A statistical reanalysis of Brachman *et al.'s* 1962 study of a human anthrax vaccine

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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 was effective against B. anthracis strains, regardless of the route of exposure. Here, the Brachman et al. (1962) field study is reexamined statistically, analyzing the vaccine's effectiveness as a function of risk levels, levels of vaccination status, types of anthrax infection, mill locations, and two study components (total versus experimental groups). Fisher's Exact Tests were used to compare the vaccine and non-vaccine groups because Fisher's Exact Tests are more accurate than the traditional chi-square tests, especially when cell sizes or probabilities are small. Numerous limitations of the trial were discovered or reaffirmed. Even taking both cutaneous and inhalational anthrax into account, we found that the vaccine's protective effects were not statistically significant ($p < 0.05$) in 75% of the mills studied. We found no evidence for the effectiveness of incomplete vaccinations, although design or reporting flaws in the original study mitigated against finding such evidence. The reanalysis of Brachman et al. (1962) does indicate that the anthrax vaccine may help provide some marginal protection against cutaneous anthrax infection; however, cutaneous anthrax is seldom fatal and usually easily cured with antibiotics. The data do not provide statistically significant evidence of protection against inhalation anthrax. In conclusion, our reanalysis indicates that Brachman et al.'s (1962) data actually fell far short, as had actually been long acknowledged by leading anthrax experts until some time after 1999, of demonstrating the efficacy of the anthrax vaccine in humans, especially with respect to inhalational anthrax infection.

Keywords: Anthrax vaccine, Inhalational Anthrax, Cutaneous Anthrax, Limitations of Research

1. Background

As observed previously [1], the safety and the efficacy of the current anthrax vaccine used by the U.S. military has been challenged [2,3,4] despite arguments in its favor [5,6]. The FDA recently issued a regulatory opinion on anthrax vaccine that was largely tied to the reputed success of the field investigations done, with a similar vaccine, in the 1950's at four textile mills. Indeed numerous recent sources have cited the 93% effectiveness rate reported by Brachman et al. [7] when discussing the efficacy of the current anthrax vaccine [5: 2105, 8:1165;9:1740;10:884). However, some researchers have admitted that the vaccine was not proven to work against inhalation anthrax; Brachman & Friedlander [11:635] as recently as 1999 admitted, "No assessment of the effectiveness of the vaccine against inhalational anthrax could be made because there were too few cases." However, more recently, Brachman et al. [12] claimed efficacy for *all* routes of infection, including *inhalational*, in the Institute of Medicine's Committee to Review the CDC Anthrax Vaccine Safety and Efficacy Research Program.

As noted previously [1], "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." Likewise, if the Brachman et al. [7] field study in fact fails "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. [1]."

Others have addressed issues of the safety of the current anthrax vaccine [3,4,13,14,15], issues of informed consent [16], and issues related to the design of the Brachman et al. [7] study [1]. However, such issues are beyond the scope of this paper. Here, our current goal was to assess whether Brachman's data had been "well-analyzed."

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2. Goals

The objective of this report was to reevaluate the reputed effectiveness of the anthrax vaccine tested in Brachman et al.'s [7,17,18] study. Was the vaccine proven to be effective against cutaneous anthrax? Was it proven to be effective against inhalational anthrax? Did 93% effectiveness actually mean that 93% of those exposed to anthrax were protected in contrast to none of those not vaccinated, a result that seems implied to the layman by the repeated emphasis on the 92.5% or 93% effectiveness result. Did the vaccine work at all the mills in the study? Did the vaccine work across all times, as well as all places tested? What factors were controlled in the study, if any? These are all questions that deserve consideration in assessing the merits of the current anthrax vaccine since the Brachman et al. [7] study is the only field study conducted in the United States reported in open sources. Indeed, the Brachman field trial is accepted by scholars as the cornerstone of the arguments favoring efficacy of anthrax vaccine for preventing cutaneous or inhalational anthrax in humans.

