

Introduction

The safety and efficacy of anthrax vaccine adsorbed in humans needs to be addressed as over 1.4 million doses have been administered to more than 440,000 U.S. citizens. Based on the first forty years of research and review this current assessment should have taken place prior to the Anthrax Vaccine Immunization Program (AVIP).

A stark divergence of the medical community's assessment of the safety and efficacy of AVA occurred at exactly the same time as the AVIP was announced. From the Brachman study in the 1950's to the submission of the IND by the Michigan Biologic Product Institute in 1996 not one published report considers the AVA as safe and effective, for the general population (i.e. mass immunizations), against all strains of anthrax, or for prophylaxis against an aerosolized exposure to anthrax spores. Indeed, even internal, unpublished materials document the severe limitations of this vaccine.

After the AVIP was announced and implemented this assessment of AVA changed dramatically. It is now safe and effective for mass immunizations, for all strains, and for protection against an aerosolized exposure to anthrax spores. This reversal of scientific opinion must be addressed. Either the first forty years of experience, research, and opinion is flawed or the last four years is flawed. I propose that it is these last four years that are suspect.

The First Forty Years

Albrink and Goodlow (American Journal of Pathology Vol. 35 No. 5) exposed chimpanzees to inhalation anthrax and published their results in 1959. Pre-exposure vaccination and post-exposure treatment was avoided. 50% of the animals survived the initial aerosol challenge. Upon a second challenge another 50% died.

The Brachman Study, conducted from 1955 through 1959 and published in 1962, was a single blind study of mill workers. While the study may have determined the general safety of a vaccine similar to AVA, efficacy was limited to cutaneous exposure from an undetermined and undefined level of exposure from anthrax strains that were not identified.

Brachman, Kaufman, and Dalldorf (Bacteriological Review Vol.30 No.3 1966) studied the effects of inhalation anthrax on the cynomolgus monkey. Five test runs occurred, three of which were considered valid. Without vaccination or treatment the highest mortality rate from anthrax was 43.8 %.

The U.S. Army patented the production process for AVA in 1965. This process would be used for the vaccine that was licensed in 1970. It must be noted that the vaccine produced by this patented process differs from the vaccine used by Brachman et al in three significant ways, manufacturing process, anthrax strain used, and constituent products. This patented vaccine was used in another study (unpublished) in several mills in the south, notably Talladega. This study was flawed in many ways. For instance, a 1968 letter from P.H. Coleman to the Division of Biologic Standards (DBS) states "As to the efficacy of the vaccine, we have no real method of determining the protection afforded." Additionally, in a memorandum from the licensing committee to Dr. M. Pittman in 1969, the committee stated, "The lack of cases of anthrax in an uncontrolled population of approximately 600 persons in a Talladega mill can hardly be accepted as scientific evidence for the efficacy of the vaccine."

Regardless, the additional standards were published in the Federal Register and the DBS honored their agreement to license the vaccine when the standards were published.

Dalldorf, Kaufman, and Brachman (Archives of Pathology Vol.92 1971) again studied cynomolgus monkeys. The highest mortality rate for untreated inhalation anthrax was 37.5%.

Two events occurred in 1985 that are critical to the first forty years of AVA science. First is the Federal Register publication of the FDA's review of biologic products titled "Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review". This Proposed Rule concludes that AVA is safe and effective, yet severely limits its application and instances where it is safe and effective. This review also indicates that it is uncertain whether or not the vaccine is effective against an aerosolized exposure of anthrax spores. No Final Rule has yet been published by FDA.

The second event of note from 1985 is the U.S. Army's Request for Proposals for a new anthrax vaccine. The need for a new vaccine is described as "There is an operational requirement to develop a safe and effective product which will protect US troops against exposure from virulent strains of *Bacillus anthracis*. There is no vaccine in current use which will safely and effectively protect military personnel against exposure to this hazardous bacterial agent." In this request to potential manufacturers of a new anthrax vaccine the current vaccines' limitations are described as "The vaccine [AVA] is, however, highly reactogenic, requires multiple boosters to maintain immunity and may not be protective against all strains of the anthrax bacillus."

Ivins (Clinical Immunology Newsletter 9:2, 1988) wrote about the need for an improved anthrax vaccine. "Immunization with MDPH-PA ...occasionally results in local pain and inflammation, and there is some evidence indicating that MDPH-PA may have diminished efficacy against certain virulent strains of *B. anthracis* (8). The need for an improved human vaccine against anthrax is apparent."

This scientific opinion is reiterated in 1989 written testimony to the Senate Committee on Governmental Affairs by Assistant Secretary of Defense Robert Barker. "The assessment in the 1986 report [1986 DoD Report on the Biological Defense Program] is accurate. Current vaccines, particularly the anthrax vaccine, do not readily lend themselves to use in mass troop immunization for a variety of reasons: the requirement in many cases for multiple immunizations to accomplish protective immunity, a higher

than desirable rate of reactogenicity, and in some cases, lack of strong enough efficacy against infection by the aerosol route of exposure.”

