Disability Among U.S. Army Personnel Vaccinated Against Anthrax

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This study was conducted to examine whether U.S. Army personnel receiving ≥1 dose of anthrax vaccine adsorbed (AVA) between March 1998 and February 2002 were at higher risk of disability than unvaccinated personnel. We studied a historical cohort study of 716,833 active-duty soldiers (154,456 vaccinated) followed for 4.25 years to determine rates of evaluation for disability discharge. Cox proportional hazards models compared estimated risk of evaluation for disability, accounting for occupation and sociodemographics. Adjusted hazard ratio (HR) and 95% confidence interval (CI) was 0.96 (CI = 0.92–0.99). Separate adjusted HRs for men, women, permanent and temporary disability, musculoskeletal and neurologic conditions were similar, ranging from 0.90 to 1.04. Latency assumptions did not affect results. Anthrax vaccination does not increase risk of disability. This finding may be partially the result of factors influencing selection for vaccination or vaccine tolerance. (J Occup Environ Med. *2004;46: 1065–1075*)

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DOI: 10.1097/01.jom.0000141664.90587.47

In 1998, the U.S. Department of Defense (DoD) initiated the Anthrax Vaccine Immunization Program (AVIP) to protect service members from anthrax spores used as biological weapons.[1] Although there was little or no evidence for adverse health effects of the anthrax vaccine,[1–6] some service members voiced concerns about perceived risks.

The only anthrax vaccine used by the military was anthrax vaccine adsorbed (AVA; BioThrax, BioPort Corp., Lansing, MI). In a recent review of the efficacy and safety of AVA, the Institute of Medicine (IOM) concluded, after reviewing some 24 published and unpublished studies, that evidence exists for "relatively frequent, mild to moderate local reactions of immediate onset following receipt of AVA" (p. 154). The rates and patterns of immediate adverse reactions to AVA were generally consistent with the reported rates of adverse reactions to other types of adult vaccinations, up to 35% of vaccinated persons in controlled studies. Systemic and severe local reactions were also reported but with frequencies generally less than 10%; all cases were reported resolved within days. The committee determined the data were insufficient to conclude that AVA either was or was not associated with persistent or later-onset health effects.[7]

Mahan et al. recently compared the prevalence of self-reported somatic and psychologic symptoms and conditions among veterans of the 1990–1991 Persian Gulf War according to self-reported receipt of anthrax vaccine.[8] The adjusted odds

of many of the outcomes included in the questionnaire were higher among respondents who recalled receipt of at least 1 dose of anthrax vaccine compared with respondents who did not recall being vaccinated against anthrax. However, among the subset of respondents with documented AVA vaccination, those who self-reported vaccination were statistically significantly more likely to report symptoms and conditions compared with those who reported not having been vaccinated against anthrax. These results suggest a substantial degree of reporting bias in the data.

Although immediate-onset, short-term reactions to the AVA have been fairly well characterized, more persistent health effects associated with AVA, or those having a delayed onset, have not been well described. In this report, we examine the evidence for persistent or later-onset health effects of AVA through an analysis comparing documented vaccination status among those seeking or granted disability discharge from the Army.

Materials and Methods

Soldiers on active duty in the U.S. Army between December 15, 1997, and December 15, 2001, were followed through February 1, 2002. The cohort was identified using data from the Total Army Injury and Health Outcomes Database (TAIHOD) maintained by the U.S. Army Research Institute of Environmental Medicine (USARIEM).

TAIHOD is a relational database containing occupational, demographic, and selected health information, including the dates and results of disability evaluations, for all individuals on active duty in the U.S. Army beginning in 1970. The structure and contents of TAIHOD have been described in detail elsewhere.[9] These data were linked by a common unique identifier to electronic immunization records provided by the Military Vaccine Agency, a component of the Office of the Army Surgeon General. With the assistance of USARIEM, a study database stripped of personal identifiers was developed.

Personnel Data

Occupational and demographic characteristics for all active-duty Army personnel were available from the TAIHOD twice annually (June and December) from 1997 through 2000. Because any individual cohort member could be represented in more than 1 personnel file, we used the first nonmissing value of any potential covariate recorded in the personnel data files.

Demographic characteristics included birth date (to calculate age), gender, race/ethnicity, marital status, and educational attainment. Date of entry into the Army was taken as the earliest nonmissing value of the recorded date of entry or the "pay entry base date," and the start of follow up was defined as the date of entry into the Army or December 15, 1997, whichever was later. December 15, 1997, was selected as the study start date because it is the date of the personnel file update most closely preceding implementation of the AVIP, allowing identification of the most appropriate population eligible for vaccination. If month or day was missing from any date variable in the TAIHOD, the value was set to "June" or "15." Other extracted occupational characteristics included duty location, which was used to identify individuals stationed in the United States or abroad, pay grade, major command code, and job coded according to Military Occupational Specialty (MOS).

The Army uses the Career Management Field (CMF) to categorize MOS. We used 9 CMFs to categorize enlisted MOS, and 1 combined category for commissioned and noncommissioned officers. The TAIHOD records 2 job codes per person, the Primary Military Occupational Specialty (PMOS), the most recent job for which training has been received, and the Duty Military Occupational Specialty (DMOS), or job assignment. In any of the semiannual personnel files evaluated, the DMOS code was 2 to 10 times more likely to be missing than PMOS (not shown). Previous analyses indicated that, when both DMOS and PMOS were recorded, the codes agreed about 90% of the time.[10] Therefore, we categorized jobs held by cohort members into CMF on the basis of PMOS.