Aside from the issue of whether the field study was well-controlled, if the claimed results from the Brachman, et al. [7] field trial fail to be supported by a detailed statistical analysis, then the whole foundation of the involuntary anthrax immunization program in the U.S. military would be undermined. Evidence of efficacy would then have to rest on animal trials, whose applicability to human situations remains uncertain at best [12].

3. Methods

The data for this reanalysis have been derived from three reports concerning an outbreak of anthrax at the Arms Mill in Manchester, New Hampshire and three other mills, identified only as M, P, and S: Brachman et al. [7,17] and Plotkin et al. [18]. Only the Arms Mill endured an "epidemic" of inhalational (and cutaneous) anthrax; the other three mills experienced occasional infections of cutaneous anthrax. In many respects, the experience at the Arms Mill deserves separate treatment, because it was substantially different from that of the other three mills and because the outcomes there are more relevant to projected military experience with inhalational anthrax as a biological weapon. Therefore, the analyses that follow will consider the Arms Mill experience separately from the other mills and will break down the outcomes on the basis of relative risk.

There were three levels of risk proposed by Brachman et al. [7,17,18]: highest risk (only associated with the carding/combing departments at the Arms Mill, 44 employees as of August 26, 1957), high risk (employees working in the picking, carding, combing, drawing, and spinning departments at each mill), and low risk (employees working in the weaving, finishing, maintenance, and office departments at each mill). Nowhere do Brachman et al. [7] specify which departments are high or low risk, but they state that only 3 of the 26 workers infected during the trial were from a low risk department. The only departments that could account for 3 workers are either weaving (3 workers) or picking, combing, and drawing (one worker each). The picking and combing departments are among the first to be exposed to incoming bales of goat hair and tend to have a higher percentage of infected workers; the only remaining department that might be classified as low risk therefore is the weaving department. Therefore, the picking, combing, and drawing departments must be high risk, as well as the spinning and carding departments, which had ten infected workers each in Brachman et al. [7].

Furthermore, results for both cutaneous and inhalation anthrax will be considered separately because of the far greater military importance of inhalation anthrax. Cutaneous anthrax is rarely fatal and in most cases, easily treated, with the appropriate antibiotics. Notably, few fatalities from cutaneous anthrax have occurred in the United States since 1940. Furthermore, while cases of cutaneous anthrax were not uncommon at the mills and in agricultural settings, there had been few inhalational cases of anthrax until 1957; other than the five cases in 1957 at the Arms Mill, there were four other cases in the United States between 1950 and 1976, with no further cases until the fall of 2001 [8:1164]. In addition, three of the mills studied in Brachman et al. [7,17,18] experienced no inhalational anthrax cases at all, suggesting perhaps a different route, process, or level of exposure to the infecting agents.

Finally, data will be analyzed first for all employees, including those partially vaccinated or who refused vaccination (designated as the TOTAL group, data from Brachman et al. [7:634], Table 2), and second for only those employees (designated Experimental group) who were vaccinated completely, either with the anthrax vaccine or with a placebo (Brachman et al. [7:640-1], Table 8). Additional analyses will be performed on the 44 employees of the Arms Mill who were at greatest risk of anthrax infection, as reported elsewhere [17, 18].

Furthermore, in order to evaluate the data from additional perspectives, to avoid bias, we analyzed the data over time, observing how the results changed from the start of the four mills project to the end and we evaluated each mill separately for all types of anthrax. We also performed some analyses based on the attrition cited in Table 8 of Brachman et al. [7:640-1] because the 92.5% effectiveness statistic widely reported was derived from data in Table 8.

In summary, our analyses will differ from previous analyses because three risk levels, three levels of vaccination status (fully vaccinated, partially vaccinated, and unvaccinated), two types of anthrax, two general locations, and two study components (total versus experimental groups) will be considered rather than looking for a single summary measure of vaccine effectiveness across those many combinations of conditions.

