Anthrax Vaccination and Risk of Optic Neuritis in the United States Military, 1998-2003

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Background: Numerous case reports have suggested a possible association between optic neuritis and receipt of several different vaccines. The most frequently identified vaccines associated with optic neuritis in the literature are influenza and hepatitis B, and a report describing 2 US military cases suggests an association with the currently used anthrax vaccine (anthrax vaccine adsorbed).

Objective: To test the hypothesis that optic neuritis may be associated with anthrax, smallpox, hepatitis B, and influenza vaccines.

Design: We conducted a matched case-control study among US military personnel from January 1, 1998, through December 31, 2003, using the Defense Medical Surveillance System. Statistical associations between vaccine exposures and optic neuritis within 6-, 12-, and 18-week study intervals were estimated through multivariable conditional logistic regression analyses.

Subjects: A total of 1131 cases of optic neuritis and 3393 controls were matched by sex, military component, and deployment status.

Results: No statistically significant associations between optic neuritis and anthrax vaccine were observed for any of the 3 study intervals: 6-week interval (odds ratio [OR], 1.18; 95% confidence interval [CI], 0.74-1.87), 12-week interval (OR, 0.92; 95% CI, 0.63-0.35), and 18-week interval (OR, 0.81; 95% CI, 0.58-1.14). Furthermore, no difference in optic neuritis risk was detected when comparing those who received no dose, 1 dose, and 2 doses of anthrax vaccine. Similarly, no statistically significant associations were observed between optic neuritis and smallpox, hepatitis B, or influenza vaccines within any of the study intervals. No vaccine to vaccine interactions were statistically significant.

Conclusions: The results from this vaccine postmarketing surveillance investigation suggest that there is no association between optic neuritis and receipt of anthrax, smallpox, hepatitis B, or influenza vaccinations in the US military, whether these vaccines are administered alone or in combination. The negative findings presented here are important to the continuing discussions regarding the safety of these vaccines.

Arch Neurol. 2006;63:871-875
We excluded all persons with any of the optic neuritis case matched to 3 controls based on sex, deployment and Department of Defense.

DEFENSE MEDICAL SURVEILLANCE SYSTEM

The DMSS is an active surveillance system administered by the Department of Defense to integrate data from medical treatment facilities, vaccination centers, and military personnel offices worldwide. Inpatient and outpatient diagnosis data are coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and medical encounter data are most comprehensive for active-duty personnel.

STUDY DESIGN

A matched case-control study design was used with each optic neuritis case matched to 3 controls based on sex, deployment during the 18 weeks preceding the diagnosis date, and the military component in which the individual served (eg, active or reserve/National Guard). The protocol for this vaccine post-marketing surveillance investigation was approved by the Centers for Disease Control and Prevention (CDC) Institutional Review Board and reviewed by the Food and Drug Administration and Department of Defense.

DEFINITION AND ASCERTAINMENT OF CASES AND SELECTION OF CONTROLS

We defined optic neuritis cases as those having a first-time diagnosis of the following ICD-9-CM codes: optic neuritis, unspecified (377.30); optic papillitis (377.31); retrobulbar neuritis, acute (377.32); and optic neuritis, other (377.39) during the period between January 1, 1998, and December 31, 2003. We excluded all persons with any of the ICD-9-CM codes representing optic neuropathies related to nutrition, toxicity, meningococcal meningitis, and syphilis (ICD-9-CM codes 377.33, 377.34, 036.81, and 094.85, respectively). From these resultant 1799 cases, 604 were excluded for having diagnoses of ischemic and compressive optic neuropathies within 1 year prior to their first diagnosis of optic neuritis, or for having an injury to the eye or orbital region within 18 weeks of optic neuritis. A further 64 were excluded because they had not completed at least 18 weeks of military service before the diagnosis. Thus, we considered 1131 persons matched to 3393 controls (n=4524) as optic neuritis cases.

Defense Medical Surveillance System diagnostic histories and administrative data for all the remaining cases were reviewed by a neuro-ophthalmologist. Cases within a predefined category of unclassifiable diagnostic certainty (defined as those diagnosed with optic neuritis but having another concurrent optic condition [eg, glaucoma, retinal scar], having numerous MS, migraine, and psychiatric diagnoses, or having a prior diagnosis of MS, neuro-ophthalmologic review. Stratified analyses were conducted for study subjects by prior diagnosis of MS, military deployment during the 18-week period preceding optic neuritis diagnosis/index date, and military component.

Fewer cases than controls (5.7% vs 7.6%, respectively) were given the anthrax vaccine within 18 weeks of the diagnosis/index date (P=.02). Of those cases receiving the anthrax vaccine, 41 (64.1%) received 1 dose and 23 (35.9%) received 2 or more doses within this study interval. Among controls receiving the anthrax vaccine, 163 (63.4%) received 1 dose and 94 (36.6%) received 2 or more doses within the 18-week study interval. Correlation tests for the administration of these vaccines showed that anthrax and smallpox vaccines were the most frequently coadministered vaccines within the 18-week study interval (P = .31).

