How "adequate and well-controlled" was the "clinical trial" of a human anthrax vaccine, 1955-1959?

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Abstract

In late 2003, the Brachman et al. (1960, 1962) field study of an earlier anthrax vaccine became the basis for an FDA regulatory determination that the currently licensed vaccine is effective against B. anthracis strains, regardless of the route of exposure. Here, the Brachman et al. (1962) field study was reexamined in terms of the validity and completeness of its experimental design. Numerous limitations with respect to the trial's experimental design were either discovered or reaffirmed. Some of these limitations have never been explained satisfactorily for more than 40 years. In conclusion, our review indicates that Brachman et al.'s (1962) experimental design actually fell far short of being able to demonstrate, conclusively, the efficacy of the anthrax vaccine in humans, especially with respect to protection against inhalation anthrax. Any claim that the early trial of the vaccine was truly "adequate and well-controlled" must depend upon a consideration of only very limited information about the numerous weaknesses of that trial's experimental design.

Keywords: Anthrax vaccine, Experimental Design, Limitations of Research

1. Background

The safety and the efficacy of the current anthrax vaccine used by the U.S. military has been challenged [1,2] despite arguments in its favor [3]. The U.S. Food and Drug Administration (FDA) has responsibility to license vaccines based on its scientific assessment of the efficacy and safety of such vaccines. On December 30, 2003 the FDA issued a regulatory opinion on anthrax vaccine, a Final Rule. FDA's Final Rule, and other assessments of the efficacy of the current anthrax vaccine in humans, are primarily tied to the reputed success of the field investigations done, with a similar vaccine, between 1955 and 1959 at four goat hair mills in the eastern United States.

The vaccine is widely quoted as having demonstrated "92.5" or "93%" effectiveness, a statistic extracted from Brachman et al., [4:634]. For example, Bales, Dannenberg, Brachman, Kaufmann, Klatsky, and Ashford [5:1165] recently stated that, "In a 1962 field investigation, an acellular anthrax vaccine was demonstrated to be 93% effective in reducing the risk for infection with B. anthracis in humans. The vaccine was subsequently recommended for persons who handle imported hair, wool, hides, or bone meal." Likewise, Friedlander, Pittman, and Parker [3:2105] stated that, with respect to the same field investigation, "Vaccination resulted in a statistically significant reduction in the incidence of anthrax in the vaccinated (1 cutaneous case) compared to the placebo group (13 cutaneous and 2 inhalational cases; 93% effective with a lower 95% confidence limit of 65%)."

The vaccine has been alleged to be effective against cutaneous anthrax, and only more recently, against inhalational anthrax, even though no new evidence from the original study has been produced to augment any claim for effectiveness against inhalational anthrax. Inglesby et al. [6:1740] recalled the field investigation and said, "A similar vaccine has been shown in 1 small placebo-controlled human trial to be efficacious against cutaneous anthrax." Brachman & Friedlander [7:635] admitted that "No assessment of the effectiveness of the vaccine against inhalational anthrax could be made because there were too few cases." Fulco, Liverman, & Sox [8:283] agreed with previous reports that "there were not enough cases of inhalation anthrax to determine if vaccination was effective against this, the most lethal form of anthrax." More recently, in stark contrast to previous conclusions, Brachman et al. [9] claimed efficacy for all routes of infection in the Institute of Medicine's Committee to Review the CDC Anthrax Vaccine Safety and Efficacy Research Program.

The validity of the design of the initial anthrax vaccine study is an important issue because it forms the foundation of claims for the current vaccine's efficacy. Demicheli, Rivetti, Deeks, Jefferson, & Pratt [10:884] concluded on the basis of both the Brachman field investigation and a Russian study that "killed anthrax vaccine is efficacious and well tolerated and should be administered to persons at high risk of the disease." Demicheli et al. [10:883] did, however, admit that Brachman et al.'s [4] reporting was not complete but still assessed the overall quality of the Brachman study as "relatively good." The Institute of Medicine's Committee to Review the CDC Anthrax Vaccine Safety and Efficacy Research Program, chaired by Dr. Brachman, observed, "A controlled trial to evaluate the safety and efficacy of this vaccine was conducted between 1955 and 1959 at goat hair-processing mills in the eastern United States

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(Brachman et al., 1962). The study indicated that the vaccine was effective in this population. [9:25]" Their report assumed that the study's design was valid enough to permit dependable conclusions about the current vaccine's efficacy and safety.

