

Anthrax Vaccine: Historical Review and Current Controversies

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Anthrax vaccine was licensed in 1970 (prior to licensing of vaccines by the Food and Drug Administration [FDA]) by the Division of Biologic Standards at the National Institutes of Health (NIH), using limited safety and efficacy data obtained in large part from studies of an earlier anthrax vaccine [1,2]. The vaccine was approved only for veterinarians and workers handling potentially infected animals or their products, and for laboratory workers researching anthrax [3]. Although efficacy had been demonstrated for cutaneous anthrax using an earlier vaccine, neither of the two studies submitted for licensure demonstrated efficacy for inhalation anthrax [1,2,4]. Cutaneous anthrax is not a fatal disease; it is easily treated with antibiotics, and therefore does not require vaccine prophylaxis.

Brachman et al. [1,5,6] studied the earlier (unlicensed) vaccine in four goat hair mills in New England and Pennsylvania. There were a total of 26 cases of anthrax at the four mills during the study. Five cases (or possibly three: the text is contradictory on this point) occurred in persons who had received some doses of vaccine, and 15 cases occurred in persons receiving placebo vaccine. Six cases occurred in workers who had chosen not to participate in the trial. The authors excluded all but one worker who developed anthrax after vaccination from the efficacy calculation, reporting that these workers were incompletely vaccinated. However, at least one of the excluded workers met the authors' inclusion criteria [1]. An efficacy rate of 92.5 % was reported, and this statistic, questionable when first published in 1962 and generated by an older vaccine, has since been used to justify use of the current, licensed anthrax vaccine.

Both the Brachman vaccine trial, and the 1960's Centers for Disease Control (CDC) observational study (which used both the former anthrax vaccine and the currently licensed vaccine), only sought adverse reactions using active surveillance for 48 hours after each dose [1,2]. There was no active surveillance for systemic reactions, and a nurse who reported multiple systemic reactions had her observations dismissed by the attending physician as "over zealous" in correspondence with CDC [2]. Data from the CDC study yielded highly variable reaction rates from one series to another, suggesting large differences between vaccine lots used and/or large differences in the recording of adverse effects by the observers. When the current vaccine received NIH approval in 1970, its label adopted Brachman's published reaction rates of 30% for local reactions and 0.2% for systemic reactions, although Brachman's study had used an earlier vaccine [3].

Following licensure, only relatively small numbers of people appear to have received anthrax vaccine in the years between 1970 and 1990. The General Accounting Office (GAO) reported in 1999 that only 200 - 2,000 people received vaccine during this period [7]. No records of use of the anthrax vaccine appear to have been kept. Distribution records indicate that 68,000 vaccine doses were shipped by the manufacturer, but some of these were sent to foreign countries and probably the bulk were used in animal experiments. Vaccine recipients were never studied systematically, records were not always kept, and the vaccine appeared to be safe.

A 1985 FDA expert panel review of anthrax vaccine concluded, "immunization with this vaccine is indicated only for certain occupational groups with risk of uncontrollable or unavoidable exposure to the organism" and "inhalation anthrax occurred too infrequently to assess the protective effect of vaccine against this form of the disease" [8]. Despite these qualifications, the decision was made in 1990 to vaccinate U.S. Armed Forces personnel with available anthrax vaccine for Operations Desert Shield and Desert Storm.

OVERLOOKED ISSUES

A number of issues appear not to have been fully considered prior to the use of anthrax vaccine in 1990, and the following concerns remain to be addressed by the current anthrax vaccine immunization program:

1. Long-term Safety

The long-term safety of the anthrax vaccine has never been established. In addition, the short-term reaction rates listed in the vaccine package insert are questionable as well. Even today, the assessment of long-term side effects for vaccines is not

required for licensure, and in general adverse reaction data are only obtained from passive post-marketing surveillance, primarily through the Vaccine Adverse Event Reporting System (VAERS), a joint effort of the CDC and FDA.

2. Spurious Efficacy Rate

The 92% efficacy rate listed on the vaccine package insert came from a different vaccine, was generous when originally calculated, pertained to goat hair mill workers facing challenge with naturally occurring strains of anthrax, and was estimated for primarily treatable, cutaneous infections.

