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Research Paper

Self-reported adverse health events following smallpox vaccination in a large prospective study of US military service members

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Abbreviations: CI, confidence interval; CMI, chronic multisymptom illness; DMDC, Defense Manpower Data Center; GWOT, Global War on Terrorism; OR, odds ratio; PCL-C, posttraumatic stress disorder (PTSD) Checklist-Civilian Version; PHQ, Patient Health Questionnaire; SF-36V, Medical Outcomes Study Short Form 36-Item Health Survey for Veterans

Key words: smallpox vaccine, questionnaires, military medicine, longitudinal studies, chronic disease, quality of life

In December 2002, the Department of Defense re-instituted smallpox vaccination for US military forces following growing concerns that smallpox might be employed as a bioterrorist weapon. More than one million service members have been given the smallpox vaccine since 2002, although there have been concerns about the safety of the vaccine. Using a large self-reported prospective database, this analysis investigated a wide variety of self-reported health outcomes and possible association with smallpox vaccination. After confirming self-reported vaccination history with electronic vaccine data, 40,472 individuals were included in the analyses, 8,793 of whom received the smallpox vaccine and 31,679 who did not. No significant adverse associations between smallpox vaccination and self-reported health outcomes, including mental and physical functioning, cardiovascular diseases, and autoimmune disorders, were found. These findings complement studies that utilize other data sources, such as electronic hospitalization records, and may be reassuring to health care providers and those who receive the smallpox vaccination.

Introduction

Smallpox immunization was first implemented in the United States military as early as 1777 and continued until 1990.¹ Millions of ordinary US citizens were routinely immunized against smallpox until the global eradication program was discontinued in 1971.² During this time of routine vaccination, acute adverse health events associated with smallpox vaccination were thoroughly described.³ Mild adverse events included swelling and tenderness of the regional lymph nodes, fever, and autoinoculation from the primary

vaccination site.³ Moderate to severe adverse reactions include bullous erythema multiforme (Stevens-Johnson syndrome), eczema vaccinatum, generalized vaccinia, progressive vaccinia, and postvaccinal encephalitis.³

More recently, the Department of Defense resumed smallpox vaccination for US military forces amid growing concerns that smallpox might be employed as a bioterrorist weapon.⁴ Following reinstatement, reported adverse events were generally mild in nature, with the exception of an increased risk of myopericarditis predominantly among white males aged 21–44 years of age. Onset of myopericarditis symptoms in these cases occurred between 2 to 25 days following primary vaccination.^{5–9}

Most evaluations of vaccine safety rely on case series or retrospective reviews of acute health care. In contrast, the Millennium Cohort Study, the largest prospective study in military history designed to follow over 140,000 US service members for 21 years from 2001 through 2022, provides a unique opportunity to evaluate a wide range of subacute or chronic health outcomes potentially associated with smallpox vaccine.¹⁰

Results

Of the 55,021 Millennium Cohort participants who completed both a baseline and follow-up questionnaire, 45,284 had concordant self-reported and electronic smallpox vaccination records. Individuals vaccinated before taking their baseline survey ($n = 74$), and individuals vaccinated during the 30 days period prior to starting or while taking their follow-up survey ($n = 283$) were excluded. In addition, individuals who deployed to the Global War on Terrorism (GWOT) before completing their baseline survey ($n = 2,378$), completed their follow-up survey during a deployment ($n = 1,672$), or who were missing demographic or military covariate data ($n = 405$) were excluded. After exclusion criteria were applied, 40,472 individuals remained for analysis, 8,793 of whom received the smallpox vaccine and 31,679 who did not.

The population was stratified by deployment status to GWOT, and characteristics of vaccinated and unvaccinated individuals

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Table 1 **Demographic characteristics of Millennium Cohort Study participants by smallpox vaccination status**