Our analyses will start with the largest groupings of data and logically break them down into smaller subsets on the basis of risk and type of anthrax experience as shown in Table 1 below. Initially, multivariate binary logistic regression analyses were used to predict infection from vaccination status, mill, and risk level, but in no analyses were mill location or risk levels significant (beyond chance) for predicting infection. In addition, partial vaccination status was never a significant predictor of infection risk, suggesting that incomplete

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vaccinations were relatively ineffective, even at preventing cutaneous anthrax infection, a situation mirrored in the three cases of anthrax found among partially vaccinated mill employees between 1962 and 1974 in an advisory panel report to the FDA [50 Federal Register 51058;5:2105]. Ultimately, for accuracy and ease of presentation, one-tailed (sided) Fisher's exact tests were used to test the association of vaccination with infection outcomes. Fisher's exact tests [19:39-40] are more accurate than the traditional chi-square tests used by Brachman et al. [7,17,18], especially when expected cell sizes or probabilities are small (as occurs often for the vaccinated but became infected cells, which should ideally be near zero, if the vaccine is working effectively). The Fisher's Exact Test gives a precisely accurate p-value or statistical significance level [20:132]. Chi-square tests depend upon assumptions about normal distributions that are good approximations in large samples, but often are less accurate for small samples or for samples including very low probabilities for some cells.

The chi-square tests for the experimental group will compare the percentage of workers becoming ill in the vaccinated group of workers compared to the placebo group of workers. The chi-square tests for the total group of workers will compare the percentage of workers becoming ill in the vaccinated group of workers compared to all other workers, including refusals, incompletes, and placebos.

4. Data Reconstruction

Table 2 illustrates the number of cases involved in each possible analysis for the mills as a total group while Tables 3 and 4 show the logical breakdowns for the mills other than the Arms Mill and for the Arms Mill itself.

Table 5 shows the reconstructed data from Brachman et al. [7,17,18] that specifies which of the 44 employees had certain jobs, previous experience with anthrax infection, antibodies to anthrax (suggesting a subclinical experience with anthrax infection), and had received either a genuine or placebo vaccination, as well as their disease outcome. Three of the titres measured after the epidemic occurred were assigned to placebo and non-placebo (but not to the vaccinated or previously had anthrax conditions) conditions because of lack of information on which specific workers within a department had been tested.

5. Results

Tables 6 through 8 present the overall findings for the Fisher's Exact Tests, assessing the relationship between vaccination status and anthrax infection outcomes. The overall results of the analyses reported in Tables 6-8 are summarized in Table 9, in which we consider the results from all of the tests previously discussed. Of the 8 significant findings for vaccine and cutaneous anthrax, none were associated with low risk conditions (workers in weaving, maintenance, finishing, or office departments). Table 9 clearly indicates that the vaccine was best described as sometimes effective against cutaneous anthrax infection and never significantly effective against inhalation anthrax. Table 10 indicates that very few workers ever became infected even when they had no previous immunity, with 20% being the highest possible percentage that could be obtained looking at the highest possible risk group at the only mill that experienced any cases of inhalational anthrax (but from a total of 20 subjects of the 1,249 in the overall study).

The figure of 92.5% effectiveness was obtained from only the experimental group of 793 subjects, who had either had complete vaccinations or complete placebo inoculations. To look at the data in a different way than Brachman had previously and to guard against possible bias, we analyzed the same group of subjects for both types of anthrax combined using the Fisher's exact test, as before. Table 11 summarizes our findings.

