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Anthrax vaccine: short-term safety experience in humans

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Abstract

Bacillus anthracis is the major terrorist and biological warfare agent of concern to civilian and military medical planners. The licensed anthrax vaccine, adsorbed (AVA) is believed to be an effective prophylactic medical countermeasure against this threat. Our objective in this report was to expand the safety database for this vaccine by assessing data on self-reported, short-term safety of AVA during more than 25 years of use, measured by local and systemic adverse events temporally associated with the administration of AVA. A minority of AVA recipients reported systemic and injection site reactions. Females reported a higher incidence of injection site and systemic adverse events than males. Data show a difference in incidence of local reactions between lots. A prospective, randomized, placebo-controlled study to actively examine reactogenicity is needed to more completely define the extent and nature of reactions associated with receipt of AVA in humans as well as to confirm the gender lot differences in local reaction rates. © 2001 Published by Elsevier Science Ltd.

Keywords: Anthrax vaccine, adsorbed; Local and systemic adverse events; Short-term safety

1. Introduction

The clinical spectrum of diseases caused by *Bacillus anthracis* includes cutaneous, gastrointestinal, and inhalational anthrax [1–4]. Cutaneous anthrax is the most common form of human infection with this organism. Anthrax spores delivered by aerosol cause inhalational anthrax, an almost uniformly fatal and extraordinarily rare natural presentation of the disease. The onset of inhalational anthrax is usually gradual and nonspecific with fever, malaise, and fatigue, which are sometimes associated with a nonproductive cough and mild chest discomfort. The initial symptoms are followed in 2–3 days by the abrupt development of severe respiratory distress with dyspnea, diaphoresis, stridor, and cyanosis. Sepsis, hypotension, and death usually follow within 24–36 h. Anthrax resulting from an accidental or purposeful release of spores is the topic of several recently published reviews [5–9].

A vaccine against anthrax has been licensed in the US since 1970 [10]. Human studies, including a field trial of a precursor protective antigen anthrax vaccine, have shown the anthrax vaccine to be both safe and effective [11–16].

A single available report suggests that there was no difference in reactogenicity between the precursor alum-precipitated anthrax protective antigen vaccine used by Brachman et al. to demonstrate efficacy [15] and the current aluminum hydroxide adsorbed vaccine (anthrax vaccine, adsorbed, AVA) [12].

In support of licensure, studies on the safety of four lots of AVA were submitted to the US Food and Drug Administration (FDA) by the Centers for Disease Control and Prevention (CDC) [11]. These studies involved approximately 7000 participants who received approximately 16,000 doses of AVA. Active monitoring showed mild local reactions ($\leq$3 cm) in 3–20% of all recipients. Reactions measuring >3 to <12 cm were reported in 1–3% of all dose recipients and severe reactions ($\geq$12 cm) in less than 1% of doses. Only four individuals (<0.06%) reported transient systemic reactions that consisted of fever, chills, nausea, and general body aches.

The objective of this report is to present data on self-reported, short-term adverse events temporally associated with AVA during more than 25 years of use to protect at-risk personnel at the United States Army Medical Research Institute of Infectious Diseases (USAMRIID), Fort Detrick, Maryland.

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2. Materials and methods

2.1. Anthrax vaccine, adsorbed

AVA is derived from sterile filtrates of an avirulent, nonencapsulated strain of *B. anthracis*. The protective component of AVA is thought to be anthrax protective antigen. The anthrax vaccine is adsorbed to aluminum hydroxide (2.4 mg/0.5 ml dose), and contains formaldehyde (0.02%) and benzethonium chloride (0.0025%). AVA is administered in a dose of 0.5 ml subcutaneously. The first three doses are given 2 weeks apart followed by three additional doses given 6 months apart (weeks 0–2–4; months 6–12–18). Subsequent booster doses are given annually as long as the risk persists. AVA vaccine production lots were assigned numerical designations before the early 1990s and alphanumerical designations thereafter.

2.2. Subjects

At-risk laboratory employees and maintenance workers at USAMRIID must be vaccinated with AVA before access is granted to biocontainment laboratories where *B. anthracis* is being studied. Most at-risk employees receive several other vaccines as well as AVA through the institute's special immunizations program (SIP) [17]. To receive this licensed vaccine, volunteers were required to read and sign an information sheet that detailed data concerning the disease and the reactogenicity of the anthrax vaccine.