3. Unapproved Indication

Because prophylaxis against biological warfare (inhalation anthrax) is not an FDA-approved indication for the vaccine, such use both during the Gulf War, and afterward, should only have been conducted using an Investigational New Drug (IND) protocol. This would have required informed consent and careful surveillance for adverse events. The Department of Defense (DOD) did obtain an IND from FDA for inhalation anthrax in 1996, which allowed studies to be performed in support of adding this indication to the vaccine label [9]. But inhalation has not yet been added to the label as a vaccine indication by the FDA, and the question of whether Armed Forces personnel can be mandated to receive a vaccination for an unapproved indication will likely require a judicial resolution.

4. Questionable efficacy for biological warfare

a) In a biological warfare setting, spore counts would be expected to be much higher than in factories, and naturally occurring anthrax strains would be specially selected for virulence, as was the Ames strain in the recent attacks, which could lower vaccine efficacy considerably.

b) Studies in a limited number of monkeys were used to support vaccine efficacy, ignoring the fact that the monkeys had been challenged with only three strains of anthrax, and that studies in vaccinated mice and guinea pigs often yielded survival rates under 25% [10].

c) The existence of genetically engineered anthrax, which had been shown to evade vaccine protection [11], was ignored.

5. Expired vaccine stockpile, improperly redated, with uncertain potency

a) The vaccine stockpile was old, and the majority of lots had expired and been redated [12]. However, there was no FDA-approved standard operating procedure for reusing expired vaccine lots. No retesting for the presence of degradants, preservative concentrations or sterility took place before reapproving the use of expired vaccine [13].

b) The DOD established its own policy for long term vaccine storage, in which experimental vaccines could be stored in bulk or in vials without any expiration date, and licensed vaccine could be stored in bulk without expiring for at least ten years [14].

c) DOD policy permitted the anthrax vaccine to be used following only a potency test, and vaccine would then be relabeled with a new expiration date. The date of manufacture would be listed as the date of the last valid potency test. Although it was later acknowledged that the potency test used for initial release of every vaccine lot, and for redating each expired lot, was unreliable [15], the vaccine stockpile, approved using this test, was not recalled or quarantined.

6. Inconsistent vaccine production

Although normally required by FDA, the manufacturer had not demonstrated lot-to-lot vaccine consistency [16]. Studies performed on one lot might not be applicable to other lots, and side effects from one lot might not be predictable based on studies from a different lot. Potency between lots could vary by a factor of 40 (4000%) [17].

7. Mandatory inspections not performed

FDA did not fulfill its obligation to inspect the anthrax vaccine portion of the manufacturing facility every two years, apparently leaving this responsibility to the U.S. Army [18, 19]. When the FDA performed a thorough inspection in February 1998, one month before the current anthrax vaccine immunization program began, it found so many problems that 11 lots of vaccine were quarantined [20] and the manufacturer "voluntarily" shut down for major repairs and renovations [21].

8. Forced plant closure for rehabilitation

Dr. Kathryn Zoon, director of the Center for Biologics at the FDA, later acknowledged that the shutdown was in response to problems at the plant [22], although initially this had been denied by DOD spokespersons. Although those renovations were completed in 1999, the FDA only allowed the manufacturer to reopen and begin shipping vaccine in January 2002, due to problems meeting current good manufacturing practices [23]. Because of continuing sterility problems in the renovated packaging suite, the manufacturer contracted with a company in Washington state (Hollister Stier) to bottle the vaccine, before FDA would relicense the product.

IS ANTHRAX VACCINE RELATED TO GULF WAR ILLNESS?

Although the DOD, Veteran's Administration and Department of Health and Human Services have spent well over 150 million dollars sponsoring over 180 studies of Gulf War Illness, not a single one of these studies has examined the relationship between the U.S.-licensed anthrax vaccine and Gulf War Illness (GWI), although 16 other Gulf War exposures have been studied (24). Instead, a series of expert panels were convened between 1994 and 1996, and were asked to comment on whether anthrax and botulinum toxoid vaccines might contribute to Gulf War illness.

Expert Panels

Since there was a paucity of published literature on anthrax vaccine, the expert panels received much of their information from DOD briefers. The NIH Technology Assessment Workshop panel stated that "No long term adverse effects have been documented" [25]. The Institute of Medicine wrote, "The Committee knows of no evidence of any chronic effect" [26]. The Persian Gulf Veterans' Coordinating Board said, "Both vaccines, anthrax and botulinum toxoid, have been used for many years without adverse effects. The Institute of Medicine, Presidential Advisory Committee and the Defense Science Board Review panels all stated that no long-term adverse effects have been documented or would be expected. Further study of the potential adverse effects of vaccines in this population is not recommended by any of the three panels, nor is it endorsed in this plan" [27].