Disability Data

Disability data files tracked all disability evaluations through February 1, 2002, including evaluations that resulted in the soldier's return to duty ("found fit"). In the case of multiple disability evaluation records for a single person, we used the earliest record available based on disability evaluation date. Individuals were excluded from analyses if their earliest disability record for the study period indicated continuation of a prior temporary disability finding, or if the result of the first disability evaluation was missing or unknown.

Disability evaluation date was defined as the earliest date for any event in the disability evaluation process (eg, hearings, notification of findings, and disposition of evaluation). Reason for disability was coded using the Veteran's Administration System for Rating Disability (VASRD) and was available for personnel discharged with permanent or temporary disability from the Army, including those not granted a specific disability benefit (ie, separated from the Army with or without severance pay) but was not available for those found fit for duty. No other data field in the disability record approximates a medical diagnosis.

Vaccination Data

The vaccination file included 1 record for each vaccination delivered since December 1997, including information on date, dose, route of administration, manufacturer, and lot number. We excluded 287 persons with any anthrax vaccinations deliv-

TABLE 1
Anthrax Vaccine Immunization Program (AVIP) Periods

Date	Substance of announcement	AVIP period
December 15, 1997	Announcement of phased program to vaccinate military personnel	
March 29, 1998	Programmatic controls in place, AVIP implementation formally begins	1: December 15, 1997 through March 29, 1999
March 30, 1999	"The 1-day policy": All military personnel and certain civilians assigned, deployed, or on temporary duty in high-threat areas and contiguous waters of Southwest Asia or the Korean Peninsula for at least 1 day	The shift from 30 days to 1 day increased the proportion of people in high-threat areas who were vaccinated
July 17, 2000	"The 30-day policy": Personnel assigned or deployed on the ground in Southwest Asia and Korea (highest threat areas) for at least 30 days, including personnel afloat on contiguous waters who have potential to be committed ashore, continue under AVIP; vaccine supplies that cannot readily be redirected to high-threat areas are to be used for personnel who have already begun the vaccination series, but who are not deployed to high-threat areas, until supplies run out	2: March 29, 1999 through July 16, 2000
November 27, 2000	Personnel assigned or deployed on the ground in Southwest Asia for more than 30 consecutive days and those afloat in the Persian Gulf who have the potential of being committed ashore; no vaccination for personnel not deployed to high-threat areas	3: July 17, 2000 through November 26, 2000; the first slowdown
		4: November 27, 2000 through June 5, 2001; the second slowdown

Source: Memoranda for the Secretary of the Army, Navy, Air Force, and Marines from the Assistant Secretary of Defense. Available at: http://www.antrhax.mil.

ered before 1997 (eg, related to service during the 1990–1991 Gulf War).

For each vaccinated person included in the study, we calculated the total number of doses delivered. In addition, we defined vaccination periods according to the dates of changes in vaccination policy (Table 1) and categorized the vaccinated population according to the period in which the first AVA dose was delivered.

Person-time was calculated from the start of follow up (defined previously) until the date of last follow up, ie, date of first disability evaluation, last date of separation from the Army without disability, or February 1, 2002, whichever came first. For vaccinated personnel, "exposed" person-time began at the date of first anthrax vaccination and continued until the date of last follow up; all person-time that accrued up to the calendar date preceding the day of first vaccination was considered "unexposed." Because little is known about the existence, nature, or timing of putative delayed adverse effects associated with anthrax vaccine, cohort members were defined as those with at least 1 person-day of follow up during the study period.

Statistical Methods

Data management and descriptive analyses were carried out using SAS.[11] Survival analyses, including use of Cox models to estimate hazard ratios (HR) and 95% confidence intervals (CI), were conducted using Stata.[12]

We examined the univariate and bivariate frequencies of all potential covariates from the vaccination, personnel, and disability datasets. We excluded from further consideration terms for which there was no difference in distribution by disability evaluation. Correlations among all occupational and sociodemographic variables were assessed using the Spearman correlation coefficient, R_{SP}. Pairs of variables with values of R_{SP} above 0.5 were examined, and the member of the pair that was most plausibly associated with risk of disability was retained for consideration in the analyses.

We measured the association between receipt of vaccination and the finding of a disability using the HR under the assumption of proportionality. Thus, reported HRs compared the estimated relative risk of a disability evaluation among persons who received vaccine relative to the unvaccinated. Risks are assumed to be constant over the timeframe in our data.

Both crude and stratum-specific HRs were calculated in preliminary analyses, the latter for strata defined by selected covariates associated with disability based on the descriptive analyses. Multivariable Cox proportional hazard models were developed as follows: any covariate that yielded a relative change of 15% in the HR for vaccination status in any

of its strata was a candidate for inclusion in the multivariable model. Confounding in the multivariable Cox models was assessed by calculating the relative change in the adjusted HR for vaccination status with the addition of terms initially excluded from the model; a 15% change in HR for vaccination was used to identify confounding. It was necessary to use this heuristic rather than to rely on traditional designations of statistical significance, because the large cohort size and large number of events resulted in a high degree of statistical power, rendering very small magnitude differences in risk statistically significant.

To determine if the risks differed for selected subgroups of the population, we developed separate multivariable Cox models for men and women, and for subsets of cases defined by primary reason for disability (musculoskeletal or neurologic) and by the result of the disability evaluation (permanent or temporary disability discharge or found fit for duty). Additional analyses were designed to account for hypothesized biologic latency and administrative latency intervals. We defined "biologic latency" as the amount of time required for a lasting biologic effect of the AVA to become apparent after vaccination, leading to evaluation for disability discharge from the Army. This question was addressed by incorporating lag times of 6, 12, and 18 months from the date of first vaccination into the overall final model.[13] "Administrative latency" refers to the amount of time needed for the processing of an individual through the Army disability system. To account for administrative latency, we constructed separate multivariable Cox models for individuals receiving their first vaccine dose during the first AVIP period (December 15, 1997–March 29, 1999) compared with those never vaccinated or vaccinated later, and first vaccinated during the second AVIP period (March 30, 1999–July 16, 2000) versus those never vaccinated or vaccinated later. The number of disability evaluations among personnel whose first vaccination was delivered during the third or fourth AVIP periods was insufficient for separate models to be constructed.

