

Anthrax Vaccination and Self-reported Symptoms, Functional Status, and Medical Conditions in the National Health Survey of Gulf War Era Veterans and Their Families

CLARE M. MAHAN, PhD, HAN K. KANG, DRPH, NANCY A. DALAGER, MS,
AND JACK M. HELLER, PhD

PURPOSE: To evaluate the health status of Gulf War veterans who reported receipt of anthrax vaccination and a small group of Gulf War veterans for whom documentation of anthrax vaccination exists.

METHODS: Among the 11,441 Gulf War veterans who completed a health survey, 4601 reported receiving the anthrax vaccine during the war; 2979 veterans reported not receiving it; 3861 were uncertain. Also, 352 of these respondents were documented by the Department of Defense as having received anthrax vaccination. We compared the medical history of these groups of veterans using multivariate analyses. Finally, we analyzed perception of exposure and its relation to reporting bias.

RESULTS: There were statistically significant differences in prevalence for almost all outcomes studied between those who reported having received anthrax vaccination and those who did not so report. However, when we compared the veterans for whom vaccination records exist to the group who self-reported that they had not received the vaccine, the significant differences in prevalence for almost all of the outcomes disappeared.

CONCLUSIONS: The extent of a reporting bias should be carefully considered when one evaluates the health consequences of anthrax vaccination based on self-reported data.

Ann Epidemiol 2004;14:81-88. © 2003 Elsevier Inc. All rights reserved.

KEY WORDS: Gulf War, Anthrax Vaccine, Information Bias, Recall Bias.

INTRODUCTION

Beginning in August 1990, US military personnel were deployed to the Gulf theater in response to Iraq's invasion of Kuwait. The Department of Defense (DoD) authorized the administration of vaccinations to these troops to protect against potential battlefield exposure to biological warfare agents, in particular, anthrax and botulism. Due to limited amounts of vaccine and vaccination protocols that called for multiple doses, not all service personnel received these vaccinations. DoD estimated that 150,000 US troops received at least one dose of the estimated 310,680 doses of anthrax vaccine sent to the Gulf theater and 8000 persons were vaccinated with botulinum toxoid with nearly 138,000 doses sent to the Gulf theater (1, 2).

Service personnel returning from the Gulf War have developed a variety of unexplained symptoms for which

the cause remains unknown. There has been much speculation as to the possible role of vaccinations in the etiology of these unexplained illnesses (3). To date, even though troops continue to be vaccinated, there have been no long-term studies to address what possible health effects may result from these specific vaccinations. Furthermore, no significant adverse effects of the vaccine have been reported in the few peer reviewed short-term studies (4-7).

The medical records from the Gulf War contain little or no information on even what vaccinations were given to the individual much less the timing or number of doses administered (8). The Office of the Special Assistant for Gulf War Illnesses indicated in their 1999 report that there was confusion about how vaccination data in the Gulf theater were to be recorded (8). There was also a consideration in not keeping shot records to avoid aiding enemy strategy. To date, DoD has been able to produce only isolated lists of small numbers of persons receiving anthrax or botulism vaccinations.

From the Veterans Health Administration, Department of Veterans Affairs, Washington, DC (C.M.M., H.K.K., N.A.D.); and US Army Center for Health Promotion and Preventive Medicine, Aberdeen Proving Ground, MD (J.M.H.).

Address correspondence and reprint requests to: Dr. Han K. Kang, Environmental Epidemiology Service, Department of Veterans Affairs, 810 Vermont Avenue, NW, Washington, DC 20420. Tel.: (202) 254-0370; Fax: (202) 254-0380; E-mail: han.kang@hq.med.va.gov

Received January 23, 2002; accepted April 1, 2003.

METHODS

National Health Survey Population

This analysis takes advantage of the health survey data collected between 1995 and 1997 for a retrospective cohort

Report Documentation Page				Form Approved OMB No. 0704-0188	
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.					
1. REPORT DATE JAN 2002		2. REPORT TYPE		3. DATES COVERED 00-00-2002 to 00-00-2002	
4. TITLE AND SUBTITLE Anthrax Vaccination and Self-reported Symptoms, Functional Status, and Medical Conditions in the National Health Survey of Gulf War Era Veterans and Their Families				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) US Army Center for Health Promotion and Preventive Medicine,5158 Blackhawk Road,Aberdeen Proving Ground,MD,21010-5403				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Same as Report (SAR)	18. NUMBER OF PAGES 8	19a. NAME OF RESPONSIBLE PERSON
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified			

Selected Abbreviations and Acronyms

aOR = adjusted odds ratio
CATI = computer assisted telephone interviewing
CHPPM = Center for Health Promotion and Preventive Medicine
CI = confidence interval
DMDC = Defense Manpower Data Center
DoD = Department of Defense
GWV = Gulf War veterans
NHS = National Health Survey of Gulf War Era Veterans and Their Families
SSN = social security number
VA = Department of Veterans Affairs

study in which health histories of a population-based sample of 15,000 troops deployed to the Gulf area were compared with those of 15,000 troops not deployed in the Gulf area. The study is entitled the "National Health Survey of Gulf War Era Veterans and Their Families" (NHS). The design, data collection methods and instruments, and results of Phase I and II have been described in earlier reports and are summarized here (9-13).

