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Research Paper

Military Hospitalizations Among Deployed US Service Members Following Anthrax Vaccination, 1998–2001

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ABSTRACT

Safety concerns have confronted the Department of Defense Anthrax Vaccine Immunization Program since inception in 1998. To determine if anthrax vaccination was associated with an increased risk of hospitalization, a historical cohort study utilizing pre- and post-anthrax-vaccination hospitalizations was undertaken and analyzed with Cox proportional hazards models. The study population consisted of 170,723 active duty US service members who were anthrax-vaccinated and deployed during the time period January 1, 1998 to December 31, 2001. Study outcomes included hospitalizations due to any-cause, 14 broad *International Classification of Diseases* diagnostic categories, autoimmune organ specific and organ non-specific hospitalizations, and asthma. After adjustment, anthrax vaccination was associated with significantly fewer hospitalizations for any-cause, diseases of the blood and blood forming organs, and diseases of the respiratory system. Comparing anthrax post-vaccination hospitalization experience with the pre-vaccination period resulted in no significant increased hazard for any of the hospitalization outcomes studied. Although there was no apparent increase in risk of morbidity in this study population, the relationship between anthrax vaccine and deployment on health outcomes among US service members needs further study.

The history and rationale behind the development of the Department of Defense (DoD) Anthrax Vaccine Immunization Program has been previously documented.[1] Since inception, this vaccine program has been surrounded by controversy, including service members who have expressed health concerns over receiving the vaccine, lapses in vaccine production, and court-ordered injunctions.[2-5]

Between May 2000 and September 2000 the US General Accounting Office conducted a stratified random survey of 1,253 Air National Guard and Air Force Reserve personnel who were currently serving or had separated.[6] Sixty-five percent of subjects responded and 41% were skeptical of the DoD biological warfare threat assessment. More than 60% were concerned about short-term and long-term health events associated with anthrax vaccination. Some researchers and members of the media have hypothesized a causal link between the anthrax vaccine and symptoms related to Gulf War service.[7,8] Case reports have identified temporal associations between anthrax vaccination and delayed-type hypersensitivity reaction,[9] hypersensitivity pneumonitis,[10] optic neuritis,[11] and pemphigus vulgaris.[12]

In response to growing concerns regarding the safety of the anthrax vaccine, a number of epidemiological studies were conducted. A review of 1,841 Vaccine Adverse Event Reporting System reports, submitted between 1998 and 2001 for adverse events associated with anthrax vaccine, found no evidence of an unusually high rate for serious adverse events or other medically important adverse events.[13] A study utilizing pre- and post-anthrax vaccination cohorts to calculate adjusted rates for over 843 specific diagnoses found positive associations, but after accounting for multiple comparisons and the potential for misclassifications, it was concluded that anthrax vaccine has few clinically significant adverse effects.[14] Using preliminary (1998) data from this study, Sato et al. assessed the relations between 14 broad categories of hospital discharge diagnoses and anthrax vaccination using Cox proportional hazards modeling and found that anthrax-vaccinated, active-duty service members were at equal or less risk of hospitalization.[15] A cohort of anthrax vaccinated active-duty health care professionals was followed 1-2 weeks post-vaccination. They also were assessed via two nested designs that used either self-reported survey data or rates from outpatient visits and hospitalizations. The authors noted that although the vaccine was considerably reactogenic, very few serious adverse events were observed.[16] A study of 1,600 scientists and maintenance workers who had received a total of 10,722 anthrax vaccine doses reported incidence rates of approximately 1% and 4% for systemic and local

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adverse events, respectively.[17] A study of US Air Force service members who had been deployed to Southwest Asia found no increase in ambulatory medical visits among anthrax vaccinees.[18] Similarly, a study of anthrax-vaccinated individuals among the Canadian military found no increased risk for medical visits within eight months of vaccination.[19] A large historical cohort study of active-duty US Army personnel found no relationship to disability evaluations.[20] Finally, the Institute of Medicine reviewed the scientific literature on the safety and efficacy of the anthrax vaccine and determined it was effective and "reasonably safe".[21] The objective of our study was to compare the adjusted risk of hospitalization among pre- and post-anthrax-vaccinated and deployed US service members who had served on active duty between 1998 and 2001.

