/preview/mmwrhtml/mm4916a1.htm

O2. 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 (Apr-May):189-202.
www.vaccines.mil/documents/library/AVEC_ms.pdf

O3. 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* 2004;13(Dec):825-40.
www.vaccines.mil/documents/library/SeverArticle.pdf

O4. 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 Rheumatology* 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 reviewed all anthrax vaccine-related reports received by VAERS. The AVEC met 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 reviewed the quality of the submitted information, evaluated the reported event in the context of expected and unexpected adverse events to vaccines, and assessed the cause-and-effect relationship of the event with the anthrax vaccine. The AVEC also looked for any clinically significant patterns in the aggregate data.

Findings: The AVEC reports that it 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.

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

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).

Citation:

O5. Niu MT, Ball R, Woo EJ, Burwen DR, Knippen M, Braun MM, and the VAERS Working Group. Adverse events after anthrax vaccination reported to the vaccine Adverse Event Reporting System (VAERS), 1990-2007. *Vaccine* 2009; 27:290-297.

Investigators: Food and Drug Administration (FDA), Center for Biologics Evaluation and Research, Office of Biostatistics and Epidemiology, Division of Epidemiology, Vaccine Safety Branch; FDA, Office of Compliance and Biologic Quality, and the VAERS Working Group.

Period of Study: 1990–2007

Participants: 4,753 reports of adverse events following receipt of AVA vaccination submitted to the Vaccine Adverse Event Reporting System (VAERS)

Vaccine Studied: Lansing formulation

Study Design: Data mining statistics using Empirical Bayesian methods to evaluate rates of reported adverse events post-vaccination with AVA in a passive surveillance system.

Findings: The analysis was an update to a previous evaluation of VAERS reports submitted for AVA and continued monitoring for potential associations between AVA vaccination and rare, serious events. The review did not find any definitive links with unexpected serious adverse events to AVA vaccination, other than injection site and some allergic reactions, which are common with other adult vaccines.

P. Reproductive Health
Female Reproductive Health Studies

Citations:

P1. Ryan MA, Smith TC, Sevick CJ, Honner WK, Loach RA, Moore CA, Erickson JD. Birth defects among infants born to women who received anthrax vaccine in pregnancy. *Am J Epidemiol* 2008;168(4):434-42. For abstract, go to: http://www.ncbi.nlm.nih.gov/pubmed/18599489?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubme

d.Pubmed_ResultsPanel.Pubmed_RVDocSum

Investigators: US Department of Defense Center for Deployment Health Research, Naval Health Research Center, San Diego, CA 92106, USA

Period of Study: 1998 to 2004

Participants: 115,169 infants born to military women. Of these 37,140 were born to women ever vaccinated against anthrax and 3,465 were born to women vaccinated in the first trimester of pregnancy.

Vaccine Studied: Lansing formulation

Study Design: Retrospective cohort study to assess the odds of birth defects among infants exposed to anthrax vaccine in the first trimester compared to infants of all other vaccinated women.

Findings: Birth defects were slightly more common in first trimester-exposed infants (odds ratio = 1.18, 95% confidence interval: 0.997, 1.41) when compared with infants of women vaccinated outside of the first trimester, but this association was statistically significant only when alternative referent groups were used. Although the small observed association may be unlikely to represent a causal relation between vaccination in early pregnancy and birth defects, this information should be considered when making decisions about administering anthrax vaccine to pregnant women.

P2. 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(Mar 27):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.

Q. Male Fertility Study

Citation: Catherino WH, Levi A, Kao T-C, Leondires MP, McKeeby J, Segars JH. The anthrax vaccine does not affect semen parameters, embryo quality, or pregnancy outcome in couples with a vaccinated male military service member. *Fertility & Sterility* 2005;83:480-3. www.vaccines.mil/documents/library/Catherino_Anthrax_Vaccine_2005.pdf

Investigators & Design: Walter Reed Army Medical Center Assisted Reproduction Technologies Program, Washington, DC.

Period of Study: October 1999 to December 2003

Vaccine Studied: Lansing formulation

Study Design: Data about anthrax vaccination was obtained from men at time of oocyte and sperm retrieval. Researchers assessed characteristics of male gametes, including 254 vaccinated men and 791 unvaccinated men. The two groups were comparable for semen concentration (million sperm per milliliter), sperm motility (movement), sperm morphology (shape), need for intracytoplasmic sperm injection, rate of fertilization of mature oocytes, embryo transfer, and clinical pregnancy.

Findings:

(a) A diagnosis of male-factor infertility was less common in anthrax-vaccinated men than in unvaccinated men.

(b) The researchers concluded that anthrax vaccination of men did not impair semen parameters, fertilization rate, embryo quality, or clinical pregnancy rates.