The Department of Defense (DoD) identified the populations from which to sample 15,000 Gulf veterans and 15,000 non-Gulf veterans. The DoD Defense Manpower Data Center (DMDC) provided military and demographic information for 693,826 US troops deployed to the Gulf area during the Gulf War. The DMDC also sampled 800,680 individuals, or approximately half of all military personnel on duty between September 1990 and May 1991 but not deployed to the Gulf.

Stratified random sampling by gender, unit component, and branch of service ensured that each subgroup was adequately represented among the Gulf veterans and non-Gulf veterans. Women, reservists, and National Guardsmen were over-sampled. The non-Gulf troops were likewise stratified and randomly sampled to mirror the number in the corresponding Gulf stratum.

Data Collection Methods and Instruments

A structured 16-page questionnaire soliciting information on veteran's health status and reproductive outcomes, exposure to possible risk factors, and confounding variables was mailed to 30,000 veterans. It was accompanied by an introductory letter regarding the purpose of the study including an explanation of informed consent, and a pre-addressed, stamped return envelope. A letter and replacement questionnaire were sent to non-respondents of the previous mailing again at 10 weeks and at 6 months. In Phase II, telephone interviews using computer assisted telephone interviewing (CATI) software were attempted on the remaining non-respondents. The same questionnaire was adopted.

Definitions of Study Subjects and Exposures

Documented exposed cohort. DoD provided the identities of 8376 Gulf War veterans who have appeared on various DoD lists of individuals who received at least one anthrax and/or botulinum toxoid vaccination while in the Gulf theater. This compilation of data contains the largest group of Gulf War veterans identified as having received anthrax vaccinations ($n = 7691$). The sources of these data were the Office of the Assistant Secretary of Defense—Health Affairs, the Walter Reed Army Medical Center, and the Army Center for Health Promotion and Preventive Medicine (CHPPM). The data were combined, duplicate entries were excluded, and Social Security numbers were confirmed against the Defense Manpower Data Center (DMDC) roster of military persons deployed to the Gulf theater between August 2, 1990 and July 31, 1991. The file of Gulf War veterans with a documented anthrax vaccination was matched to the 11,441 Gulf deployed veterans who responded in Phase I or II of the National Health Survey of Gulf War Era Veterans and Their Families (9). Record linkage produced 352 persons who responded to the survey questionnaire and who appeared on the list of 7691 veterans who received at least one anthrax vaccination (Documented DoD Group).

Self-reported as Exposed. On the survey instrument, participants were asked,

"Have you taken or received any of the following while in the military...

... Anthrax vaccine (injection): NO; DON'T KNOW; YES

IF YES, when was the MOST RECENT TIME that you had this medication?

____/____MONTH/YEAR"

Included in this list of nine specific pills and vaccines were three types of pills (malaria, ciprofloxacin, and pyridostigmine) and six types of vaccines (anthrax, typhoid, botulism, immune globulin, plague, and meningococcus). Among the 11,441 Gulf War veterans, a total of 4601 Gulf veterans (40.2%) self-reported (S-R) on the survey instrument that they had received anthrax vaccination and 2979 (26.0%) reported that they had not received anthrax vaccine. The remaining 3861 (33.7%) were uncertain or did not answer the question.

Definitions of Outcomes

Health history and exposure data collected from veterans included: presence of various symptoms, medical and psychological conditions, exposures in the Gulf theater, self assessed health status, measures of functional impairment, and health care utilization. Basic demographic data and military variables (date of birth, gender, marital status, race, branch, rank, MOSC, unit component) came from DMDC

and VA records. A self-reported symptom inventory, comprised of 48 items representative of the symptoms commonly reported by outpatients was used to assess the prevalence of somatic and psychological symptoms (14). Information on the time of onset and severity of symptoms was also collected. The guideline for reporting a symptom experienced during the past year as "severe" was that its presence was sufficient to seek medical advice, take prescription drugs, lose work, or limit routine activities. All these outcomes are fully described for the entire cohort of 11,441 Gulf veteran respondents and 9476 non-Gulf veteran respondents elsewhere (9).