Because AVA was associated with deployment to areas considered at high threat for purposeful anthrax exposure, we hypothesized that personnel selected for vaccination represented some ill-defined subset of the Army that might be more "combat-ready" than average, possibly having unmeasured characteristics such as higher levels of physical fitness, which reduced their likelihood of injury or decreased their likelihood of becoming disabled, once injured. Therefore, we developed separate multivariable Cox models for subgroups of the population whose duty location was Southwest Asia after June 1998 (just after the implementation of the AVIP in that region) or South Korea after December 1998 (just after the AVIP was implemented there). We expected that these subgroups would represent populations that were relatively homogeneous with respect to factors correlated with selection for deployment.

Finally, we examined various measures of exposure in addition to ever/never vaccinated against anthrax during the study period. These included the number of doses delivered and delivery of doses from specific lots.

The May test was used to assess the goodness of fit of the Cox models.[14] Again, because of the very large number of events in this cohort, the traditional 0.05 level of statistical significance was not a useful criterion. Therefore, we elected to compare observed and predicted values within deciles of risk computed by the May test, and examined the Arjas plots to identify areas of better and worse correspondence between observed and predicted survival. Because our assessment of the fit of the final models is not grounded in explicit statistical theory, model diagnostics are available for review on request.

Results

After dropping fewer than 1% of records for outlying values of age (younger than 16 or older than 35 years at entry into the Army), or invalid dates, and records missing all data values, 716,833 persons with at least 1 day of follow-up time were included in the cohort; 154,456 (22%) had at least one dose of AVA during the study period.

The prevalence of anthrax vaccination was between 18% and 24% in each category of the demographic variables analyzed (Table 2). Among occupational characteristics, the prevalence of vaccination was lowest for personnel with the shortest duration of service and those never stationed abroad (9% and 11%, respectively). Prevalence of vaccination was also low for members of the U.S. Army Pacific and the Recruiting Command (9% and 12%, respectively). The highest vaccination prevalence was for personnel stationed abroad at any time during the study period (46%). Likelihood of vaccination was also high for certain of the major commands (eg, at least 30% of members of the 8th U.S. Army [Korea], Special Operations and the Signal Command). When dates of program implementation were taken into account, vaccination coverage was quite complete in regions specifically targeted by the AVIP: 89% of personnel stationed in Southwest Asia on or after June 1998 and 96% of those stationed in South Korea on or after December 1998 received at least one dose of AVA (Table 2).

As shown in Table 3, 4% of the cohort (29,332 of 716,833) was evaluated for disability discharge from the Army during the study period, of whom 4386 (15%) had at least one dose of AVA. The unadjusted rate of disability evaluation was about twice as high for unvaccinated compared with vaccinated personnel: 140 and

TABLE 2
Vaccination Prevalence by Demographic and Occupational Characteristics at Beginning of Follow up for 716,833 Active Duty Army Personnel Included in the Study

	Percent Vaccinated	No. Vaccinated	No. Total
Gender			
Male	22.31	134,306	602,123
Female	17.61	20,103	114,151
Race/ethnicity			
White	20.46	88,872	434,398
Black	23.78	43,522	182,981
Hispanic	21.50	11,846	55,100
Other	23.34	10,102	43,288
Age quintiles			
16–20 yr	21.26	43,899	206,474
21–22 yr	21.00	19,909	94,816
23–26 yr	22.08	31,175	141,179
27–33 yr	23.63	34,580	146,345
34–65 yr	19.44	24,893	128,019
Education			
At most high school/alternate	22.02	118,644	538,801
Any college/graduate school	19.77	25,438	128,641
Marital status			
Married	21.51	67,034	311,691
Not married	21.56	80,977	375,592
Pay grade			
Enlisted grades 1–3	20.77	60,193	289,876
Enlisted grades 4–6	23.33	58,982	252,825
Enlisted grades 7–9	18.31	10,258	56,038
Warrant and commissioned officers	20.87	18,805	90,087
Duration of service quintiles			
1–919 days	8.67	12,459	143,666
920–1570 days	26.49	37,970	143,357
1571–3012 days	25.48	36,477	143,156
3013–5680 days	25.52	36,591	143,376
5681–17768 days	21.61	30,959	143,278
Stationed abroad during study period			
Never	10.74	53,211	495,635
Ever	45.77	101,245	221,198
Stationed in Southwest Asia, June 1998* or later			
No	11.14	349	562,377
Yes	88.86	2783	154,456
Stationed in South Korea, December 1998* or later			
No	3.35	14,426	562,377
Yes	95.65	41,157	154,456
Career management field†			
Support/administration	20.41	18,745	91,826
Electronic equipment repair	27.48	13,114	47,723
Communication/intelligence	20.90	13,459	64,393
Health care	16.59	7720	46,546
Technical/allied specialties	22.26	4139	18,596
Infantry/gun crews	22.13	32,631	147,454
Electronic/mechanical equipment repair	24.16	20,732	85,801
Craftsworkers	16.19	1982	12,244
Service/supply	20.45	14,909	72,916
Officers	20.87	18,805	90,087
Major Command code			
Forces Command	26.38	57,302	217,220
Training and Doctrine Command	19.43	45,091	232,052
Fifth Corps (Europe)	13.13	5733	43,649
Medical Command	14.14	5358	37,902
8th US Army (Korea)	38.72	10,310	26,627
US Army Pacific	8.96	1844	20,587
Special Operations Command	39.57	6244	15,779
Recruiting Command	11.77	1152	9790
Signal Command	27.92	2692	9643
Intelligence and Security Command	20.14	1808	8975
Other	16.01	9477	59,207

*The AVIP was implemented in Southwest Asia in March 1998 and in South Korea in August 1998.
†Career management field groups jobs based on Primary Military Occupational Specialty.