Baseline Characteristics	Deployed to GWOT				Not deployed to GWOT			
	Vaccinated n = 7,003		Unvaccinated n = 2,352		Vaccinated n = 1,790		Unvaccinated n = 29,327	
	n	%*	n	%	n	%	n	%
Gender								
Male	5,694	81.3	1,883	80.1	1,256	70.2	20,042	68.3
Female	1,309	18.7	469	19.9	534	29.8	9,285	31.7
Birth year								
Before 1960	1,056	15.1	511	21.7	400	22.3	8,242	28.1
1960-1969	2,814	40.2	1,001	42.6	760	42.5	11,676	39.8
1970-1979	2,730	39.0	751	31.9	530	29.6	8,429	28.7
1980 or later	403	5.8	89	3.8	100	5.6	980	3.3
Marital status								
Not married	2,552	36.4	734	31.2	642	35.9	9,537	32.5
Married	4,451	63.6	1,618	68.8	1,148	64.1	19,790	67.5
Race/ethnicity								
White non-Hispanic	4,924	70.3	1,740	74.0	1,260	70.4	21,081	71.9
Black non-Hispanic	761	10.9	218	9.3	185	10.3	3,586	12.2
Other	1,318	18.8	394	16.8	345	19.3	4,660	15.9
Service								
Army	3,705	52.9	738	31.4	1,035	57.8	13,781	47.0
Air Force	2,415	34.5	1,174	49.9	416	23.2	8,521	29.1
Navy and Coast Guard	535	7.6	381	16.2	300	16.8	5,812	19.8
Marine Corps	348	5.0	59	2.5	39	2.2	1,213	4.1
Rank								
Enlisted	5,203	74.3	1,660	70.6	1,208	67.5	21,056	71.8
Officer	1,800	25.7	692	29.4	582	32.5	8,271	28.2
Occupational category								
Combat specialists	1,715	24.5	561	23.9	395	22.1	5,354	18.3
Health care specialists	563	8.0	152	6.5	484	27.0	3,849	13.1
Other occupation	4,725	67.5	1,639	69.7	911	50.9	20,124	68.6

GWOT, global war on terrorism; *Percentages rounded and may not sum to 100.

within each group are shown in Table 1. Notably, a higher proportion of vaccinees were younger, not married, and in the Army. Frequencies of selected, new-onset self-reported health conditions at follow-up were examined by deployment and vaccination status (Table 2).

Adjusted odds ratios of self-reported new-onset health conditions among smallpox-vaccinated participants compared to unvaccinated participants stratified by deployment status are presented in Table 3. Only one significant association was observed between smallpox vaccination status and the self-reported new-onset health conditions. Deployed vaccinees were significantly less likely to report "other autoimmune disorders" including multiple sclerosis, lupus, ulcerative colitis, rheumatoid arthritis, and Crohn's disease between baseline and follow-up than were deployed, unvaccinated individuals.

Discussion

Since December 2002, approximately 1.2 million US military members have been inoculated against smallpox as part of a national program to immunize health care workers, first responders, and military personnel against the potential use of this virus as a biological weapon.¹¹ The resumption of smallpox vaccinations has raised concerns about this vaccine's safety for veterans and the general public. Reports have suggested an increased risk for myopericarditis.^{5,7,8}

Other short-term morbidities may be associated with the smallpox vaccine as well.^{4,12} Although smallpox vaccinations are currently being monitored for short-term adverse events,^{13,14} no surveillance system is in place to monitor potential long-term adverse outcomes. Using data from Millennium Cohort Study responders, the current report describes an examination of potential long-term subjective health consequences of smallpox vaccination. This investigation found no significant increase in self-reported symptoms or conditions associated with smallpox vaccination over the average 2.7 years follow-up period.

A primary objective of this study was to investigate whether smallpox vaccination causes a decline in physical and/or mental functioning as measured by the Medical Outcomes Study Short Form 36—Item Health Survey for Veterans (SF-36V). This objective was established because previous studies have reported that 20–40% of smallpox vaccine recipients report headaches following smallpox vaccination.^{12,15,16} Additionally, a postvaccination surveillance study of more than 900 laboratory workers found frequent reports of musculoskeletal pain and fatigue.¹⁵ However, no differences were found in SF-36V mental component or physical component summary scores among deployed and nondeployed smallpox vaccinees when compared with unvaccinated peers; nor were there increased odds for mental health disorders, symptoms of chronic multisymptom

Table 2 **Frequency distribution of new-onset outcomes, stratified by smallpox vaccination and deployment status among Millennium Cohort Study participants**