Statistical Methods

We measured the association between receipt of anthrax vaccine (both by the self-reported responses in the survey questionnaire and by the documented DoD record) and the various health outcomes described above. First, we compared the morbidity experience of the three self-reported history groups: 4601 S-R yes, 2979 S-R no, and 3861 S-R unknown. The variable which identified the three self-reported groups was transformed to two indicator variables: $X_1 = 1, 0$ and $X_2 = 0, 1$. "S-R no" served as the reference category. A multiple logistic regression model was set up in which morbidity experience (a binary variable) was regressed on these two indicator variables as well as on several other independent variables. Demographic, military factors, and confounding variables contained in the models included gender (male vs. female), age in 1991 (<30 vs. ≥ 30 years), race (white vs. other), marital status (single vs. ever married), rank (officer or warrant vs. enlisted), branch of service (Navy and Air Force personnel were categorized as non-ground troops, and Army and Marines were categorized as ground troops), unit component (active duty vs. reserve or National Guard), current smoker (within past 12 months), and current alcohol use (within past 12 months). Also included in the regression model was a variable representing other vaccines administered (typhoid, botulinum toxoid, immune globulin, plague, and meningococcus). This variable was coded as the sum of the number of vaccines received, other than anthrax, and ranged from 0 to 5. The coefficients of the two indicator variables were used to assess the association between the self-reported group identity and the morbid outcomes. Adjusted odds ratios (aORs) and 95% confidence intervals (CI) were estimated (15). This process was repeated for 4 disability/utilization indices, 31 medical conditions, and 48 symptoms.

Subsequent Comparison with "Documented DoD Group"

Second, we compared the morbidity experience of the 352 veterans with documented anthrax vaccination according to DoD records with the group who self-reported as negative (2979 S-R no). For these comparisons we used the stratified

Cochran-Mantel-Haenszel analysis to estimate ORs and 95% CI adjusted for confounders (16). These confounding factors were number of vaccines received other than anthrax (≤ 2 vs. ≥ 3 vaccines), gender, branch, and unit component. Data analysis was performed using the Statistical Analysis System (15).

Stratification of "Documented DoD Group"

Third, we estimated the prevalence of disability indices, medical conditions, and symptoms for the documented group stratified by the three self-reported categories of anthrax vaccination: S-R yes ($n = 260$), S-R no ($n = 34$), S-R unknown ($n = 58$). The non-parametric Wilcoxon signed-ranks test was used to assess whether the prevalence in S-R yes group was the same as the prevalence in the S-R no group considering all outcomes summarized (17).

RESULTS

The percent distributions of selected demographic, military characteristics, and confounders among the Gulf veterans who participated in the survey are presented in Table 1, stratified by the three groups defined by self-report of anthrax vaccination, and for the small group of Gulf War veterans for whom documentation of anthrax vaccination exists. The groups differed significantly in characteristics. The "Documented DoD Group", when compared with the group who reported having received the vaccine, were more likely to be female ($p = 0.0030$); unmarried individuals ($p = 0.0031$); who were ground troops (i.e., served in the army and marines) ($p < 0.0001$); and served in the reserves ($p < .0001$) at the time of the Gulf War. The distributions of number of vaccines received, other than anthrax, were different ($p < 0.0001$). Adjustment was made for most of these differences in the analysis (see footnotes to Tables 2, 3, and 4).

The 4601 veterans who reported having received the vaccine differed from the 2979 negatively reporting group in characteristics of gender, ($p < .0001$); rank, ($p = 0.0064$); serving as ground troops ($p < 0.0001$); and reserve or National Guard rather than active duty, ($p < .0001$). History of smoking within the past 12 months differed between the S-R yes and S-R no groups ($p = 0.0219$); as well as number of vaccines received other than anthrax ($p < 0.0001$). In the multivariate logistic analysis of outcomes, adjustment was made for all these factors as well as for other demographic variables.

The prevalences of functional impairment, limitation of employment, and medical care utilization due to illness are presented in Table 2. Those who reported that they had received anthrax vaccination list higher rates of disability

TABLE 1. Percent distribution of selected characteristics for 11,441 Gulf War veterans according to self-report of anthrax vaccination and for exposed group documented to have received anthrax vaccination

Characteristics	Anthrax vaccination			Documented DoD (N = 352)
	S-R Yes (N = 4601)	S-R Unknown (N = 3861)	S-R No (N = 2979)	
Gender				
Male	78.6	83.6	82.8	71.6
Female	21.4	16.4	17.2	28.4
Age (mean age in yrs in 1991) (interquartile range)	30.8 23-37	29.8 23-35	30.7 24-36	31.5 23-39
Race				
White	74.9	71.5	74.7	77.0
Black	18.2	20.3	18.6	15.3
Other	6.8	8.2	6.7	7.7
Marital status				
Single	41.5	44.3	40.6	49.7
Married	52.4	50.8	54.9	44.3
Other	6.1	4.9	4.5	6.0
Rank				
Officer	13.2	8.3	16.4	13.6
Warrant	1.6	1.3	0.8	2.0
Enlisted	85.2	90.4	82.8	84.4
Branch of service				
Air Force	8.6	9.4	22.4	3.4
Army	74.4	64.6	44.3	96.6
Marine	11.3	12.6	9.1	0.0
Navy	5.7	13.4	24.2	0.0
Unit type				
Active duty	28.6	38.5	49.1	4.8
National Guard	31.2	28.8	23.3	22.4
Reserve	40.2	32.7	27.6	72.7
Alcohol use (past 12 months)	76.1	75.6	76.6	75.6
Cigarettes (past 12 months)	34.9	35.7	32.3	31.2
Number of Vaccines (other than anthrax)				
0	10.5	37.1	29.3	19.6
1	20.8	27.4	27.3	22.4
2	28.8	20.6	25.8	23.0
3	21.5	11.0	13.3	20.7
4	10.5	3.4	3.6	11.1
5	7.9	0.4	0.7	3.1