2.3. Follow-up clinical visits

Adverse events were self-reported. Any event temporally associated with vaccination and reported by vaccines was recorded as an adverse event. As a general rule, employees reported adverse events requiring treatment or those adverse events they believed should be recorded in their health records. When a subject returned to the clinic to report an adverse event, a clinic staff member evaluated the subject, recorded reactions in the volunteer's clinic record, and entered the data into the special immunizations database. The dimensions of injection site erythema and induration were measured and recorded by clinic staff.

2.4. Statistics

The individual's dose of vaccine was the experimental unit for all safety evaluations. Demographic and adverse event data were obtained for all doses and subjects. Adverse event data were gathered for all doses and stratified by gender, age, and race/ethnicity. The statistical significance of gender and age was tested by Fisher's exact test for each adverse event. Race/ethnicity differences in the reporting frequency of local adverse events were evaluated by Fisher's exact test and logistic regression controlling for gender and age. Only European–Americans, African–Americans, Hispanic–Americans, and Asian–Americans received sufficient numbers of doses for statistical comparison. Euro–Americans received over 90% of doses and served as the referent group.

The incidence of erythema and/or induration (E/I) is described for each of doses 1–6. Relative risk (with 95% CI) was estimated for gender differences for erythema and induration events combined. To assess if females were more prone to large local inflammatory reactions, we stratified dimensions of E/I and assessed incidences by gender. The ability of the preceding dose to predict systemic or local adverse events to the next dose was tested by logistic regression adjusted for gender and by Fisher's exact test only in the first six doses. We looked for a correlation between severe reactions to one dose and a subsequent severe reaction to the next dose of AVA. Differences between lots were tested by analysis of variance (ANOVA) with adjustment for gender. All tests were at the 95% confidence level [18].

3. Results

3.1. Demographics

A total of 1583 volunteers received 10,722 doses (median of six doses/person) of AVA between 1973 and 1999 (Table 1). The preponderance of recipients were male, European–American, and 40 years of old or younger. Two hundred seventy-three volunteers received 10 doses or more of AVA and 46 received 20 or more doses.

3.2. Systemic adverse events

Of 10,722 doses administered, 1% (101/10,722) were associated with one or more systemic events. Systemic adverse events (such as headache, malaise, myalgia, fever, nausea, vomiting, dizziness, chills, diarrhea, hives, anorexia, arthralgias, diaphoresis, blurred vision, generalized itching

Table 1
Demographics of AVA recipients at USAMRIID

	Number of volunteers: $N = 1583$ (N%)	Doses of AVA: $N = 10722$ (N%)
Gender		
Males	1249 (79)	8797 (82)
Females	334 (21)	1925 (18)
Age (years)		
18–40	1279 (81)	7676 (72)
>40	304 (19)	3046 (28)
Race/ethnicity		
European–American	1353 (85.5)	9388 (87.6)
African–American	131 (8.3)	809 (7.5)
Hispanic–American	52 (3.3)	291 (2.7)
Asian–American	43 (2.7)	215 (2.0)
Native American	2 (0.1)	10 (0.1)
Other	2 (0.1)	9 (0.1)

and sore throat) were associated with 1% (78/7795) of doses in the primary vaccination series (first six doses) and 0.8% (23/2927) of subsequent doses. The most frequently reported systemic adverse event was headache (0.4% of doses). Headache (male 27/8797 versus female 13/1925; $P = 0.023$), dizziness (male 4/8797 versus female 6/1925; $P < 0.004$), and hives (male 0 versus female 4/1925; $P < 0.002$) were reported proportionately more often by females. Systemic adverse events were not associated more frequently with either age group, or race/ethnicity.

Fever, with temperatures ranging from 38.1 to 39.4°C, was recorded in volunteers after eight (0.1%) doses. Low-grade temperature elevations measuring 37.2–38°C occurred in 23 (0.2%). Females had higher rates of fever (4/1925, $P = 0.023$) and of low-grade temperature elevations (10/1925, $P = 0.04$) than males. One female volunteer developed an acute demyelinating disorder 8 days after receiving the second dose of AVA. She had received the first dose 42 days before the onset of symptoms. The patient recovered completely and resumed work within 3 months. No additional doses of vaccine were given and she has remained asymptomatic.

