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Comprehensive systematic surveillance for adverse effects of Anthrax Vaccine Adsorbed, US Armed Forces, 1998–2000

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Abstract

Routine vaccinations of US military personnel with Anthrax Vaccine Adsorbed began in 1998. To systematically identify clinical diagnoses reported more frequently after vaccination than before, all military personnel were retrospectively assigned to pre- or post-vaccination cohorts. Cohort assignments were based on vaccination statuses each day of the 3-year surveillance period. For each cohort, rates of hospitalizations and ambulatory visits for 843 specific diagnoses were calculated using data in a public health surveillance system. Compared to the pre-vaccination cohort, the post-vaccination cohort had statistically higher rates of hospitalizations for 17 diagnoses, of ambulatory visits for 34 diagnoses, and in both clinical settings for one diagnosis (malaria). After accounting for systematic differences in coding/reporting and residual confounding, the number and nature of clinical diagnoses more frequent after anthrax vaccination than before were consistent with expectations due to random variation. This surveillance suggests that Anthrax Vaccine Adsorbed has few, if any, clinically significant adverse effects.

Keywords: Surveillance; Anthrax vaccine; Safety

1. Introduction

Inhalational anthrax is the highly lethal clinical expression of infection of the respiratory tract with *Bacillus anthracis* [1–5]. Because its spores are relatively easy to grow, store, and aerosolize, *B. anthracis* is a leading choice for use in biological weapons [1–4,6–10]. To enhance national security and to protect the health of its servicemembers, the US Department of Defense (DoD) began a program in 1998 to vaccinate all members of the US Armed Forces with Anthrax Vaccine Adsorbed, the only vaccine currently licensed for use in humans [11,12].

The safety of the anthrax vaccine has received significant public and scientific attention [5,13–16]. Studies done prior to the vaccine's licensure in 1970 revealed that the types and frequencies of side effects were comparable to those of many other licensed vaccines [5,13,17,18]. However, pre-licensing studies, which typically monitor a relatively small number of volunteers for short periods, may not be able to detect rare adverse effects, may not predict adverse effects in demographically diverse populations, and may fail to identify adverse effects with long latency periods [19,20]. No significant adverse effects have been identified since the vaccine was licensed [5,13,18,21].

The Vaccine Adverse Events Reporting System (VAERS), jointly operated by the Food and Drug Administration and the Centers for Disease Control and Prevention, is a national repository of post-licensure reports of vaccine adverse effects that are voluntarily submitted by manufactures, health care workers, patients, family members, and others [22,23]. VAERS and the DoD Anthrax Vaccine Immunization Program have received numerous reports of adverse effects temporally related to anthrax vaccinations of US servicemembers. However, VAERS has significant limitations for vaccine safety monitoring in general [20,22–26]. For example, there is an unknown and variable amount of underreporting to VAERS; thus, it is difficult to reliably measure incidence rates of vaccine-associated adverse effects. VAERS does not receive data regarding morbidity among non-vaccinated individuals; thus, rates of illnesses and injuries among vaccinated and non-vaccinated individuals from the same populations cannot be compared. Finally, the lack of standardization of reporting limits the ability of VAERS to detect and characterize rare or unusual vaccine-associated events.

The public health surveillance system that supports the US Armed Forces [27] provides a unique capability to

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systematically assess morbidity that may be related to anthrax vaccine. In the US Armed Forces, hospitalizations and ambulatory visits of all active duty servicemembers are routinely documented in standardized, automated records that are transmitted to and integrated in a centralized, comprehensive public health surveillance database. In the database, records that document the natures, dates, and locations of nearly all medical encounters of all active duty servicemembers are linked to records that document, for example, demographic characteristics, military experiences, and dates and locations of anthrax vaccinations. In turn, the clinical experiences of all recipients of anthrax vaccine can be compared with the contemporaneous experiences of all non-recipients in the same population.