68.4 per 100,000 person-months, respectively. Overall, women were nearly twice as likely as men to be evaluated for disability, regardless of vaccination status. Other demographic and occupational characteristics were associated with disability evaluation to varying degrees.

The overall unadjusted HR and CI for disability evaluation was 0.77 (CI = 0.74–0.79), suggesting that personnel exposed to at least one dose of AVA had, on average, 23% lower risk of undergoing evaluation for disability compared to unvaccinated persons (not shown). The magnitude of the unadjusted HRs for the separate models stratified by each of the demographic and occupational characteristics was consistently between approximately 0.7 and 0.9, indicating minimal modification of the effect of anthrax vaccination on risk of undergoing evaluation for disability (not shown). As seen in Table 4, after adjustment for potential confounding by duty location (ever/never abroad), Major Command, and race (white/nonwhite), the overall adjusted HR for disability evaluation among those vaccinated was 0.96 (CI = 0.92–0.99). The HR for men, adjusted for duty location, Major Command, and Career Management Field (CMF), was also 0.96 (CI = 0.92–1.00). For women, the multivariable model, adjusted for duty location, Major Command, race, CMF, and quintiles of age, yielded an HR of 1.04 (CI = 0.96–1.13).

The 10 most common reasons for permanent or temporary disability discharge, as determined by the primary VASRD code in the disability record, are shown stratified by vaccination status in Table 5. Nine of the 10 were identical for vaccinated and unvaccinated persons, accounting for 97% of disabilities in each group. Nevertheless, we evaluated the possibility that the musculoskeletal or neurologic disability might be more clearly associated with AVA than the combined outcome of evaluation for any type of disability. As shown in Table 4, the HR for musculoskeletal

TABLE 3
Disability Evaluation Prevalence by Demographic and Occupational Characteristics at Beginning of Follow Up of 716,833 Active-Duty Army Personnel

	Evaluated for disability			
	Percent	No.	Total	Rate/100,000 person- months
Anthrax-vaccinated				
No	4.44	24,946	562,377	140.0
Yes	2.84	4386	154,456	68.4
Gender				
Male	3.70	22,263	602,123	108.1
Female	6.19	7063	114,151	195.7
Race/ethnicity				
White	4.23	18,393	434,398	127.4
Black	4.17	7624	182,981	118.7
Hispanic	3.27	1800	55,100	98.6
Other	3.44	1491	43,288	99.4
Age quintile				
16–20 yr	3.18	6562	206,474	109.6
21–22 yr	4.22	4005	94,816	136.0
23–26 yr	5.13	7242	141,179	151.9
27–33 yr	4.98	7285	146,345	127.4
34–65 yr	3.31	4238	128,019	88.2
Education				
At most high school/alternate	4.51	24,283	538,801	139.8
Any college/graduate school	2.62	3372	128,641	68.5
Marital status				
Married	4.52	14,074	311,691	122.6
Not married	3.77	14,167	375,592	123.3
Pay grade				
Enlisted grades 1–3	3.94	11,411	289,876	136.9
Enlisted grades 4–6	5.56	14,047	252,825	155.6
Enlisted grades 7–9	2.39	1338	56,038	65.7
Warrant and commissioned officers	1.67	1504	90,087	41.5
Duration of service quintiles				
1–919 days	5.14	7386	143,666	295.4
920–1570 days	3.89	5580	143,357	126.0
1571–3012 days	4.71	6737	143,156	121.5
3013–5680 days	4.59	6576	143,376	110.1
5681–17768 days	2.13	3053	143,278	52.8
Stationed abroad during study period				
Never	4.58	22,680	495,635	144.1
Ever	3.01	6652	221,198	78.4
Southwest Asia June 1998 or later				
No	4.10	29,276	713,701	121.5
Yes	1.79	56	3132	39.7
South Korea December 1998 or later				
No	4.17	28,135	674,250	125.3
Yes	2.81	1197	42,583	67.4
Career management field*				
Support/administration	4.31	3959	91,826	128.3
Electronic equipment repair	4.56	2177	47,723	142.4
Communication/intelligence	4.26	2742	64,393	136.7
Health care	5.45	2537	46,546	163.0
Technical/allied specialties	3.76	699	18,596	110.0
Infantry/gun crews	4.24	6259	147,454	132.1
Electronic/mechanical equipment repair	4.57	3919	85,801	141.3
Craftsworkers	4.78	585	12,244	148.0
Service/supply	4.81	3504	72,916	148.9
Officers	1.67	1504	90,087	41.5
Major Command code				
Forces Command	4.93	10,701	217,220	144.1
Training and Doctrine Command	3.38	7852	232,052	116.2
Fifth Corps (Europe)	4.42	1930	43,649	117.1
Medical Command	5.86	2220	37,902	165.7
8th US Army (Korea)	3.81	1015	26,627	103.0
US Army Pacific	5.14	1059	20,587	139.6
Special Operations Command	3.66	578	15,779	94.6
Recruiting Command	2.94	288	9790	70.9
Signal Command	4.44	428	9643	126.3
Intelligence and Security Command	4.20	377	8975	121.5
Other	2.75	1629	59,207	73.7

*Career management fields group job codes based on Primary Military Occupational Specialty.