3.3. Local adverse events

One or more local or injection site reactions were reported in 3.6% (383/10,722) of doses of AVA. The most common local reactions were erythema and induration, which occurred in 3.2% (338/10,722 doses). Local reactions were associated with 3.6% (281/7795) of the first six doses, and 3.5% (102/2927) of subsequent doses. Of 161/6212 reactions reported by males to doses 1–6, 0.6, 49.1, and 50.3% were reported at 30 min, 24 and 48 h, respectively. Of 136/1583 reactions in females during doses 1–6, 4.4, 55.2, and 40.4% were reported at 30 min, 24 and 48 h, respectively.

Injection site reactions were more common among females and volunteers of 40 years of old (Table 2). In addition, edema and lymphadenopathy were more commonly reported by females.

We examined in greater detail the effect of gender on the frequency and severity of E/I during each of the first six doses of AVA. The incidence of E/I for males was generally low and did not vary significantly for doses 1–6. However, for females, injection site E/I peaked at 10.8% at dose 2 and gradually decreased to 5.4% at doses 5 and 6 (Table 3).

To determine if females had a higher frequency of large lesions, the dimensions of E/I were stratified: <50, 50–120 and >120 mm, and sorted by gender (Table 4). Females had higher incidences (with relative risks as high as 9) for all size stratifications, except the largest (>120 mm).

A logistic regression model was used to examine the impact of race/ethnicity on local reactions to AVA, because gender and age were correlated with increased frequency of certain local adverse events, these parameters were controlled for in the model. Although we found that certain local adverse events were reported by racial groups at different frequencies, statistically significant differences in reporting were noted only between European–Americans and African–Americans. The findings included erythema (244/9388 versus 13/809; $P = 0.018$), in duration (268 versus 14; $P = 0.018$), and injection site warmth (97 versus 3; $P = 0.04$) with European–Americans reporting each of these reactions more commonly than African–Americans.

No individual reported abscess, cyst formation, or necrosis during the study period.

3.4. Gender and prior reaction as predictors of adverse events at next dose

A logistic regression model was applied to evaluate whether E/I associated with a prior AVA injection predicted E/I with a next injection in either gender during the administration of the first six doses, controlling for vaccine lot. Prior E/I reactions were associated with an increase in the odds of subsequent E/I reactions in the same subject with the next injection ($P = 0.0001$; odds ratio = 13; 95% CI = 8.7–21). However, the majority of E/I reactions followed injections with no E/I, thus limiting the value of

Table 2
Frequency of injection site reactions among AVA recipients by gender and age

Adverse event	Gender			*P*-value	Age (years)		*P*-value
	Total: $N = 10{,}722$ (*N*%)	Male: $N = 8797$ (*N*%)	Female: $N = 1925$ (*N*%)		18–40: $N = 7676$ (*N*%)	>40: $N = 3046$ (*N*%)	
Induration	295 (2.8)	174 (2.0)	121 (6.4)	<0.001	239 (3.1)	56 (1.8)	<0.001
Erythema	271 (2.5)	147 (1.7)	124 (6.3)	<0.001	220 (2.9)	51 (1.7)	<0.001
Tenderness	186 (1.7)	117 (1.3)	69 (3.6)	<0.001	149 (1.9)	37 (1.2)	0.009
Warmth	104 (1.0)	58 (0.7)	46 (2.4)	<0.001	86 (1.1)	18 (0.6)	0.012
Pruritis site	84 (0.8)	37 (0.4)	47 (2.4)	<0.001	69 (0.9)	15 (0.5)	0.038
Lymph node	12 (0.1)	5 (0.1)	7 (0.4)	0.002	11 (0.1)	1	0.198
Arm motion limitation	10 (0.1)	6 (0.1)	4 (0.2)	0.09	9 (0.1)	1	0.3
Edema	8 (0.1)	3	5 (0.3)	0.006	7 (0.1)	1	0.45
Rash	5	3	2 (0.1)	0.22	3	2	0.63