Category*	Deployed to GWOT				Not deployed to GWOT			
	Vaccinated		Unvaccinated		Vaccinated		Unvaccinated	
	n	%	n	%	n	%	n	%
Mental component summary score [†]								
No change	4,040	59.1	1,408	61.2	995	57.1	17,259	60.2
Increased by 5 or more points	1,076	15.7	389	16.9	338	19.4	5,170	18.0
Decreased by 5 or more points	1,718	25.1	505	21.9	411	23.6	6,240	21.8
Physical component summary score [†]								
No change	4,476	65.5	1,514	65.8	1,141	65.4	18,716	65.3
Increased by 5 or more points	964	14.1	331	14.4	272	15.6	4,912	17.1
Decreased by 5 or more points	1,394	20.4	457	19.9	331	19.0	5,041	17.6
Mental health disorder [‡]								
No	5,601	89.5	1,916	91.9	1,456	91.7	23,181	91.7
Yes	657	10.5	169	8.1	132	8.3	2,086	8.3
Symptoms of CMI [§]								
No	5,334	85.1	1,872	88.2	1,444	91.0	23,045	90.0
Yes	933	14.9	250	11.8	143	9.0	2,575	10.1
Chronic fatigue syndrome [¶]								
No	6,808	99.2	2,304	99.3	1,740	99.6	28,424	99.2
Yes	56	0.8	17	0.7	7	0.4	224	0.8
Headache ^{¶, #, **}								
No	5,121	87.6	1,786	90.2	1,328	90.3	21,348	90.9
Yes	722	12.4	194	9.8	143	9.7	2,148	9.1
Chest pain ^{¶, #, **}								
No	6,084	94.0	2,081	94.9	1,585	95.6	25,490	95.3
Yes	392	6.1	111	5.1	73	4.4	1,255	4.7
Heart condition ^{¶, ††}								
No	6,273	96.8	2,084	96.3	1,564	96.8	25,265	96.3
Yes	208	3.2	80	3.7	52	3.2	960	3.7
Hypertension [¶]								
No	6,105	94.9	2,057	94.4	1,518	93.0	24,086	93.5
Yes	331	5.1	121	5.6	114	7.0	1,683	6.5
Anemia [¶]								
No	6,640	99.2	2,251	99.1	1,665	99.1	26,969	98.6
Yes	52	0.8	21	0.9	15	0.9	371	1.4
Diabetes [¶]								
No	6,862	99.5	2,304	99.1	1,748	99.2	28,364	99.0
Yes	37	0.5	21	0.9	14	0.8	292	1.0
Other autoimmune disorder ^{¶, ††}								
No	6,642	98.6	2,211	97.8	1,706	98.6	27,144	97.8
Yes	98	1.5	49	2.2	25	1.4	608	2.2

CMI, chronic multisymptom illness; GWOT, Global War on Terrorism; PHQ, Patient Health Questionnaire (PHQ). * Sample size changes for each outcome based on the number missing the outcome or reported having the outcome at baseline. Percentages rounded and may not sum to 100. † No change = a <5 point change on the MCS or PCS score from first to second survey. ‡ Excludes alcohol abuse. § Defined as reporting persistent or recurring problems with one or more symptoms from at least two of the following clusters: general fatigue, mood and cognitive abnormalities, and musculoskeletal pain. ¶ Self-reported positive response to "In the last three years, has your doctor or other health professional told you that you have any of the following conditions?" # Self-reported response to "bothered a lot" to "During the last four weeks, how much have you been bothered by any of the following problems?" ** Self-reported positive response to "During the last 12 months, have you had persistent or recurring problems with any of the following conditions?" †† Excludes chest pain. ‡‡ Multiple sclerosis, lupus, ulcerative colitis, rheumatoid arthritis, Crohn's disease.

illness (CMI), chronic fatigue syndrome, or headache among smallpox vaccinated compared with unvaccinated US service members. These findings provide strong evidence that most symptoms of headache, musculoskeletal pain, and fatigue do not lead to long-term decrements in mental or physical functioning.

In this study, no association was found between smallpox vaccination and chest pain or a heart condition. This may indicate that either few myopericarditis cases are being diagnosed as either

chest pain or a heart condition, or that a significant number of other chest pain or heart condition etiologies dilute any association between smallpox vaccination and any chest pain or heart condition attributable to myopericarditis. The lack of association found here does not refute the relationship between smallpox vaccination and myopericarditis; it may only imply that such cases are either too infrequent to be detected in this sample, or chest pain in such cases resolves over time.