A 1990 review of military medicine by Takafuji and Russell (Infectious Disease Clinics of North America Vol. 4. No. 1) describes AVA as “a limited use vaccine” and “experimental”.

Hambleton and Turnbull (Bacterial Vaccines 1990) described the efficacy of protective antigen vaccines as follows, “Despite their effectiveness in protecting against industrially acquired anthrax, the present human vaccines do have deficiencies. For example, three doses at short intervals are required initially and there is a requirement for repeated booster doses; also, the vaccine gives rise to a variable degree of reactogenicity, which may be rather more than localized. Of perhaps more obvious concern are reports...that the protective antigen vaccines are unable to give protection, in guinea pigs at least, against certain virulent strains of *B. anthracis*. For the above reasons, there is currently interest in developing a human vaccine that lacks side effects, requires fewer doses to achieve and maintain long-term immunity, and is effective against all virulent strains.”

Ivins, Welkos, et al (Infection and Immunity Vol. 58 No. 2, 1990) wrote, “Undesirable characteristics of this vaccine include the need for multiple boosters and the reduced ability to protect laboratory animals against certain virulent strains of *B. anthracis*...such as the Ames strain.”

Iacono-Connors, Welkos, et al (Infection and Immunity Vol. 59 No. 6, 1991) reiterated the guinea pig as good animal model for anthrax testing. “The Hartley guinea pig was established previously as a good animal model for testing the protective immunogenicity of anthrax vaccines.”

A 1992 memorandum from B. Ivins to A. Friedlander begins “Although there is no data on MDPH-PA efficacy in humans, there is considerable information on its efficacy in guinea pigs and rhesus monkeys. In all experiments the dose of MDPH-PA was 0.5 ml.

In 1986 Little and Knudson (*Infect. Immun.*, 52:509-512) noted that MDPH-PA protected against challenge by the Vollum 1B strain of Bacillus anthracis, but afforded little or no protection against certain other strains (Table 1).”

The second edition of the textbook *Vaccines* published in 1994 includes AVA for the first time with a chapter authored by Brachman and Friedlander. This chapter is critical of the vaccine in terms of safety and efficacy.

Ivins, Welkos, and Nelson (*Vaccine* Vol. 12 No. 10, 1994) again use Hartley guinea pigs as the animal model for anthrax testing.

In 1995 the U.S. Army recognized the need to amend the AVA license. In a letter to R. Myers of the Michigan Department of Public Health AVA was defined as “not licensed for aerosol exposure expected in a biological warfare environment.” The letter also highlights the current technological limitations of determining efficacy, “In addition, there are no data to demonstrate that the human antibodies are exactly the same as those raised in the monkeys that were protected against a lethal aerosol challenge. Furthermore, cell-mediated immunity (CMI) in actively immunized monkeys may contribute to protection against aerosol challenge, and there is no comparative CMI data on monkeys and humans immunized against anthrax.”

A 1995 report in *Vaccine* by Ivins, Fellows, et al summarizes the difficulties in determining the actual immune responses that elicit protection, whether an to what degree humoral and/or cell mediated immunity are responsible for protection.

In 1996 an IND was submitted that would change the AVA license to show a specific indication for inhalation anthrax.

In addition to these instances in the first forty years of AVA history, the manufacturing facility itself has not been without criticism. A massive renovation occurred in 1990/91. The entire production process was changed. Stainless steel replaced glass lined

equipment. Ceramic filters replaced glass sintered filters. The sterilization process changed. The only change reported to FDA was the fact that the facility was being augmented with two additional production lines.

The AVA produced with this new equipment was different from that produced from the originally licensed and approved production line as discussed in the 1994 article by Ivins, Fellows, and Nelson published in *Vaccine* (Vol. 12 No. 10).

Three employees of the Michigan facility filed suit in 1998 for royalties on AVA. They contend that the significant changes they made to the production process in 1990 resulted in a “new” anthrax vaccine, that they had in fact “invented” a new anthrax vaccine. Their sworn testimony describes in detail the various changes made and the resultant new product. No clinical studies of safety and efficacy have been conducted with this newly invented vaccine.

The FDA has continually found fault with the product itself from at least 1990. In every inspection that FDA looked at AVA production, discrepancies were noted that violated current Good Manufacturing Practices (cGMP). The list of violations is too long to compile in this statement. However, several examples follow. In one inspection multiple cases of microbial contamination were noted in various sublots, to include the detection of penicillin. The presence of penicillin requires the destruction of the batches so contaminated. This did not occur. Also noted was the lack of integrity of the filter system. This system is the only step in the production process that ensures the removal of organic material from the final product.