The evidence for efficacy of the current anthrax vaccine is a central issue of a lawsuit brought by service members against the Department of Defense (DoD) and the Food and Drug Administration (FDA). If a vaccine is offered to an individual for a purpose for which it was not intended or known to be effective (not a licensed indication), then that individual should have the right to informed consent, even if in the military (10 U.S. Code, Section 1107). The defendants in John Doe #1 et al. v. Donald H. Rumsfeld, et al., (U. S. District Court for the District of Columbia, Civil Action No. 03-707) concede that the FDA's "effectiveness determination is based on the adequate and well-controlled study conducted by Drs. Brachman, Gold, Plotkin, Fekety, Werrin, and Ingraham." The defendants argue that the FDA's action in approving the anthrax vaccine for inhalational anthrax was "rational and supported by the evidence." Therefore, if the design of the Brachman et al. [4] field study in fact is not sufficiently strong to be able to support the efficacy of the current vaccine in humans for protection against inhalational anthrax, then much of the argument for efficacy of the vaccine against inhalational anthrax would be invalidated, as well as the validity of the FDA's Final Rule.

Objections to the current anthrax vaccination program may be raised on the basis of ethics and informed consent [11], or safety [2;8:13;12;13] but such issues are beyond the scope of this paper. However, numerous objections to the experimental design can be raised. We decided to review those issues briefly so readers would understand more clearly the historic and scientific background of the development of the human anthrax vaccine.

2. Summary of Brachman et al. (1962)

The U.S. Army began a field trial of what is now an older version of a human anthrax vaccine in 1955. Eventually, four textile mills that processed imported goat hair for suit interlinings were selected for participation in the study. The mills were probably selected on the basis of having had relatively high rates of anthrax infection previously; all four mills averaged 1.2 cases per 100 mill employees per year, a total of 130 cases between 1948 and the initiation of the study at each of the mills. In February 1955, the study began at Mill S with 273 workers and continued there until June 1958, with eleven workers contracting cutaneous anthrax during that time, one of them after being vaccinated and another after partial vaccination. The trial was extended to Mill M with 200 workers in May 1955 and continued there until late March 1959; only three workers developed cutaneous anthrax. The trial at Mill P with 144 workers did not begin until June 1956 and continued until late March 1959, with three workers developing cutaneous anthrax, the last in March 1959 after partial vaccination. The fourth Mill, Mill A, the Arms Mill in Manchester, New Hampshire became involved in the trial in May 1957 with 632 workers. However, after an epidemic of inhalational anthrax that began in late August, the trial was discontinued in November 1957, after which all that mill's workers were vaccinated. That epidemic left four workers dead of inhalational anthrax and infected five others, one with inhalational anthrax and four with cutaneous anthrax. The identities of mills M, P, and S, as well as most of the workers who were infected with anthrax, including those who died, have remained a secret. Based on relative rates of person-months of exposure, Brachman et al. [4] calculated the effectiveness of the vaccine as 92.5%, usually rounded up to 93% in recent reports. The initial pool of workers was 1,330. It appears that the researchers would initially randomly select workers into treatment and placebo groups and then ask for volunteers, after removing those who appeared to have had previous anthrax infections (N = 81). It is not clear if previous infection was determined from company medical records or worker self-report or both. Those who refused did not participate. Some workers started receiving either genuine or placebo vaccinations but dropped out of the program, becoming "incompletes." Among the 793 workers who did not refuse to participate and who did not become incompletes, 379 (47.8%) were vaccinated with anthrax vaccine and 414 (52.2%) received placebo vaccine. Numerous other workers fell out of the study, either by choice or because they left the mills for employment elsewhere. At the end of the study, only 287 (23.0%) of the original 1,249 workers were still participating, as well as only 190 (24.0%) of the original 793 workers in the complete vaccine or placebo group.

Of the 379 vaccinated workers, only one developed cutaneous anthrax (0.3%); of the 414 placebo cases, 15 (3.6%) developed cutaneous or inhalational anthrax. Among the 456 refusals and incompletes, 10 (2.2%) developed cutaneous or inhalational anthrax. Overall, anthrax infection rates were low, even among those with presumably no protection in spite of, in some cases, years of exposure to anthrax spores in the work environment.