The associations between smallpox vaccination and autoimmune diseases were also examined, including diabetes, and a combined “other” group of autoimmune disorders. Although no associations were found between diabetes and smallpox vaccination, a significantly lower odds ratio was found for other autoimmune disorders among the deployed, vaccinated participants than among deployed, unvaccinated participants. This category combined multiple sclerosis, lupus, ulcerative colitis, rheumatoid arthritis, and Crohn’s disease. While it is unlikely that deployers who are vaccinated are less likely to develop an autoimmune disease, it is possible that some of the unvaccinated participants developed one of these autoimmune diseases after completing the first questionnaire, which precluded them from receiving a smallpox vaccination. This could have artificially inflated the rate of autoimmune disorders among the unvaccinated group. There seems to be no plausible biological mechanism for a protective effect of developing fewer autoimmune diseases among vaccinated deployers. The significance of this association could also be due to chance, as a result of multiple comparisons.

These analyses did have some limitations. The Millennium Cohort response rate to enrollment invitation was 37%, and therefore participants may not be representative of the US military in general.¹⁰ Recent reports confirm, however, that the Millennium Cohort baseline sample had minimal response bias and was representative of the larger military with respect to demographic, health, and exposure characteristics.^{10,17-25} Also, since smallpox vaccination is associated with deployment, and since deployment is health-dependent, stratification was applied in an attempt to mitigate the effect deployment may have on health, independent of smallpox vaccination. Furthermore, while the Millennium Cohort Study provides an excellent opportunity to examine health outcomes longitudinally, these data were not collected for the purposes of this specific study. For example, the study was never intended to analyze rare outcomes, nor was it possible to adjust for multiple vaccines, and with an average of 30 months between baseline and follow-up surveys, health outcomes with long latency may have been missed. Additionally, the timing between survey collection and vaccination was not controlled, thus individuals may have taken their baseline survey more than one year before receiving the vaccine, which may have allowed baseline factors to change prior to vaccination for reasons unrelated to vaccination. Finally, the use of standardized instruments for self-reported data as surrogate for clinician diagnosis is imperfect.

Despite these limitations, this study has several strengths. Previous research investigating health effects related to the smallpox vaccine have been primarily case studies or retrospective designs. The current study is the first large, prospective, epidemiologic investigation to report on potential associations between self-reported symptoms and conditions and smallpox vaccination. Ascertaining vaccination status by both electronic vaccination record and self-report should have reduced potential misclassification of exposure bias. The large sample of both men and women, along with many variables to adjust for confounding, allowed for a robust investigation of the potential association between self-reported symptoms and conditions with smallpox vaccination.

In summary, we identified a study population of more than 9,000 deployed and 31,000 nondeployed members of the Millennium Cohort Study with confirmed smallpox vaccination status. Analyses were stratified by deployment status to adjust for

possible confounding. No significant adverse associations were found between smallpox vaccination and self-reported health outcomes, including mental and physical functioning, cardiovascular diseases, and autoimmune disorders. These findings may be reassuring regarding smallpox vaccine safety, and complement studies that use other data sources to evaluate the relationship between smallpox vaccination and long-term health.

Methods

Study population and data sources. In 2001, the Millennium Cohort Study began to collect and evaluate population-based data on behavioral and occupational risk factors related to military service that might be associated with adverse health outcomes.^{10,26} Those invited to participate in the first panel were a randomly selected subgroup of all US military personnel serving in 2000. Service members who had deployed to Southwest Asia, Bosnia, or Kosovo between January 1, 1998, and September 1, 2000, members of the Reserve or National Guard, and women were oversampled to ensure sufficient power to detect differences in these smaller population subgroups.

The Millennium Cohort participants who consented and enrolled in the first panel and completed the first follow-up questionnaire between June 2004 and February 2006 ($n = 55,021$; 71%) were included in the current study. Participants were excluded from the analyses for the following reasons: (1) their self-reported vaccination status did not agree with their vaccination status in military electronic data; (2) they were vaccinated and/or deployed in support of the GWOT prior to starting the baseline questionnaire; (3) they were vaccinated during the 30 day period prior to starting or while taking their follow-up survey; (4) they had not completed their first deployment to GWOT at the time of their follow-up questionnaire; or (5) they had incomplete demographic, smallpox vaccination, or military-specific data. When available, self-reported data were used to supplement missing data from personnel records to minimize the number of participants removed from analyses due to missing data.

