

**Surveillance of Adverse Effects
of Anthrax Vaccine Adsorbed**

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Army Medical Surveillance Activity
Directorate of Epidemiology and Disease Surveillance
US Army Center for Health Promotion and Preventive Medicine

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EXECUTIVE SUMMARY

Background. Future adversaries of the United States may have biological weapons that employ *Bacillus anthracis*, the bacterium that causes anthrax. In response to this threat, the Department of Defense implemented the Anthrax Vaccine Immunization Program in March 1998. This program requires that all military personnel receive Anthrax Vaccine Adsorbed (AVA). While pre-licensure studies and post-licensure uses of AVA have documented its safety, there remain concerns regarding its widespread use. In response to these concerns, the Department of Defense implemented surveillance to detect potential adverse medical effects of AVA.

Methods. The source of data for the surveillance is the Defense Medical Surveillance System (DMSS). The surveillance is designed to continuously, systematically, and comprehensively monitor all medical encounters of all individuals who served in an active component of the U.S. Armed Forces since January 1998. In order to detect potential adverse medical effects of AVA, rate ratios are calculated that compare rates of hospitalizations and ambulatory visits between cohorts of postimmunization and preimmunization individuals. All illnesses and injuries that result in a hospitalization or ambulatory visit are specified by codes of the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*. These codes are examined at two levels of diagnostic detail: in 14 major categories and for 824 specific diagnoses. Rate ratios were adjusted for potentially confounding differences between the cohorts in military experience, medical history, and demographic characteristics with procedures of Poisson regression.

Results. This periodic analysis included 4.2 million person-years of active military service of which 18% was postimmunization. Surveillance from January 1998 to December 2000 revealed the following:

Hospitalizations:

- Crude and adjusted rates for all major categories were lower in the postimmunization than in the preimmunization cohort.
- Adjusted rates of hospitalization for 17 specific diagnoses were statistically higher in the postimmunization than in the preimmunization cohort.
- Compared to the last quarterly report, 3 diagnoses were added and 5 were deleted from among diagnoses considered nominally “statistically significant.”

Ambulatory visits:

- Crude and adjusted rates for all major categories were lower in the postimmunization than in the preimmunization cohort.
- Adjusted rates of ambulatory visits for 34 specific diagnoses were statistically higher in the postimmunization than in the preimmunization cohort.
- Compared to the last quarterly analysis, 7 diagnoses were added and 12 were deleted from the list of diagnoses considered nominally “statistically significant.”

Incident visits:

- Crude and adjusted rates for all major categories were lower in the postimmunization than in the preimmunization cohort.
- Adjusted incidence rates for 27 specific diagnoses were statistically higher in the postimmunization than in the preimmunization cohort.

Periodicity of analyses. The surveillance periods that define the scopes of these quarterly analyses lengthen over time. While the start dates of surveillance periods remain the same (1 January 1998), end dates advance to keep pace with the ongoing vaccination program. Specifically, end dates of the surveillance periods that are used for quarterly analyses are the latest dates for which all data required for analysis are integrated in the DMSS. The next periodic analysis is scheduled for July 2001.

INTRODUCTION

Adversaries of the United States may have biological weapons that use *Bacillus anthracis*, the bacterium that causes the disease anthrax. There is evidence that seven nations have pursued biological weapons programs and one terrorist group has already used *B. anthracis* (Inglesby, 1999; Mazzuchi, 2000). *B. anthracis* is a choice agent for biological weapons for the following reasons: large quantities can be produced easily and stored for years; it can be delivered by a variety of systems; and inhalation is almost always fatal (Inglesby, 1999; Friedlander, 1999). Since natural immunity to *B. anthracis* is rare, in 1997, the US Secretary of Defense directed the implementation of the Anthrax Vaccine Immunization Program (Memorandum, 1998). The goal of this program is to protect every member of the US Armed Forces from *B. anthracis* by immunizing them with Anthrax Vaccine Adsorbed (AVA).