Multiple regulatory and production violations render the AVA produced from 1990 to the present as adulterated. As a matter of public safety, it is illegal to ship or distribute adulterated biologic products.

A host of military medical officers wrote an article in JAMA (Vol. 278 No. 5) titled "Clinical Recognition and Management of Patients Exposed to Biological Warfare Agents". They summarize as follows, "If the cause is identified quickly, appropriate therapy can be initiated and the impact of a terrorist attack greatly reduced." It is also acknowledged that "There is insufficient data regarding efficacy against inhalational anthrax in humans..."

In the same issue of JAMA several of these same officers wrote another article in which they report that "...anthrax is readily treatable by commonly available antibiotics..."

Ivins, Pitt, Fellows, et al (Vaccine Vol. 16 No. 11/12, 1998) wrote that "Results of recent studies show that anthrax vaccines vary in their efficacy among different species...Indeed, in these studies, there was no anti-PA ELISA titer, TN titer, or SI level that would serve as a surrogate marker or immunity to an aerosol anthrax spore challenge." They additionally find fault with AVA. "The exact composition of the AVA used in these studies is difficult to assess due to non-quantitative desorption of protein from the Alhydrogel adjuvant. The formaldehyde excipient in AVA also complicates analysis, in that it causes considerable modification of the proteins in the licensed vaccine."

Fellow, Linscott, and Ivins presented efficacy data to the International Anthrax Conference in September 1998. Their study results of diverse anthrax strains and AVA showed that prophylaxis/survival of more than 50 % occurred against 6 of the 33 anthrax strains. 27 of the 33 strains had less than a 50 % survival rate.

Gu, Leppla, and Klinman (Vaccine Vol. 17, 1999) wrote that "Previous studies showed that humoral responses are not solely responsible for protection against *B. anthracis*...For example, Ivins et al showed that there was no correlation between the

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titer of anti-PA antibodies and survival from bacterial infection, indicating that a cell-mediated immune response may contribute to clearing of anthrax infections.”

Brachman and Friedlander revised the chapter in the textbook Vaccines third edition. What did not change however was their assessment that “The current vaccine is unsatisfactory for several reasons. The vaccine is composed of an undefined crude culture supernatant adsorbed to aluminum hydroxide. There has been no quantification of the protective antigen content of the vaccine or of any of the other constituents, so the degree of purity is unknown. Standardization is determined by an animal potency test. The undefined nature of the vaccine, and the presence of constituents that may be undesirable may account for the level of reactogenicity observed.”

A group of medical professionals wrote an article for JAMA in 1999 titled “Anthrax as a Biological Weapon”. This group, including Friedlander, states only that “A similar vaccine has been shown in 1 small placebo-controlled human trial to be efficacious against cutaneous anthrax.”

The Last Two Years

This review of AVA over the years reveals that it has been the purview of the U.S. military since its inception. The Department of Defense has sponsored all the studies. The Department of Defense owns the patent. The Department of Defense has furnished and financed the only licensed facility. The published studies have been by military officers. Until the AVIP very few reviews had been conducted or published by civilians.

Since the inception of AVIP the Department of Defense has stated, in congressional testimony, education packets for servicemembers, and Internet sites, that the vaccine is safe and effective against inhalation anthrax. Yet the material published by military medical officers contradicts this. Until Friedlander et al (JAMA Vol. 282 No. 22, 1999) every published article criticized AVA to one degree or another. This most recent article

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is definitive in nature by its use of numerous references to unpublished information purporting to the safety and efficacy of the vaccine.

No data has been made available for public review that supports this watershed change in opinion.

Discussion

AVA received little attention from the medical community or regulatory oversight prior to AVIP. The vaccine resided in the research labs of the U.S. military where only 7900 doses were administered through 1995 (National Academy Press, Health Consequences of Service During the Persian Gulf War: Initial Findings and Recommendations for Immediate Action, 1995).

The U.S. military is virtually the sole proprietor and source of any safety and efficacy data for AVA. As such, the current military opinion of AVA must be addressed in the following context.

Either the first forty years of data, observation, and opinion is wrong, or the last two years of data, observation, and opinion is wrong.

Either Brachman, Albrink, Kaufman, Dalldorf, etc. wrongly observed that inhalation anthrax is not uniformly fatal, or inhalation anthrax is uniformly fatal as per today's military position.

Either AVA is efficacious or the Coleman letter and multiple other references to the vaccine's lack of proven effectiveness are wrong.

Either the 1985 and 1989 U.S. military references to AVA as not well suited to mass immunizations and limited efficacy against inhalation anthrax is wrong or the current military opinion is wrong.

Either AVA is efficacious against all known strains as purported by the current military opinion or the work of Ivins and many others indicating limited effectiveness against numerous strains is wrong.