Presidential Advisory Committee on Gulf War Illnesses

The Presidential Advisory Committee on Gulf War Veterans' Illnesses (PAC) produced three reports as further information about Gulf War exposures came to light [28-30]. Their 1996 Final Report stated, "The Committee concludes it is unlikely that health effects reported by Gulf War veterans today are the result of exposure to the botulinum toxoid or anthrax vaccines, used alone or in combination." They cited five references, all to DOD briefers. Their 1997 Special Report emphasized the fact that problems associated with investigational vaccine use stemming from the Gulf War were being repeated in the Bosnia conflict: specifically, the investigational Tick-Borne Encephalitis vaccine was being used without informed consent, required record-keeping and surveillance for adverse effects. The PAC then repeated its comment from an earlier report, "The issue of accurate medical and vaccination records is central to the concerns of many ill veterans, and the absence of records has been suggested by some as evidence that the government is engaging in a cover up of its own pre-deployment practices."

Lost Immunization Records: Fort Bragg Study

Although the DOD has said that nearly all the Gulf War immunization records have been lost, other documents indicate that the records may instead have been classified [31]. Pittman et al. [32] studied the effect of booster doses of anthrax and botulinum toxoid vaccine on 400 active duty personnel at Fort Bragg in 1994, who had received initial doses of the vaccines at the time of the Gulf War. Gulf War immunization records with the number of doses and dates received were retrieved for every study participant. The fact that Pittman et al [32] were able to obtain all the desired information on Gulf War vaccinations for over 400 Fort Bragg personnel, suggests that the availability of records may depend on the purpose for which they are required.

Systemic reactions occurred in 44% of the Fort Bragg recipients of the anthrax and botulinum toxoid vaccine boosters. Since vaccinees received a dose of each vaccine simultaneously in opposite arms, it is uncertain how many reactions were due to anthrax vaccine alone. Twenty volunteers had "severe" symptoms, which were not described further [33]. This study also found that at 30 days post-vaccination, 3.2 % of the subjects continued to suffer from adverse systemic reactions. Data are not available to show whether the reactions resolved. This appears to be an unprecedented rate of long-term reactions, but it was not investigated further.

This study's results [32], never published in their entirety, were presented in a much more favorable light in a JAMA review, coauthored by the study's principal investigator, who provided the following brief summary of the study: "Of 486 subjects who received AVA (anthrax vaccine adsorbed), 21% had local erythema and/or induration. In 5%, the erythema or induration was 5 cm or more. No reaction caused lost time from work and all resolved without sequellae. Systemic reactions could not be ascribed solely to AVA as recipients received botulinum toxoid as well" [34]. This summary entirely avoids mention of systemic reactions, and claims that all reactions fully resolved. However, the unpublished data show that 3.2% of vaccinees had persisting reactions one month later, when the investigators stopped collecting adverse event reports.

Epidemiologic Analysis

What then can be said about Gulf War Illness and anthrax vaccination? Several recent studies suggest that there is a relationship. The first examined Armed Forces personnel from the United Kingdom who had received British anthrax vaccine, which is similar but not identical to the vaccine used on U.S. personnel [35]. The authors found that "vaccination against biological warfare and multiple routine vaccinations were associated with the CDC multi-symptom syndrome (which was a definition of Gulf War Illness used by the authors) in the Gulf War cohort." An accompanying commentary said "vaccination against plague and anthrax before deployment to the Gulf correlated highly with illness. The investigators speculated that these vaccines, more so than the routine ones given to service personnel, had unanticipated effects" [36]. Some of the investigators of this study later claimed that the vaccines were not associated with GWI when given prior to, instead of following, deployment [37] but withdrew this claim when their analysis was shown to be flawed [38].

The second study, of Gulf War and Gulf "era" veterans from Kansas, compared Gulf War veterans who received deployment vaccines with Gulf-era veterans who were prepared with vaccines but ultimately not deployed to the Gulf, and with non-vaccinated, Gulf-era veterans [39]. It was found that 4% of non-deployed, non-vaccinated veterans reported symptoms meeting the case definition for Gulf War illness, that 12% of the non-deployed but vaccinated veterans met the GWI case definition, and that 34% of the Gulf War deployed veterans met the case definition. Unfortunately, this study did not break down the vaccines into the types received. Gulf War veterans were not necessarily informed of what vaccines were administered, and generally do not have complete vaccination records from the war [40, 41] but it can be assumed that the majority of vaccinated Gulf era veterans and deployed Gulf War veterans probably received similar, non-routine immunizations.