Our results in Table 11 indicate that the vaccine failed to show statistically significant benefit in 75% of the mills tested, including even the one mill where inhalation anthrax occurred. It is of interest that the results in Table 11 were not statistically significant for the Arms Mill. Brachman et al. [17:14] reported that the results for the Arms Mill, identified only as a goat-hair processing mill in Manchester, New Hampshire in their report [17:6-7], were significant ($p < 0.05$, two-sided) but they used a standard chi-square test; had they used a precise Fisher's Exact Test they would have reported non-significant findings ($p < 0.13$, two-sided). Even so, Brachman et al. [17:21] admitted that "Anthrax vaccine containing alum-precipitated protective antigen appeared to afford protection to those who received it, but this impression could not be confirmed statistically," perhaps because [17:20] the "vaccinated group was not at as high a risk as the placebo or uninoculated control groups" for exposure to the most virulent forms of anthrax encountered at the Arms Mill during the epidemic in 1957 or because the weaknesses in the design of the study meant that [17:20] "The efficacy of the anthrax cell-free antigen as a vaccine was not fairly tested in this epidemic." Brachman et al. [17:20] did refer to an unpublished report that would later be published [7] as evidence for the efficacy of the vaccine when results from all the other mills were combined. However, it must be noted that Brachman et al. [17] used 300 cases as their total for the experimental group at the Arms Mill but used 313 cases for the same group in their later report [7].

As another challenge to our previous results, we turned to Table 8 in Brachman et al. [7:640-641], which had been used to obtain the 92.5% effectiveness figure. Table 8 lists the "person months" of exposure for high and low risk workers based on their vaccination/placebo inoculation status, for periods of six, six, twelve, twelve, and twelve months after the field test began at each mill. We divided the person months by the number of months, as appropriate, and reanalyzed the data for the most recent number of persons in the last reporting period for each mill. This approach was conservative because we assumed that all those who became infected remained in the final count of workers whereas all the workers who had dropped from the study had avoided infection. We found that the vaccine was not effective against the combined types of anthrax infection at mill A (Fisher's Exact Test, $p = 0.147$), mill M ($p = 0.211$), or mill P ($p = 0.423$), but was effective at mill S ($p = 0.010$), with most Mill S workers avoiding infection whether vaccinated (98.6%) or not (87.1%). Overall, combining all four mills, the Fisher's

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Exact Test was significant (p = 0.003), with most workers avoiding infection whether vaccinated (99.3%) or not (92.9%). Thus, even with our conservative procedures, designed to favor the hypothesis that the vaccine is effective, only one of the four mills (Mill S) yielded a significant result in favor of the vaccine.

The Assistant Secretary of Defense for Health Affairs has asserted a "grave harm to the armed forces in not vaccinating" against a "continuing significant threat" of anthrax [21]. Admittedly (according to DoD) if much larger exposures were encountered by service members, then a vaccine that might protect against the lower levels of exposure experienced by the mill workers might not work under more demanding conditions. Previously, the Secretary of the Army had acknowledged the fact that not all vaccinated soldiers would necessarily acquire immunity and that unforeseen adverse side effects were quite possible, when Mr. Caldera, authorizing indemnification of the anthrax vaccine manufacturer, stated, "…the obligation assumed by MBPI under this contract involves unusually hazardous risks associated with the potential for adverse reactions in some recipients and the possibility that the desired immunological effect will not be obtained by all recipients. The size of the proposed vaccination program may reveal unforewarned idiosyncratic adverse reactions. Moreover, there is no way to be certain that the pathogen used in tests measuring vaccine efficacy will be sufficiently similar to the pathogen that U.S. forces might encounter to confer immunity."[1]

We also looked at how the experimental group would have fared over time, from the start of the four mills project in February 1955. Table 12 documents those results.

What we see in Table 12 is that the program failed to yield any significant results for the first 20 months of its existence (February 1955 to late August 1956). Finally, by January 1957, a statistically significant result had been obtained for Mill S, which would remain the only mill to ever yield a statistically significant result for (cutaneous) anthrax. It was not until May 20, 1957, about the same time as the Arms Mill vaccination program began, that the overall significance for the first three mills combined finally reached below the $p < 0.01$ level, which – after nearly 30 months of field testing – probably assured the vaccine producers that their product was at least marginally effective and perhaps could stand up to a more rigorous challenge (i.e., against inhalational anthrax), should that occur by chance, of course, at any of the mills. Coincidentally, just such a more rigorous challenge occurred at the Arms Mill in Manchester New Hampshire near the end of August 1957, after the testing and vaccination program had begun at this mill in May 1957 [17:13], fortuitously allowing all employees in the experimental group just enough time to receive at least three inoculations before the epidemic began.