Table 3
Incidence and relative risk of E/I by dose and gender for AVA doses 1–6

Dose	Number of subjects: E/I	Number of subjects: E/I (%)	*P*-value	RR (95% CI)
Gender (overall)				
Male	8600	197 (2.2)		
Female	1784	141 (7.3)	<0.0001	3.3 (2.7, 4.0)
Dose 1				
Male	1217	33 (2.6)		
Female	318	16 (4.8)	0.051	1.8 (1.0, 3.3)
Dose 2				
Male	1185	31 (2.5)		
Female	288	35 (10.8)	<0.0001	4.3 (2.7, 6.8)
Dose 3				
Male	1162	15 (1.3)		
Female	291	21 (6.7)	<0.0001	5.3 (2.8, 10.1)
Dose 4				
Male	975	25 (2.5)		
Female	243	19 (7.3)	<0.0009	2.9 (1.6, 5.2)
Dose 5				
Male	829	22 (2.6)		
Female	193	11 (5.4)	0.045	2.1 (1.0, 4.2)
Dose 6				
Male	707	12 (1.7)		
Female	140	8 (5.4)	0.012	3.2 (1.3, 7.8)

Table 4
Frequency and relative risk of E/I by lesion size and gender for all AVA doses and for each of doses 1–6[a]

Dose	Number of subjects: E/I	<50 mm (*N*%)	*P*-value	RR (95% CI)	50–120 mm (*N*%)	*P*-value	RR (95% CI)	>120 mm (*N*%)	*P*-value	RR (95% CI)
Gender (overall)										
Male	8600	107 (1.2)			78 (0.9)			12 (0.1)		
Female	1784	65 (3.5)	<0.001	2.9 (2.1, 3.9)	67 (3.5)	<0.001	4.0 (2.9, 5.6)	9 (0.5)	0.005	3.6 (1.5, 8.5)
	10384	172 (1.6)			145 (1.4)			21 (0.2)		
Dose 1										
Male	1217	29 (2.3)			3 (0.3)			0		
Female	318	14 (4.2)	0.085	1.8 (0.97, 3.4)	2 (0.6)	0.279	2.5 (0.4, 15)	0	–	–
Dose 2										
Male	1185	14 (1.2)			17 (1.4)			0		
Female	288	14 (4.6)	<0.001	4.0 (1.9, 8.2)	15 (5.0)	<0.001	3.5 (1.7, 6.9)	6 (2.0)	<0.001	–
Dose 3										
Male	1162	8 (0.7)			5 (0.4)			2 (0.2)		
Female	291	7 (2.4)	0.019	3.4 (1.3, 9.4)	12 (4.0)	<0.001	9 (3.3, 26)	2 (0.7)	0.182	4.0 (0.6, 28)
Dose 4										
Male	975	11 (1.1)			14 (1.4)			0		
Female	243	9 (3.6)	0.011	3.2 (1.3, 7.6)	10 (4.0)	0.017	2.8 (1.3, 6.2)	0	–	–
Dose 5										
Male	829	13 (1.5)			7 (0.8)			2 (0.2)		
Female	193	5 (2.5)	0.362	1.6 (0.6, 4.5)	6 (3.0)	0.024	3.6 (1.2, 11)	0	1.0	–
Dose 6										
Male	707	7 (1.0)			5 (0.7)			0		
Female	140	4 (2.8)	0.096	2.8 (0.8, 9.6)	3 (2.1)	0.135	3.0 (0.7, 12)	1 (0.7)	0.166	–

[a] *P*-values and percentages are based on separately comparing each lesion size to subjects with no lesion.

Table 5
Relative risk of E/I as predictor of E/I at next dose (same lot) by gender for the first six doses of AVA

	Prior dose	Next dose	Total	*P*-value	RR (95% CI)
Males					
Positive	18	64	82		
Negative	55	3527	3582		
Total	73	3591	3664	<0.0001	14.3 (8.8, 23)
Females					
Positive	21	40	61		
Negative	42	799	841		
Total	63	839	902	<0.0001	6.9 (4.3, 10.9)

this observation. Age was not significant in the logistic regression model of predicting an adverse event to the next dose.

Gender differences in the effect of AVA injection-related E/I on the risk for E/I at the next injection were examined using 2×2 contingency tables (Table 5). Among females, 5% (42/841) had injection E/I reactions not associated with prior injection-related E/I. On the other hand, of those with prior injection-related E/I, 34% (21/61) had next injection E/I, controlling for vaccine lot ($P =< 0.0001$; RR = 6.9; 95% CI 4.3, 10.9).

For males, 1.5% (55/3582) experienced injection-related E/I reactions in the absence of prior injection-related E/I. Of males with prior injection-related E/I reactions, 22% (18/82) had E/I reactions related to the next injection, controlling for vaccine lot ($P =< 0.0001$; RR = 14.3; 95% CI 8.8, 23).