In support of the Kansas study's results [39] are many anecdotal reports of vaccinated, non-deployed veterans from throughout the United States who have also developed illnesses resembling GWI. This group is important to study because their vaccine exposure is isolated from all other Gulf War exposures, and because the veterans are ineligible to receive evaluations, treatment and benefits for illnesses incurred as a result of Gulf War service. If vaccination is shown to have caused their illness, they too should be treated and compensated. The Institute of Medicine recommended in October 2000 that immunized and non-immunized, deployed and non-deployed veterans for whom vaccination records can be found (4 cohorts) should be studied for long-term adverse health outcomes [33].

The third study of Canadian GW veterans was published on the Department of National Defense website [42]. It found a significant relationship between non-routine, biological warfare vaccinations and chronic fatigue syndrome, a common finding in GWS.

A fourth study of British GW veterans was published in April 2001 [43]. It did not look at specific deployment vaccines, but instead evaluated the number of vaccinations received in relation to GWS. It said, "Consistent, specific and credible relations, warranting further investigation, were found between health indices and two exposures: the reported number of inoculations, and days handling pesticides."

A fifth (VA Environmental Epidemiology Service) study was presented in January 2001 [44] but has yet to be published. Veterans were divided into those who thought they had received anthrax vaccine, and those who thought they had not. The group who believed themselves to have been vaccinated was twice as likely to report a multitude of symptoms as those who believed they had not received the vaccine.

ADVERSE EVENT REPORTING

Universal anthrax vaccination for U.S. Armed Forces personnel began in March of 1998. In the first 11 months 550,000 doses of the vaccine were administered, but only 39 VAERS reports had been filed with the FDA. The Defense Department, in Congressional testimony, reported that the total adverse reaction rate was only 0.007% and that anthrax vaccine was safer than childhood vaccines. This number was arrived at by taking the total number of reports to FDA and calling it the sum total of all adverse events, despite the fact that only a small fraction of adverse events are reported to the VAERS database.

It was later learned that the policy for reporting adverse events had been changed prior to instituting the anthrax vaccine program. Military medical personnel were instructed that only adverse reactions that resulted in hospitalization, or lost duty time of greater than 24 hours could be reported to FDA, unless contamination of a vaccine lot was suspected [45]. This kept the reporting rate artificially low. Obstacles in filing reports were reported in Congressional testimony in July 1999 [46] and the reporting restrictions were changed within days [47]. Currently over 1700 VAERS reports have been filed, with a reporting rate of 87 per 100,000 doses administered [48], higher than for other licensed vaccines. Almost one-

half (46%) of the anthrax VAERS reports do not state that the reported reaction had resolved at the time the report was filed [48], and it is not known how many of the reactions persist indefinitely.

An "anthrax vaccine expert committee" was created by the DOD and the Department of Health and Human Services to review every adverse reaction report sent to FDA. This committee has reported that there is no unusual pattern of adverse events.

Adverse reaction reports submitted to VAERS are filed by phone or letter, and then converted by an FDA contractor to a series of acceptable terms for the VAERS system. The conversion of native language to "COSTART" terms is cumbersome, and the final computerized reports can be difficult to evaluate with respect to symptoms suffered, disease severity and reaction duration. Despite these problems, one of us found that 10% of the anthrax vaccine VAERS reports appeared to meet the CDC's own definition of Gulf War Illness [49]. The anthrax VAERS reports frequently list fatigue, cognitive problems and musculoskeletal pains, which are hallmarks of both Gulf War illnesses [24,35,39,49] and the reactions experienced following anthrax vaccination [50].

THE TRIPLER STUDY

The DOD initiated a study at Tripler Army Medical Center, Hawaii in September 1998 to explore the issue of systemic reactions following anthrax vaccine and to look for long-term problems [51]. A total of 603 medical personnel were enrolled in an observational trial with no control group. In April 1999 the GAO reported that 43% of vaccine recipients had had mild systemic reactions and 5% had moderate or severe systemic reactions after one of the first four vaccine doses [19]. GAO later presented additional data from the study showing that over 60% of males reported muscle soreness following each vaccination and 60 to 80% of females reported this; 2-5% of males and 4-14% of females sought medical attention after one of their first three vaccinations; and 1-2% of males and 4-5% of females missed at least one shift of work after inoculation [51]. This study has yet to be published.