P-values for continuity adjusted chi-square test of independence between characteristic and groups (S-R Yes vs. S-R No) are: for gender, $p < 0.0001$; age: (<30 vs. ≥ 30 years), $p = 0.8685$; race: white vs. non-white, $p = 0.8015$; marital status: single vs. married and other, $p = 0.4302$; rank: enlisted vs. officer and warrant, $p = 0.0064$; branch of service: ground troops vs. non-ground, $p < 0.0001$; unit type: active duty vs. National Guard vs. Reserves, $p < 0.0001$; history of smoking during past 12 months: yes vs. no, $p = 0.0219$; alcohol use past 12 months: yes vs. no, $p = 0.6138$; number of vaccines other than anthrax (0,1,...,5), $p < 0.0001$; number of vaccines other than anthrax (≤ 2 vs. ≥ 3), $p < 0.0001$. P-values for continuity adjusted chi-square test of independence between characteristic and groups (Documented DoD vs. S-R Yes) are: for gender, $p = 0.0030$; age: (<30 vs. ≥ 30 years), $p = 1.000$; race: white vs. non-white, $p = 0.4281$; marital status: single vs. married and other, $p = .0031$; rank: enlisted vs. officer and warrant, $p = 0.7415$; branch of service: ground troops vs. non-ground, $p < 0.0001$; unit type: active duty vs. National Guard vs. Reserves, $p < 0.0001$; history of smoking during past 12 months: yes vs. no, $p = 0.1832$; alcohol use past 12 months: yes vs. no, $p = 0.8824$; number of vaccines other than anthrax, (0,1,...,5), $p < 0.0001$; number of vaccines other than anthrax (≤ 2 vs. ≥ 3), $p < 0.0754$.

P-values for continuity adjusted chi-square test of independence between characteristic and groups (Documented DoD vs. S-R No) are: for gender, $p < 0.0001$; age: (<30 vs. ≥ 30 years), $p = 0.9976$; race: white vs. non-white, $p = 0.3717$; marital status: single vs. married and other, $p = 0.0012$; rank: enlisted vs. officer and warrant, $p = 0.5077$; branch of service: ground troops vs. non-ground, $p < 0.0001$; unit type: active duty vs. National Guard vs. Reserves, $p < 0.0001$; history of smoking during past 12 months: yes vs. no, $p = 0.7276$; alcohol use past 12 months: yes vs. no, $p = 0.7140$; number of vaccines other than anthrax (0,1,...,5), $p < 0.0001$; number of vaccines other than anthrax (≤ 2 vs. ≥ 3), $p < 0.0001$.

and utilization of health care services, as measured by at least one clinic or doctor visit within the previous 12 months, other than for a routine physical examination or vaccination. They also report more hospitalizations within the previous 12 months than the other two groups defined by self-report.

Gulf veterans who self-reported that they had received the anthrax vaccination reported the presence of chronic dis-

ease conditions at one and one-half to two times more frequently than Gulf veterans who reported that they did not receive the vaccine (Table 3). The results of the multivariate regression analyses in which the reference category for the odds ratios was self-report "no" are presented where the statistics estimated for selected medical conditions, from among the 31 studied, are ranked in decreasing order of prevalence of the condition in the self-report "yes" group.

TABLE 2. Prevalence and adjusted odds ratios of functional impairment, limitation of employment, and medical care utilization due to illness among 11,441 Gulf War veterans according to self-report of anthrax vaccination; also for 352 Gulf War veterans for whom anthrax vaccination is documented in DoD records

Conditions	Self-reported anthrax vaccination			Documented DoD (N = 352)	Adjusted odds ratio (95% CI) [†]		
	Yes (N = 4601)	Unknown (N = 3861)	No (N = 2979)		Anthrax Vaccination Yes [‡]	Unknown [‡]	DoD*
Functional impairment**	32.7	28.6	19.1	26.0	1.73 (1.54-1.96)	1.58 (1.41-1.79)	1.20 (0.91-1.60)
Limitation of employment***	21.3	17.9	10.2	17.3	2.13 (1.83-2.48)	1.86 (1.60-2.16)	1.56 (1.12-3.17)
Clinic visit [§]	55.7	48.4	45.6	54.3	1.36 (1.22-1.50)	1.14 (1.04-1.26)	1.25 (0.97-1.60)
Hospitalization [¶]	8.8	7.6	6.3	9.4	1.22 (1.00-1.48)	1.21 (0.99-1.47)	1.34 (0.89-2.01)

*Positive response to the question, "Thinking back over the past 2 weeks, did you stay in bed or at home all or part of any day because you did not feel well or as a result of illnesses or injury?"