For this report, we examined all clinical encounters of all active duty servicemembers in US military hospitals and clinics during a 3-year surveillance period to identify diagnoses that were more frequent after vaccination than before. Diagnoses that were statistically significantly over represented among vaccine recipients in hospital or ambulatory settings were considered "screen positive" diagnoses. Diagnoses that were screen positive in each clinical setting were compared with each other and to adverse effects that were anecdotally reported to VAERS and/or to the Department of Defense Anthrax Vaccine Immunization Program. The results were assessed with consideration of known and suspected determinants of "false screen positive" diagnoses.

2. Methods

2.1. Data sources

The Defense Medical Surveillance System (DMSS) [27] was the source of all data used for this surveillance. Records in the DMSS document demographic characteristics and military experiences of all individuals on active duty in the US Armed Forces (since 1990); all hospitalizations (since 1990) and ambulatory visits (since 1997) of active duty servicemembers in fixed US military medical facilities worldwide; and all injections (since 1998) of Anthrax Vaccine Adsorbed. The quality of the hospitalization data is comparable to that of other large health services databases (e.g. Health Care Financing Administration, large insurers) [28].

2.2. Surveillance period and population base

All individuals who served on active duty in the US Armed Forces at any time between January 1, 1998 and December 31, 2000, were included in the surveillance. Follow-up of each servicemember began either at the start of the surveillance period or upon his/her entry into active military service (whichever was later) and ended either at the end of the surveillance period or upon his/her termination of active military service (whichever was earlier).

2.3. Pre- and post-vaccination cohorts

Servicemembers were sorted into pre- and post-vaccination cohorts based on their vaccination statuses each day of the 3-year surveillance period. Individuals transitioned from the pre-vaccination to the post-vaccination cohort on the days they received their first injections of anthrax vaccine.

2.4. Clinical outcomes

For each hospitalization and ambulatory clinic visit in a fixed US military hospital or ambulatory clinic, a diagnosis indicating the primary reason for the encounter is routinely recorded using codes of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). For this surveillance, we examined all three-digit level diagnoses included in 14 of the 17 major diagnostic categories of the ICD-9-CM. The major diagnostic categories that were excluded were "complications of pregnancy, childbirth, and the puerperium" (ICD-9-CM codes: 630–676), "congenital anomalies" (ICD-9-CM codes: 740–759) and "factors influencing health status and contact with health services" (ICD-9-CM codes: V01–V82). Diagnoses in the "diseases of the genitourinary system" category were analyzed separately among males and females.

2.5. Data analysis

Rates of hospitalizations and ambulatory visits for 843 separate illness and injury diagnoses were calculated for each cohort. Rate ratios were used to compare rates of hospitalizations and ambulatory visits between the cohorts. Rate ratios were adjusted using Poisson regression models (PROC GENMOD, SAS®, SAS Institute, Cary, NC) with up to 11 covariates. The covariates were: age, gender, race/ethnicity, military grade, calendar time, military hospitalization prior to the study, military occupation category, trainee status, deployment in Bosnia or Southwest Asia, and assignment within the continental United States. The analysis accounted for all changes in covariate-specific exposure statuses during the surveillance period.

A parsimonious model was developed for each diagnosis in each clinical setting to enhance data dispersion, model fit, and the validity of confidence interval estimation. Each model was fit by examining the relationship of each covariate along with vaccination status to each diagnosis in each clinical setting. Covariates that were significantly related (χ^2 P-value < 0.1) to each diagnosis in each setting were included along with vaccination status in the final regression model for that outcome in that setting. In each clinical setting, multivariate models were not developed for diagnoses that were reported fewer than five times in either cohort.

2.6. Previously reported adverse effects

Since the program began, adverse events associated with anthrax vaccination were reported to the VAERS [29] and/or

the Department of Defense Anthrax Vaccine Immunization Program [30]. From these sources, a list was created of possible adverse effects that were clinically significant and could be described by three-digit ICD-9-CM codes. This list contained 40 diagnosis-specific ICD-9-CM codes.