THE DOVER STUDY

Because of a large number of adverse reactions following anthrax vaccination at Dover Air Force Base, Delaware, the base commander Colonel Felix Grieder called a "time out" for the vaccination program in May 1999 so that reactions could be investigated, and Defense Department staff could answer questions. Within a week, the vaccine program restarted. Both Col. Grieder and the two nurses who ran the base clinic were soon replaced. The remaining medical staff were reportedly unsympathetic to reports of illness developing after vaccination, and have denied that any reactions on the base were due to anthrax vaccine.

In this setting, a Dover pilot initiated her own study of adverse reactions, sending questionnaires to 250 people in her squadron. The response rate was about 55%, and over 50% of respondents reported one or more medical problems which began shortly after vaccination. Only 8% of these problems resolved within a short period of time [52].

INSTITUTE OF MEDICINE REVIEWS

In March of 2000 at the request of the DOD and VA, an Institute of Medicine Committee investigating Gulf War illness reported on the evidence for safety of anthrax vaccine [33, 53]. They stated, "The committee concludes that in the peer reviewed literature there is inadequate, insufficient evidence to determine whether an association does or does not exist between anthrax vaccination and long term adverse health outcomes."

Two new Congressionally mandated Institute of Medicine committees have been constituted to further examine the anthrax vaccine for safety and efficacy, and to advise the CDC and DOD on proposed research on the licensed anthrax vaccine. Both committees will produce final reports in October 2002.

STRATEGIC CONSIDERATIONS

Does vaccination of troops against biological warfare agents make strategic sense? The military's Defense Advanced Research Projects Agency produced a list of over 65 naturally occurring pathogens that could be used as biological warfare agents. In addition there are an infinite number of virulent microorganisms that may be created using genetic engineering [54]. There exist less than 10 effective vaccines against these agents. It takes an estimated 10 years, once one is aware of a microbial pathogen, to develop an effective and safe vaccine against it. The fact that the United States did not have an

effective and safe anthrax vaccine at the time of the Gulf War, and still does not have one eleven years later, makes this perfectly clear.

Furthermore, if the DOD vaccinates its troops against anthrax, an enemy can just pick a different microorganism to use [54]. If an enemy genetically engineers a new, virulent organism, we will not even be able to begin developing a vaccine against it until after it has presented itself, in other words, after it has been used. And vaccinating troops does not protect civilians, who are thought by many to be a more logical target for bioterrorism. For these simple reasons, the use of vaccines against the threat of biological warfare will never provide an effective defense [54].

Finally, a U.S. House of Representatives report on anthrax vaccine reviewed all aspects of the mandatory anthrax vaccine immunization program and in March 2000 recommended that it be stopped, and that the vaccine be used only with informed consent [53].

THE JOINT VACCINE ACQUISITION PROGRAM, AND FDA'S RESPONSE

The anthrax vaccine was to be the first immunization in a much larger program termed the Joint Vaccine Acquisition Program. This program was created to develop, test, license, manufacture and eventually administer over a dozen vaccines against biological warfare threats to all U.S. Armed Forces personnel [56]. These newer vaccines, planned primarily for military use, may be associated with similar problems as the anthrax vaccine. Furthermore, it is expected that there will be difficulty testing these vaccines for efficacy in humans, as the diseases they are protecting against are rare, and situations in which the diseases occur at high frequency are hard to find. To overcome this hurdle, the FDA has proposed new regulations for biological warfare vaccines, which would eliminate the requirement for efficacy studies to be conducted in humans, allowing animal efficacy studies to be used for licensure [57]. There have been additional hints that FDA is considering dropping the requirement for human safety studies before licensing some vaccines. The Center for Biologics' Annual Report for 1999 mentions the difficulties obtaining efficacy data in humans, but then suggests that safety trials in humans will be omitted as well [58]. Since one does not need to expose human volunteers to pathogens to collect data on safety of drugs and vaccines, and since animal studies do not provide an accurate assessment of product safety, it is difficult to understand FDA's rationale for omitting human testing before licensure. FDA itself is helping to develop newer vaccines against anthrax [59]. It is hard to see how FDA will be able to ensure adequate oversight for vaccines developed by its own staff.

Dr. Katherine Zoon, the Director of the FDA's Center for Biologics Evaluation and Research, has advocated rapid approval of new biological warfare vaccines. She has written, "after these vaccines are licensed and administered, the safety and adverse reactions of these vaccines should be assessed" [60]. We should be deeply concerned by FDA's suggestion that human safety studies can be eliminated prior to new vaccine licensure, and that post-marketing surveillance alone will be adequate to assure vaccine safety.