3. Problems with Brachman et al.'s Design

First, the field study provided complete anthrax vaccinations to only 379 (30.3%) of the 1,249 participants. Adding in the placebo vaccinations, the total increases to 793 (63.5%). Ideally, one would want to administer genuine vaccine to approximately half of the subjects in a study in order to have the most powerful statistical test of the effectiveness of the vaccine. The study fell short of the ideal in this regard, due to a high rate of refusals at some of the mills and numerous "incompletes."

Another ideal for experimental designs is for a study to be "double-blind," that neither the subjects nor the researchers in direct contact with the subjects know which groups are treatment and which are control. However, an earlier report by the Institute of Medicine [8:282] indicated that this ideal was probably not met: "The study subjects did not know whether they had received the active vaccine or placebo; the article does not state whether the investigators were also blinded to the allocation."

Secondly, an unknown number of workers received partial vaccinations; the lack of clarity is a result of Brachman et al. (1962) reporting partial vaccinations and partial placebo inoculations together, rather than separately. Specifically, 116 (9.3%) of the 1,249 workers received partial vaccinations. That omission is important because it has prevented other researchers

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from ever analyzing the difference in effectiveness between partial vaccinations and partial placebo inoculations. The omission also weakens the ability of researchers to test the effectiveness of partial vaccinations because the "partial vaccination" group includes both those who received genuine vaccine and those who received placebo vaccine. One could statistically test the effects of partial vaccination but any legitimate effect of partial vaccination with the actual vaccine would be weakened by the presence of recipients of the placebo vaccine. This weakness of the study makes it impossible to determine exactly how many injections of the vaccine, below the recommended amount, are actually needed to provide an adequate level of immunity.

Thirdly, it is not clear how the design took into account certain unusual classifications of workers. For example, the departure of former workers and the arrival of new workers complicated the design in unknown ways. Brachman, Plotkin, Bumford, & Atchison [14:14] admit that two new workers who had not had a chance to receive either the vaccine or placebo (because they had started working at Mill A in mid-August 1957) had become infected. Thus, new workers who became ill were counted in the observational group, but it is not clear if new workers who did not become infected were added to the unvaccinated observational group. Likewise, Brachman et al. [4:642] admit that two workers at the Arms Mill were inadvertently given the first injection of the vaccine even though they had contracted cutaneous anthrax previously, implying that the study's attempts to remove workers with prior immunity to anthrax as a result of previous infections were not always successful. It is also possible that some workers had experienced subclinical cases of anthrax and had developed immunity without being aware of it. Yet the procedures used for screening those with previous clinical or subclinical infections were not specified, complicating interpretation of the study's experimental design.

Low retention rates were a fourth problem with the study's design. What we do know from Table 3 [4:635] is that of the 793 members of the experimental group (those who received either full vaccinations or full placebo inoculations) only 190 (24.0%) remained in the evaluation program after having had four booster inoculations. Thus, 76.0% of the experimental group did not complete the full study. Of those 116 who failed to complete their initial series of real or placebo vaccinations, there were 73 (62.9%) remaining at the end, admittedly a higher percentage than for the experimental group (24.0%) Such different retention rates remain troubling from a scientific perspective. Finally, with respect to retention rates, among the 340 workers who refused the vaccine, only 24 (a mere 7.1%) remained at the end of the study. The differences between these retention rates for the three groups (7.1%, 24.0%, and 62.9%) are very significant by chi-square ($df = 2$) = 153.7 ($p < 0.001$), though they yield an overall retention rate of 23% (287/1249). On the other hand, Brachman et al. [4: 635] provided no information in Table 3 about the differential retention rates between the placebo and the genuinely vaccinated groups (we know that together only 190/793 (24.0%) workers in the experimental group remained in the study as of their fourth booster inoculation). Brachman et al. [4] also failed to report if there were significant differences in attrition rates across the four mills studied, a weakness that could further complicate the valid interpretation of their results. It is not clear what factors may have led workers to quit the project, but those unknown factors may have confounded differences between the vaccinated and unvaccinated groups and subsequent rates of anthrax infection. For example, twice as many placebo workers (15/414 or 3.6%) became infected with anthrax during the study as did workers who refused to participate in the program (6/340 or 1.8%). While the percentages were not different statistically ($p < .17$), such differences suggest there may be other ways in which the various groups differed but that were not controlled in the study's design.