DEFINITION OF VACCINE EXPOSURE

We ascertained the date of each case’s first diagnosis of optic neuritis and determined all vaccinations received during each of the following 3 prior study intervals from the electronic record: 6 weeks (42 days), 12 weeks (84 days), and 18 weeks (126 days). For each of the 3 matched controls, we determined all vaccinations during the 3 intervals predating their index date. We focus on reporting statistical test results for the 18-week study interval because the onset of a vaccine-mediated optic neuritis would typically be expected to occur within this time period following vaccination, and of the 3 study intervals, this period is composed of the most vaccinations received by the study subjects.

RESULTS

The descriptive epidemiology of optic neuritis cases and their matched controls is presented in Table 1. Statistically significant differences between cases and controls were found for race, age, service branch, and occupational category.

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Table 2 presents results from the multivariable conditional logistic regression model, after adjusting for age, race, ethnicity, military service branch, occupational category, previous MS diagnosis, and other vaccinations (smallpox, hepatitis B, and influenza). A statistically non-significant negative association was observed (odds ratio [OR], 0.81; 95% confidence interval [CI], 0.58-1.14) between anthrax vaccine administration and optic neuritis for the 18-week study interval. In addition, no statistically significant associations were observed for anthrax vaccine administered during the 12- and 6-week study intervals (OR, 0.92; 95% CI, 0.63-1.35; and OR, 1.18; 95% CI, 0.74-1.87, respectively); however, there were progressively fewer study subjects available for each of these comparative analyses. Similarly, no statistically significant associations were observed between optic neuritis and prior receipt of smallpox, hepatitis B, or influenza vaccination within any of the 3 study intervals. No difference in adjusted risk of optic neuritis was detected when comparing those who received no doses of anthrax vaccine with those receiving 1 dose (OR, 0.82; 95% CI, 0.55-1.21), and to those receiving 2 or more doses during the 18-week study interval (OR, 0.81; 95% CI, 0.48-1.38). Furthermore, no vaccine to vaccine interactions achieved statistical significance in the final model. We conducted a separate analysis excluding those cases having unclassifiable diagnostic certainty and observed only minor differences between these results and the multivariate conditional logistic regression results for the full sample presented in Table 2. We also conducted separate stratified conditional multivariable analyses for only those study subjects who had no prior diagnosis of MS, were not deployed within the 18-month interval, and were in the active component of the US military. Again, no significant differences were observed between results for these strata and for the full sample. This investigation found no evidence that receipt of anthrax vaccine is associated with the onset of optic neuritis in the US military population. In addition, no statistically significant associations were observed between optic neuritis and prior receipt of smallpox, hepatitis B, and influenza vaccinations within any of the 3 study intervals. Moreover, no statistically significant interactive effect on optic neuritis risk was observed, and there were no significant differences in the risk for developing optic neuritis when we restricted our analysis to study subjects having high diagnostic certainty, no prior history of MS, no deployment in the prior 18-week interval, and only active component personnel. This vaccine postmarketing surveillance investigation of whether anthrax vaccine is possibly associated with optic neuritis in the US military was selected as a priority adverse event topic for study by the CDC’s Vaccine Analytic Unit with input from a workgroup of the National Vaccine Advisory Committee. With questions concerning the safety of anthrax vaccine raised by the media, by some scientists, and by some members of the Armed Forces, some scientists, and by some members of the Armed Forces.
In an expanded clinical evaluation, members of the An- 
cine alone (CDC, unpublished data, August 24, 2005). 
the authors were unable to detect common epitopes shared 
by both the anthrax vaccine and the retina/optic nerve 
in support of this hypothesized pathogenic mechanism. 

The CDC and Food and Drug Administration’s jointly 
administered, passive surveillance system, the Vaccine 
Adverse Event Reporting System, has received 7 reports 
of optic neuritis following receipt of the anthrax vac- 
cine alone (CDC, unpublished data, August 24, 2005). 
In an expanded clinical evaluation, members of the An-
trax Vaccine Expert Committee reviewed all Vaccine Ad-
verse Event Reporting System reports from 1998 through 
2001 considered possibly associated with the receipt of 
the anthrax vaccine. The authors suggested a possible 
association between optic neuritis and prior receipt of the 
anthrax vaccine, possibly as a result of a potential immune-mediated response to optic nerve 
antigens that was stimulated by the vaccine. However, 
the authors were unable to detect common epitopes shared 
by both the anthrax vaccine and the retina/optic nerve 
in support of this hypothesized pathogenic mechanism. 