For many vaccines, post-marketing surveillance is essentially limited to VAERS reporting, and as discussed above, VAERS reporting is of limited usefulness. Expecting passive post-marketing surveillance to provide timely and adequate warning of vaccine problems is unrealistic. If the case of anthrax vaccine is an example, the military will do its best to prevent meaningful vaccine oversight and may cover up adverse reactions. Active surveillance for long-term vaccine reactions is clearly needed. It should take place prior to vaccine licensure, and should use cohorts of adequate size to discover serious reactions that might occur in 0.1% or more of vaccine recipients.

SUMMARY

The current anthrax vaccine has not been shown to be safe or effective. As a military vaccine, its production has bypassed civilian standards for inspections, consistency, good manufacturing practices, and expiration dates. Potency is uncertain, and adverse reactions have been ignored, despite the fact that the vaccine has engendered very high rates of adverse event reports. Gulf War Illness appears to be, at least in part, a consequence of anthrax vaccination. The Defense Department has tried to control the reporting of vaccine-related adverse events, and has withheld release of adverse event data. Large numbers of recently vaccinated Armed Forces personnel are ill, many with symptom clusters that resemble Gulf War Illnesses. The FDA has not properly performed many of its oversight duties for anthrax vaccine, and proposes to further weaken its own standards for vaccine licensure, possibly eliminating human studies. This would severely undermine new vaccine safety and efficacy for both civilians and the military. The history of the anthrax vaccine program presages potentially very serious problems with the vaccines yet to be licensed, and should provide a clarion call for oversight of all military vaccines by an independent civilian authority.