**Positive response to the question, "Are you limited in your employment or the kind of work you can do around the house because of any impairment or health problems?"

***Clinic visit because of illness during past 12 months.

§Hospitalization because of illness during past 12 months.

CI: Confidence interval.

†Adjusted odds ratios (95% CI) were derived from logistic models. Reference category was self-report "No." Adjustment was made for number of vaccines received other than anthrax (0,1,...,5); gender (male vs. female); age in 1991 (<30 vs. ≥30 yrs.); race (white vs. other); marital status (single vs. ever married); rank (officer or warrant vs. enlisted); branch of service (non-ground troops vs. ground troops); unit component (active duty vs. National Guard or Reserves); current alcohol use (within past 12 months); and current cigarette use (within past 12 months).

‡Adjusted odds ratios (95% CI) for documented vaccination by DoD records relative to self-report "No" were derived through stratified Cochran-Mantel-Haenszel (15) analysis. Adjustment was made for variables that were correlated with both exposure (anthrax vaccine) and outcome (condition). These confounding factors included number of vaccines received other than anthrax, (≤2 vs. ≥3); gender (male vs. female); branch of service (non-ground troops vs. ground troops); unit component (active duty vs. National Guard or Reserves).

The self-reporting of anthrax vaccination was significantly associated with each of the chronic medical conditions even while controlling for other covariates. This was true for both self-report "yes" with reference category self-report "no", as well as for self-report "unknown" with reference category self-report "no." However, when one compares the "Documented DoD Group" to the self-report "no" group (n = 2979), the adjusted ORs show no association between receipt of anthrax vaccine and onset of the medical conditions for five of the eight studied (Table 3).

The prevalences of severe symptoms are presented in Table 4 for all three self-report groups for the ten most frequently reported severe symptoms in the self-report "yes" group. Several symptoms were twice as prevalent in those who self-reported having received the vaccine, when compared with the self-report "no" group, chiefly fatigue, joint aches, anxiety, depression, sleep difficulty, and reflux. The self-reporting of anthrax vaccination was significantly associated with each symptom after adjustment for other factors and confounders for both the comparison of S-R yes with

TABLE 3. Prevalence and adjusted odds ratios of selected self-reported medical conditions among 11,441 Gulf War veterans according to self-report of anthrax vaccination; also for 352 Gulf War veterans for whom anthrax vaccination is documented in DoD records

Conditions	Self-reported anthrax vaccination			Documented DoD (N = 352)	Adjusted odds ratio (95% CI) [†]		
	Yes (N = 4601)	Unknown (N = 3861)	No (N = 2979)		Anthrax vaccination Yes [‡]	Unknown [‡]	DoD*
Dermatitis	34.9	28.4	18.7	29.7	1.85 (1.64-2.09)	1.62 (1.44-1.83)	1.39 (1.06-1.82)
Gastritis	33.8	27.4	18.1	28.9	1.85 (1.64-2.09)	1.55 (1.38-1.75)	1.46 (1.11-1.92)
Arthritis	29.9	24.2	18.6	26.4	1.51 (1.33-1.70)	1.30 (1.14-1.47)	1.22 (0.93-1.62)
Frequent diarrhea	29.5	23.5	13.8	23.8	1.93 (1.69-2.20)	1.69 (1.48-1.93)	1.39 (1.03-1.86)
Hair loss	22.0	19.8	11.8	16.3	1.87 (1.62-2.16)	1.73 (1.50-1.99)	1.25 (0.90-1.73)
Migraines	21.2	19.1	13.6	15.9	1.42 (1.23-1.63)	1.37 (1.19-1.57)	0.96 (0.69-1.34)
Lumbago	18.5	16.3	9.4	14.4	1.83 (1.56-2.14)	1.82 (1.56-2.13)	1.30 (0.92-1.86)
Bronchitis	16.4	12.4	10.2	13.0	1.33 (1.14-1.56)	1.22 (1.04-1.42)	1.14 (0.79-1.65)

†CI: confidence interval.

‡Adjusted odds ratios (95% CI) were derived from logistic models. Reference category was self-report "No." Adjustment was made for number of vaccines received other than anthrax (0,1,...,5); gender (male vs. female); age in 1991 (<30 vs. ≥30 yrs.); race (white vs. other); marital status (single vs. ever married); rank (officer or warrant vs. enlisted); branch of service (non-ground troops vs. ground troops); unit component (active duty vs. National Guard or Reserves); current alcohol use (within past 12 months); and current cigarette use (within past 12 months).