2.7. Assessments of screen positive diagnoses

Clinical outcomes that were statistically significantly (95% confidence intervals excluding 1.0) over represented in the post-vaccination cohort relative to the pre-vaccination cohort were considered "screen positive" diagnoses. For each screen positive diagnosis, we examined the locations and timing of all reports of the diagnosis in both clinical settings. We attempted to identify significant regional differences in the proportions of cases hospitalized versus managed as outpatients (e.g. differences in hospital utilization in the US versus overseas) and unusual uses of specific diagnoses from specific locations (e.g. aberrant coding and/or miscoding of diagnoses).

3. Results

3.1. Population base

During the surveillance period, approximately 2.0 million individuals were followed for 4,106,512 person-years of active military service. During follow-up, approximately 23% (n = 454,145) of all servicemembers received at least one dose of anthrax vaccine, and approximately 18% (n = 738,382 person-years) of total follow-up time was after an initial anthrax vaccine dose (post-immunization) (Table 1).

Table 1
Demographic and military characteristics of individuals included in surveillance, active duty members, US Armed Forces, 1998–2000

Characteristic	Percent (of person-years)	
	Pre-immunization cohort	Post-immunization cohort
Age (years)		
18–24	39.0	40.6
25–34	36.3	37.6
35–65	24.8	21.8
Deployment status		
No	99.0	97.3
Yes	1.0	2.7
Grade		
Enlisted	83.3	86.9
Officer	16.7	13.1
Initial training period (first 6 months of service)		
No	92.1	99.5
Yes	7.9	0.5
Race/ethnicity		
Other	33.5	35.4
White	66.5	64.6
Service		
Army	34.8	33.4
Air Force	26.2	25.6
Marine Corps	11.3	17.9
Navy	27.7	23.1
Gender		
Female	15.1	10.0
Male	84.9	90.0
Previous hospitalization (in military)		
No	96.9	96.0
Yes	3.1	4.0
Residence		
In the US	77.8	65.8
Outside the US	22.2	34.2
Period of observation		
January 1998–June 1999	55.6	25.8
July 1999–December 2000	44.4	74.2
Military occupation group		
Combat	19.8	25.6
Medical	9.2	4.6
Other	71.0	69.8

Number of individuals: pre-immunization 2,013,179; post-immunization 454,145. Doses of Anthrax Vaccine Adsorbed: pre-immunization 0; post-immunization 1,845,374. Observation time: pre-immunization 3,368,130 person-years; post-immunization 738,382 person-years.

3.2. Frequencies and crude rates of medical encounters

During follow-up, there were 136,314 hospitalizations and 15,465,744 ambulatory visits of US servicemembers. Overall, hospitalization and ambulatory visit rates were higher in the pre-immunization than the post-immunization cohort (crude hospitalization rate, pre-immunization: 33.7 per 1000 person-years [p-yrs]; post-immunization: 27.4 per 1000 p-yrs; hospitalization rate ratio, pre:post-immunization:1.23; crude ambulatory visit rate, pre-immunization: 3900 per 1000 p-yrs; post-immunization: 2753 per 1000 p-yrs; ambulatory visit rate ratio, pre:post-immunization: 1.42). In addition, in every major diagnostic category, rates of hospitalizations and ambulatory visits were higher in the pre-immunization than the post-immunization cohort (data not shown).