REFERENCES

- [1] Brachman PS, Gold H, Plotkin S, Fekety FR, Werrin M, Ingraham NR. Field evaluation of a human anthrax vaccine. *American J Public Health* 1962; 52: 632-645.
- [2] Centers for Disease Control. Observational study of anthrax vaccine, 1960s. (Report obtained by FOIA to CDC, August 2000).
- [3] Bioport. Anthrax vaccine adsorbed. Package Insert March 1999. Online: <http://www.bioportcorp.com/Anthraxins.htm> (accessed 6/99)
- [4] Pittman M. HEW Memorandum to Reference File no. 67-70, November 2, 1970.
- [5] Plotkin SA, Brachman PS, Utell M, Bumford FH, Atchison MM. An epidemic of inhalation anthrax, the first in the twentieth century. I. Clinical features. *Am J Medicine* 1960; 992-1001.
- [6] Brachman PS, Plotkin SA, Bumford FH, Atchison MM. An epidemic of inhalation anthrax, the first in the twentieth century. II. Epidemiology. *Am J Hygiene* 1960; 72: 6-23.
- [7] Sharma S. Verbal testimony: DOD's mandatory anthrax vaccine immunization program for military personnel. Hearing before the House Subcommittee on national security, veterans affairs and international relations. April 29, 1999. Serial No. 106-26. U.S. Government Printing Office, Washington, 1999.
- [8] FDA. Biological products: Bacterial vaccines and toxoids: Implementation of efficacy review. Proposed rule. *Federal Register* 1985; 50(240): 51002-51117.
- [9] Michigan Biologic Products Institute. Investigational New Drug Application BB-IND 3723, September 20, 1996.
- [10] Nass M. Anthrax vaccine: Model of a response to the biological warfare threat. *Infectious Disease Clinics of North America* 1999; 13: 187-208. Online: <http://www.anthraxvaccine.org/AVmodel.htm>
- [11] Pomerantsev AP, Staritsin NA, Mockov YUV, Marinin LI. Expression of cereolysin AB genes in Bacillus Anthracis vaccine strain ensures protection against experimental hemolytic infection. *Vaccine* 1997;15: 1846.
- [12] MBPI Confidential Analytical Laboratory Anthrax Potency Review. AVA Lots manufactured 1990-1997. Prepared by R. Merriman, 12/8/97. page 1.
- [13] FDA Memorandum from Jeanne Novak to Carolyn Hardegree. December 10, 1997. Online: <http://www.anthraxvaccine.org/suppdocs/doc5.htm>
- [14] DOD document DASG-HCD-D: Medical Biological Warfare Defense Plan (undated, unclassified), signed by Brig. Gen. Bruce T. Micketinac; Online: <http://www.anthraxvaccine.org/suppdocs/doc12.htm>
- [15] Ivins BE, Fellows PF, Nelson GO. Efficacy of a standard human anthrax vaccine against Bacillus anthracis spore challenge in guinea pigs. *Vaccine* 1994; 12: 872.
- [16] Institute of Medicine. Chemical and Biological Terrorism: Research and Development to Improve Civilian Medical Response. National Academy Press: Washington DC, 1999, pp134-136.
- [17] Ivins BE, Fellows PF, Nelson GO. Efficacy of a standard human anthrax vaccine against Bacillus anthracis spore challenge in guinea pigs. *Vaccine* 1994; 12: 872.
- and Personal communication: Ivins BE, 9/98.
- [18] FDA Form 483 Inspectional Observations, 18-27 November 1996 for Michigan Biologics Product Institute.
- [19] Chan K-C. Medical Readiness: Safety and efficacy of the anthrax vaccine. GAO Report T-NSIAD-99-148. April 29, 1999.
- [20] FDA. Letter from Zoon KC to Myers R. April 28, 1998.
- [21] Letter from Lt. Gen. Ronald R. Blanck (US Army Surgeon General) to the Editor, Belleville Illinois News-Democrat. May 29, 1998.
- [22] Zoon K. The Defense Department's Universal Anthrax Vaccine Program. Testimony before the Senate Armed Services Committee, July 12, 2000. Federal News Service 2000.
- [23] FDA Form 483 Inspectional Observations for Bioport Corp. 10-26 October 2000.
- [24] Research Working Group of the Persian Gulf Veterans Coordinating Board. Annual Report to Congress: Federally sponsored research on Gulf War veterans' illnesses for 1998. Department of Veterans Affairs, June 1999.
- [25] National Institutes of Health Technology Assessment Workshop Panel. The Persian Gulf Experience and Health. *JAMA* 1994; 272: 391-396.
- [26] Institute of Medicine. Health Consequences of Service During the Persian Gulf War: Recommendations for research and information systems. National Academy Press: Washington DC, 1996.
- [27] Persian Gulf Veterans Coordinating Board. A Working Plan for Research on Persian Gulf Veterans' Illnesses. November 1996. Online: <http://www.gulfink.osd.mil/varpt/framing.html>
- [28] Presidential Advisory Committee on Gulf War Veterans' Illnesses. Interim Report. Washington DC: U.S. Government Printing Office: February 15, 1996. Online: <http://www.gwvi.ncr.gov/interim.html>
- [29] Presidential Advisory Committee on Gulf War Veterans' Illnesses. Final Report. Washington DC: U.S. Government Printing Office: December 31, 1996. Online: <http://www.gwvi.ncr.gov/toc-f.html>
- [30] Presidential Advisory Committee on Gulf War Veterans' Illnesses. Special Report. Washington DC: US Government Printing Office: October 1997. Online: <http://www.gwvi.ncr.gov/toc1.html>
- [31] Joint Staff Action Processing Form, Action # J-4A01206-91, and ASD (HA) Memo SF601 22 July 1991. Online: <http://www.anthraxvaccine.org/testimon.htm>
- [32] Pittman PR, Sjogren MH, Hack D, Franz D, Makuch RS, Arthur JS. Serologic Response to Anthrax and Botulinum Vaccines (Protocol NO, FY 92-95, M109, Log No.A-5747) Final Report to the US FDA. Fort Detrick, MD; US Army Medical Research Institute of Infectious Diseases.
- [33] Institute of Medicine. Gulf War and Health, vol. 1: Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines. National Academy Press: Washington, DC, 2000.
- [34] Friedlander AM, Pittman PR, Parker GW. Anthrax vaccine: Evidence for safety and efficacy against inhalational anthrax. *JAMA* 1999; 282: 2104-6.
- [35] Unwin C, Blatchley N, Coker W, Ferry S, Hotoph M, Hull L, Ismail K, Palmer I, David A, Wessely S. Health of UK servicemen who served in Persian Gulf War. *Lancet* 1999; 353: 169-178.
- [36] Straus SE. Commentary. *The Lancet* 1999; 353: 162-163.
- [37] Hotoph M, David A, Hull L, Ismail K, Unwin C, Wessely S. Role of vaccinations as risk factors for ill health in veterans of the Gulf War: Cross sectional study. *BMJ* 2000; 320: 1363-1367.
- [38] Hotoph M. Reanalysis of Gulf war vaccination data does not contradict findings. *BMJ* 2000; 321: 761-2.
- [39] Steele L. Prevalence and patterns of Gulf War Illness in Kansas Veterans. *Am J Epidemiology* 2000; 152: 991-1001.
- [40] OSAGWI (Office of the Special Assistant to the Secretary of Defense for Gulf War Illnesses). Military medical recordkeeping during and after the Gulf War: Interim Report. Washington, DC. U.S. Department of Defense 1999. Online: <http://www.gulfink.osd.mil/mrk/>
- [41] OSAGWI (Office of the Special Assistant to the Secretary of Defense for Gulf War Illnesses). Information Paper: Vaccine Use During the Gulf War. Washington, DC. US Department of Defense 2000. Online: <http://www.gulfink.osd.mil/va/>
- [42] Canadian Department of National Defense website: www.dnd.ca/menu/press/Reports/Health/health_study_eng_1.htm and Online: http://www.dnd.ca/menu/press/Reports/Health/health_study_eng_1.htm