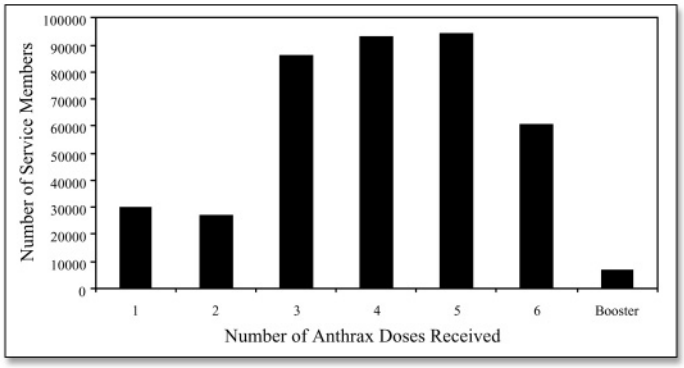

Figure 1. Distribution of the number of anthrax doses received among anthrax-vaccinated US service members serving on active duty 1998-2001.

METHODS

Data. Methods used to assemble the analytic cohort were previously described.[15] A historical cohort design was used to gather electronically available demographic, military-specific, and health outcomes data. Demographic data were obtained from the Defense Manpower Data Center, and anthrax vaccination status was obtained from the Defense Enrollment Eligibility Reporting System. Hospital discharge diagnoses assigning an *International Classification of Diseases*, Ninth Revision, Clinical Modifications (ICD-9-CM) code were obtained from the Standard Inpatient Data Record and the Health Care Service Record. All files were obtained in electronic format and were linked by personal identifiers.

Study population. All US service members who had served on active duty a minimum of 30 consecutive days or longer between January 1, 1998, and December 31, 2001, were identified and described. However, to account for unmeasured confounding, and to decrease heterogeneity among subjects, the analytic cohort was restricted to those service members who had received one or more anthrax vaccinations and had been deployed to high-threat areas, such as southwest Asia and received one or more pay entitlements. Months deployed was estimated based on the number of months these entitlements were received.

Outcomes. The objective of this study was to identify any yet-to-be-known severe adverse health effects, excluding mortality and pregnancy-related outcomes, associated with anthrax vaccination. Outcomes were limited to hospitalizations to focus on severe morbidity and to minimize possible misclassification associated with ambulatory diagnoses or self-reported morbidity. A priori outcomes included any-cause hospitalization, hospitalizations among 14 broad ICD-9-CM categories as described by Sato et al.,[15] autoimmune organ-specific or organ-non-specific disease hospitalizations,[22] and specific diagnoses thought to possibly manifest from vaccine exposure.[9-12]

Statistical analyses. Pearson chi-square tests and t tests were used to calculate univariate measures of association for demographic and military-specific variables. Those variables significant at $p \leq 0.15$ were entered into a post-vaccination versus pre-vaccination multivariable Cox proportional hazards model. Post-vaccination person-time was calculated by cumulating successive 42-day risk windows following each recorded anthrax dose. For example, if the member remained on the correct dosing schedule, he or she would remain under constant observation until 42 days after the third dose. Post-vaccination person-time began on the day vaccinated and continued until whichever of the following occurred first: (1) the date of first admission, (2) the date of separation from the military, (3) 42 days after date vaccinated, or (4) the end of the study, December 31, 2001. Forty-two day observation periods were chosen as the best compromise between identifying acute outcomes that may be associated with anthrax vaccination yet preventing spurious associations simply due to temporal sequencing. Three previous studies regarding vaccine safety suggest the use of risk periods somewhere between 30-days and 6-weeks.[23-25] Pre-vaccination person-time was set at 130 days prior to first vaccination, which corresponded to the mean length of follow-up for all post-vaccination person-time. To account for the correlation between a subject's pre-vaccination and post-vaccination hospitalizations, multivariable models used a sandwich estimated covariance structure to better calculate the standard error in parameter estimates.[26] All final models were adjusted for gender, age, race/ethnicity, branch of service, rank, military occupation as specified in the DoD Occupational Conversion Index,[27] marital status, and months deployed. Reference cell coding was used to produce dummy variables for all categorical variables, and no statistical adjustments were made to account for possible spurious findings due to multiple comparisons. All multivariable analyses excluded hospitalizations as a result of complications of pregnancy, childbirth, and the puerperium (ICD-9-CM codes 630-677), congenital anomalies (740-759), and certain conditions originating in the perinatal period (760-779), which are currently being analyzed separately. Data management and statistical analyses were performed using SAS® Version 9.0 (SAS Institute, Cary, NC).