*Adjusted odds ratios (95% CI) for documented vaccination by DoD records relative to self-report "No" were derived through stratified Cochran-Mantel-Haenszel (15) analysis. Adjustment was made for variables that were correlated with both exposure (anthrax vaccine) and outcome (medical condition). These confounding factors included number of vaccines received other than anthrax, (≤2 vs. ≥3); gender (male vs. female); branch of service (non-ground troops vs. ground troops); unit component (active duty vs. National Guard or Reserves).

TABLE 4. Prevalence and adjusted odds ratios of selected self-reported severe symptoms among 11,441 Gulf War veterans according to self-report of anthrax vaccination; also for 352 Gulf War veterans for whom anthrax vaccination is documented in DoD records

Symptoms	Self-reported anthrax vaccination			Documented DoD (N = 352)	Adjusted odds ratio (95% CI) [†]		
	Yes (N = 4601)	Unknown (N = 3861)	No (N = 2979)		Anthrax vaccination Yes [‡]	Unknown [‡]	DoD*
Joint aches or pain	21.8	16.8	9.7	16.5	2.05 (1.76-2.39)	1.76 (1.51-2.06)	1.50 (1.08-2.10)
Running nose	21.7	17.8	12.9	20.5	1.53 (1.33-1.76)	1.43 (1.24-1.64)	1.32 (0.96-1.81)
Headaches	21.4	17.7	11.3	16.8	1.69 (1.46-1.95)	1.53 (1.32-1.77)	1.18 (0.85-1.64)
Back pain/spasms	20.4	18.5	12.4	13.1	1.54 (1.34-1.78)	1.51 (1.31-1.74)	0.98 (0.69-1.40)
Anxious, irritable or upset	19.2	15.1	8.2	15.0	2.02 (1.72-2.38)	1.75 (1.49-2.06)	1.46 (1.03-2.07)
Excessive fatigue	18.8	13.4	7.1	14.3	2.19 (1.85-2.60)	1.83 (1.54-2.18)	1.62 (1.14-2.31)
Sleep difficulty	18.3	13.8	7.6	15.1	2.04 (1.72-2.40)	1.71 (1.44-2.02)	1.57 (1.11-2.21)
Awaken tired or worn out	17.8	13.8	7.8	14.0	1.86 (1.57-2.19)	1.62 (1.38-1.92)	1.33 (0.93-1.91)
Been depressed or blue	15.4	11.8	6.7	12.1	1.94 (1.62-2.31)	1.65 (1.38-1.97)	1.43 (0.99-2.06)
Reflux, heartburn, indigestion	14.8	11.9	6.7	12.0	1.93 (1.62-2.31)	1.72 (1.44-2.06)	1.65 (1.13-2.43)

[†]CI: confidence interval.[‡]Adjusted odds ratios (95% CI) were derived from logistic models. Reference category was self-report "No." Adjustment was made for number of vaccines received other than anthrax (0, 1, ..., 5); gender (male vs. female); age in 1991 (<30 vs. ≥30 yrs.); race (white vs. other); marital status (single vs. ever married); rank (officer or warrant vs. enlisted); branch of service (non-ground troops vs. ground troops); unit component (active duty vs. National Guard or Reserves); current alcohol use (within past 12 months); and current cigarette use (within past 12 months).

*Adjusted odds ratios (95% CI) for documented vaccination by DoD records relative to self-report "No" were derived through stratified Cochran-Mantel-Haenszel (15) analysis. Adjustment was made for variables that were correlated with both exposure (anthrax vaccine) and outcome (severe symptom). These confounding factors included number of vaccines received other than anthrax, (≤2 vs. ≥3); gender (male vs. female); branch of service (non-ground troops vs. ground troops); unit component (active duty vs. National Guard or Reserves).

the reference category S-R no as well as for the comparison of S-R unknown with S-R no. Again, when we compare the "Documented DoD Group" with S-R no, the associations disappear for five of the ten symptoms (Table 4). The ORs, adjusted for number of vaccines received other than anthrax, gender, ground vs. non-ground troops, and unit component show no association between documented anthrax vaccination and symptoms of severe degree for five of the ten symptoms. From a non-parametric viewpoint, however, for four of the four indices (Table 2), for seven of the eight medical conditions (Table 3), and for nine of

the ten symptoms (Table 4), the adjusted odds ratios are above 1.0.

Next, we analyze the role perception of exposure plays with over-reporting. In Table 5, the prevalences of the four health care indices and top ranked eight major conditions are presented for the "Documented DoD Group," stratified by the three self-reported responses. For each of the 12 indices/conditions, the prevalence for S-R yes group is greater than the prevalence for the S-R no group. In Table 6, the prevalences of the major symptoms are presented in a similar manner; for nine of the ten symptoms, the prevalence for S-R yes is greater than the prevalence for S-R no. This consistent pattern of the prevalences for the self-reported

TABLE 5. Prevalence of disability, health care utilization, and selected medical conditions among 352 Gulf War veterans for whom anthrax vaccination records exist in DoD stratified by self-reported response to question on anthrax vaccination

Indices/conditions	Documented DoD N = 352		
	Yes N = 260	Unknown N = 58	No N = 34
Functional impairment	30.3	13.8	14.7
Limitation of employment	19.9	12.3	5.9
Clinic visit	58.1	41.4	47.1
Hospitalization	10.0	8.6	5.9
Dermatitis	31.2	28.1	20.6
Gastritis	32.6	20.7	14.7
Arthritis	29.3	19.0	17.6
Frequent diarrhea	28.8	12.1	5.9
Hair loss	17.1	17.2	8.8
Migraines	17.6	12.3	8.8
Lumbago	14.5	17.2	8.8
Bronchitis	14.6	6.9	11.8

Significance probability for Wilcoxon signed ranks test, $p < .01$ (2-tailed) (17).