R. Dosing Change Studies

Citations:

R1. 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. www.vaccines.mil/documents/library/Antibody_resp.pdf

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.

R2. Marano N, Plikaytis BD, Martin SW, Rose C, Semenova VA, Martin SK, et al. Effects of a reduced dose schedule and intramuscular administration of Anthrax Vaccine Adsorbed on immunogenicity and safety at 7 months. *JAMA* 2008;300(13): 1532-1543.

Investigators: Centers for Disease Control and Prevention sponsored Anthrax Vaccine Research Program Working Group. Congressionally-mandated phase 4 clinical trial.

Period of Observation: May 2002 to February 2003

Participants: 1005 voluntary participants

Vaccine Studied: Lansing formulation

Study Design: Randomized clinical trial to evaluate alternate regimens for anthrax vaccine adsorbed (AVA). Researchers enrolled 1,005 participants across five study centers. Participants were randomized into one of six groups: Group 1 received the first four doses of AVA subcutaneously (SQ) according to the licensed schedule (0, 2, and 4 weeks, and 6 months); Group 2 received AVA via intramuscular (IM) route at the same intervals; Group 3, 4, and 5 received AVA via IM route at 0 and 4 weeks and 6 months and placebo at week 2; these groups were combined for analyses; and Group 6 was split into two subgroups 6a and 6b, which received placebo via IM route and SQ, respectively, at 0, 2, and 4 weeks and 6 months.

Findings: Immunogenicity at month 7 among individuals (Groups 3, 4, and 5) who received the reduced dose regimens of AVA, 4-IM and 3-IM, was non-inferior to the immunogenicity among those who received the licensed AVA regimen of 4-SQ infections; thus, demonstrating that an immune

response is achievable when the dose at week 2 is eliminated and the route of administration is changed from SQ to IM. The study results also showed that injection site adverse events (AEs) occurred less frequently when AVA was administered IM compared to SQ.

S. USAMRIID Dose-Reduction / Route-Change Studies

Citations:

S1. 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. www.vaccines.mil/documents/library/Immunogenicity.pdf

S2. 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* 2001;18:213-6. www.vaccines.mil/documents/library/Vaccine19(2-3)213-6.pdf

S3. See also: Pittman PR. Aluminum-containing vaccine associated adverse events: Role of route of administration and gender. *Vaccine* 2002;20:S48-50. www.vaccines.mil/documents/library/VaccineS48-50.pdf

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.

Note: The Centers for Disease Control & Prevention is currently conducting an expanded version of the dose-reduction/route-change study at five clinical trial sites in a double-blinded, randomized, placebo-controlled manner. The five sites are Baylor College of Medicine, Emory University, Mayo Clinic, University of Alabama-Birmingham, and the Walter Reed Army Institute of Research. The study group reports no unexpected findings to date. CDC submitted data to the FDA in January 2005 that could support a change in route of administration from subcutaneous to intramuscular and dropping of dose 2 (the week-2 dose).

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.

T. Naval Institute for Dental and Biomedical Research.

Citation: Lininger LA, Cullum ME, Lyles MB, Bienek DR. The impact of incomplete vaccination schedules on the magnitude and duration of protective antigen-specific IgG responses in recipients of the US licensed anthrax vaccine. *Vaccine* 2007;25(9):1619-25.

Investigators: Scientists from the Naval Institute of Dental and Biomedical Research, Great Lakes, IL, and the US Navy Bureau of Medicine and Surgery, Washington, DC.

Period of Observation: Enrollment occurred from October 2004 to April 2005 (during the AVA pause).

Participants: 363 volunteers (military personnel) who had zero to six anthrax vaccine adsorbed (AVA) vaccinations 3-57 months earlier.

Vaccine Studied: Lansing formulation

Study Design: Cross-sectional analysis of serum anti-protective antigen (PA) concentration in 363 individuals who had received six or fewer US licensed anthrax vaccinations. The investigators collected and tested blood samples from each of the individuals. Blood specimens were blinded by assignment of random identification numbers to those conducting the enzyme-linked immunosorbent assay (ELISA) test to detect anthrax vaccine-induced serum antibody concentrations. Linear regression analyses were used to evaluate the relationships between specimen antibody concentration and the number of vaccinations, sample collection time, and time since last AVA vaccination. The goal of the study was to determine if mean anti-protective antigen (anti-PA) IgG serum increases after each additional AVA vaccination.

Findings: Concentrations of specific antibody rose with increasing doses of AVA ($P \leq 0.001$, $r=0.73$). A marked difference in anti-PA concentration was observed between the primary series (one to three doses) and four to six doses in vaccinated individuals. Univariate regression analyses ($r=-0.07$) suggest that the magnitude of the anti-PA serum antibody level does not significantly decrease with time after administration of one or more AVA doses.