RESULTS

We identified 2,251,678 US service members who had served on active duty a minimum of 30 consecutive days or longer between January 1, 1998, and December 31, 2001. This group comprised predominantly white, non-Hispanic males aged 17–24 years. Additionally, the largest groups consisted of service members who were enlisted, members of the Army, and served as infantry, gun crews, or other combatant occupations (Table 1). Among this population, 398,464 service members had received one or more anthrax vaccinations (Fig. 1). When compared with non-anthrax-vaccinated service members, this group had disproportionately higher percentages of males, was predominantly 25–34 years of age, served in the Air Force or Marine Corps, and were married. Anthrax-vaccinated service members spent on average 3.7 times (3.13 months vs. 0.85 months) as many months deployed during the study period than did the non-anthrax-vaccinated personnel (Table 1). All differences between the frequency distribution among anthrax-vaccinated and non-anthrax-vaccinated service members were statistically significant ($p < 0.001$) using either Pearson's chi-square or t test. Regression diagnostics found no evidence of multicollinearity or violation of assumption of proportional hazards.

The cohort for multivariable modeling was restricted to those 170,723 service members who had received one or more anthrax vaccinations and had been deployed (Table 2). Compared to any-cause hospitalizations occurring prior to anthrax vaccination, the hazard for post-vaccination hospitalizations were statistically increased for women, those greater than or equal to 45 years of age, serving in the Army, enlisted, or were health care workers. Black non-Hispanic and other race/ethnicities were at significantly less risk than white non-Hispanic members. In Cox proportional hazards multivariable models that compared pre-vaccination hospital diagnoses to post-vaccination hospital diagnoses, adjusted hazard ratios (HRs) were calculated for the 14 broad categories of ICD-9-CM codes within the group of anthrax-vaccinated service members (Table 3). Statistically significant decreased hazard ratios post-vaccination were observed for any-cause hospitalization (adjusted hazard ratio [HR], 0.88; 95% confidence interval [CI],

Table 1 **Demographic and military profile of all service members serving on active duty, and meeting enrollment criteria, by vaccination status, 1998-2001**

		Anthrax vaccine	
	Total	**Vaccinated**	**Unvaccinated**
Gender*			
Female	343,906 (15.3)	42,488 (10.7)	301,418 (16.3)
Male	1,907,772 (84.7)	355,976 (89.3)	1,551,796 (83.7)
Age, y*			
17–24	862,452 (38.3)	126,708 (31.8)	735,744 (39.7)
25–34	836,070 (37.1)	176,892 (44.4)	659,178 (35.6)
35–44	444,374 (19.7)	84,953 (21.3)	359,421 (19.4)
45	108,782 (4.8)	9,911 (2.5)	98,871 (5.3)
Race/Ethnicity*			
White non-Hispanic	1,501,028 (66.7)	258,264 (64.8)	1,242,764 (67.1)
Black non-Hispanic	435,208 (19.3)	79,309 (19.9)	355,899 (19.2)
Hispanic	186,995 (8.3)	35,906 (9.0)	151,089 (8.1)
Other	128,447 (5.7)	24,985 (6.3)	103,462 (5.6)
Service*			
Army	796,660 (35.4)	127,068 (31.9)	669,592 (36.1)
Navy/Coast Guard	645,806 (28.7)	92,190 (23.1)	553,616 (29.9)
Air Force	507,343 (22.5)	108,372 (27.2)	398,971 (21.5)
Marine Corps	301,869 (13.4)	70,834 (17.8)	231,035 (12.5)
Rank*			
Enlisted	1,951,139 (86.7)	342,994 (86.1)	1,608,145 (86.8)
Officer	300,539 (13.3)	55,470 (13.9)	245,069 (13.2)
Occupational category*			
Infantry, gun crews, seamen	519,255 (23.1)	102,353 (25.7)	416,902 (22.5)
Mechanical equipment repair	368,282 (16.4)	77,509 (19.4)	290,773 (15.7)
Functional support and admin	345,164 (15.3)	60,445 (15.2)	284,719 (15.4)
Electrical repair	206,003 (9.2)	37,891 (9.5)	168,112 (9.1)
Service and supply	184,521 (8.2)	35,348 (8.9)	149,173 (8.1)
Communication/intelligence	179,850 (8.0)	33,195 (8.3)	146,655 (7.9)
Health care	163,695 (7.3)	18,449 (4.6)	145,246 (7.8)
Construction	67,359 (3.0)	12,037 (3.0)	55,322 (3.0)
Other technical and specialty	55,062 (2.5)	10,586 (2.7)	44,476 (2.4)
Other and missing	162,487 (7.2)	10,651 (2.7)	151,836 (8.1)
Marital status*			
Married	1,126,411 (50.0)	226,347 (56.8)	900,064 (48.6)
Single	1,125,267 (50.0)	172,117 (43.2)	953,150 (51.4)
Months deployed	1.26	3.13	0.85