3.3. Hospitalizations

Multivariate models were not developed for 445 diagnoses that accounted for fewer than five hospitalizations each in one or both cohorts. For 17 (4.3%) of the 398 diagnoses for which multivariate models were developed, adjusted hospitalization rates were statistically significantly higher in the post-immunization relative to the pre-immunization cohort (Table 2). Thirteen screen positive diagnoses could be attributed, at least in part, to regional differences in hospital utilization practices; for these diagnoses, individuals were much more likely to be hospitalized if they were diagnosed outside the US. One screen positive

Table 2
Hospitalization diagnoses with rate ratios statistically significantly above 1.0, post-immunization vs. pre-immunization, active duty members, US Armed Forces, 1998–2000

ICD-9-CM code(s)	Description	Anthrax immunization status				Adjusted rate ratio (post:pre)	95% Confidence interval	Comment
		Post-immunization		Pre-immunization				
		Number	Rate per 100,000	Number	Rate per 100,000			
084	Malaria	67	8.8	82	2.4	2.88	2.04–4.05	1
110	Dermatophytosis	5	0.7	10	0.3	4.54	1.24–16.65	2
217	Benign neoplasm of breast	19	2.5	13	0.4	8.92	4.06–19.60	2
233	Carcinoma in situ of breast and genitourinary system	19	2.5	38	1.1	3.58	1.98–6.47	2
354	Mononeuritis of upper limb and mononeuritis multiplex	57	7.5	169	4.9	1.61	1.18–2.21	
374	Other disorders of eyelids	16	2.1	56	1.6	2.16	1.19–3.90	2
377	Disorders of optic nerve and visual pathways	22	2.9	33	1.0	2.74	1.56–4.80	2
454	Varicose veins of lower extremities	34	4.5	93	2.7	1.66	1.09–2.51	2
470	Deviated nasal septum	128	16.9	325	9.5	1.52	1.23–1.87	2
541	Appendicitis, unqualified	95	12.5	312	9.1	1.38	1.09–1.74	2
550	Inguinal hernia	321	42.4	988	28.8	1.45	1.27–1.66	2
603	Hydrocele	28	4.1	43	1.5	2.83	1.71–4.68	2
610	Benign mammary dysplasias	13	17.0	12	2.3	4.96	2.23–11.05	2
622	Non-inflammatory disorders of cervix	77	100.5	75	14.5	5.37	3.81–7.57	2
732	Osteochondropathies	41	5.4	111	3.2	1.45	1.01–2.09	
735	Acquired deformities of toe	117	15.4	247	7.2	1.86	1.48–2.32	2
983	Toxic effect of corrosive aromatics, acids, and caustic alkalis	7	0.9	14	0.4	2.76	1.06–7.15	

Comment (1): associated with service in Korea; comment (2): more likely to be hospitalized if diagnosed overseas than in US.

Table 3
Ambulatory visit diagnoses with rate ratios statistically significantly above 1.0, post-immunization vs. pre-immunization, active duty members, US Armed Forces, 1998–2000