Either AVA is licensed for its intended use as per today's military opinion or the former commanders at USAMRIID, Takafuji and Russell article detailing AVA as limited use and always experimental are wrong.

Either the guinea pig is a good animal model, although it is not producing the desired results for the military's current position, or the work done to date describing the various known and unknown immune response mechanisms is wrong.

Either Brachman and Friedlander are wrong in their description of AVA as "unsatisfactory, undefined, crude, reactogenic, etc. (Vaccines, 2nd and 3rd editions) or the vaccine is satisfactory, defined, benign, etc.

Either the vaccine is not licensed as per the 1995 letter by U.S. Army or it is licensed as per today's military opinion.

Either the FDA has mis-identified multiple violations of cGMP, contamination of product, unapproved equipment and changes to same, extending vaccine beyond expiration dates without approval or the existence of standard procedures, etc., or these violations of the Federal Food, Drug, and Cosmetic Act and Public Health Service Act occurred.

Either the vaccine produced from the 1990/91 timeframe to the present is different than that approved by NIH (and then FDA) or the principal operators of the production process during that time frame lied in their sworn testimony.

Either the FDA has published a Final Rule on AVA classifying it as Category I and approved for sale and distribution or FDA has yet to determine and publish its findings and rule on AVA.

Either antibiotics, after an inhalation exposure, work as discussed by Friedlander and others in JAMA (1999) or they don't.

Either the composition of the vaccine is known and thereby its safe use by humans or the work done by Ivins, Pitt, Fellows, Friedlander, Brachman, etc. describing the lack of known composition is wrong.

Either formaldehyde does not affect the proteins in the vaccine and thereby the very basics of the vaccine itself, or formaldehyde does affect the proteins and thereby the composition of the vaccine as given servicemembers.

Either there is a correlation of immunity with anti-PA titers in laboratory animals and thereby an assumption of immunity in humans with similar anti-PA titers or the work of CDC personnel (Gu, Leppla, Klinman, 1999) is wrong.

Either published, peer reviewed data is acceptable science or the recent article by Friedlander (JAMA, 1999) is acceptable science.

The CDC/FDA have collected over 1500 VAERS reports since AVIP started. Walter Reed Medical Center has personnel assigned to handle the multiple severe adverse reaction cases being presented from around the services. Many of these 1500 plus reports list one to several of the symptoms associated with Gulf War Syndrome as their reaction to the anthrax vaccine. Statistically, AVA is the most highly reported vaccine in the VAERS system to date. If one were to extrapolate the reaction rate to the general population, annual VAERS reports would number several hundred thousand per year. At the present time, approximately 11,000 to 12,000 VAERS are filed per year for the entire population and for all vaccines. In the last eighteen months, over 1100 VAERS

have been filed on AVA alone, in a population that is generally loath to self-reporting of medical ailments.

Either AVA is highly reactogenic and responsible for the myriad ailments afflicting the vaccine recipients as reported through VAERS or a sudden unknown affliction, similar to Gulf War Syndrome, is affecting vast numbers of servicemembers whose only common thread is AVA.

Animal data is being gathered to determine the efficacy of AVA against inhalational anthrax in humans. The immune response of animals will be used to determine efficacy. The safety of the vaccine in these animals is not being observed or tested. Recent work in animals has raised serious questions about vaccine safety. Wilkie, Hogenesch, Dean, Dodds, Thornton, Kass, Philips, and others have published research in Veterinary Allergy & Clinical Immunology, Advances in Veterinary Medicine, etc. identifying and demonstrating the negative affects of vaccination in animals. These disorders generally center on autoimmune problems.

Either the entire range of issues should be examined with animal models to include safety testing, or animal models should be discarded.

Conclusion

The Gulf War represented a quantum increase in vaccine recipients. Those vaccinated represented a vastly larger population than all previously inoculated humans combined. The safety implications and efficacy limitations were previously known. Multiple organizations chartered to investigate Gulf War Illness have failed to adequately address the cause and effect of this and other vaccines. Thus the safety of AVA must continue to be derived from previously published material and from the only new source of data, VAERS. Those safety implications are just now becoming substantiated.

Absent political and public pressure the first forty years provided objective analyses of the vaccine, to include its attributes and its faults. The decision to proceed with AVIP

required a foundation on which to base the program. This statement attempts to define that foundation and the contradictions it is based upon.

These contradictions present a quandary. Either the first forty years of data and opinion are faulty or the foundation that AVIP relies upon is faulty. In the meantime, hundreds of thousands of servicemembers health and well-being are at risk as the safety of this vaccine is slowly realized. At risk also is the military mission. If the vaccine is not as effective as the current opinion purports, then servicemembers and the mission are at risk because they do not have the protection the AVIP guarantees.