TABLE 4
Adjusted Hazard Ratios (HR) and 95% Confidence Intervals (CIs) Comparing Risk of Disability Evaluation Among Vaccinated and Unvaccinated Personnel in the US Army: Overall and by Subgroups

	Adjusted HR*	95% CI
Overall†	0.96	0.92–0.99
Men‡	0.96	0.92–1.00
Women†‡§	1.04	0.96–1.13
Primary disability		
Musculoskeletal†‡	0.99	0.95–1.04
Neurologic†‡§	1.02	0.89–1.17
Result of evaluation		
Fit for duty†‡§‖	0.90	0.79–1.02
Temporary disability discharge‡§	0.91	0.82–1.00
Permanent disability discharge†‡	0.99	0.95–1.04
Lagged follow up¶		
6 mo (24,095 cases/668,618)	0.94	0.91–0.98
12 mo (19,868 cases/619,589)	0.97	0.94–1.01
18 mo (15,535 cases/558,886)	1.01	0.97–1.05
First dose of AVA		
AVIP priod 1†‡	1.04	1.00–1.09
AVIP priod 2†	0.84	0.79–0.89
Duty location**		
Southwest Asia June 1998 or later†‖††	1.23	0.58–2.59
South Korea December 1998 or later†‡§‖	0.17	0.12–0.23

*HR, hazard ratio. The unvaccinated group is the referent. All models except for the subset stationed in Southwest Asia or South Korea included indicators for ever-stationed abroad during follow up (referent = no) and Major Command (see Table 4 for list; referent = Forces Command).

†Adjusted for nonwhite race (referent = white race).

‡Adjusted for Career Management Field (see Table 4 for list; referent = Support/Administration).

§Adjusted for quintiles of age (see Table 4 for list; referent = 16 to 20 yr).

‖Adjusted for female gender (referent = male gender).

¶Final overall model plus duration of service, and follow up lagged from study entry date.

**Models for subsets of personnel stationed in Southwest Asia and South Korea did not include indicators for stationed abroad or Major Command.

††Adjusted for marital status (referent = married).

disability discharge, adjusted for duty location, Major Command, and race, was 0.99 (CI = 0.95–1.04). The HR for neurologic disability discharge, adjusted for duty location, Major Command, race, CMF, and age, was 1.02 (CI = 0.89–1.17). When we redefined the end point as "result of disability evaluation," ie, soldier found fit for duty, or granted temporary or permanent disability discharge, the magnitudes of the adjusted HR (0.90 [CI = 0.79–1.02], 0.91 [CI = 0.82–1.00], and 0.99 [CI = 0.95–1.04], respectively) were similar to the overall HR = 0.96 (Table 4).

The risk of disability evaluation for personnel first vaccinated during the earliest AVIP period compared with those never vaccinated or vaccinated later was 1.04 (CI = 1.00–1.09), adjusted for duty location, Major Command, race, and CMF (Table 5). After adjustment for duty location, Major Command, and race, personnel first vaccinated during the second AVIP period showed a lower risk of disability evaluation compared with those who were never vaccinated or vaccinated later (HR = 0.84 [CI = 0.79–1.02]). Introducing lag times of 6, 12, and 18 months from first vaccination date did not substantially change the HR from its overall value (Table 4).

For the subgroup of the population whose duty location was Southwest Asia after June 1998 (the implementation of the AVIP in that region), the HR was 1.23 (CI = 0.58–2.59), adjusting for race, age, gender, and marital status, indicating a 23% increase in risk of disability evaluation associated with vaccination in the subgroup. In contrast, the HR for the subgroup stationed in South Korea after December 1998 was 0.17 (CI = 0.12–0.23) (adjusted for race, CMF, age, and gender), indicating an 83% decrease in risk of disability evaluation.

Results of the models based on various exposure measures are shown in Table 6. There was an inverse association between risk of disability evaluation and number of doses of AVA eventually received. Compared with unvaccinated persons, the adjusted risks of disability evaluation for 1, 2, and 3 or more doses of AVA were 1.83 (CI = 1.60–2.10), 1.64 (CI = 1.43–1.87), and 0.91 (CI = 0.87–0.94), respectively.

We evaluated the risk of disability evaluation for persons who received at least one dose from a given AVA lot number compared with all unvaccinated personnel. As shown in Table 6, the risk of disability evaluation was slightly higher for those with exposure to vaccine from older lots. The magnitude of the HR comparing vaccinated with unvaccinated was highest for people exposed to the oldest batches of AVA, but only reached as high as 1.13 (CI = 1.00–1.28) for lot FAV030, which expired in early 1999. No other lot, including lots contemporary to FAV030, was associated with an increase in risk of disability evaluation.

Discussion

We aimed to assess differences in the rates of evaluation for disability in the U.S. Army that might be associated with vaccination against anthrax. This end point was chosen to reflect longer-lasting or later-onset sequelae of exposure to AVA than would be apparent in analyses of inpatient or outpatient care. However, due to the relative recency of AVIP implementation, and the resulting short fol-

TABLE 5
Ranking of Primary Reason for Disability Discharge Among Vaccinated and Unvaccinated Personnel the US Army

	Vaccinated (*N* = 4035)			Unvaccinated (*N* = 22,437)		
Rank	**Primary VASRD* group**	**No.**	**Percent**	**Primary VASRD* group**	**No.**	**Percent**
1	Musculoskeletal conditions	2919	72.3	Musculoskeletal conditions	15,818	70.5
2	Neurologic and convulsive disorders	312	7.7	Neurologic and convulsive disorders	1735	7.7
3	Respiratory conditions	271	6.7	Respiratory conditions	1561	7.0
4	Psychologic disorders	202	5.0	Psychologic disorders	1187	5.3
5	Digestive conditions	62	1.5	Digestive conditions	450	2.0
6	Cardiovascular conditions	53	1.3	Cardiovascular conditions	425	1.9
7	Endocrine conditions	52	1.3	Endocrine conditions	334	1.5
8	Skin conditions	34	0.8	Genitourinary conditions	177	0.8
9	Genitourinary conditions	28	0.7	Skin conditions	167	0.7
10	Auditory problems	25	0.6	Visual problems	149	0.7

*Veteran's Administration System for Rating Disability.