*Tests of statistical significance for the difference between anthrax-vaccinated and non-anthrax-vaccinated service members were based on Pearson chi-square test or t test, and were <0.001. Occupational categories based on the Department of Defense *Occupational Conversion Index*.

0.81–0.97), infectious or parasitic hospitalizations (adjusted HR, 0.59; 95% CI, 0.42–0.82), as well as hospitalizations associated with the blood and blood forming organs (adjusted HR, 0.54; 95% CI, 0.33–0.87) and the respiratory and digestive systems (adjusted HR, 0.66; 95% CI, 0.50–0.87 and adjusted HR, 0.80; 95% CI, 0.66–0.97, respectively). Using the pre-vaccination versus post-vaccination Cox proportional hazards modeling, no other statistically significant associations were observed between anthrax vaccination and hospitalizations for a wide range of outcomes. Cox proportional hazards models could not be run for systemic lupus erythematosus, fibromyalgia, motor neuron disease including amyotrophic lateral sclerosis; peripheral neuropathy, hypersensitivity pneumonitis, immune pneumonitis, or myocarditis and pericarditis as there were no hospitalizations during the post-vaccination period.

DISCUSSION

This 4-year historical cohort study used a large anthrax-vaccinated deployed US military population and adjusted for multiple potentially confounding variables to compare the hazard of hospitalization using a pre-vaccination verses post-vaccination model. We report significantly decreased hazard ratios for hospitalizations due to any-cause, infectious or parasitic diseases of the blood and blood forming organs, as well as respiratory and digestive systems. Conversely, there were no significant increased hazards for any outcomes investigated.

Finding increased adjusted hazards for any-cause hospitalization among members of the Army and enlisted ranks, and decreased adjusted hazards among black non-Hispanic and others is curious, but not uncommon. Four previous studies reporting any-cause hospitalizations among US service members also found increased risk, of approximately the same magnitude, for enlisted ranks and members of the Army, but varying results for race/ethnicity.[28-31] Increased risk among Army personnel most likely represents service-specific differences in hospitalization policies. One explanation for an increased risk among enlisted is that proportionally more enlisted are young and single in comparison to officers, and a common policy within the military is to hospitalize service members who have no other caretakers, such as a spouse, if the condition warrants this level

of care. This may result in proportionally more enlisted being hospitalized for conditions of similar severity when compared to officers. A decreased hazard for any-cause hospitalization among black non-Hispanic and others can not be readily explained and may represent residual confounding.

These findings support a similar study of US Army medical personnel that found decreased, but non-significant, risk post-vaccination for hospitalizations due to any-cause and diseases of the digestive system.[16] Although it is theoretically possible for anthrax vaccination to provide a protective effect against illness, the more likely explanation is that our post-vaccination versus pre-vaccination models were slightly biased by events occurring prior to and during deployment. For example, service members who have an impending deployment may elect to undergo elective hospital procedures prior to deployment. Additionally, once deployed there is both limited access to hospitals, and electronic reporting of hospitalizations may not be as complete as for those occurring in a non-deployed setting. It may be possible in the future to better define this effect given that anthrax vaccination is currently being administered on a voluntary basis to members of the US military.[32,33] Should there be sufficient numbers of anthrax vaccinated and non-vaccinated personnel deploying to the same region, this will create a unique opportunity to study anthrax vaccinated and non-vaccinated groups that are likely comparable with respect to confounding factors associated with being deployed.