AVA is a noninfectious filtrate of an attenuated strain of *B. anthracis* that is adsorbed to aluminum hydroxide adjuvant. The primary immunizing series consists of six subcutaneous injections given at baseline, 2 weeks, 4 weeks, 6 months, 12 months, and 18 months. Booster immunizations are required annually to maintain immunity (Friedlander, 1999). The US Food and Drug Administration licensed AVA in 1970. Between 1970 and 1990, individuals with frequent occupational exposures to *B. anthracis* (e.g., veterinarians, abattoir workers, laboratory workers) were the primary users of the vaccine. In 1991, approximately 150,000 military personnel deployed for Operation Desert Storm received about 250,000 doses of AVA.

Pre- and post-licensure studies have documented the safety of AVA. In general, adverse reactions are mild inflammatory reactions that manifest as swelling and erythema at injection sites (Friedlander, 1999; Brachman, 1962; Demicheli, 1998). Less frequent reactions include edema of the forearm, nodules (local and distant to injection sites), malaise, lassitude, headaches, fever, chills, nausea, heartburn, and body, joint, and muscle aches (Friedlander, 1999; Brachman, 1962; Demicheli, 1998). Even though the results of studies document the vaccine's safety and show that adverse reactions to AVA are similar to those of other vaccines, there remain concerns about the use of AVA in large populations.

The safety of AVA, as with other licensed vaccines, is monitored through the Vaccine Adverse Events Reporting System (VAERS), a national system of vaccine safety surveillance that is jointly operated by the Food and Drug Administration and the Centers for Disease Control and

Prevention. However, the VAERS, like many other passive surveillance systems, has significant shortcomings (Rosenthal, 1995; Ellenberg, 1997). For example, there is significant underreporting to the VAERS, particularly of adverse events that are less serious or delayed in onset. Also the VAERS lacks standard definitions for adverse events. As a result, similar clinical events may be reported differently, different clinical events may be reported identically, reports may be inaccurate and vague, and as a result, clusters of events may be difficult to detect and characterize. Finally, since numbers and characteristics of recipients of vaccines are unknown, rates of reported adverse events cannot be calculated or compared to baseline rates of similar events in unvaccinated control populations. Despite its shortcomings, however, the VAERS has been and remains a useful tool for detecting clinical signals of adverse events of vaccines.

Medical surveillance of anthrax vaccination described in this report is designed to complement rather than replace the oversight provided by the VAERS. Our project provides continuous, systematic, and comprehensive surveillance of the complete spectrums of morbidity that affect both vaccine recipients and contemporaneous non-recipients. In turn, adverse health effects of the vaccination, if any, can be disentangled from the background of morbidity that affects all military personnel and targeted for more detailed investigation. This report summarizes the results of the second periodic surveillance analysis.

METHODS

The source of all data used in analyses is the Defense Medical Surveillance System. This system provides a longitudinal record of demographic characteristics, military experiences, medical events, and immunization records for all members of the active component of the US military services. Demographic characteristics documented in the system include age, gender, and race. Military experience data include military occupational histories, periods of service, and locations of assignments. Medical event data are derived from administrative records of all medical encounters at military hospitals and clinics. The medical reasons for inpatient and outpatient encounters are specified by codes of the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). Immunization records track dates and types of inoculations. This surveillance system is routinely and systematically maintained, updated, and monitored for quality by the Army Medical Surveillance Activity of the United States Army Center for Health Promotion and Preventive Medicine, Washington, DC.

For this report, we conducted population-based surveillance of active duty military personnel between January 1998 and December 2000. Medical encounters were examined at two levels of diagnostic detail, as specified within the classification of ICD-9-CM codes. Individuals could contribute one medical event per three-digit ICD-9-CM diagnosis per day. We examined 14 of the 17 major categories of illness and injury. We excluded the categories of complications of pregnancy, childbirth, and the puerperium; congenital anomalies; and certain conditions originating in the perinatal period. Pregnancy-related codes were excluded because pregnancy is a contraindication for vaccination. Congenital disorder-related codes were excluded because they are, by definition, unrelated to AVA. Within the major categories, we examined 824 three-digit diagnoses. Due to biological differences, diagnoses in the genitourinary system category were examined separately for males and females.