TABLE 6. Prevalence of severe symptoms among 352 Gulf War veterans for whom anthrax vaccination records exist in DoD stratified by self-reported response to question on anthrax vaccination

Symptoms	Documented DoD N = 352		
	Yes N = 260	Unknown N = 58	No N = 34
Joint aches pain	17.7	12.1	15.2
Runny nose	22.8	10.3	20.6
Headaches	18.1	17.5	5.9
Back pain/spasms	14.2	12.1	5.9
Anxious, irritable or upset	18.0	8.6	2.9
Excessive fatigue	17.4	6.9	2.9
Sleep difficulty	17.8	8.6	5.9
Awaken tired or worn out	17.1	6.9	2.9
Been depressed or blue	14.2	6.9	5.9
Reflux, heartburn, indigestion	12.0	10.5	14.7

Significance probability for Wilcoxon signed ranks test, $p < .01$ (2-tailed) (17).

exposure groups is considered as evidence of reporting bias, $p < .01$.

DISCUSSION

In a health survey of 15,000 Gulf War veterans, we found significant differences in the prevalence for almost all symptoms, functional status, and disease status categories between those who reported having received the anthrax vaccine ($n = 4601$) and those who did not so report ($n = 2979$). Information on the receipt of anthrax vaccine was collected from the veteran through the postal survey instrument or through a telephone interview. As in any survey, self-reported data need to be evaluated for a possibility of recall bias (18).

The self reported anthrax vaccination data collected in the National Health Survey and a DoD list of Gulf War veterans who were documented as vaccinated allowed us to evaluate the possible recall bias. For the small group of 352 veterans who responded to the survey and were also on the DoD list, we have their responses to the question on anthrax vaccination by self-report. In this group, 34 (9.7%) self-reported "no, not vaccinated for anthrax," another 56 (15.9%) self-reported "don't know," while 260 (73.9%) self-reported "yes vaccinated"; the remaining 2 (0.6%) did not answer the anthrax vaccine question. Based on the data, the sensitivity of S-R could be calculated as 73.9% ($260/352 \times 100$) and the false-negative of S-R, 26.1%. However, since we do not have a "documented not vaccinated" group, we could not calculate the specificity or the false-positive rate. During the Gulf War, there were not widespread procedures in place for maintaining immunization records. Many expert panels have recommended efforts to improve record keeping and environmental monitoring in future deployments (19-22).

A higher prevalence of any health outcome associated with anthrax vaccination is expected in the "Documented DoD Group" of 352 veterans more frequently than "Self-Report, yes" group of 4601 veterans because all of the 352 veterans are considered vaccinated, while some unknown number of "Self-Report, yes" veterans were not vaccinated, unless the specificity of self report is nearly 100%. The 100% specificity is unlikely because DoD estimated approximately 150,000 of 697,000 (22%) Gulf veterans received at least one dose of anthrax vaccine, while in the population-based survey, 4601 of 11,441 (40%) respondents reported receiving anthrax vaccination. Without exception, "Self-Report, yes" group reported higher prevalence of each of 22 health outcomes presented in Tables 2, 3, and 4. When a comparison is made for each outcome between "Self-Report, yes" group ($n = 4601$) and "Self-Report, yes" among "Documented

DoD Group" ($n = 260$), there is no significant difference in prevalence for 21 of the 22 health outcomes.

Stratification of the "Documented DoD Group" into the three self-reported responses yields further demonstration of the effect of perception of vaccination on over-reporting. If the prevalence in the "S-R yes" group is higher than in the "S-R no" group, one may conclude that the difference is due to perception rather than to actual effect of the anthrax vaccine. Conversely, if there were no difference in the prevalence of a given outcome by self-reported anthrax vaccination status within the "Documented DoD Group," this may lead to the conclusion that the significant association found for the corresponding outcome in the larger samples in Tables 2, 3 and 4 could not be due to reporting bias. The consistent pattern of the higher prevalence of abnormal outcomes in the "S-R yes" group compared with the "S-R no" group (signed-ranks test) for all outcomes summarized (Tables 5 and 6) is considered as evidence for rejecting the hypothesis of no reporting bias.