Table 2 **Characteristics and risk for any-cause hospitalization among anthrax-vaccinated deployed US service members serving on active duty, 1998-2001**

	Deployed (n = 170,723)		
	No. (%)	HR* (95% CI)	*P* Value
Gender			
Female	22,221 (13.0)	1.65 (1.45–1.88)	<0.001
Male	148,502 (87.0)	1.00	
Age, y			
17–24	59,233 (34.7)	1.00	0.014
25–34	72,536 (42.5)	1.04 (0.94–1.16)	
35–44	34,486 (20.2)	1.11 (0.98–1.27)	
45	4,468 (2.6)	1.71 (1.34–2.18)	
Race/Ethnicity			
White non-Hispanic	104,887 (61.4)	1.00	<0.001
Black non-Hispanic	37,745 (22.1)	0.85 (0.76–0.94)	
Hispanic	16,847 (9.9)	0.87 (0.74–1.01)	
Other	11,244 (6.6)	0.77 (0.64–0.93)	
Service			
Army	82,576 (48.4)	1.86 (1.66–2.09)	<0.001
Navy/Coast Guard	14,344 (8.4)	1.00	
Air Force	28,939 (17.0)	1.00 (0.89–1.12)	
Marine Corps	44,864 (26.3)	1.14 (0.98–1.34)	
Rank			
Enlisted	148,223 (86.8)	1.47 (1.28–1.68)	<0.001
Officer	22,500 (13.2)	1.00	
Occupational category			
Infantry, gun crews, seamen	40,839 (23.9)	0.96 (0.82–1.12)	0.722
Mechanical equipment repair	26,747 (15.7)	0.94 (0.80–1.11)	
Functional support and admin	29,600 (17.3)	0.92 (0.77–1.10)	
Electrical repair	14,700 (8.6)	1.00	
Service and supply	18,032 (10.6)	1.00 (0.82–1.21)	
Communication/intelligence	14,403 (8.4)	0.86 (0.71–1.05)	
Health care	11,168 (6.5)	1.32 (1.05–1.66)	
Construction	4,238 (2.5)	1.04 (0.80–1.35)	
Other technical and specialty	4,753 (2.8)	0.81 (0.59–1.10)	
Other and missing	6,243 (3.7)	1.07 (0.78–1.46)	
Marital status			
Married	98,476 (57.7)	0.97 (0.89–1.07)	0.846
Single	72,247 (42.3)	1.00	

No, number; HR, hazard ratio; CI, confidence interval. *Adjusted for all other variables listed in the table. Occupational categories based on the Department of Defense *Occupational Conversion Index*.

This study has a number of strengths. The large sample size and 4-year study duration allowed adequate power to examine the association between anthrax vaccination and specific diagnoses except those with very low incidence of hospitalization. Ascertainment of electronic inpatient hospital discharge diagnoses from the standardized DoD reporting systems provides a high degree of assurance that there was minimal misclassification of ICD-9-CM-coded diagnoses when compared with ambulatory visit data records. Observing no increased hazard for any-cause hospitalizations among deployed service members is reassuring. Although it has been hypothesized that post-deployment illnesses may be related to a long-term shift in cytokine response from a Th1 to a Th2 pattern, and that this change is triggered by relations between multiple vaccinations, deployment, stress, and insecticides, this theory is not supported by these findings.[34-37]

Studying vaccine effects within the US military has unique challenges. Service members selected for deployment and subsequent anthrax vaccination may be healthier than those who do not deploy. Those selected for deployment generally begin anthrax vaccination shortly prior to deployment, and the limitations of hospitalization data in the deployed setting have been previously discussed. These challenges often make the assessment of post-vaccination adverse health events difficult, and become problematic when attempting to identify a comparable reference group. We decided to compare anthrax vaccine recipients' pre-vaccination hospitalization experience with that following vaccination, within the same person. Although utilizing deployed service members as their own controls reduced the analytic cohort to only those who had been deployed and received the anthrax vaccination, this decreased heterogeneity among exposed and non-exposed groups reduced the potential for unmeasured confounding to affect study results.