ICD-9-CM code(s)	Description	Anthrax immunization status				Adjusted rate ratio (post:pre)	95% Confidence interval	Comment
		Post-immunization		Pre-immunization				
		Number	Rate per 100,000	Number	Rate per 100,000			
001	Cholera	81	10.7	41	1.2	4.67	3.13–6.99	2
002	Typhoid and paratyphoid fevers	376	49.6	128	3.7	25.68	20.86–31.61	2
010	Primary tuberculous infection	180	23.8	804	23.4	1.72	1.45–2.04	2
022	Anthrax	7,771	1025.8	623	18.2	109.50	100.67–119.11	2
062	Mosquito-borne viral encephalitis	85	11.2	192	5.6	1.59	1.23–2.07	2
084	Malaria	241	31.8	660	19.2	1.46	1.25–1.71	1
142	Malignant neoplasm of major salivary glands	120	15.8	397	11.6	1.56	1.26–1.93	
156	Malignant neoplasm of gallbladder and extrahepatic bile ducts	38	5.0	54	1.6	2.92	1.90–4.50	
179	Malignant neoplasm of uterus, part unspecified	9	1.2	41	1.2	4.42	1.99–9.79	2
182	Malignant neoplasm of body of uterus	67	8.8	110	3.2	4.16	3.04–5.69	
184	Malignant neoplasm of other and unspecified female genital organs	43	5.7	78	2.3	3.76	2.54–5.57	
199	Malignant neoplasm without specification of site	615	81.2	2,557	74.5	1.19	1.09–1.31	
229	Benign neoplasm of other and unspecified sites	673	88.8	2,276	66.3	1.60	1.46–1.76	
261	Nutritional marasmus	6	0.8	7	0.2	4.36	1.46–13.05	
266	Deficiency of B-complex components	202	26.7	954	27.8	1.21	1.04–1.42	2
302	Sexual deviations and disorders	944	124.6	4,200	122.4	1.09	1.02–1.18	
388	Other disorders of ear (noise induced hearing loss)	6,554	865.2	27,959	815.0	1.07	1.04–1.10	
415	Acute pulmonary heart disease	215	28.4	817	23.8	1.24	1.06–1.45	
429	Ill-defined descriptions and complications of heart disease	948	125.1	4,814	140.3	1.35	1.26–1.46	2
435	Transcient cerebral ischemia	490	64.7	2,640	77.0	1.16	1.05–1.28	
452	Portal vein thrombosis	14	1.8	16	0.5	3.15	1.51–6.60	
519	Other diseases of respiratory system	2,154	284.3	9,738	283.9	1.16	1.10–1.21	
537	Other disorders of stomach and duodenum	472	62.3	913	26.6	2.91	2.58–3.28	2
781	Symptoms involving nervous and musculoskeletal systems	3,131	413.3	6,736	196.4	1.57	1.50–1.65	2
796	Other non-specific abnormal findings	13,597	1794.9	24,981	728.2	2.32	2.26–2.37	
867	Injury to pelvic organs	54	7.1	179	5.2	1.48	1.08–2.02	
876	Open wound of back	77	10.2	260	7.6	1.34	1.03–1.75	
884	Multiple and unspecified open wound of upper limb	2,007	264.9	4,764	138.9	1.79	1.69–1.89	
894	Multiple and unspecified open wound of lower limb	2,104	277.7	2,188	63.8	3.58	3.36–3.82	
895	Traumatic amputation of toe(s) (complete) (partial)	35	4.6	75	2.2	1.93	1.27–2.93	
897	Traumatic amputation of leg(s) (complete) (partial)	72	9.5	230	6.7	1.58	1.20–2.08	
903	Injury to blood vessels of upper extremity	83	11.0	146	4.3	1.72	1.29–2.28	
991	Effects of reduced temperature	439	58.0	2,011	58.6	1.16	1.04–1.30	
999	Complications of medical care, not elsewhere classified	716	94.5	2,568	74.9	2.02	1.85–2.20	

Comment (1): associated with service in Korea; comment (2): isolated coding/reporting: clustering of reports of ICD-9-CM code.

diagnosis—malaria—was strongly associated with assignment to Korea, a malaria endemic region.

3.4. Ambulatory visits

Multivariate models were not developed for 93 diagnoses that accounted for fewer than five ambulatory visits each in one or both cohorts. For 34 (4.5%) of the 750 diagnoses for which multivariate models were developed, adjusted ambulatory visit rates were statistically significantly higher in the post-immunization relative to the pre-immunization cohort (Table 3). Isolated coding patterns (i.e. discrete clusters of infrequently used ICD-9-CM codes) accounted for some, if not all, of the excess visits for 10 of the screen positive diagnoses. Again, one screen positive diagnosis—malaria—was strongly associated with assignment to Korea.

3.5. Relationship between screen positive diagnoses in the hospital and ambulatory settings

Malaria was the only diagnosis that was screen positive in both the hospital and ambulatory clinic settings (Tables 2 and 3).

3.6. Previously reported adverse events

Of 40 diagnoses that had been reported as potential adverse effects of vaccination, none was associated with a significantly higher rate of hospitalizations and one (ICD-9-CM code: 429: ill-defined descriptions and complications of heart disease) was reported at a significantly higher rate in the ambulatory setting in the post-immunization relative to the pre-immunization cohort (Table 4). A single installation accounted for 63% of all outpatient diagnoses of "ill-defined descriptions and complications of heart disease" in 1998–1999—but only 2% in 2000. Of note, the same installation accounted for 58% of all outpatient reports of this diagnosis in 1997, the year before the start of the DoD Anthrax Immunization Program.