To determine if a trend existed toward more severe E/I lesions after prior experience of such lesions, regardless of the severity, contingency tables were generated with lesion size stratified. Severity of prior E/I did not predict the severity of such reactions after the next dose (when the reactions occurred) controlling for vaccine lot (data not shown). Females with the most severe E/I reactions (>120 mm) did not report E/I lesions at a higher rate after the next dose.

3.5. Effect of lot on adverse events

Thirty-two lots of AVA were administered to at-risk individuals at USAMRIID between 1973 and 1999. The number of doses of AVA per lot (for 19 lots in which at least 50 doses were used) ranged between 52 and 1702. Injection-related E/I reaction rates ranged from 0 to 20.6 (males) and 33.3% (females) as a function of lot (Table 6). Lots were tested for differences in E/I rates from a recent lot (FAV038, 11/429 E/I reactions, 2.6%) after adjusting for gender. There was a significant gender effect ($P < 0.0001$) and a significant lot effect ($P < 0.0001$). The gender-adjusted odds ratio confidence intervals of E/I reaction in each lot relative to the "recent" lot, after adjusting for multiple comparisons (confidence level set to 99.75% by the Bonferroni method), showed that lots 10, FAV006 and FAV008 were elevated but did not reach statistical significance. Lots 16 and 9 were significantly lower in E/I rates than the "recent" lot based on confidence intervals less than 1.0. No single lot was associated with the largest areas (≥120 mm) of E/I at the injection site. Lots for which the number of doses was not adequate to allow statistical comparison did not show an increased rate of adverse events.

Table 6
Incidence of injection site reaction by AVA production lot among AVA recipients in order of decreasing frequency

Lot	First dose			Last dose			Duration (years)	Female		Male	
	Year	Month	Day	Year	Month	Day		*N*	*N*: local reaction (%)	*N*	*N*: local reaction (%)
9	1975	April	17	1990	August	29	15.4	1	0	82	0
10	1977	October	5	1980	January	16	2.3	27	9 (33.3)	204	42 (20.6)
13	1979	July	31	1982	July	26	3	133	8 (6.0)	684	19 (2.8)
12	1981	March	31	1983	May	10	2.1	115	1 (0.9)	474	2 (0.4)
16	1983	May	6	1985	October	2	2.4	180	0	931	1 (0.1)
19	1986	February	21	1991	June	25	5.3	252	10 (4.0)	1205	12 (1.0)
18	1987	April	14	1989	September	15	2.4	124	2 (1.6)	659	18 (2.7)
FAV001	1990	May	8	1991	August	29	1.3	52	7 (13.5)	226	10 (4.4)
FAV004	1991	January	28	1991	March	5	0.1	20	5 (25.0)	54	1 (1.9)
FAV008	1991	January	29	1997	June	26	6.4	293	47 (16.0)	1409	43 (3.1)
FAV006	1991	March	5	1992	June	16	1.3	88	16 (18.2)	340	24 (7.1)
FAV012	1994	March	9	1995	September	12	1.5	47	3 (6.4)	247	2 (0.8)
FAV018	1994	September	13	1997	August	14	2.9	113	5 (4.4)	625	5 (0.8)
FAV022	1995	October	24	1996	June	26	0.7	76	2 (2.6)	344	4 (1.2)
FAV032	1996	October	29	1998	December	23	2.1	50	4 (8.0	189	1 (0.5)
FAV016	1997	January	9	1998	September	24	1.7	184	8 (4.3)	610	8 (1.3)
FAV034	1999	January	5	1999	February	19	0.1	29	3 (10.3)	72	0
FAV036	1999	February	23	1999	April	16	0.1	13	0	39	0

4. Discussion

Wright et al. [14] analyzed 1936 injections in 660 persons who received an alum-precipitated protective antigen anthrax vaccine. They reported the rate of significant systemic and local adverse events (E/I >5 cm) to be 0.7 and 2.4%, respectively, during the initial three doses. The corresponding incidences for subsequent injections were 1.3 and 2.7%. During his field study of Wright's vaccine, Brachman et al. [15] noted a 0.2% overall frequency of systemic reactions, consisting of malaise and lassitude and, less commonly, fever and chills. Minimal local reactions measuring 1–2 cm were noted by Brachman et al. to occur in approximately 30% of recipients. Moderate reactions measuring >5 cm in diameter occurred in 4% of recipients of the second injection. More severe local reactions occurred less frequently and consisted of extensive edema of the forearm in addition to the local inflammation. Puziss and Wright [12] provided the only study that compared the alum-precipitated aerobic protective antigen and AVA in humans. Although few details are provided in the publication, the authors concluded that "the rates of occurrence of erythema, edema, or pruritis at the site of injection were low in both groups, and did not appear to be different. No systemic reactions were observed".