6. Conclusions

The reanalysis of Brachman et al. [7] reaffirms that the anthrax vaccine probably helps provide some marginal protection against cutaneous infection. However, it appears that the majority of mill workers avoided infection, even if they had not had previous clinical cases of anthrax nor any detectable subclinical cases, as assessed by detectable antibody titres. Moreover, the data simply do not provide statistically significant evidence of protection against inhalation anthrax. While that result may be attributed to too few cases or low statistical power, it would have taken an increase of 60% to 150% more cases of inhalational anthrax among unvaccinated workers (three more cases) in the various groups in order to achieve statistical significance for inhalational anthrax prevention. Coupled with the fact that some vaccines that protect against cutaneous infectious diseases are known to fail against inhalational versions of the same disease [22,23,24], the existing evidence is insufficient to determine how much, if any, protection against inhalation anthrax was afforded by this previous version of anthrax vaccine.

Even taking both types of anthrax into account, we found that the vaccine's protective effects were not significant in 75% of the mills tested, which paralleled our findings in Table 10, in which 75% of the specific statistical tests conducted were not significant.

A "best case scenario" to demonstrate vaccine protection was creating by forming a cohort of unvaccinated subjects with no prior immunity, who were working in the highest risk areas, at only the Arms Mill, and only during the epidemic there. Even so, the results were not significant ($p < 0.05$) by Fisher's Exact Test, which is most appropriate for such small samples.

To summarize, the reanalysis of Brachman et al. [7] does indicate that the anthrax vaccine may help provide some marginal protection against cutaneous infection. The data do not provide statistically significant evidence of protection against inhalation anthrax, which is the source of the military's interest in anthrax [25:471]. That outcome should not come as a shock – Colonel Friedlander himself said in 1997, as he did later in 1999 with Brachman [11:635], with reference to the Brachman et al. [7] study, "There were insufficient cases of inhalational anthrax to determine whether the vaccine was effective against this form of the disease [25:474]." In addition, numerous objections to the experimental design, aside from the statistics used, can be raised. In conclusion, our reanalysis indicates that Brachman et al.'s [7,17,18] data actually fall far short of demonstrating the efficacy of the anthrax vaccine in humans, especially with respect to inhalational anthrax infection. Given the uncertainty associated with the benefits of the vaccine, greater weight should be given to potential risks associated with the current vaccine when risk-benefit ratios with respect to the current anthrax vaccine are considered.

We acknowledge that, after 1999, later reports [12] seem to have, somehow, found new scientific evidence to provide statistically significant, and incontrovertible support for the efficacy of the anthrax vaccine against inhalational anthrax infection in humans. Certainly, we can understand the political pressure that might have been brought to bear to find such a

[1] Memorandum of Decision, dated 3 September 1998, Subject: Indemnification for Michigan Biologics Products Institute

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"new" answer, but that should not overrule the traditional requirement for "revised" scientific answers to have specific empirical foundations in published peer-reviewed sources. Our research suggests that the Brachman et al. [7] study was not adequate for use as a principal source for revising our understanding of the protective effects of anthrax vaccine against inhalational anthrax. Given that understanding, one must wonder what was the source – and was it a *scientifically* valid source? Lacking that, we can only conclude that the FDA's action in approving the current anthrax vaccine was not supported by the evidence from Brachman et al. [7, 17, 18], as demonstrated here, and therefore was not rational from a strictly scientific perspective. Therefore, the U.S. military's current approach of universal mandatory vaccination with an anthrax vaccine of clearly (as shown here) questionable efficacy and, as discussed elsewhere [2,3,4,14,15] uncertain safety, must be deemed inappropriate, if not illegal [16].