4. Discussion

Our general approach to this surveillance was to compare the complete spectrums of morbidity that affected all immunized and unimmunized members of the US Armed Forces during contemporaneous periods of follow-up. Specifically, in both the hospital and ambulatory settings, we classified diagnoses as "screen positive" if their post- to pre-immunization adjusted relative rates statistically significantly exceeded 1.0. We then compared screen positive diagnoses in each clinical setting to potential adverse effects that had been reported through other monitoring systems. After we considered the likely effects of other sources of screen positive diagnoses (i.e. systematic error, residual confounding, random variation), we concluded that there were few if any significant adverse effects of anthrax vaccination among US servicemembers.

Our approach was based on the assumption that adverse effects of vaccination would increase the rates of "indicator" conditions among vaccinees (relative to the rates of the same conditions during the same periods among non-vaccinees). Over time, indicator conditions would emerge in our analyses as screen positive diagnoses—and as such, they would be detectable "signals" of vaccine adverse effects.

Unfortunately, however, screen positive diagnoses include not only "true positive" signals of vaccine adverse effects but also "false positive" signals. In turn, "false positive" signals result from systematic misclassifications of exposure and outcome states, uncontrolled (residual) confounding, and random variation of rates of illnesses and injuries over time. Interpretations of the results of our analyses must account for the likely effects of these determinants of "false positive" signals.

In this analysis, misclassifications of exposure (e.g. immunization status) and outcome (e.g. medical encounters, diagnoses) states undoubtedly accounted for several false positive signals of vaccine adverse effects. In a database of the nature, size, and scope of the Defense Medical Surveillance System, misclassifications of exposures and/or outcomes are inevitable due to system limitations, administrative errors, and individual oversights. For example, servicemembers who received anthrax immunizations prior to the start of the DoD Anthrax Immunization Program were misclassified as "pre-immunization" until they were immunized during the study period. Also, in rare instances, immunizations (e.g. anthrax, typhoid) and diagnostic procedures (e.g. TB skin tests) for specific diseases were reported using codes for the diseases themselves (e.g. anthrax, typhoid, tuberculosis).

Residual confounding was a second source of false positive signals. Through multivariate analyses, we attempted to control for the most significant differences between the immunized and unimmunized cohorts. However, there were some unaccounted for (residual) differences between the cohorts that were undoubtedly confounding. For example, in general, servicemembers who are immunized are healthier than those who are not (e.g. due to medical exemptions); servicemembers who deploy or are assigned overseas are healthier than their counterparts who are ineligible (often for medical reasons) for such assignments [31–34]; and medical encounters in treatment facilities on permanent military installations are more completely ascertained than those onboard ships or in deployed clinics and hospitals. Finally, there are regional, local, and assignment-related differences in endemic disease and injury hazards, in access to and utilization practices regarding health care resources (e.g. inpatient versus outpatient care for similar conditions), and in the natures, durations, and intensities of military and off-duty activities.

In addition, during the surveillance period, anthrax immunizations were required before assignments to certain

Table 4
For anecdotally reported adverse events associated with anthrax immunization, crude and adjusted rates of hospitalizations and ambulatory visits among active duty members, US Armed Forces, 1998–2000

