MONITORING ANTHRAX VACCINE SAFETY IN U.S. MILITARY SERVICE MEMBERS ON ACTIVE DUTY: SURVEILLANCE OF HOSPITALIZATIONS IN TEMPORAL ASSOCIATION WITH IMMUNIZATION, 1998

P. A. Sato
R. J. Reed
T. C. Smith
L. Wang

Report No. 00-29

Approved for public release; distribution unlimited.

NAVAL HEALTH RESEARCH CENTER
P. O. BOX 85122
SAN DIEGO, CA 92186-5122

BUREAU OF MEDICINE AND SURGERY (MED-02)
2300 E ST. NW
WASHINGTON, DC 20372-5300
MONITORING ANTHRAX VACCINE SAFETY IN U.S. MILITARY SERVICE MEMBERS ON ACTIVE DUTY: SURVEILLANCE OF HOSPITALIZATIONS IN TEMPORAL ASSOCIATION WITH IMMUNIZATION, 1998

NAVAL HEALTH RESEARCH CENTER
DoD Center for Deployment Health Research
P.O. Box 85122
San Diego, CA 92186-5122

Paul A. Sato, MD, MPH, Robert J. Reed, MS, Tyler C. Smith, MS, Linda Wang, BS

Report No. 00-29 was supported by [the Office of Naval Research, Arlington, VA, under Work Unit No. 60002]. The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. Government. Approved for public release; distribution is unlimited. Human subjects participated in this study after giving their free and informed consent. This research has been conducted in compliance with all applicable Federal Regulations governing the Protection of Human Subjects in Research.

ABSTRACT

We studied military medical hospitalizations for possible temporal associations with anthrax immunization in U.S. military personnel on active duty in 1998. Anthrax immunization, demographic, and hospitalization data were linked and analyzed using Cox proportional hazards modeling for hospitalization within 42 days of an anthrax vaccine dose. Discharge diagnoses were aggregated into 14 International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic categories. Approximately 11% of active-duty personnel received one or more doses of anthrax vaccine during 1998; those anthrax immunized were more likely to be younger and male. Lower hospitalization rates were observed in the anthrax-immunized, across doses and diagnostic categories. Adjusted risk ratios for hospitalization by diagnostic category suggests that anthrax-immunized active-duty service members were at equal or lesser risk of hospitalization than the nonimmunized.

INTRODUCTION

The value of anthrax as a biological weapon stems from its high stability in spore form, from the relative absence of natural immunity in industrialized nations, and from the severity of disease in its inhalation form. The threat posed by anthrax to the U.S. military prompted the Secretary of Defense, in December 1997, to order a mandated program for anthrax immunization of all U.S. military personnel. This program is currently being implemented. Phase I, an accelerated immunization program for personnel who were already deployed in Southwest Asia, began in March 1998, as tensions with Iraq over United Nations weapons inspections increased. In August of the same year, the program was extended to personnel assigned or rotating to high threat areas. Ensuing phases of the immunization program will begin in subsequent years.

As of April 12, 2000, a total of 425,976 service members had received 1,620,793 anthrax vaccine doses. Approximately 500 service members have...
refused anthrax vaccine immunization, despite the administrative or disciplinary action that may result. Concerns that there may be long-term severe and/or permanent adverse effects to immunization have been among the reasons for refusing immunization. In response to these concerns, we initiated a study to monitor anthrax vaccine safety. The study uses available U.S. Department of Defense (DoD) data to assess hospitalizations that occur in close temporal proximity to anthrax immunization. We report here on findings for calendar year 1998.

MATERIALS AND METHODS

Personal identifying information was used for matching and linking immunization, demographic, and hospitalization data during data analysis. Such identifying information was kept in secure conditions designed to assure confidentiality and privacy. All identifying information was disassociated and deleted from the analytical data set once linking was complete.

Anthrax Immunization Status Data
Anthrax immunization status was determined from records maintained by the Defense Eligibility Enrollment Reporting System (DEERS) at the Defense Manpower Data Center, Seaside, California. Anthrax immunization data for 1998 on record as of December 31, 1999, were obtained. Anthrax dose sequence number and date of dose administration, among other variables, were used in these analyses.

Demographic Data
Demographic data for service members were also obtained from DEERS. Data for all U.S. military personnel on active duty for all or part of 1998, and on record as of December 31, 1999, were used. DEERS contains data on changes of military assignment, contingency deployments, as well as on dates of accession to and/or discharge from military service, among others.

Hospitalization data
A database containing the Standard Inpatient Data Record (SIDR) for all hospitalizations at military medical treatment facilities (MTFs) is maintained at Fort Detrick, Maryland. This database contains up to 8 hospitalization discharge diagnoses coded in International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) format. Other information available in this database includes length of hospital stay, dates of admission, and dates of discharge.