However, from Table 8 [4: 640-641], we can estimate the retention rates at the end of the study, regardless of the previous number of inoculations for each mill. It appears that the retention rates for the four mills varied considerably. For example, from Table 2 [4: 634], Mill P started with 19 high risk workers who were vaccinated and with 22 high risk workers who were inoculated with placebo vaccine. Likewise, Mill P started with 22 low risk workers who were vaccinated and with another 22 low risk workers who received placebo. Altogether, Mill P began with 85 workers in the experimental group, which would translate into approximately 510 (85 x 6) person-months exposure over six months. However, Table 8 [4: 640-641] shows Mill P having only 453 person-months exposure in the first six-month evaluation period, a retention rate of 453/510 (88.8%). In its last available evaluation period, which was 12 months long, Mill P had only 156 person-months or 78 person-months over six months on average. Thus the final apparent retention rate for Mill P appears to have been 78/510 (15.3%). Similar figures for Mills A, M, and S were, respectively, 1740/1878 (92.3%), 477/984 (48.5%), and 399/1386 (28.8%). These estimates are conservative because workers who received incomplete vaccinations were not included in the initial totals, which would have enlarged the denominator in the previous statistics. Even if one were to use slightly different methods of calculating the retention rates, it would appear that substantial differences would still emerge among the mills with respect to their retention rates.

Whatever factors drove the differences in worker retention rates in the field trial, those factors were far more influential with respect to retention than the vaccine was at reducing anthrax rates. When external factors are not well-controlled but are far more powerful than the independent variable, the interpretation of the results of such a study are jeopardized. If Brachman et al. [4] had reported the breakdown of the partial inoculations, it might have been possible to control statistically for the study's retention problems, but that breakdown was not reported. Nevertheless, such limitations have not impacted the confidence often placed in the results of this trial.

Fourth, the vaccine was clearly administered only to volunteers [14:13-14] and it remains unclear how the group of volunteers was similar to or different from the group of non-volunteers. From Table 2 [4: 634], it is apparent that refusal rates differed considerably among the mills -- 284/632 (44.9%) for Mill A, 24/200 (12.0%) for Mill M, 31/144 (21.5%) for Mill P, and 1/273 (0.4%) for Mill S, with an overall refusal rate of 340/1249 (27.2%). Refusal rates also differed as a function of high risk versus low risk workers, with 89/589 (15.1%) of high

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risk workers refusing to participate, compared to 251/660 38.0%) of low risk workers. Differences in susceptibility to anthrax infection between the two groups (age, gender, preexisting health or genetic conditions, etc.) might well account for differences in outcome since the assignments to volunteer/non-volunteer groups were not randomized, as usually done in well-controlled experimental designs. Refusal rates did not parallel previous infection rates (1948 to start of study at each mill) among workers at the four mills, infection rates (Table 1 in [4: 633]) of 1% (Mill A), 1.4% (Mill M), 0.6% (Mill P), and 1.0% (Mill S) even though they appeared related to the relative risk status of each worker.

Fifth, it appears that the randomization procedures were done before the list of volunteers was obtained rather than afterwards [14:14], allowing for the possibility that factors associated with volunteering could confound the differences between the vaccinated and placebo groups.

Sixth, the length of time that each mill remained part of the study varied from a few months to over three years, creating substantial differences in possible exposure durations for each worker, both to anthrax spores and to the possibility of continuing vaccination.

Seventh, Brachman et al. [14] carefully reviewed the records of the Arms Mill and found not even one case of inhalational anthrax in the Mill from 1941 to July 1957, highlighting the unusual nature of the epidemic that occurred at the Arms Mill in the fall of 1957. Even though Brachman et al. [14:11] noted that anthrax bacilli were recovered from three of the Arms Mill victims and tested on laboratory animals (with LD_{50} of 6,000 inhaled spores for monkeys and 50,000 for guinea pigs and with virulence equivalent to "the most virulent laboratory-selected strain," it is not clear that anyone publicly reported the causative strain of anthrax. It was referred to by Brachman, et al. [14:20] as the "Manchester strain," even though it arguably did not originate in that locality, since the goat hair used came from Iran, Iraq, and Pakistan [14:8]. One would have expected the particular strain of that disease to have been identified in order to know against what strain the vaccine might have been effective. It would be very helpful to know if the strain was the Ames strain manufactured by the United States Army or whether it was a different strain, perhaps one manufactured by the former Soviet Union, or a naturally occurring strain.