ICD-9-CM code(s)	Diagnosis	Hospitalizations			Ambulatory visits		
		Crude rate (per 100,000 person-years)		Adjusted rate ratio (post:pre)	Crude rate (per 100,000 person-years)		Adjusted rate ratio (post:pre)
		Post	Pre		Post	Pre	
047	Meningitis due to enterovirus	11.1	16.3	0.71	11.6	20.1	0.61
204	Lymphoid leukemia	0.7	1.0	0.57	38.7	39.6	0.96
205	Myeloid leukemia	0.9	1.4	0.59	21.0	35.9	0.58
206	Monocytic leukemia	–	0.1	–	–	0.5	–
207	Other specified leukemia	–	0.0	–	–	0.2	–
208	Leukemia of unspecified cell type	0.1	0.3	–	4.8	7.8	0.57
240	Simple and unspecified goiter	0.4	0.4	–	22.6	34.9	0.76
241	Non-toxic nodular goiter	3.4	3.9	1.13	76.8	128.1	0.75
242	Thyrotoxicosis with or without goiter	1.8	3.8	0.52	167.8	276.3	0.75
244	Acquired hypothyroidism	0.1	0.3	–	450.5	666.8	0.81
245	Thyroiditis	0.3	0.8	–	24.0	50.8	0.63
246	Other disorders of thyroid	0.4	0.4	–	67.2	76.3	0.96
250	Diabetes mellitus	9.0	13.3	0.64	612.2	1,085.9	0.63
296	Affective psychoses	83.7	120.5	0.70	2,236.6	4,193.1	0.67
340	Multiple sclerosis	4.4	3.0	1.30	71.4	125.6	0.62
357	Inflammatory and toxic neuropathy[a]	1.7	2.7	0.69	49.8	61.3	0.88
410	Acute myocardial infarction	9.5	11.3	0.99	9.4	23.1	0.57
411	Other acute ischemic heart disease	5.1	6.2	1.00	11.1	15.3	0.78
413	Angina pectoris	1.6	2.1	0.73	35.8	55.4	0.74
414	Other chronic ischemic heart disease	13.2	17.4	0.97	143.1	327.9	0.58
420	Acute pericarditis	2.4	2.0	1.15	12.1	13.9	0.73
421	Acute and subacute endocarditis	0.3	0.6	–	3.3	3.8	0.73
422	Acute myocarditis	0.5	0.5	–	1.1	0.9	0.75
423	Other diseases of pericardium	2.1	2.8	0.73	13.1	22.2	0.68
424	Other diseases of endocardium	2.8	3.5	0.78	89.4	161.1	0.73
425	Cardiomyopathy	1.5	2.3	0.60	33.7	56.6	0.63
426	Conduction disorders	4.0	4.5	0.95	28.0	44.2	0.68
427	Cardiac dysrhythmias	23.1	29.5	0.78	300.8	480.9	0.72
428	Heart failure	0.4	1.0	–	13.9	22.8	0.69
429	Ill-defined descriptions of heart disease	1.6	1.9	0.78	125.1	140.3	1.35[b]
695	Erythematous conditions	1.5	0.9	1.66	156.0	245.9	0.86
710	Diffuse diseases of connective tissue[c]	1.7	1.8	1.15	76.3	153.5	0.63
711	Arthropathy associated with infections	3.7	5.1	0.63	34.8	40.3	0.78
712	Crystal arthropathies	–	–	–	5.8	5.6	0.73
713	Arthropathy with other disorders	–	–	–	2.9	2.8	0.82
714	Rheumatoid arthritis	0.9	0.6	1.46	129.9	202.8	0.76
715	Osteoarthrosis and allied disorders	12.7	17.8	0.72	1,224.6	1,594.7	0.83
716	Other and unspecified arthropathies	3.2	3.7	0.90	623.3	664.6	0.97
719	Other and unspecified disorder of joint	15.0	17.6	0.74	15,740.9	21,697.9	0.81
785	Symptoms of cardiovascular system	5.4	5.2	0.95	701.5	1,118.7	0.78

[a] Includes Guillain–Barre syndrome and inflammatory demyelinating diseases.
[b] Statistically significant: adjusted rate ratio > 1.0 with $\alpha < 0.05$.
[c] Includes systemic lupus erythematosis.

relatively "high risk" regions, locations, and military units. Thus, some diagnoses may have been screen positive because of risks or health care practices inherent to certain assignments—rather than adverse effects related to pre-assignment immunizations. In this analysis, for example, malaria was the only diagnosis that was screen positive in both the inpatient and outpatient settings. Malaria is endemic in Korea, more than half of all cases acquired in Korea have delayed (months to years) clinical manifestations, and most cases with long incubation periods present during subsequent assignments outside of Korea [35,36]. Because US servicemembers received anthrax immunizations prior to Korea assignments, the strong association between anthrax vaccination and subsequent malaria was almost certainly due to confounding.