In summary, this survey data along with the DoD list of Gulf War veterans who received anthrax vaccine provide an opportunity to evaluate the long-term health consequences of anthrax vaccination. Although those who reported having received the vaccine reported higher prevalence of adverse health outcomes in all instances, the increases are likely due to reporting bias. The possibility of a reporting bias should be carefully considered when one evaluates the health consequences of anthrax vaccination based on self-reported vaccination data.

This project received support from the Medical Research Service, Office of Research and Development, Department of Veterans Affairs.

REFERENCES

1. Christopher GW, Cieslak TJ, Pavlin JA, Eitzen EM Jr. Biological warfare: A historical perspective. *JAMA*. 1997;278:412-417.
2. Committee on Veterans' Affairs. US Senate. Report of the Special Investigation Unit on Gulf War Illnesses. 105th Congress, 2nd session, S. Prt. 105-139/Pt. 2. Oct 5-9, 1998, Washington, DC: Government Printing Office; 1998.
3. Fulco CE, Liverman CT, Sox HC, eds. Gulf War and Health. v.1. Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines. Washington DC: Institute of Medicine, National Academy Press; 2000.
4. Hoffman K. Surveillance for adverse events associated with anthrax vaccination, US Department of Defense, 1998-2000. *Morb Mortal Wkly Rep*. 2000;49(16):341-345.
5. Pittman PR, Hack D, Mangiafico J, Gibbs P, McKee Jr. KT, Friedlander AM, Sjogren MH. Antibody response to a delayed booster dose of anthrax vaccine and botulinum toxoid. *Vaccine*. 2002;20:2107-2115.
6. Wiesen AR, Littell CT. Relationship between prepregnancy anthrax vaccination and pregnancy and birth outcomes among US Army Women. *JAMA*. 2002;287:1556-1560.

7. Joellenbeck LM, Zwanziger LL, Durch JS, Strom BL, eds. *The Anthrax Vaccine: Is it Safe? Does it work?* Washington DC: Institute of Medicine, National Academy Press; 2002.
8. OSAGWI (Office of the Special Assistant for Gulf War Illnesses). *Military Medical Recordkeeping during and after the Gulf War. Interim Report.* Washington, DC: US Department of Defense; 1999.
9. Kang HK, Mahan CM, Lee KY, Magee CA, Murphy FM. Illnesses among United States Veterans of the Gulf War: A Population Based Survey of 30,000 Veterans. *J Occup Environ Med.* 2000;42:491-501.
10. Kang HK, Magee CA, Mahan CM, Lee KY, Murphy F, Jackson LJ, et al. Pregnancy outcomes among US Gulf War veterans: a population-based survey of 30,000 veterans. *Ann Epidemiol.* 2001;11:504-511.
11. Kang HK, Mahan CM, Lee KY, Murphy FM, Simmens SJ, Young HA, et al. Evidence for a deployment related Gulf War Syndrome by factor analysis. *Arch Environ Health.* 2002;57:61-68.
12. Kang HK, Natelson BH, Mahan CM, Lee KY, Murphy FM. Post-traumatic Stress Disorder and Chronic Fatigue Syndrome-like illness among Gulf War Veterans: A population-based survey of 30,000 Veterans. *Am J Epidemiol.* 2003;157:141-148.
13. Kang HK, Dalager NA, Ishii EK, Mahan CM, Bullman TA. The role of sexual harassment and assault in PTSD among Gulf War Veterans. Submitted for publication.
14. Cameron L, Leventhal EA, Leventhal H. Seeking medical care in response to symptoms and life stress. *Psychosom Med.* 1995;57:37-47.
15. SAS Institute Inc. *SAS OnlineDoc. Version 8.* Cary, NC: SAS Institute Inc; 1999.
16. Stokes ME, Davis CS, Koch GG. *Categorical Data Analysis Using the SAS System.* 2nd ed. Cary, NC: SAS Institute Inc.; 2000.
17. Lehmann EL. *Nonparametrics: Statistical Methods Based on Ranks.* San Francisco: Holden-Day, Inc; 1975, 123-32.
18. McCauley LA, Jous SK, Spencer PS, Lasarev M, Shuell T, and Members of the Portland Environmental Hazards Center. Strategies to assess validity of self-reported exposures during the Persian Gulf War. *Environ Res.* 1999;81:195-205.
19. Institute of Medicine. *Strategies to Protect the Health of Deployed US Forces: Medical Surveillance, Record Keeping, and Risk Reduction.* Washington, DC: National Academy Press; 1999.
20. National Research Council. *Strategies to Protect the Health of Deployed US Forces: Analytical Framework for Assessing Risks.* Washington, DC: National Academy Press; 2000.
21. National Research Council. *Strategies to Protect the Health of Deployed US Forces: Detecting, Characterizing, and Documenting Exposures.* Washington, DC: National Academy Press; 2000.
22. National Research Council. *Strategies to Protect the Health of Deployed US Forces: Force Protection and Decontamination.* Washington, DC: National Academy Press; 2000.