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Table 1. Reconstruction of Brachman data (1,249 cases)

\Mill	Risk Level	Vaccine Status	Total Number of Workers Studied	Number of Cutaneous Cases	Number of Inhalation Cases
A	High	Yes	59	0	0
M	High	Yes	42	0	0
P	High	Yes	19	0	0
S	High	Yes	89	1	0
A	High	Placebo	60	0	1
M	High	Placebo	49	3	0
P	High	Placebo	22	1	0
S	High	Placebo	95	8	0
A	High	Incomplete	11	0	0
M	High	Incomplete	8	0	0
P	High	Incomplete	15	2 (Vaccine, Placebo)	0
S	High	Incomplete	31	1 (Vaccine)	0
A	High	Refused	70	2	3
M	High	Refused	8	0	0
P	High	Refused	10	0	0
S	High	Refused	1	1	0
A	Low	Yes	90	0	0
M	Low	Yes	31	0	0
P	Low	Yes	22	0	0
S	Low	Yes	27	0	0
A	Low	Placebo	104	1	1
M	Low	Placebo	42	0	0
P	Low	Placebo	22	0	0
S	Low	Placebo	20	0	0
A	Low	Incomplete	24	1 (Placebo)	0
M	Low	Incomplete	4	0	0
P	Low	Incomplete	13	0	0
S	Low	Incomplete	10	0	0
A	Low	Refused	214	0	0
M	Low	Refused	16	0	0
P	Low	Refused	21	0	0
S	Low	Refused	0	0	0
Total			1,249	21	5

NOTE: Derived from Tables 2, 4, and 5 in Brachman et al. [7:634, 636-7]. The total group consists of all 1,249 workers; the "experimental" group consists of only those 793 workers in either the vaccinated (complete) group or the placebo (complete) group, omitting those who refused or did not complete their inoculations, whether vaccine or placebo.

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Table 2. Breakdown of analyses for all mills combined

Analysis	Mills	Groups	Risk Levels	Type Infection	Remarks (cases)
1	All	Total	Both	Cutaneous	1,249
2			Low	Cutaneous	660
3			High	Cutaneous	589
4			Both	Inhalation	1,249
5			Low	Inhalation	660
6			High	Inhalation	589
7	All	Experi-mental	Both	Cutaneous	793
8			Low	Cutaneous	358
9			High	Cutaneous	435
10			Both	Inhalation	793
11			Low	Inhalation	358
12			High	Inhalation	435

Table 3. Breakdown of analyses for all mills except the Arms Mill, Manchester, New Hampshire

Analysis	Mills	Groups	Risk Levels	Type Infection	Remarks (cases)
1	M,P, S	Total	Both	Cutaneous	617
2			Low	Cutaneous	228
3			High	Cutaneous	389
4	M,P, S	Experi-mental	Both	Cutaneous	480
5			Low	Cutaneous	164
6			High	Cutaneous	316

NOTE: Since none of the three mills ever experienced a case of inhalation anthrax, analyses were not performed for that as an outcome. Analysis eventually revealed that no cases of anthrax infection occurred within the low risk group.

Table 4. Breakdown of analyses for Arms Mill only

Analysis	Mills	Groups	Risk Levels	Type Infection	Remarks (cases)
1	Arms	Total	Both	Cutaneous	632
2			Low	Cutaneous	432
3			High	Cutaneous	200
4			Highest	Cutaneous	44
5			Both	Inhalation	632
6			Low	Inhalation	432
7			High	Inhalation	200
8			Highest	Inhalation	44
9	Arms	Experi.	Both	Cutaneous	313
10			Low	Cutaneous	194
11			High	Cutaneous	194
12			Both	Inhalation	313
13			Low	Inhalation	194
14			High	Inhalation	119
15			Highest	Inhalation	21

NOTE: Because no cutaneous cases occurred for the highest risk cases in the experimental group, only inhalation anthrax is used as an outcome variable for the highest risk cases in the experimental group.