In the hospital setting, 17 (4.3%) of 398 diagnoses that were included in the final analyses were screen positive. Fourteen screen positive diagnoses could be related to regional differences in hospital utilization practices or to a region-specific risk (Table 2). Thus, only three screen positive diagnoses (0.8% of the total screened) could not be attributed to a specific source of confounding.

In the outpatient setting, 34 (4.5%) of 755 diagnoses that were included in the final analyses were screen positive. Ten screen positive diagnoses were related to isolated coding patterns, and one was attributable to a region-specific risk (Table 3). Thus, 23 screen positive diagnoses (3.0% of the total screened) could not be attributed to misclassification or residual confounding.

Random variation of rates over time was the final determinant of false positive signals. During any given period of time, identical cohorts will have different rates of many illnesses and injuries; and by chance alone, some of the differences in rates will be nominally statistically significant. Given the screening cutpoint we used, we anticipated that approximately 2.5% of all diagnoses would be screen positive by chance (i.e. approximately 10 in the hospital setting and 19 in the outpatient setting). We also expected that the diagnoses that were screen positive by chance would be different in the inpatient and outpatient settings. In fact, the screen positive diagnoses that could not be attributed to misclassifications or residual confounding were approximately equal to the numbers anticipated; also, as expected, they were different in the inpatient and outpatient settings. Overall, the findings suggest that few (if any) screen positive diagnoses were true positive signals of adverse effects of anthrax vaccination.

Finally, our results provide little evidence that any of 40 diagnoses that had been reported as potential clinically significant adverse effects of vaccination were true adverse effects. Of the 40 diagnoses we examined, none accounted for significantly higher rates of hospitalizations and only one was associated with a significant excess of ambulatory visits in the immunized versus unimmunized cohort (Table 4). The aberrant use of ICD-9-CM code 429 (ill-defined descriptions and complications of heart disease) at a single installation during the first 2 years of the surveillance period accounted for excess ambulatory visits for that diagnosis among vaccine recipients overall. It is likely, therefore, that this screen positive diagnosis was a false positive signal. The overall lack of correspondence between previously reported adverse effects and screen positive diagnoses in either clinical setting suggests that most (if not all) of anecdotally reported adverse events either occurred among vaccinees at rates consistent with background rates, did not result in hospitalizations or clinic visits, were reported with ICD-9-CM codes that were not included in our "sentinel" list, or were rare (idiosyncratic) reactions.

Comprehensive systematic screening of diagnosis-specific adjusted relative rates is intended to identify relatively extreme statistical relationships between post-immunization status and specific diagnoses. To this end, we used a nominal *P*-value as a cutpoint to identify a group of diagnoses that would be likely to include significant adverse effects, if any existed. The screening is neither intended to nor is it capable of assessing causality. Assessments of causality require information more detailed than that routinely collected for medical surveillance purposes and analysis methods that consider, for example, biological plausibility, specific temporal relationships, medical histories, comorbidities, behavioral and other illness and injury risk factors, concurrent vaccinations, and variations in health care access, usage, and reporting. Until detailed investigations of nominally significant associations are completed, screen positive diagnoses should not be considered vaccine adverse effects [37,38].

In summary, despite the limitations of our analyses, the results together with those of other monitoring efforts [5,30,31,38] (such as VAERS) provide unprecedented oversight of the safety of the anthrax vaccination program. Results of surveillance efforts to date suggest that Anthrax Vaccine Adsorbed has few if any significant adverse health effects.

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