There are limitations to this study that also must be considered. The analysis was limited to hospital discharge diagnoses. Although these outcomes were used for the reasons above, there are a number of disease outcomes of potential interest that normally do not result in hospitalization. Furthermore, we were not able to assess hospitalizations once a service member was no longer on active duty, and hospitalizations occurring while in a deployed status may not be

Table 3 **Adjusted hazard of hospitalization among post-anthrax-vaccinated compared with pre-anthrax-vaccinated deployed US service members serving on active duty, 1998-2001**

	Deployed (n = 227, 741)		
	Cases		
Category (*ICD-9-CM* codes)	**Pre-vaccination**	**Post-vaccination**	**Hazard Ratio (95% CI)**
Any cause*	1,191	1,164	0.88 (0.81–0.97)
Infectious/parasitic (001–139)	107	68	0.59 (0.42–0.82)
Neoplasms (140–239)	25	37	1.11 (0.62–2.01)
Endocrine, nutritional, metabolic (240–279)	74	69	0.90 (0.63–1.28)
Blood and blood-forming organs†	51	33	0.54 (0.33–0.87)
Mental disorders (290–319)	149	173	1.15 (0.91–1.46)
Nervous system (320–389)	52	37	0.76 (0.47–1.21)
Circulatory system (390–459)	56	70	1.15 (0.79–1.67)
Respiratory system (460–519)	144	99	0.66 (0.50–0.87)
Digestive system (520–579)	263	244	0.80 (0.66–0.97)
Genitourinary system (580–629)	97	103	0.93 (0.68–1.27)
Skin and subcutaneous tissues (680–709)	72	62	0.85 (0.59–1.23)
Musculoskeletal and connective tissue (710–739)	152	170	0.90 (0.70–1.15)
Ill-defined conditions (780–799)	162	140	0.80 (0.62–1.02)
Injury and poisoning (800–999)	296	337	1.01 (0.85–1.19)
Autoimmune organ—specific diseases‡	10	12	1.18 (0.46–2.99)
Autoimmune organ—non-specific diseases‡	2	2	0.58 (0.06–5.73)
Asthma (493)	11	10	0.79 (0.30–2.06)

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; CI, confidence interval. *Excludes complications of pregnancy, childbirth and the puerperium (*ICD-9-CM* codes 630-676 and 740-779). †*ICD-9-CM* codes 280-289. ‡Follows categorical definitions found in Haynes, BF, Fauci AS. Disorders of the immune system. In: Fauci AS. Braunwald E, Isselbacher KJ, et al., eds. *Harrison's Principles of Internal Medicine.* 14th ed. New York, NY: McGraw-Hill Health Professions Division; 1998:1753-4.

recorded consistently across all services and locations. Sato et al. observed that those who receive anthrax vaccination are a select and healthy active duty population when compared to those US service members who do not deploy, making it very difficult to assemble an active duty comparison group of similar health.[15] For this reason, we adapted a post-vaccination versus a pre-vaccination analytic model. Cox proportional hazards modeling allowed adjustment for confounding due to age, but we were aware that there may be confounding due to time. The Institute of Medicine Report on the safety of anthrax vaccine describes this effect and how this bias is likely to produce a spurious positive association between vaccination and hospitalizations in the post-vaccination period as the cohort regresses towards average health.[21] Because the average length of follow-up post-vaccination was 130 days, and because a comparable length of follow-up pre-vaccination was used, we do not believe time contributed a significant bias to this study, as most individuals were observed for a year or less. Analyses support this belief as most hazard ratios are less than 1.0 rather than above 1.0. Additionally, employing a post-vaccination versus a pre-vaccination analytic model may produce spurious associations because service members with certain diagnoses are excluded from vaccination.

Alternatively, a case-series analysis may have been used.[38] Case series analyses are a powerful analytic method when the vaccination coverage is high for the population being studied, and the cost of assembling a cohort is high. However, in this instance a cohort design was chosen to allow the investigation of a large number of outcomes. Additionally, using electronic data sources to assemble the cohort, identify those vaccinated, and link to hospitalization data was relatively inexpensive.

We utilized 42-day windows of observation following each anthrax vaccination. Although this has merit to decrease the inclusion of non-causal hospitalizations, we were unable to assess disease outcomes with long latency, such as neoplasms.

In conclusion, we constructed a large, historical prospective cohort of anthrax vaccinated and deployed US service members. Hospital diagnoses were obtained for 130 days prior to and for 42-day intervals following each anthrax vaccination. We found no positive association between anthrax vaccination and hospitalization among the14 broad ICD-9-CM categories investigated. Additionally, we found no evidence of an association between anthrax vaccination and hospitalization due to a number of specific disease outcomes, such as autoimmune diseases, asthma, amyotrophic lateral sclerosis, systemic lupus erythematosus, or fibromyalgia. Vaccine safety within military populations remains an important issue, and further study is warranted in an attempt to overcome potential challenges associated with confounding that results from subsequent deployment after receipt of vaccination.

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