Table 5. Reconstruction of data from Tables 4 and 5 (Brachman et al., [17:13-14])

Case No.[a]	Job	Had Anthrax Before	Previous Titres	Vaccine	Became Sick
1	Fixer	Yes			
2	Fixer	Yes			
3	Fixer	Yes			
4	Fixer	Yes			
5	Fixer			Placebo	
6	Fixer			Placebo	Inhalation
7	Fixer				Inhalation
8	Fixer			Placebo	
9	Fixer				Cutaneous
10	Fixer				Cutaneous
11	Fixer			Placebo	
12	Oiler	Yes			
13	Oiler			Yes	
14	Oiler		Yes		
15	Oiler				
16	Oiler				
17	Gillbox			Yes	
18	Gillbox			Yes	
19	Gillbox			Yes	
20	Gillbox		Yes	Placebo	
21	Gillbox				
22	Gillbox		Yes		
23	Gillbox				
24	Other	Yes			
25	Other				
26	Other				
27	Noil Remover			Yes	
28	Noil Remover				Inhalation
29	Noil Remover				Inhalation
30	Stripper		Yes		
31	Fixer			Yes	
32	Fixer			Yes	
33	Fixer			Yes	
34	Fixer		Yes	Placebo	
35	Fixer			Placebo	
36	Fixer			Placebo	
37	Fixer				
38	Fixer				
39	Fixer		Yes		
40	Gillbox			Yes	
41	Gillbox			Yes	
42	Gillbox			Yes	
43	Gillbox		Yes	Placebo	
44	Gillbox			Placebo	
Totals	44	6	7	11	6

[a]Cases 1-26 were in the carding department; 27-44 in the combing department.

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Table 6. Breakdown of analyses for all mills combined

Analysis	Mills	Groups	Risk Leveles	Type Infection	Results
1	All	Total	Both	Cutaneous	Yes (.005)
2			Low	Cutaneous	No
3			High	Cutaneous	Yes (.002)
4			Both	Inhalation	No
5			Low	Inhalation	No
6			High	Inhalation	No
7	All	Experi-mental	Both	Cutaneous	Yes (.001)
8			Low	Cutaneous	No
9			High	Cutaneous	Yes (.002)
10			Both	Inhalation	No
11			Low	Inhalation	No
12			High	Inhalation	No

Under results, YES indicates that the Fisher's Exact Test yielded a statistically significant result, with that result shown in parentheses. NO indicates that the result was not statistically significant ($p > 0.05$).

Table 7. Breakdown of analyses for all mills except the Arms Mill, Manchester, New Hampshire

Analysis	Mills	Groups	Risk Levels	Type Infection	Results
1	M,P,S	Total	Both	Cutaneoous	Yes (.004)
2			Low	Cutaneous	No Disease
3			High	Cutaneous	Yes (.003)
4	M,P,S	Experi-mental	Both	Cutaneous	Yes (.002)
5			Low	Cutaneous	No Disease
6			High	Cutaneous	Yes (.003)

NOTE: Since none of the three mills ever experienced a case of inhalation anthrax, analyses were not performed for that as an outcome. No significant results were obtained in logistic regression for Mill or Risk factors or for partial vaccination in any of the analyses within Table 7. Under results, "Yes" indicates that the Fisher's Exact Test yielded a statistically significant result, with that result shown in parentheses. "No" indicates that the result was not statistically significant ($p > 0.05$).