TABLE 6
Vaccination Characteristics, Disability Evaluation, and Adjusted Hazard of Disability Evaluation for 154,456 Vaccinated Army Personnel

	With characteristic		Evaluated for disability		
Vaccine characteristic	**No.**	**Percent**	**No.**	**Percent**	**HR* (CI)**
No. of doses					
1 dose†	6529	4.23	215	3.29	1.83 (1.60–2.10)
2 doses	6987	4.52	237	3.39	1.64 (1.43–1.87)
>3 doses	140,940	91.25	3934	2.79	0.91 (0.87–0.94)
Any dose from lot‡					
FAV017 (Feb 6, 1999)§	42,637	27.60	1362	3.19	1.00 (0.94–1.06)
FAV030 (Feb 23, 1999)	6757	4.37	282	4.17	1.13 (1.00–1.27)
FAV034 (Feb 23, 1999)	14,998	9.71	529	3.53	1.02 (0.93–1.11)
FAV036 (Mar 16, 1999)	28,690	18.57	1093	3.81	1.04 (0.98–1.11)
FAV033 (Aug 27, 1999)	24,083	15.59	758	3.15	0.98 (0.91–1.06)
FAV038 (Jan 15, 2000)	36,675	23.74	1126	3.07	0.92 (0.87–0.98)
FAV019 (Feb 6, 2000)§	4341	2.81	141	3.25	0.80 (0.68–0.95)
FAV020 (Feb 6, 2000)§	15,050	9.74	530	3.52	0.83 (0.76–0.91)
FAV037 (Feb 25, 2000)	32,993	21.36	837	2.54	0.81 (0.75–0.87)
FAV043 (Mar 12, 2000)	12,613	8.17	371	2.94	0.91 (0.82–1.01)
FAV041 (Apr 5, 2000)	26,007	16.84	755	2.90	0.83 (0.77–0.90)
FAV024 (Apr 22, 2000)§	29,985	19.41	847	2.82	0.83 (0.77–0.89)
FAV008 (Aug 4, 2000)§	13,819	8.95	205	1.48	0.56 (0.49–0.65)
FAV031 (Oct 6, 2000)§	34,186	22.13	792	2.32	0.74 (0.69–0.80)
FAV044 (Feb 3, 2001)	41,349	26.77	829	2.00	0.70 (0.65–0.76)
FAV047 (Sep 8, 2001)	34,900	22.60	672	1.93	0.67 (0.62–0.73)
FAV048 (Apr 13, 2002)	30,321	19.63	485	1.60	0.59 (0.54–0.65)
Other§	11,095	7.18	315	2.84	0.91 (0.81–1.02)

*Hazard ratio and 95% confidence interval for subset of vaccinated cohort defined by each vaccine characteristic compared with unvaccinated cohort, adjusted for race/ethnicity, ever stationed abroad, and major command.

†*n* = 6529 had only 1 vaccination dose within the study period.

‡Lot number (original expiration date). Exposure defined as: 0 = unvaccinated (referent); 1 = vaccinated, but not from the specified lot number; 2 = vaccinated, at least 1 dose from the specified lot number.

§Indicated lots were used at various times and had potency dating extensions.

low-up time (a maximum of just over 4 years), these analyses cannot be used to evaluate the association between AVA exposure and conditions with expected long latency or induction times. By using data derived from uniformly collected databases, these analyses were also designed to address the likely biases inherent in analyses that require recall of vaccination and self-reported symptom status to detect cases. We included all disability evaluations, rather than only those resulting in discharge from the Army, to identify all personnel who perceived themselves, or were perceived by their commanders, to be experiencing a work-limiting health problem.

Although the unadjusted rate of disability evaluation for vaccinated personnel was about half that ob-

served for the unvaccinated (Table 3), there was essentially no difference in the risk of disability evaluation for the vaccinated versus unvaccinated after adjustment for occupational and sociodemographic factors (HR = 0.96, Table 4). The adjusted hazard ratios for the various subgroups analyzed separately, including gender-specific analyses, were all of about the same magnitude.

We hypothesized that the slightly lower (4%) risk of disability among the vaccinated compared with the unvaccinated might be the result of selection for "combat readiness" arising from the targeted nature of AVIP implementation. "Combat readiness" may be associated with higher levels of fitness, physical training, and/or resilience to injury, and might be reflected by the very low rates of disability discharge for the vaccinated. A similar theory was proposed by the IOM committee to explain lower rates of inpatient and outpatient care among vaccinated compared with unvaccinated active-duty military personnel. This pattern of lower risks for health outcomes among subsets of the population has been dubbed the "healthy warrior effect."[7]

To investigate the possibility of unmeasured selection bias resulting from the healthy warrior effect, we completed subanalyses for individuals whose duty location was in Southwest Asia or South Korea after the implementation of AVIP in those regions. We assumed these subgroups were homogeneous with respect to selection for "deployability." For the group stationed in Southwest Asia, vaccination with AVA appeared to increase the risk of disability evaluation slightly, with an adjusted HR = 1.23 (CI = 0.58–2.59). In contrast, vaccinated personnel stationed in South Korea had substantially lower risks of disability evaluation compared with unvaccinated personnel in that region: HR = 0.17 (CI = 0.12–0.23). We have no explanation to propose for the inconsistency in these findings.