A subject experienced a hospitalization event if he or she was discharged from an MTF with a diagnosis classified under one of 14 targeted ICD-9-CM diagnostic categories (Table I). Anthrax-immunized service members experienced a hospitalization event if it occurred within 42 days following an anthrax vaccine dose. This 0- to 42-day time window is consistent with conventions described in the literature. Nonimmunized service members experienced an event if they were hospitalized any time between January 1 and December 31, 1998.

Objective
We studied military hospitalizations in temporal association with anthrax immunization in U.S. military personnel on active duty in 1998. Adjusted risk ratios (ARRs) with 95% confidence intervals (CIs) for hospitalization comparing anthrax immunized with nonimmunized service members were computed to study this association.

Statistical analysis
Chi-square tests and t-tests for associations were used to determine possible predictors of hospitalization. Variables with p values of #0.15 obtained from these tests were included in subsequent model analyses. A multivariable Cox proportional hazards
model was used with a manual, backward, stepwise model-building process to compare risk for hospitalization between anthrax-immunized and nonimmunized service members. Data management and statistical analysis were performed using SAS Version 6 software (SAS Institute, Cary, NC).

Person-years of observation were counted for anthrax immunized, within the 42-day window, from the date of immunization until whichever of the following occurred first: (a) the date of first admission, (b) the date of next anthrax vaccine dose, (c) the date of separation from military service, or (d) December 31, 1998. Person-years for nonimmunized service members were calculated from January 1, 1998, until whichever of the following occurred first: (a) the date of first admission, (b) the date of separation from military service, or (c) December 31, 1998. Subsequent hospitalizations within the same diagnostic category for any service member, in either group, were not counted as events.

The following covariates were included in the final model to adjust for contributing effects: prior hospitalization between January 1 and December 31, 1997; gender; age (quartile groupings: 16-21, 22-26, 27-33, and ≥34 years); marital status (married, not married); and race/ethnicity (white, black, Hispanic, other). Additional covariates included paygrade (enlisted, warrant officer, commissioned officer), duty occupational category (divided into 10 major groupings per DoD Occupational Conversion Index), branch of service, deployment status (deployed prior to January 1, 1998, deployed during study period, deployed during study period, and deployed four or more times during career), and date of separation from active-duty military service.

**RESULTS**

**Demographic Profiles**

The demographic characteristics of anthrax-immunized service members were compared with the entire active-duty population (Table II). There was a slightly greater proportion of men among the anthrax immunized in 1998, and they were also younger than the active-duty population as a whole.

**Anthrax Immunization Status**

DoD-wide, 11.3% of active-duty service members had received at least one dose of anthrax vaccine in 1998. There was a generally proportionate representation of Army, Navy, Air Force, and Marine Corps personnel (Table III).

**Hospitalizations**

For anthrax-immunized service members, there were 719 unique hospitalizations within 14 ICD-9-CM diagnostic categories during 28,619 person-years of observation. Among the nonimmunized, there were 47,391 hospitalizations during 1,248,332 person-years of observation. Table I provides a summary of ICD-9-CM diagnostic categories and the abbreviations for the categories used in Figures 1 and 2.

Anthrax-immunized service members had lower rates of hospitalization across doses and diagnostic categories. All point estimates of ARR by diagnostic category were less than 1.0. For 7 of 14 categories (Fig. 2), the 95% CI around ARR included 1.0. The 95% CI for the 7 other ICD-9-CM diagnostic categories did not include 1.0, suggesting that immunized active-duty service members were significantly less likely to be hospitalized for conditions in these diagnostic categories than their nonimmunized counterparts (Fig. 2).

**DISCUSSION**

We report on data from the first year of a multi-year study designed to monitor anthrax vaccine safety in U.S. military service members on active duty. Through surveillance of hospitalizations in MTFs, we have sought to monitor ICD-9-CM category-specific risks associated with anthrax immunization. These data refer to only calendar year 1998.

In our results, anthrax immunization was not associated with an increased risk for
hospitalization within 42 days following immunization. Immunized service members were at equal or lesser risk for hospitalization than nonimmunized service members during the period of observation. Nonetheless, this study had a number of limitations.

First, there is a potential confounder that may explain some of our results. Figure 2 shows that the point estimates for the ARR in anthrax-immunized personnel are lower across all diagnostic categories. Some part of this effect could be due to the fact that a majority of those immunized in 1998 were likely among the forward deployed or deployable, among those stationed overseas, and/or among those stationed in high threat areas. If selection for deployment is biased in favor of the healthier service member, it may well be expressed among the deployed and/or deployable as a decreased risk of hospitalization, particularly for routine or nonurgent hospitalizations that may be deferred until the end of deployment. This effect, thought to be transient, was seen in hospitalizations among service members deployed to the Gulf War in 1991.8 We attempted to control for this "healthy deployment effect" by including the prior hospitalization covariate in our explanatory model. Additional methods for adjusting for this effect are being investigated.