U. Army Medical Surveillance Activity.

Citation: Singer DE, Schneerson R, Bautista CT, Rubertone MV, Robbins JB, Taylor DN. Serum IgG antibody response to the protective antigen (PA) of Bacillus anthracis induced by anthrax vaccine adsorbed (AVA) among U.S. military personnel. Vaccine Feb 2008(26);869-873

Investigators: Division of Retrovirology, Walter Reed Army Institute of Research and U.S. Military HIV Research Program, Rockville, MD, USA; National Institute of Child Health and Human Development, NIH, Bethesda, MD, USA; Army Medical Surveillance Activity, USA Center for Health Promotion and Preventive Medicine, Washington, DC, USA; and VaxInnate Corporation, 3 Cedar Brook Drive, Cranbury, NJ, USA.

Period of Observation: Doses and serum collection took place from January 1996 to October 2002.

Participants: All active duty or former active military personnel with both AVA vaccination information and appropriate serum samples available in the DoDSR were selected as study subjects, as of October 2002.

Vaccine Studied: Lansing formulation

Study Design: Retrospective study of number of doses of AVA and serum IgG antibody of protective antigen among individuals who received AVA from January 1996 to October 2002. This study did not involve notifying the study participants.

Findings: Anti-PA IgG concentrations were measured by ELISA. All 246 vaccinees had low but detectable pre-immunization anti-PA IgG (GMC 1.83 _g/mL). Three doses elicited a GMC of 59.92 _g/mL and a seroconversion rate of 85.3%, four doses elicited a GMC of 157.44 _g/mL and 67.9% and the sixth of 276.95 _g/mL and 45.5%, respectively. The forth dose elicited 100% seroconversion compared to the pre-immunization level. These results should facilitate comparison between different immunization schedules and new vaccines.

International Studies
V. Canadian Forces Safety

Citation: Hunter D, Zoutman D, Whitehead J, Hutchings J. Health effects of anthrax vaccination in the Canadian Forces. *Military Medicine* 2004;169:833-8. www.anthrax.mil/documents/library/anthraxvaccinestudy.pdf

Investigators: Investigators from Queen's University, Kingston, Ontario, Canada

Period of Observation: February 1996 to August 2000

Participants: 403 anthrax-vaccinated personnel deployed to the Persian Gulf, contrasted with 445 unvaccinated personnel deployed to Kosovo.

Vaccine Studied: Lansing formulation

Study Design: Quasi-experimental cohort study

Findings: No statistically significant differences between groups were seen in the percent change before and after vaccination in the number of chart entries for specific diagnoses and symptoms. Time trends in rates showed no unexplained increases in the rate of diagnosis and symptoms in the vaccinated group after vaccination. This study found no evidence that anthrax vaccination resulted in an increase in adverse health effects in an 8-month period after return from deployment.

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), viral-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 2-5 days.

W. United Kingdom Armed Forces Safety

Citation: Murphy D, Hull L, Horn O, Jones M, Marteau T, Hotopf M, Rona RJ, Wessely S. Anthrax vaccination in a military population before the war in Iraq: side effects and informed choice. *Vaccine* 2007; 25(44): 7641-8.

Investigators: Investigators from the Institute of Psychiatry, Kings College London, Psychological Medicine, Weston Education Centre, Cutcombe Road, London SE5 9RJ, United Kingdom and the Department of Psychology and Genetics Research Group, King's College London, United Kingdom.

Period of Observation: June 2004 and March 2006

Participants: 5302 participants assigned to an Iraq War Cohort study combined with 607 service personnel from a longitudinal study.

Miscellaneous

X. Mycoplasma Study

Citation: Hart MK, DelGiudice RA, Korch GW. Absence of Mycoplasma contamination in anthrax vaccine. *Emerging Infectious Diseases* 2002;7:94-6. 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.

Y. Vaccine Analytic Unit

Citation: Payne DC, Franzke LH, Stehr-Green PA, Schwartz B, McNeil MM. Development of the Vaccine Analytic Unit's research agenda for investigating potential adverse events associated with anthrax vaccine adsorbed. *Pharmacoepidemiol Drug Saf* 2007;16(1):46-54.

Investigators: Representatives from the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the Department of Defense that make up the Vaccine Analytic Unit (VAU). The National Vaccine Advisory Committee (NVAC) conducted an independent review and ranked the findings.

Vaccine Studied: Anthrax Vaccine Adsorbed (Lansing formulation)

Study Design: Meta-analysis of public health literature, surveillance data, and clinical sources to identify potential adverse events related to the anthrax vaccine adsorbed (AVA).