Initially, all military personnel were classified as pre-immunization. On the day of an individual's first AVA immunization, he/she transitioned into the post-immunization cohort. Rate ratios were used to compare rates of hospitalizations, ambulatory visits, and incident visits between the two cohorts. Incident visits refer to the first occurrences (per person) of medical care for given diagnoses regardless of the locations or settings. Rate ratios were adjusted using Poisson regression models with up to 11 covariates. The covariates were chosen based on their crude (unadjusted) associations with either the rate of hospitalization, the prevalence of AVA

immunization, or both. The covariates that were included were: age, gender, race/ethnicity, branch of service, hospitalization history, primary occupation, training period, deployment history, assignment location, military grade, and calendar year (table 1).

Utilizing Poisson regression, we examined each covariate along with AVA status in relation to every diagnostic code in each clinical setting. Covariates that were significantly related (χ^2 p-value < 0.1) to each diagnosis in each clinical setting were included along with AVA status in final multivariate regression models. Separate parsimonious models were developed for each diagnostic outcome in each clinical setting to enhance data dispersion, model fit, and the validity of confidence interval estimation. Estimates were not computed for diagnoses with fewer than five cases in the post-immunization cohort.

RESULTS

Surveillance Population. This analysis followed all 2.0 million individuals who served on active duty in US military service during the period from January 1998 to December 2000. The surveillance period started three months before the initiation of the Anthrax Vaccine Immunization Program. As of December 2000, 2 million injections had been given to 448,330 individuals. Of the total follow-up time of 4.2 million person-years, 757,540 years (18%) occurred after an injection of AVA, or “post-immunization,” and 3,430,459 years (82%) occurred before an injection of AVA, or “pre-immunization.”

Rates of hospitalization for any reason differed across demographic and military experience strata (table 1). Individuals in the following strata were more likely than their counterparts to be hospitalized: those less than 24 years of age, women, Army personnel, those with a previous hospitalization, those in the health care field, those in the first 6 months of service, those not on major deployments to Bosnia or Southwest Asia, and enlisted personnel.

For hospitalizations, ambulatory visits, and incident visits, the counts, crude rates, and adjusted rate ratios are presented in the Appendix for all major categories and specific diagnoses.

Hospitalizations. For the surveillance period, there were 115,549 hospitalizations during the pre-immunization follow-up and 20,765 hospitalizations during the post-immunization follow-up. Hence, a hospitalization for any reason was less likely (crude rate ratio = 0.81) during post-immunization relative to pre-immunization. None of the major categories of hospitalizations had adjusted rate ratios that were greater than 1.0 with 95% confidence intervals that excluded 1.0. Seventeen three-digit diagnoses had adjusted rate ratios that were greater than 1.0 with 95% confidence intervals that excluded 1.0 (table 2). Since the last report, five diagnoses were no longer statistically significant (gout (274), acute pharyngitis (462), other disorders of liver (573), infertility, male (606), and fracture, one or more fingers (816)). Since the last report, three diagnoses became statistically significant (mononeuritis of upper limb and mononeuritis multiplex (354), osteochondropathies (732), and toxic effects of corrosives (983)).