A different form of selection bias might exist that would affect likelihood of exposure rather than outcome. Specifically, all unvaccinated personnel who would have been eligible to participate in the AVIP, but who were due to be discharged for disability before their scheduled vaccination, were by definition unexposed; their disability evaluations and person-time would be attributed to the unvaccinated group. Similarly, all personnel who received at least one dose of AVA, by definition, remained on active duty long enough to be vaccinated. These definitions, although standard, create a potential for survival bias in the calculation of the HRs that might increase the magnitude of any apparent protective effect of AVA exposure on short- or long-term health effects. If operating, this bias would be impossible to address with current research methods.

Most temporary adverse events after anthrax vaccination are musculoskeletal or neurologic.[7] In this cohort, there were no meaningful differences in the risk of specific types of disability granted for the vaccinated versus unvaccinated personnel. Not only were the reasons for permanent and temporary disability discharge nearly identically distributed for the two groups, the adjusted HRs for both musculoskeletal and neurologic disability discharge and for the various disability evaluation results (eg, fit for duty, temporary or permanent disability discharge) were all approximately 1.0. However, the relatively broad range of diagnoses included within many of the VASRD categories could have masked associations with more specific illnesses or conditions.

Because we wanted to be as inclusive as possible, cohort members were defined as those with at least one person-day of follow up during the study period. This approach implicitly assumes that adverse effects of AVA might become apparent within one day of vaccination. We also tested two alternative assumptions, namely, 1) that personnel vaccinated earlier in calendar time were at higher risk of disability evaluation than personnel vaccinated later, in case the passage of time would allow for the administrative processing of a disability evaluation to be completed (administrative latency); and 2) that adverse effects of AVA would not become apparent until 6, 12, or 18 months after vaccination (biologic latency).

The data weakly supported the hypothesized need to consider an administrative latency interval. When the exposed group was restricted to persons whose first AVA dose was delivered during the earliest AVIP period, December 1997–March 1999, the adjusted HR was slightly elevated (1.04), indicating a 4% increase in risk of disability evaluation for vaccinated compared with unvaccinated persons. The HR was attenuated to 0.84 when exposure was restricted to first dose received during the second AVIP period, March 1999–July 2000, supporting the theory that this and later groups had insufficient opportunity for long-term health effects to develop or be recognized sufficiently to initiate the disability determination process. The number of cases among those first vaccinated in AVIP periods 3 and 4 was insufficient to permit separate analysis of those subgroups (not shown), and this observation also supports the hypothesized need for an adequate administrative latency interval to elapse. In contrast, including lag times of 6, 12, and 18 months from date of first AVA dose did not result in any substantial change in HR (Table 4), indicating that the biologic latency intervals (lag times) we evaluated were either inappropriate or unnecessary.

Investigators used data from the Defense Military Surveillance System to conduct analyses at the request of the IOM that also aimed to elucidate latency intervals for the development of delayed-onset health