In an analysis of DMSS diagnostic codes for anthrax-
immunized and nonimmunized US service personnel from 
1998 through 2000, Lange et al18 reported a statistically 
significant elevated postvaccination adjusted rate ratio 
of 2.74 (95% CI, 1.56-4.80) for the nonspecific 3-digit 
ICD-9-CM code 377 (disorders of optic nerve and visual 
pathways). The authors’ conclusions were limited by this 
broad definition of optic disorders and the lack of any 
diagnostic validation; nonetheless, the optic disorders re-
mained rare with a prevaccination diagnosis rate of 1 of 
100 000 person-years and a postvaccination diagnosis rate 
of 2.9 of 100 000 person-years. 

DeStefano et al2 investigated whether several vaccines 
were associated with MS and optic neuritis using the Vac-
cine Safety Datalink database. These investigators found 
no statistically significant increased risk associated with 
hepatitis B, tetanus, influenza, measles/mumps/rubella, 
measles, and rubella vaccines. Furthermore, no statisti-
cally significant associations were observed between the 
administration of these immunizations during 3 study in-
tervals (<1 year, 1-5 years, and >5 years) and the devel-
opment of MS or optic neuritis. The authors concluded 
that vaccinations do not cause central nervous system de-
myelination and do not trigger its clinical presentation 
among persons having subclinical disease, although other 
researchers contend that insufficient evidence exists from 
which to state this definitively. 

Particular strengths of this vaccine postmarketing sur-
veillance investigation included the availability of the large 
DMSS database for studying this extremely rare diagnos-
tic endpoint. No previously published epidemiologic study 
is known to have possessed a sufficiently large sample 
size to enable calculation of specific vaccine exposure risks 
within 6-, 12- and 18-week postvaccination intervals. Our 
investigation’s relatively brief exposure intervals tend to 
lesser the opportunity for chance causations to be in-
troduced in the analysis. It is well accepted that the on-
set of vaccine-mediated optic neuritis would typically oc-
cur within several weeks after vaccination. We were also 
able to adjust for any potential effects from other (small-
pox, hepatitis B, and influenza) vaccines administered to 
study subjects within the same study intervals as an-
thrax vaccine. In addition, we assessed individual ef-
fects and possible interactions between these vaccines. 

A possible weakness of our study is the omission to con-
duct a medical record review to confirm the diagnosis of 
optic neuritis. Nevertheless, we consider that the level of 
diagnostic validity was probably high because this spe-
cific condition is typically associated with an acute, se-
vere presentation which would likely result in the patient 
being clinically investigated and diagnosed by an ophthal-
mologist. While medical records were not reviewed as part 
of this study, we retrieved complete DMSS diagnostic 
histories of all cases, which were individually reviewed 
for diagnostic quality by an experienced neuro-ophtal-
mologist. In addition, when we repeated our analysis 
and excluded those cases suggested by this neuro-
ophthalmic review to be of an unclassifiable diagnostic va-
didity, the results did not change substantially. While some 
nondifferential misclassification of exposures or diag-
noses is possible, it is unlikely that it would have pro-
duced sufficient bias to change our results or conclu-
sions. We could not rule out an infectious cause for a 
minority of cases, particularly those having diagnosed 
chronic sinusitis or unspecified viral infections within 18 
weeks of the optic neuritis diagnosis. 

Compared with controls, subjects were more likely to 
be older than 35 years and less likely to fall within the 18-
to 25-year-old group. This age imbalance between cases 
and controls is significant in that demyelinating optic neu-
ritis generally has the highest incidence in persons younger 
than 35 years; however, it is not clear whether this age re-
relationship exists with potential vaccine-mediated optic neu-
ritis. We believe that any possible confounding effect of 
age was adequately controlled in the multivariable logis-
tic regression analyses, and using a continuous age vari-
able in the model produced almost identical, statistically 
non-significant results as those reported in Table 2. 

Finally, the lack of any appreciable differences be-
tween our multivariate conditional logistic regression re-
sults and the results from our separate analyses (which 
excluded those subjects having unclassifiable diagnostic 
certainty, prior diagnosis of MS, deployments within the 
18-month study interval, and reserve and National Guard 
personnel) suggest that the full sample results pre-
sented in Table 2 sufficiently explain the data. In sum-
mary, the results of this vaccine postmarketing surveil-
ance investigation contribute to evidence that there is 
no association between optic neuritis and anthrax, small-
pox, hepatitis B, and influenza vaccines, whether admin-
istered alone or in combination. 

Accepted for Publication: February 13, 2006.

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Acknowledgment: We thank the following individuals for their valuable contributions to this investigation: John Moran, MD, MPH, Frank DeStefano, MD, MPH, John Iskander, MD, MPH, Col Mark V. Rubertone, MD, MPH, Col John D. Grablestein, RPh, PhD, Col Renata J. M. Engler, MD, Robert Ball, MD, MPH, Dale R. Burwen, MD, MPH, and Emily Jane Woo, MD, MPH. We would like to specifically thank our prior and current National Vaccine Advisory Committee work group members Jeffrey P. Davis, MD, Mary Beth Koslap-Petraco, MS, CPNP, David S. Stephens, MD, and Gary D. Overturf, MD.

REFERENCES


Announcement

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