Ambulatory Clinic Visits

For the surveillance period, there were 13,380,501 ambulatory visits during the pre-immunization follow-up and 2,085,243 ambulatory visits during the post-immunization follow-up. Hence, an ambulatory clinic visit for any reason was less likely (crude rate ratio = 0.71)

during post-immunization relative to pre-immunization. None of the major categories of ambulatory clinic visits had adjusted rate ratios that were greater than 1.0 with 95% confidence intervals that excluded 1.0. Thirty-four three-digit diagnoses had adjusted rate ratios that were greater than 1.0 and 95% confidence intervals above 1.0 (table 3). Since the last report, twelve diagnoses were no longer statistically significant (malignant neoplasm of other sites, digestive organs (159), malignant neoplasm of connective tissue (171), other benign neoplasm of connective tissue (215), benign neoplasm of breast (217), redundant prepuce and phimosis, male (605), other disorders of female genital organs (629), symptoms of nutrition, metabolism, development (783), traumatic amputation of fingers (886), late effects of musculoskeletal tissue injuries (905), foreign body in anus/rectum (937), injury to nerve roots, spinal plexus (953), poisoning by agents acting on muscles (975)). Since the last report, seven diagnoses became statistically significant (malignant neoplasm w/o specification of site (199), transient cerebral ischemia (435), other diseases of the respiratory system (519), injury to pelvic organs (867), open wound of back (876), traumatic amputation of toe(s) (895), injury of blood vessels of upper extremity (903)).

Incident Visits

For the surveillance period, there were 5,806,145 incident visits during the pre-immunization follow-up and 850,480 incident visits during the post-immunization follow-up. Hence, an incident clinic visit for any reason was less likely (crude rate ratio = 0.66) during post-immunization relative to pre-immunization. None of the major categories of incident visits had adjusted rate ratios that were greater than 1.0 with 95% confidence intervals that excluded 1.0. Twenty-seven three-digit diagnoses had adjusted rate ratios that were greater than 1.0 and 95% confidence intervals above 1.0 (table 4). Of these 27 diagnoses, one diagnosis (malaria (084)) was statistically significant in both the hospital and ambulatory settings; 22 diagnoses were statistically significant in the ambulatory setting only; and 4 diagnoses were not statistically significant in either the hospital or ambulatory setting.

COMMENT

This surveillance was designed to use existing data sources and analysis capabilities to compare the complete spectrums of morbidity that affect anthrax vaccine recipients and contemporaneous non-recipients. The purpose is to detect “signals” of possible adverse effects of vaccination that may be appropriate for detailed investigation. Data analysis methods were designed to document *statistical* relationships between specific diagnoses and prior anthrax vaccination. The analyses, however, were not intended and are inherently unable to determine *causal relationships* between specific disorders and AVA vaccination.

Several limitations in methods should be considered in interpreting the findings. First, more than 2,000 separate comparisons were made during the analyses for this report. Thus, by chance alone, we expected that some diagnoses would be statistically associated with, but not physiologically related to, anthrax vaccination (false positive statistical associations). Using a threshold of statistical significance of $p = .05$ (two-tailed), we anticipated that approximately 2.5% ($n=25$) of the endpoints screened during each analysis would be false positive statistical associations. In our analyses of the hospitalization, ambulatory visit, and incident visit data, there were 17, 34, and 27 diagnoses, respectively, that had adjusted rate ratios significantly greater than 1.0. It is likely, therefore, that most or all of the positive signals that were detected represent false positive statistical associations rather than true effects of AVA. Second, despite efforts to control for confounding differences between the immunized and non-immunized cohorts, there was undoubtedly “residual confounding.” For example, the higher rates among vaccine recipients of certain injuries (e.g., open wound of back, effects of reduced temperature) and infectious illnesses (e.g., malaria) were almost certainly related to undocumented differences in the nature, durations, intensities, and locations of hazardous training and off-duty activities. Our ability to further reduce confounding is limited by the nature of the data in the Defense Medical Surveillance System.

Clearly, assessments of causality require information that is more detailed than that routinely collected for medical surveillance purposes. In addition, causality assessments require analytic methods that consider, for example, biological plausibility, temporal relationships, medical histories, co-morbidities, competing risks, vaccines given at the same time as AVA, and differences in health care access and usage (e.g., deferred diagnoses or treatments during certain assignments/deployments, inpatient versus outpatient diagnostic/surgical procedures). Despite the limitations of this analysis, however, the results together with those of other monitoring efforts, such as VAERS, provide unprecedented oversight of the safety of the anthrax vaccination program.