Using a passive adverse event reporting mechanism, we noted a systemic reaction rate of 1% and a local reaction rate of 3.6% for the subcutaneously administered AVA. E/I >5 cm occurred at a rate of 1.6% of all doses. These rates compare favorably with the rates recorded by Wright et al. [14] with the precursor alum-precipitated vaccine, but are lower than those reported by Brachman et al. [15]. This difference can likely be attributed solely to passive versus active surveillance.

We found headache to be the most common systemic complaint, followed by malaise, myalgia, and fever. Headache, malaise, fever, dizziness, and hives were more common among females. When recorded in the clinic, fever with temperature above 38.1°C occurred more commonly in females ($P = 0.04$).

The most common injection site reactions were induration, erythema, tenderness, warmth, and pruritis. Subcutaneous nodules occurred frequently among AVA recipients, but were not always recorded because both recipients and clinic personnel considered them routine. Darlow et al. [16], who administered 1057 doses of an alum-precipitated protective antigen anthrax vaccine to 373 persons, wrote of subcutaneous nodules, "a further reaction type in the form of a small pain-less persistent nodule was often observed; but, as these nodules never progressed to abscesses, always developed late, and bore no relation to the occurrence of other signs, records were discontinued".

We determined that females and individuals younger than 41 years of old had higher frequencies of injection site reactions, such as induration, erythema, tenderness, warmth, and local pruritis. Females also reported more lymph node enlargement, arm motion limitation, and edema (Table 2). European–Americans reported E/I and injection site warmth significantly more often than African–Americans; this discrepancy may reflect a difference in reporting rates rather than a biologic difference as there were no statistical differences in local reactions for other race/ethnicity categories compared to European–Americans or the incidences were too small for statistical comparisons.

Among individuals who experienced a reaction to a dose of AVA, most subsequent doses were administered without sequelae. However, both gender and prior E/I were associated with a higher probability of E/I after the next dose of AVA. The relative risk of a repeat reaction, if the recipient was female, was 6.9 (CI: 4.4, 10.7); if the recipient was male, the relative risk was 14 (CI: 8.8, 23). The absolute number of individuals with repeat reactions was low; thus, the relative contribution of repeat reactions to the total reaction rate of a given dose was low.

Individuals with E/I did not demonstrate a propensity for same size or larger lesions after subsequent doses of AVA. In particular, females with E/I lesions >120 mm were not at increased risk for large lesions after the next dose. Indeed, after a large E/I reaction, most had no reaction to a subsequent dose of AVA.

This study of passively reported adverse events undoubtedly underestimates the true incidence of reactions, especially less severe reactions, due to the limitations of the data collection system. However, as has been demonstrated on a national scale by the vaccine adverse events reporting systems (VAERS), spontaneously reported data are useful in that trends may be recognized [19]. The present study provides more than 25 years of observation for reaction patterns associated with AVA. During this period, many vaccine lots were produced, allowing for assessment of association between vaccine lots and safety.

In summary, we found that administration of AVA over a prolonged time interval to laboratory workers and maintenance personnel was associated with an overall low frequency of self-reported systemic (1%) and local (3.6%) adverse events. Injection site inflammation, including erythema, induration, and subcutaneous nodules, occurred with higher frequency in females. For a given individual, it was not possible to predict who would develop an adverse event to AVA, be it local or systemic. However, for an individual who had a reaction, the odds of a reaction to the subsequent dose of AVA were higher than if no prior reaction had occurred. The Department of Defense recently instituted a large-scale program to protect personnel considered to be at risk of exposure to anthrax. This report presents the type and duration of common adverse events the military can expect from its immunization program which medical personnel might be required to evaluate. A prospective, randomized, placebo-controlled assessment of reactions recorded in the context of active follow-up will be necessary to more precisely define and

quantify the scope and extent of reactogenicity for this product.

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