Findings: The review by the VAU produced over 100 potential adverse events and of these only 11 topics were recommended for further study. Based on the NVAC independent review, the NVAC identified the following adverse event topics for study: arthritis, optic neuritis, and Stevens-Johnson syndrome/Toxic epidermal necrolysis. Systemic lupus erythematosus (SLE) and multiple, near-concurrent military vaccinations were added based on emerging public health and military concerns.

Z. Anthrax Vaccine and Immunogenicity

Citation: Grabenstein JD. Countering Anthrax: Vaccines and Immunoglobulins. *Vaccine* 2008;46:129-136.

AA. Case Reports

AA1. Swanson-Biearman B, Krenzelok EP. Delayed life-threatening reaction to anthrax vaccine. *Journal of Toxicology & Clinical Toxicology* 2001;39:81-4.

AA2. Kerrison JB,Lounsbury D, Thirkill CE, Lane RG, Schatz MP, Engler RM. Optic neuritis after anthrax vaccination. *Ophthalmology* 2002;109:99-104.

AA3. Greidanus TG, Honl BA. Delayed-type hypersensitivity reaction to anthrax vaccine. *Military Medicine* 2002;167:74-75.

AA4. Timmer SJ, Amundson DE, Malone JE. Hypersensitivity pneumonitis following anthrax vaccination. *Chest* 2002;122:741-5.

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

AA5. Chopra A, Drage LA, Hanson EM, Touchet NL. Stevens-Johnson syndrome after immunization with

smallpox, anthrax, and tetanus vaccines. *Mayo Clin Proceedings* 2004;79(Sep):1193-6.

AA6. Gilson RT, Schissel DJ. Recurrent, localized urticaria and erythema multiforme: a review and management of cutaneous anthrax vaccine-related events. *Cutis* 2004;73(May):319-25.

AA7. Muellenhoff M, Cukrowski T, Morgan M, Dorton D. Oral pemphigus vulgaris after anthrax vaccine administration: association or coincidence? *Journal of the American Academy of Dermatology* 2004;50(Jan):136-9.

AA8. Pande H, Lacy BE, Crowell MD. Inflammatory causes of gastroparesis: Report of five cases. *Digestive Diseases & Sciences* 2002;47(Dec):2664-8.

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Joellenbeck LM, Zwanziger L, Durch JS, Strom BL, editors. *The Anthrax Vaccine: Is it Safe? Does it Work?* Washington, DC: National Academy Press, April 2002, xxi + 265 pages. www.nap.edu/catalog/10310.html

Summary for General Public: www.iom.edu/Object.File/Master/4/149/0.pdf

Summary for Policy Makers: www.iom.edu/Object.File/Master/4/150/0.pdf

Civilian panels that evaluated the anthrax vaccine for effectiveness and safety

FDA Panel on Bacterial Vaccines and Toxoids, 1978, 1985.

Advisors to the Food and Drug Administration.
Food and Drug Administration. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review. *Federal Register* 1985;50(Dec 13):51002-117. http://www.vaccines.mil/documents/library/fed_reg.pdf

See also: Food & Drug Administration. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review; Anthrax vaccine adsorbed; Final order. *Federal Register* 2005(Dec 19);70:75180-98. www.fda.gov/cber/rules/bvactoxanth.pdf

Armed Forces Epidemiological Board (AFEB), 1994 to present.

Advisors to the Assistant Secretary of Defense for Health Affairs and the Surgeons General of the Armed Forces. Recommendations: August 1994, November 1996, April 1998, March 2000, March 2002. www.anthrax.mil/resource/library/afeb.asp

Cochrane Collaboration, 1998, 2004.

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(May-Jun):880-4. Updated in 2004.

Working Group on Civilian Biodefense.

Inglesby TV, Henderson DA, Bartlett JG, et al. Anthrax as a biological weapon: Medical and public health management. *Journal of the American Medical Association* 1999;281(May 12):1735-45. www.jama.ama-assn.org/cgi/reprint/281/18/1735.pdf

Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a biological weapon, 2002: Updated recommendations for management. *Journal of the American Medical Association* 2002;287(May 1):2236-52. www.jama.ama-assn.org/cgi/content/short/287/17/2236

Advisory Committee on Immunization Practices (ACIP).

Advisors to the Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices. Use of anthrax vaccine in the United States. *Morbidity and Mortality Weekly*

Report (MMWR) 2000;49(RR-15) (Dec 15):1-20. www.cdc.gov/mmwr/PDF/rr/rr4915.pdf

Anthrax Vaccine Expert Committee (AVEC).

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(Apr-May):189-202. http://www.vaccines.mil/documents/library/AVEC_ms.pdf

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