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Table 1. Covariates included in surveillance

Covariate Exposure level	Person-years at exposure level	Relative rate of hospitalization	Relative rate of immunization
Age			
17-24	1,652,571	1.33	1.14
25-34	1,525,382	-	1.14
35-65	1,010,046	1.14	-
Gender			
Women	593,310	1.61	-
Men	3,594,689	-	1.47
Race/ethnicity			
Other	1,419,851	1.00	1.08
White, non-Hispanic	2,768,149	-	-
Service			
Army	1,456,760	1.93	1.16
Air Force	1,078,507	1.29	1.17
Marine Corps	527,310	1.46	1.67
Navy	1,125,422	-	-
Military hospitalization since July 1997			
No	4,051,830	-	1.25
Yes	136,169	6.59	-
Occupation			
Combat	880,778	-	2.20
Medical	347,224	1.30	-
Other	2,959,997	0.98	1.79
Training period (first 6 months of service)			
No	3,912,642	-	14.57
Yes	275,357	1.65	-
Deployed to Bosnia or Southwest Asia			
No	4,135,188	1.59	-
Yes	52,811	-	2.04
Assigned within United States			
Yes	3,166,046	0.92	-
No	1,021,953	-	1.59
Grade			
Enlisted	3,517,993	1.64	1.27
Officer	670,006	-	-
Year			
1998 - June 1999	2,105,966	1.07	-
July 1999 - 2000	2,082,033	-	2.87
Anthrax immunization status			
Post-immunization	757,540	-	-
Pre-immunization	3,430,459	1.23	-

- Denotes referent group

Table 2. Hospitalization diagnoses with rate ratios above 1.0, U.S. Armed Forces, Active Duty, 1998-2000

ICD-9-CM Code(s)	Description	Adjusted rate ratio all visits	Comment ¹
084	Malaria	2.88	Associated with service in Korea
110	Dermatophytosis	4.54	Hospital utilization overseas ²
217	Benign neoplasm of breast	8.92	Hospital utilization overseas
233	Carcinoma in situ of breast and genitourinary system	3.58	Hospital utilization overseas
354	Mononeuritis of the upper limb and mononeuritis multiplex	1.61	
374	Other disorders of eyelids	2.16	Hospital utilization overseas
377	Disorders of optic nerve and visual pathways	2.74	Hospital utilization overseas
454	Varicose veins of lower extremities	1.66	Hospital utilization overseas
470	Deviated nasal septum	1.52	Hospital utilization overseas
541	Appendicitis, unqualified	1.38	Hospital utilization overseas
550	Inguinal hernia	1.45	Hospital utilization overseas
603	Hydrocele	2.83	Hospital utilization overseas
610	Benign mammary dysplasias	4.96	Hospital utilization overseas
622	Noninflammatory disorders of cervix	5.37	Hospital utilization overseas
732	Osteochondropathies	1.45	
735	Acquired deformities of toe	1.86	Hospital utilization overseas
983	Toxic effects of corrosives...	2.76	

1. Comment provided when patterns in the data may be relevant to interpreting results.

2. Hospital utilization overseas: Servicemembers with this diagnosis were more likely to be hospitalized if assigned overseas than in the US.

Table 3. Ambulatory visit diagnoses with rate ratios above 1.0, U.S. Armed Forces, 1998-2000