The Defense Manpower Data Center (DMDC) provided demographic and military-specific data from electronic personnel files, including gender, date of birth, marital status, race/ethnicity, deployment experience (no deployment experience in support of GWOT between 2001 and 2006 or deployment experience in support of GWOT between 2001 and 2006), rank, service component (active duty or Reserve/National Guard), service branch (Army, Air Force, Navy/Coast Guard, or Marine Corps), and primary military occupation.

Smallpox vaccination data. Self-reported smallpox vaccination status was obtained from the Millennium Cohort Study 2004-2006 questionnaire that asked, “In the past three years have you received the smallpox vaccine?” Vaccination status was confirmed through electronic smallpox vaccination records obtained from the Defense Enrollment Eligibility Reporting System at DMDC. Participants were classified as vaccinated if they endorsed vaccination in the questionnaire and if an electronic record of smallpox vaccination in the three years prior to completing the follow-up questionnaire was present in the DMDC vaccination database. Participants were classified as unvaccinated if they endorsed that they had not received the smallpox vaccination in the questionnaire and if there was no electronic record of smallpox vaccination in the three years prior to completing the follow-up questionnaire in the DMDC vaccination database.

Table 3 Results of multivariable logistic regression: Adjusted odds of self-reported health conditions in smallpox vaccinees by deployment status

Category	Deployed to GWOT OR* (95% CI)	Not deployed to GWOT OR* (95% CI)
Mental component summary score [†]		
No change	1.00	1.00
Increased by 5 or more points	0.89 (0.77-1.02)	1.14 (1.00-1.30)
Decreased by 5 or more points	0.98 (0.87-1.11)	1.13 (1.00-1.27)
Physical component summary score [†]		
No change	1.00	1.00
Increased by 5 or more points	0.90 (0.77-1.03)	0.93 (0.81-1.07)
Decreased by 5 or more points	0.90 (0.80-1.03)	1.11 (0.98-1.27)
Mental health disorder [‡]		
No	1.00	1.00
Yes	0.96 (0.79-1.15)	0.98 (0.81-1.18)
Symptoms of CMI [§]		
No	1.00	1.00
Yes	0.97 (0.83-1.14)	0.89 (0.74-1.06)
Chronic fatigue syndrome [¶]		
No	1.00	1.00
Yes	0.78 (0.45-1.38)	0.53 (0.25-1.12)
Headache ^{¶, #, **}		
No	1.00	1.00
Yes	1.03 (0.86-1.23)	1.03 (0.86-1.24)
Chest pain ^{¶, #, **}		
No	1.00	1.00
Yes	0.89 (0.71-1.12)	0.92 (0.72-1.17)
Heart condition ^{¶, ††}		
No	1.00	1.00
Yes	0.81 (0.61-1.06)	0.90 (0.68-1.20)
Hypertension [¶]		
No	1.00	1.00
Yes	0.92 (0.73-1.14)	1.13 (0.93-1.38)
Anemia [¶]		
No	1.00	1.00
Yes	0.74 (0.43-1.26)	0.68 (0.40-1.14)
Diabetes [¶]		
No	1.00	1.00
Yes	0.58 (0.33-1.01)	0.86 (0.50-1.47)
Other autoimmune disorder ^{¶, ††}		
No	1.00	1.00
Yes	0.52 (0.36-0.75)	0.70 (0.47-1.04)

Abbreviations: CMI, chronic multisymptom illness; CI, confidence interval; GWOT, global war on terrorism; OR, odds ratio; PHQ, patient health questionnaire. * Adjusted for smoking status, possible alcohol abuse, rank, and occupation at baseline as well as gender, birth year, and combat exposure. † No change = a change of less than 5 points on the MCS or PCS score from first to second survey. ‡ Excludes alcohol abuse. § Defined as reporting persistent or recurring problems with one or more symptoms from at least two of the following clusters: general fatigue, mood and cognitive abnormalities, and musculoskeletal pain. ¶ Self-reported positive response to "In the last three years, has your doctor or other health professional told you that you have any of the following conditions?" # Self-reported response "bothered a lot" to "During the last 4 weeks, how much have you been bothered by any of the following problems?" ** Self-reported positive response to "During the last 12 months, have you had persistent or recurring problems with any of the following conditions?" †† Excludes chest pain. ‡‡ Multiple sclerosis, lupus, ulcerative colitis, rheumatoid arthritis, Crohn's disease.