- [43] Cherry N. Health and exposures of United Kingdom Gulf War veterans. Part II: The relation of health to exposure. *Occup Environ Med* 2001; 58: 299-306.
- [44] Mahan CM, Kang HK, Ishii EK et al. Anthrax vaccination and self-reported symptoms, functional status and medical conditions in the national health survey of Gulf War era veterans and their families. Environmental Epidemiology Service, Veterans Health Administration, Washington, DC.
- [45] Secretary of the Navy. DON Anthrax Vaccination Implementation Program (AVIP). April 29, 1998. SECNAVINST 6230.4.
- [46] Piel M. Verbal testimony to House Subcommittee on National Security, Veterans Affairs and International Relations, July 21, 1999. Online: www.house.gov/reform/ns/hearings/testimony/piel.htm
- [47] Surgeon General NOTAM Risk Management Lessons. SG NOTAM 99-005. 30 July 1999.
- [48] Mootrey GT. The Vaccine Adverse Event Reporting System and Anthrax Vaccine. Presented to the Institute of Medicine Committee on anthrax vaccine safety and efficacy, October 3, 2000.
- [49] Fukuda K, Nisenbaum R, Stewart G, Thompson WW, Robin L, Washko RM, Noah DL, Barrett DH, Randall B, Herwaldt BL, Mawle AC, Reeves WC. Chronic multisymptom illness affecting Air Force veterans of the Gulf War. *JAMA* 1998; 280: 981-988.
- [50] Nass M. Testimony: DOD's Mandatory Anthrax Vaccine Immunization Program for Military Personnel. Hearing before the House Subcommittee on National Security, Veterans Affairs and International Relations. April 29, 1999. Serial No. 106-26. US Government Printing Office 1999. Online: <http://www.house.gov/reform/ns/hearings/testimony/nass2.htm>
- [51] Chan K-C. Medical Readiness: Issues Concerning the Anthrax Vaccine. July 21, 1999. GAO Report GAO/T-NSIAD-99-226.
- [52] Tanner J. Dover study of adverse reactions following anthrax vaccine. Unpublished. Online: <http://www.anthraxvaccine.org>
- [53] Institute of Medicine Committee on Health Effects Associated with Exposures During the Gulf War. An assessment of the safety of the anthrax vaccine: A Letter Report. March 30, 2000. National Academy Press, Washington DC. Online: <http://www.nap.edu/catalog/9811.html>
- [54] Nicolson GL, Nass M, Nicolson NL. The anthrax vaccine controversy. Questions about its efficacy, safety and strategy. *Med Sentinel* 2000; 5: 97-101.
- [55] U.S. House of Representatives, Committee on Government Reform. Unproven Force Protection. US Government Printing Office. 17 February, 2000. Online: <http://www.house.gov/reform/ns/reports/anthrax1.pdf>
- [56] Joint Vaccine Acquisition Program environmental impact statement. Online: <http://www.jpobd.net/jvap/fpea.htm>
- [57] Federal Register vol 64, no. 192. Oct 5, 1999 DHHS FDA 21 CFR Parts 314 and 601, pp53960-70.
- [58] FDA. CBER Annual Report, FY 1999. Online: <http://www.fda.gov/cber/inside/annrpt.htm#bioterr>
- [59] Gu ML, Leppla SH, Klinman DM. Protection against anthrax toxin by vaccination with a DNA plasmid encoding anthrax protective antigen. *Vaccine* 1999; 17: 340-344.
- [60] Zoon KC. Vaccines, pharmaceutical products, and bioterrorism: Challenges for the U.S. Food and Drug Administration. *Emerg Infect Dis* 1999; 5: 534-536.