Second, although personnel on active duty are generally required to obtain their health care at an MTF, some hospitalizations of service members on active duty occur in non-DoD facilities, mainly through DoD-sponsored health plans (TriCare and CHAMPUS). This is thought to be infrequent, especially for service-related events. Nonetheless, we are currently planning to incorporate data from hospitalizations in non-MTFs that are billed to TriCare and CHAMPUS health plans into future years of our multi-year study. Non-MTF hospitalizations may also be more likely among service members in units deployed to areas where MTFs are few in number or far away in distance, such as in Southwest Asia. This may also explain some of the apparent decreased risk for hospitalization among anthrax-immunized personnel. Most of these cases should eventually appear in SIDR hospitalization databases; they would likely be medically evacuated back to the United States or to the nearest MTF as soon as their condition stabilized, and rehospitalized for further evaluation and treatment.

Finally, as previously mentioned, these data are from the first year of a multi-year study, and they reflect only the first year of the DoD’s current anthrax immunization program. As a result, anthrax-immunized service members contributed less than 3% of the total observation time contributed by all service members on active duty, and only slightly more than 11% had received at least one dose of anthrax vaccine.

The number of person-years of observation in the anthrax immunized should increase rapidly as additional years of data are obtained. This will provide the study with greater statistical power, permitting examination of potential associations between anthrax vaccine and specific diagnoses that have been alleged or found to be associated with the use of vaccines, such as serum sickness, other hypersensitivity reactions, and Guillain-Barré syndrome.6

ACKNOWLEDGMENTS

We are indebted to the staff at Defense Manpower Data Center, Seaside, California, for their assistance and support. We are also indebted to the advice of Neal A. Halsey, MD (Institute for Vaccine Safety, Johns Hopkins University, Baltimore, MD) and LTC Phillip R. Pittman, MC, USA (U.S. Army Medical Research Institute for Infectious Diseases, Fort Detrick, MD) in the preparations for this study.

Naval Health Research Center Technical Report No. 00-29
REFERENCES


TABLE I. Summary Of ICD-9-CM Diagnostic Categories Used In Study Analysis

<table>
<thead>
<tr>
<th>ICD-9-CM Diagnostic Category</th>
<th>ICD-9-CM Codes in Category</th>
<th>Abbreviations Used in Figures 1 and 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious and parasitic diseases</td>
<td>001-139</td>
<td>Infectious</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>140-239</td>
<td>Neoplasms</td>
</tr>
<tr>
<td>Endocrine, nutritional and metabolic diseases, and immunity disorders</td>
<td>240-279</td>
<td>Endocrine</td>
</tr>
<tr>
<td>Diseases of the blood and blood forming organs</td>
<td>280-289</td>
<td>Blood</td>
</tr>
<tr>
<td>Mental disorders</td>
<td>290-319</td>
<td>Mental</td>
</tr>
<tr>
<td>Diseases of the nervous system and sense organs</td>
<td>320-389</td>
<td>Nervous</td>
</tr>
<tr>
<td>Diseases of the circulatory system</td>
<td>390-459</td>
<td>Circulatory</td>
</tr>
<tr>
<td>Diseases of the respiratory system</td>
<td>460-519</td>
<td>Respiratory</td>
</tr>
<tr>
<td>Diseases of the digestive system</td>
<td>520-579</td>
<td>Digestive</td>
</tr>
<tr>
<td>Diseases of the genitourinary system</td>
<td>580-629</td>
<td>Genitourinary</td>
</tr>
<tr>
<td>Diseases of the skin and subcutaneous tissue</td>
<td>680-709</td>
<td>Skin</td>
</tr>
<tr>
<td>Diseases of the musculoskeletal system and connective tissue</td>
<td>710-739</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Symptoms, signs, and ill-defined conditions</td>
<td>780-799</td>
<td>Ill-defined</td>
</tr>
<tr>
<td>Injury and poisoning</td>
<td>800-999</td>
<td>Injury</td>
</tr>
</tbody>
</table>
TABLE II. Demographic And Military Profile Of All Service Members On Active Duty Compared With Those Anthrax Immunized, 1998