ICD-9-CM Code(s)	Description	Adjusted rate ratio all visits	Comment ¹
001	Cholera	4.68	Isolated coding pattern ²
002	Typhoid and paratyphoid fevers	25.68	Isolated coding pattern
010	Primary tuberculous infection	1.71	Isolated coding pattern
022	Anthrax	109.50	Isolated coding pattern
062	Mosquito-borne viral encephalitis	1.59	Isolated coding pattern
084	Malaria	1.46	Associated with service in Korea
142	Malignant neoplasm of major salivary glands	1.56	
156	Malignant neoplasm of gallbladder and bile ducts	2.92	
179	Malignant neoplasm of uterus, part unspecified	4.42	Isolated coding pattern
182	Malignant neoplasm of body of uterus	4.16	
184	Malignant neoplasm of other female genital organs	3.76	
199	Malignant neoplasm without specification of site	1.19	
229	Benign neoplasm of other and unspecified sites	1.60	
261	Nutritional marasmus	4.36	
266	Deficiency of B-complex components	1.21	Isolated coding pattern
302	Sexual deviations and disorders	1.09	
388	Other disorders of ear	1.07	Noise induced hearing loss
415	Acute pulmonary heart disease	1.24	
429	Ill-defined descriptions of heart disease	1.35	Isolated coding pattern
435	Transient cerebral ischemia	1.16	
452	Portal vein thrombosis	3.15	
519	Other diseases of the respiratory system	1.16	
537	Other disorders of stomach and duodenum	2.91	Isolated coding pattern
781	Symptoms involving nervous and musculoskeletal	1.57	Isolated coding pattern
796	Other nonspecific abnormal findings	2.32	
867	Injury to pelvic organs	1.48	
876	Open wound of back	1.34	
884	Multiple and unspecified open wound of upper limb	1.79	
894	Multiple and unspecified open wound of lower limb	3.58	
895	Traumatic amputation of toe(s) (complete) (partial)	1.93	
897	Traumatic amputation of leg(s) (complete) (partial)	1.58	
903	Injury of blood vessels of upper extremity	1.72	
991	Effects of reduced temperature	1.16	
999	Complications of medical care, not elsewhere classified	2.02	

1. Comment provided when patterns in the data may be relevant to interpreting results.

2. Isolated coding pattern: Clustering of cases of infrequently used diagnoses.

Table 4. Incident visit diagnoses with rate ratios above 1.0, U.S. Armed Forces, 1998-2000

ICD-9-CM Code(s)	Description	Adjusted rate ratio	Comment ¹
001	Cholera	4.56	Isolated coding pattern ²
002	Typhoid and paratyphoid fevers	21.68	Isolated coding pattern
010	Primary tuberculous infection	1.53	Isolated coding pattern
022	Anthrax	90.33	Isolated coding pattern
036	Meningococcal infection	2.10	Isolated coding pattern
062	Mosquito-borne viral encephalitis	1.39	Isolated coding pattern
084	Malaria	1.52	Associated with service in Korea
182	Malignant neoplasm of body of uterus	4.23	Isolated coding pattern
199	Malignant neoplasm without specification of site	1.67	
215	Other benign neoplasm of connective tissue	1.13	
229	Benign neoplasm of other and unspecified sites	1.57	
261	Nutritional marasmus	4.48	
266	Deficiency of B-complex components	1.67	Isolated coding pattern
388	Other disorders of ear	1.09	Noise induced hearing loss
429	Ill-defined descriptions of heart disease	1.32	Isolated coding pattern
519	Other diseases of the respiratory system	1.19	
537	Other disorders of stomach and duodenum	3.17	Isolated coding pattern
605	Redundant prepuce and phimosis (males only)	1.19	Isolated coding pattern
629	Other disorders of female genital organs	4.00	Isolated coding pattern
781	Symptoms involving nervous and musculoskeletal	1.36	Isolated coding pattern
796	Other nonspecific abnormal findings	2.48	
876	Open wound of back	1.33	
884	Multiple and unspecified open wound of upper limb	1.66	
894	Multiple and unspecified open wound of lower limb	3.45	
903	Injury of blood vessels of upper extremity	1.64	
991	Effects of reduced temperature	1.34	
999	Complications of medical care, not elsewhere classified	2.54	

1. Comment provided when patterns in the data may be relevant to interpreting results.

2. Isolated coding pattern: Clustering of cases of infrequently used diagnoses.