Self-reported health outcomes. The baseline and follow-up Millennium Cohort Study questionnaires assess physical health, mental health, and other health outcomes. The SF-36V, which is a modified version of the Short Form 36 and part of the Millennium

Cohort questionnaire, was used to compare changes in mental and physical health.²⁷⁻³¹ Like the original SF-36, the SF-36V includes eight health scales that can be summarized into two summary scores, the mental component summary and the physical component summary.^{32,33} Higher scores are associated with better health status. Changes in summary scores between baseline and follow-up were examined.

The Millennium Cohort baseline questionnaire includes the question, "Has your doctor or other health care professional ever told you that you have any of the following conditions?" This question was used to determine if participants reported having chronic fatigue syndrome, headaches, chest pain, a heart condition, hypertension, anemia, diabetes, or other autoimmune disorders at baseline. Participants who reported "no" on the baseline questionnaire for one of these conditions were included in the study for analysis of that particular condition. On the follow-up questionnaire, participants who reported "yes" to the question "In the last three years, has your doctor or other health care professional told you that you have any of the following conditions?" were included in the study as having new-onset of the condition of interest. Two additional questions on the survey instrument were also available to define new-onset headaches and/or chest pain between baseline and follow-up. Finally, symptoms of CMI were defined as new onset of reporting persistent or recurring problems with one or more symptoms from at least two of the following clusters: general fatigue, mood and cognitive abnormalities, and musculoskeletal pain.³⁴

A measure of mental health was based on two standardized instruments: the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PHQ)³⁵⁻³⁷ and the posttraumatic stress disorder (PTSD) Checklist-Civilian Version (PCL-C).^{38,39} Using standardized scoring algorithms,³⁵⁻³⁷ the PHQ provides a psychosocial assessment based on scores of several health concepts. The PCL-C is a 17-item self-report measure of PTSD symptoms that requires responders to rate the severity of each symptom during the past 30 days on a 5-point Likert scale (from 1 = not at all to 5 = extremely). Participants were identified as having PTSD

if they reported a moderate or greater level of at least one intrusion symptom, three avoidance symptoms, and two hyperarousal symptoms,⁴⁰ and had a total score of 50 or more on a scale of 17 to 85.^{38,39,41,42} Using this instrument with a cutoff

of 50 has been reported to be highly specific (specificity = 99%) in comparison with other instruments and other cutoff values.⁴³ For the purposes of this report, major depression, panic disorder, other anxiety disorders, bulimia nervosa, binge-eating disorders, and PTSD are reported in one mental health variable.

Statistical analysis. A descriptive investigation was completed to compare vaccinated and unvaccinated participants, stratified by GWOT deployment experience. Multivariable logistic regression was used to assess associations between self-reported health outcomes and vaccination status, adjusting for gender, birth year, rank, occupation, combat exposure, self-reported smoking status, and alcohol abuse at baseline.

Regression diagnostics, including examining covariates for multicollinearity and goodness of fit test, were performed. All data analyses were completed using SAS Version 9.1.3 (SAS Institute, Inc., Cary, NC).

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Note

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14. ABSTRACT (maximum 200 words)

In December 2002, the Department of Defense re-instituted smallpox vaccination for US military forces following growing concerns that smallpox might be employed as a bioterrorist weapon. More than one million service members have been given the smallpox vaccine since 2002, although there have been concerns about the safety of the vaccine. Using Millennium Cohort study data, this prospective analysis investigated a wide variety of self-reported health outcomes and possible association with smallpox vaccination. After confirming vaccination history with electronic vaccine data, 40,472 individuals were included in the analyses, 8,793 of whom received the smallpox vaccine and 31,679 who did not. No significant adverse associations between smallpox vaccination and self-reported health outcomes, including mental and physical functioning, cardiovascular diseases, and autoimmune disorders, were found. These findings complement studies that utilize other data sources, such as electronic hospitalization records, and may be reassuring to health care providers and those who receive the smallpox vaccination.

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smallpox vaccine, questionnaires, military medicine

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