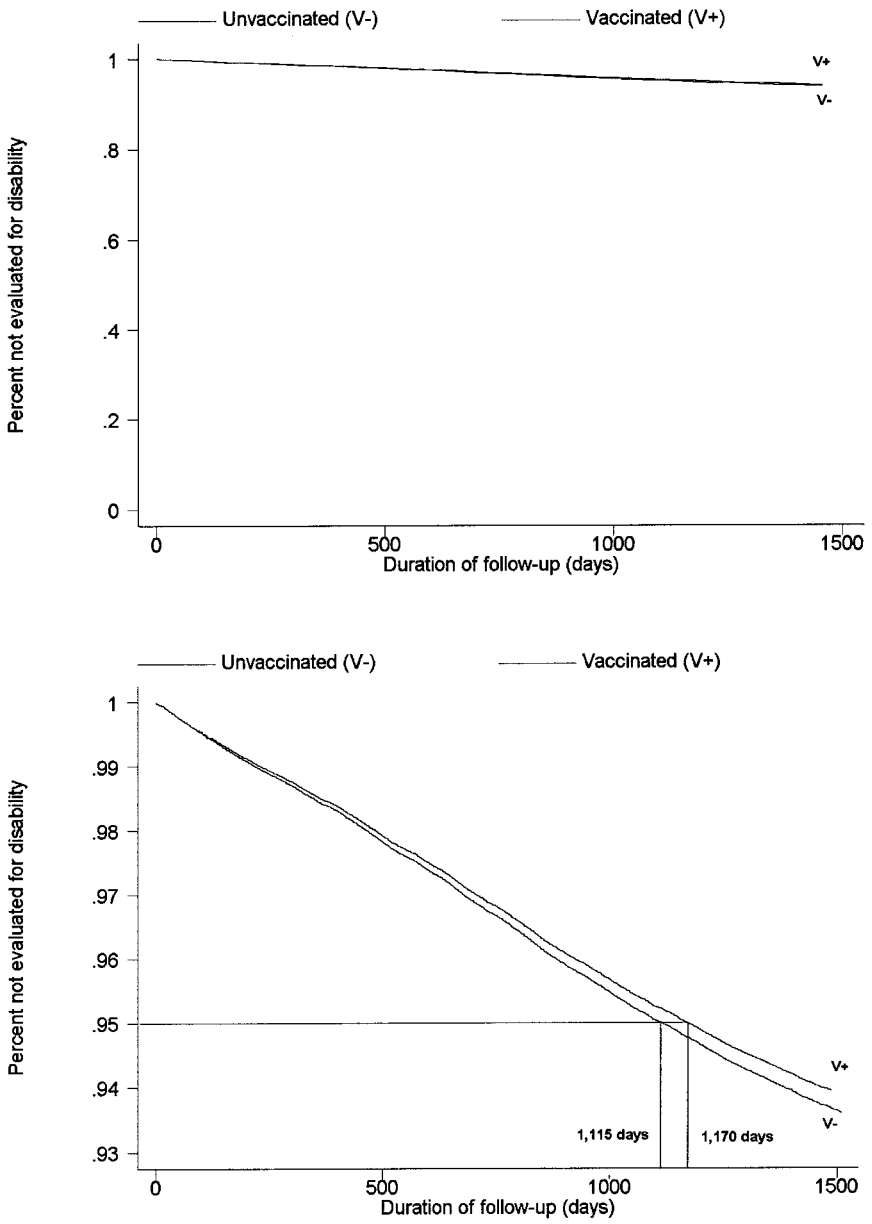

Fig. 1. Adjusted survivorship function for U.S. Army personnel vaccinated (V+) and unvaccinated (V-) against anthrax shown over the whole range and for the 93rd percentile of survivorship.

effects that might be associated with AVA exposure. They calculated rates of inpatient care for vaccinated persons before vaccination compared with rates in time windows of 0 to 45 days and >45 days after first AVA exposure. The overall hospitalization rates were about the same for all 3 time periods. Of the more than 800 specific diagnoses evaluated, 13 showed rate ratios statistically significantly above 1.0 for the first postvaccination window compared with prevaccination time, and 20 diagnoses had rate ratios above 1.0 for the later time window compared with prevaccination time. However, no biologically explicable patterns emerged when the particular diagnoses with elevated rates during the two postvaccination time windows were compared.[7,15]

If biologic and administrative latencies were not important considerations in our analyses, then the observed increase in HR for those whose first dose was delivered during the earliest AVIP period could be associated with the use of older, stockpiled lots of AVA used during that time. As shown in Table 6, the magnitude of the risk was highest for individuals receiving doses from the oldest lots. The effect of other time-dependent factors such as the age and duration of service of the personnel on active duty during the earliest phase of the AVIP probably do not explain this association. As shown in Tables 2 and 3, there was no strong association between these covariates and either the likelihood of vaccination or disability evaluation.

For most of the analyses reported here, we focused on one definition of vaccination status: the receipt of at least one dose of AVA. Overall, 3% of the disabled and 4% of the nondisabled received at least one dose of AVA during the study period (Table 2). In analyses to investigate alternative exposure definitions, we found a decrease in risk of disability evaluation with number of AVA doses received (Table 6). One explanation for this finding is that personnel less able or willing to tolerate exposure to AVA might be removed from the population at risk after the first one or two doses, which could be another indication of selection bias resulting from the healthy warrior effect.

A similar question was addressed by the DMSS study in analyses that compared hospitalization rates before and after vaccination according to the number of doses of AVA eventually received. For nearly all diagnoses evaluated, the prevaccination hospitalization rate was lowest for those service members who eventually received the largest number of doses of vaccine. This finding was interpreted by the IOM committee as an indication of the healthy warrior effect.[7]

On the other hand, the first three AVA doses were scheduled for delivery every two weeks. If personnel unable to tolerate the vaccine were selectively removed from the population, it would have been necessary

for their health effects to be detected and labeled "debilitating" within a month or less of receiving their first dose. In the present study, the minimum duration of follow up for vaccinated persons was 96 days. Therefore, the healthy warrior effect is a less likely explanation for this finding than the need for an adequate administrative latency interval to elapse between vaccination and disability evaluation, as discussed previously.

To put into context the observed overall HR of 0.96, the covariate adjusted survivorship functions for vaccinated and unvaccinated personnel, evaluated at the 50th percentile of risk, are shown in the Figure 1. Because disability evaluation was rare in both groups, the functions appear to be nearly flat and nearly superimposed when plotted over their whole range (0–100% surviving), as shown in the top panel. The bottom panel of the figure, therefore, shows the curves plotted for the 93rd through the 100th percentile of survivorship. This can be used to estimate the difference in the amount of follow-up time accrued before disability evaluation for each group (vaccinated and unvaccinated) at any of the top seven percentiles of survivorship. On average, 95% of those vaccinated against anthrax remained in service without a disability evaluation for 1170 days (3.2 years), whereas 95% of those not vaccinated against anthrax remained in service without a disability evaluation for 1115 days (3.05 years); the difference between groups is 51 days. A difference such as this has no likely causal association with anthrax vaccination.

Overall, the disability evaluation rate in the Army was very low for the 4.25 years covered by this study, and there appeared to be little, if any, effect of exposure to AVA on the risk of disability evaluation. The small negative association that we observed might be partially explained by the determinants of eligibility for vaccination or vaccine tolerance; it is unlikely that a large positive association was masked by these potential biases. We conclude that exposure to AVA is not associated with an increase in risk of evaluation for disability discharge from the U.S. Army.

Acknowledgments

The authors thank the following individuals: Mr. Brendan Bartley and Mr. Jeffrey Williams from USARIEM for abstracting the files for analysis from the TAIHOD database. Mr. Richard Houser provided the AVIP vaccination data and patiently answered our many questions. Dr. Carol Bigelow and Dr. David Hosmer provided statistical advice. Dr. Edwin van Wijngaarden and Dr. Kenneth Mundt reviewed the analytical approach. Mr. Michael Schmidt assisted in generating the covariate-adjusted survivorship curves. Dr. van Wijngaarden and Dr. Diane Mundt reviewed an early draft of the final report. The authors also appreciate the continuing support and collaboration of Dr. Paul Amoroso, USARIEM.

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