<table>
<thead>
<tr>
<th>Gender</th>
<th>All Active-Duty Personnel</th>
<th>Anthrax-Immunized</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>Male</td>
<td>1,210,251</td>
<td>86.0</td>
</tr>
<tr>
<td>Female</td>
<td>196,779</td>
<td>14.0</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>#19</td>
<td>164,299</td>
</tr>
<tr>
<td></td>
<td>20-24</td>
<td>409,959</td>
</tr>
<tr>
<td></td>
<td>25-29</td>
<td>285,932</td>
</tr>
<tr>
<td></td>
<td>30-34</td>
<td>228,707</td>
</tr>
<tr>
<td></td>
<td>35-39</td>
<td>199,347</td>
</tr>
<tr>
<td></td>
<td>40-44</td>
<td>83,425</td>
</tr>
<tr>
<td></td>
<td>45-49</td>
<td>28,032</td>
</tr>
<tr>
<td></td>
<td>50+</td>
<td>8,017</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>910,123</td>
<td>68.8</td>
</tr>
<tr>
<td>Black</td>
<td>277,654</td>
<td>21.0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>102,944</td>
<td>7.8</td>
</tr>
<tr>
<td>Other</td>
<td>31,929</td>
<td>2.4</td>
</tr>
<tr>
<td>Service</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Army</td>
<td>475,582</td>
<td>33.8</td>
</tr>
<tr>
<td>Navy</td>
<td>366,867</td>
<td>26.1</td>
</tr>
<tr>
<td>Air Force</td>
<td>359,853</td>
<td>25.6</td>
</tr>
<tr>
<td>Marine Corps</td>
<td>171,199</td>
<td>12.2</td>
</tr>
<tr>
<td>Other</td>
<td>34,217</td>
<td>2.4</td>
</tr>
<tr>
<td>Military paygrade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enlisted</td>
<td>880,090</td>
<td>63.1</td>
</tr>
<tr>
<td>Officer</td>
<td>515,271</td>
<td>36.9</td>
</tr>
</tbody>
</table>

Naval Health Research Center Technical Report No. 00-29
TABLE III. Anthrax Immunization Status By Service And By Number Of Anthrax Vaccine Doses Given, 1998

<table>
<thead>
<tr>
<th>Number of Doses</th>
<th>Total</th>
<th>Army</th>
<th>Navy</th>
<th>Air Force</th>
<th>Marine Corps</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
<td>Number</td>
<td>%</td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>1</td>
<td>159,386</td>
<td>11.32</td>
<td>60,761</td>
<td>12.78</td>
<td>36,652</td>
<td>9.99</td>
</tr>
<tr>
<td>2</td>
<td>142,004</td>
<td>10.09</td>
<td>53,016</td>
<td>11.15</td>
<td>32,516</td>
<td>8.86</td>
</tr>
<tr>
<td>3</td>
<td>121,591</td>
<td>8.64</td>
<td>44,201</td>
<td>9.29</td>
<td>28,465</td>
<td>7.76</td>
</tr>
<tr>
<td>4</td>
<td>28,756</td>
<td>2.04</td>
<td>9,969</td>
<td>2.10</td>
<td>6,237</td>
<td>1.70</td>
</tr>
<tr>
<td>5</td>
<td>487</td>
<td>0.03</td>
<td>173</td>
<td>0.04</td>
<td>31</td>
<td>0.01</td>
</tr>
<tr>
<td>6</td>
<td>203</td>
<td>0.01</td>
<td>69</td>
<td>0.01</td>
<td>15</td>
<td>0.00</td>
</tr>
<tr>
<td>Booster doses</td>
<td>0</td>
<td>0.00</td>
<td>0</td>
<td>0.00</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Zero doses</td>
<td>1,248,332</td>
<td>88.68</td>
<td>414,821</td>
<td>87.22</td>
<td>330,215</td>
<td>90.01</td>
</tr>
<tr>
<td>All active duty</td>
<td>1,407,718</td>
<td></td>
<td>475,582</td>
<td></td>
<td>366,867</td>
<td></td>
</tr>
</tbody>
</table>

Naval Health Research Center Technical Report No. 00-29
Fig. 1. Hospitalization rates by ICD-9-CM diagnostic category and anthrax vaccine dose, 1998. U.S. military service members on active duty.

Fig. 2. Adjusted risk ratios for hospitalization with 95% confidence intervals, by ICD-9-CM diagnostic category, 1998. U.S. military service members on active duty.
We studied military medical hospitalizations for possible temporal associations with anthrax immunization in U.S. military personnel on active duty in 1998. Anthrax immunization, demographic, and hospitalization data were linked and analyzed using Cox proportional hazards modeling for hospitalization within 42 days of an anthrax vaccine dose. Discharge diagnoses were aggregated into 14 International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic categories. Approximately 11% of active-duty personnel received one or more doses of anthrax vaccine during 1998; those anthrax immunized were more likely to be younger and male. Lower hospitalization rates were observed in the anthrax immunized, across doses and diagnostic categories. Adjusted risk ratios for hospitalization by diagnostic category suggests that anthrax-immunized active-duty service members were at equal or lesser risk of hospitalization than the nonimmunized.