Table 8. Breakdown of analyses for Arms Mill only

Analysis	Mills	Groups	Risk Levels	Type Infection	Results
1	Arms	Total	Both	Cutaneoous	No
2			Low	Cutaneous	No
3			High	Cutaneous	No
4			Highest	Cutaneous	No
5			Both	Inhalation	No
6			Low	Inhalation	No
7			High	Inhalation	No
8			Highest	Inhalation	No
			Highest	Both Combined	No (*)
9	Arms	Experi-mental	Both	Cutaneous	No
10			Low	Cutaneous	No
11			High	Cutaneous	No Disease
12			Both	Inhalation	No
13			Low	Inhalation	No
14			High	Inhalation	No
15			Highest	Both Combined	No

(*) Vaccine worked by chi-square test but not by Fisher's exact test; if those (13 of the 44 cases) with suspected natural immunity were removed from the analysis. Under results, "Yes" indicates that the Fisher's Exact Test yielded a statistically significant result, with that result shown in parentheses. "No" indicates that the result was not statistically significant ($p > 0.05$).

Table 9. Summary of significant findings

Tests	Cutaneous Anthrax	Inhalational Anthrax
Number of Statistical Tests Conducted	19	13
Number of Statistical Tests With Disease Outcomes	16	0
Number of Significant Statistical Tests With Disease Outcomes	8	0
Percentage of Significant Tests	50	0

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Table 10. Detailed results for anthrax vaccination for high risk worker groups only

Groups	Type Infection	Percent Unvaccinated Protected (Not Infected)	Percent Vaccinated Protected (not infected)	Results
All Mills				
All	Cutaneous	95.3	99.5	(p=.002)
Exper.	Cutaneous	94.7	99.5	(p=.002)
All	Iinhalation	98.9	100.0	n.s.
Exper.	Inhalation	99.6	100.0	n.s.
Three Mills				
All	Cutaneous	93.3	99.3	(p=.003)
Exper.	Cutaneous	92.8	99.3	(p=.003)
Arms Mill				
All	Cutaneous	98.6	100.0	n.s.
Exper.	Cutaneous	No cases	No cases	
All	Inhalation	97.2	100.0	n.s.
Exper.	Inhalation	98.3	100.0	n.s.
Arms Mill Highest Risk - All	Cutaneous	93.9	100.0	n.s.
	Cutaneous (among those with no previous immunity)	90.0	0.0	n.s.
	Inhalation	87.9	100.0	n.s.
	Inhalation (among those with no previous immunity)	80.0	100.0	n.s.
Highest Risk – Exper.	Inhalation	90.0	100.0	n.s.
	Inhalation (among those with no previous immunity)	85.7	100.0	n.s.

Table 11. Effectiveness of Anthrax vaccine against both types of Anthrax combined for each of four mills in the experimental group

Mill	Healthy Vaccinated (%)	Healthy Placebo (%)	Fisher's Exact Test	Vaccine Effective
A	100.0	98.1	.087	No
M	100.0	97.6	.254	No
P	100.0	97.1	.363	No
S	99.1	93.6	.019	Yes

Table 12. Changes in significance over time for the four mills apparent effectiveness of anthrax vaccine

Date	Mills	Subjects	Ratio of Infections Placebo/ Vaccinated	Fisher's Exact Test	Percent Healthy Vaccinated versus Placebo
Feb-May 1956	S Only	231	5/1	0.104	99.1/95.7
Feb-May 1956	S and M	395	5/1	0.129	99.5/97.6
June 1956	S/M/P	480	5/1	0.129	99.6/98.0
Sep 1 1956	S/M/P	480	7/1	0.044[a]	99.6/97.2
Jan 1957	S/M/P	480	8/1	0.025[b]	99.6/96.8
May 1957	S/M/P	480	9/1	0.014[c]	99.6/96.4
June 1957	S/M/P/A[d]	480[e]	10/1	0.008[f]	99.6/96.0

[a]Mills by each are not significant!
[b]Mill S is significant by itself (0.032)
[c]Mill S only is significant by itself (0.017)
[d]but A not ready yet
[e]soon to be 793 when adding Mill A
[f]Mill S only is significant by itself (0.017)

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