Finally, it should be added that nowhere did Brachman et al. [4] report statistical analyses of the vaccine's effectiveness that controlled for mill location, risk levels, age, race, gender of workers, or other factors that might have been of interest, as did Wiesen & Littell [15] in a recent analysis of anthrax vaccination and pregnancy outcomes (not to mention the retention issues discussed earlier). Our point is that quite an argument can be made to dispute the notion that the study was "well-controlled." At the very least, it was not well-controlled from the perspective of a multivariate statistical analysis controlling for numerous potential confounding factors.

The Brachman et al. [4] study was also limited not only in terms of what it did, but in terms of what it didn't do. In fact, FDA has recently noted [16:2] that "a window of opportunity for preventive therapy exists between the time of inhalation of aerosolized spores of B. anthracis and development of signs and symptoms of disease." The basis for FDA's statement is (1) Army research [3:1242] on non-human primates that "clearly showed that complete, long-term survival, after discontinuance of antibiotics, occurred when postexposure antibiotic treatment was combined with vaccination" and (2) the results in exposed postal workers none of whom developed anthrax after starting prophylactic antibiotics while asymptomatic. The recent success of post-exposure prophylaxis with vaccine and antibiotics after the 2001 anthrax letter attacks, along with Friedlander, et al.'s [3] results, appear to have convinced the CDC [17] that post-exposure prophylaxis with antibiotics and vaccine has as much statistical validity as pre-exposure immunization with a highly reactive [12] vaccine. Yet, the Brachman et al. [4] study did not include a post-exposure prophylaxis treatment group (for both vaccinated and placebo groups), making it impossible to determine the relative effectiveness of treating anthrax infections by vaccination alone, by vaccination and antibiotics, or by antibiotics alone. Regardless of the ethics of such an experiment, the lack of alternative treatments remains a weakness of the original Brachman et al. [4] study. Even among those who fell ill with inhalational anthrax in the study, there was no systematic attempt to administer adequate levels of antibiotics as early as possible, even after the first cases had occurred (and the local medical community presumably having been advised of the risk of mill workers contracting inhalational anthrax – at least that would have been the logical thing to have been done, if only in hindsight) [18].

4. Discussion

Readers might object, however, that the flaws in design might not be nearly substantial enough to influence the outcome of the study with respect to the efficacy of the vaccine. For example, if 99% of those vaccinated were protected from anthrax infection in contrast to only 50% of those not vaccinated, it could be argued that the 49% difference was so substantial as to override any errors associated with design flaws. It would be a valid argument, if the effect of the vaccine were so dramatic. However, vaccination raised protection rates against anthrax infection from 96.4% to 99.7% among the 793 workers in the experimental group in the study, a difference of only 3.3 percent, a difference small enough to perhaps compare with the errors associated with the study's flaws in design.

Uncertainty associated with retention rates and refusal rates clouds the clarity of the study's design. Without information on partial vaccinations, we cannot distinguish the effects of partial vaccination with placebo versus genuine vaccine. It is not clear how workers with previous anthrax infections were screened nor under what conditions and how incoming workers were admitted to the study. Numerous factors (risk level, gender, mill, age, etc.) were not controlled statistically in the estimation of the vaccine's effectiveness. The way in which the Brachman et al. [4] study was conducted leaves many questions unanswered and falls far short of an ideal experimental design in numerous ways. In conclusion, our review indicates that Brachman et al.'s [4] experimental design actually falls far short of being able to demonstrate conclusively the efficacy of the current anthrax vaccine in humans. Given the uncertainty associated with the benefits of the vaccine, greater weight should be given to potential risks associated with the current

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vaccine when risk-benefit ratios with respect to the current anthrax vaccine are considered. Leaning on the Brachman et al. [4] study to justify the current vaccine's effectiveness is more akin to wishful thinking than to science in our opinion. Clearly, the debate about anthrax vaccine's safety and effectiveness [19, 20] and the role of vaccines in Gulf War illness [21] will continue, regardless of the measure of faith placed in the original human trials of the anthrax vaccine [4], but the evidence suggests that the Brachman et al. [4] study had numerous and considerable limitations in its design that tend to limit its usefulness for promoting human anthrax vaccine's effectiveness, especially with respect to protecting against inhalation anthrax.

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