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ORIGINAL REPORT

Safety of anthrax vaccine: a review by the Anthrax Vaccine Expert Committee (AVEC) of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS)

John L. Sever*[1], Alan I. Brenner[2], Arnold D. Gale[3], Jerry M. Lyle[4], Lawrence H. Moulton[5] and David J. West[6]

[1]*Departments of Pediatrics, Obstetrics and Gynecology, Microbiology and Immunology, The Children's National Medical Center, George Washington University, School of Medicine, Washington, DC, USA*
[2]*Metro West Medical Center, Framingham, MA, USA*
[3]*Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA, USA*
[4]*1686 Chimney House Road, Reston, VA, USA*
[5]*Departments of International Health and Biostatistics, Room W5515, The Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD, USA*
[6]*406 W. Prospect Avenue, North Wales, PA, USA*

SUMMARY

Purpose To assess the safety of a licensed anthrax vaccine given to nearly 400 000 US military personnel, reports of adverse events (AEs) submitted to the Vaccine Adverse Event Reporting System (VAERS) were reviewed and evaluated medically.

Methods The Anthrax Vaccine Expert Committee (AVEC), a civilian panel of private-sector physicians and other scientists, reviewed 602 VAERS reports using a Delphic approach (structured expert consensus) to assess the causal relationship between vaccination and the reported AEs and sought to identify unexpected patterns in the occurrence of medically important events. Reports were entered into a database and used to profile AEs with respect to person, type/location, relative frequency, severity/impact, concomitant illness or receipt of other drugs or vaccines, and vaccine lot.

Results Nearly half the reports noted a local injection-site AE, with more than one-third of these involving a moderate to large degree of inflammation. Six events qualified as serious AEs (SAEs), and all were judged to be certain consequences of vaccination. Three-quarters of the reports cited a systemic AE (most common: flu-like symptoms, malaise, rash, arthralgia, headache), but only six individual medically important events were judged possibly or probably due to vaccine (aggravation of spondyloarthropathy (2), anaphylactoid reaction, arthritis (2), bronchiolitis obliterans organizing pneumonia).

Conclusions Since some cases of local inflammation involved distal paresthesia, AVEC recommends giving subcutaneous injections of AVA over the inferior deltoid instead of the triceps to avoid compression injury to the ulnar nerve. At this time, ongoing evaluation of VAERS reports does not suggest a high frequency or unusual pattern of serious or other medically important AEs. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS — anthrax vaccine; vaccine safety; Vaccine Adverse Event Reporting System (VAERS)

INTRODUCTION

Anthrax is a serious disease caused by the bacterium *Bacillus anthracis*. It occurs in three forms: cutaneous, gastrointestinal and inhalational.[1,2] Inhalational anthrax is of special concern because *B. anthracis*

* Correspondence to: John L. Sever, Departments of Pediatrics, Obstetrics and Gynecology, Microbiology and Immunology, The Children's National Medical Center, George Washington University, 111 Michigan Avenue, N.W., Washington, DC 20010-2970, USA. Tel: (202) 884-4132. Fax: (202) 884-3051.
E-mail: jsever@cnmc.org

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spores can easily be weaponized and dispersed in an aerosol.[3] Inhaled spores initiate an infection whose early symptoms resemble those of many benign respiratory infections. However, inhalational anthrax progresses rapidly, causing abrupt respiratory distress with hemorrhagic necrosis of pulmonary and thoracic tissues resulting in massive septicemia and toxemia. Mortality rates are high even with intensive antibiotic therapy and are nearly 100% without therapy. At least 17 nations are believed to have offensive biological weapons programs that could include *B. anthracis*,[4] and Iraq has specifically acknowledged weaponizing anthrax.[5] Recent illnesses and deaths in the US associated with exposure to spores of *B. anthracis* in mail further underscore the grave potential this bacterium has as an instrument of bioterrorism.

The Department of Defense (DoD) is vaccinating US Armed Forces personnel with a anthrax vaccine licensed in 1970 that previously had limited use.[6] As of December 1999, the Anthrax Vaccine Immunization Program (AVIP) had administered more than 1.3 million doses of vaccine to nearly 400 000 military personnel and civilian employees of DoD.[6] When AVIP is fully implemented, more than 2.2 million personnel (all of the 1.37 million Active duty forces and 890 000 selected members of the 1.35 million Reserve forces) will be scheduled to receive vaccine each year.[7]

Anthrax vaccine is made from a sterile filtrate of a microaerophilic culture of an attenuated, non-encapsulated, non-proteolytic strain of *B. anthracis*.[8,9] Protective antigen (PA) is the predominant protein immunogen in the vaccine, although vaccinated animals have also been shown to develop antibodies against other toxin proteins present in small amounts (e.g. lethal factor (LF) and edema factor (EF)).[10,11] The culture filtrate is adsorbed to aluminum hydroxide to create the final vaccine. Accordingly, this vaccine, Anthrax Vaccine Adsorbed, is denoted throughout the remainder of the paper as AVA. AVA is administered as a primary series of six subcutaneous injections at 0, 2 and 4 weeks and 6, 12 and 18 months, followed by annual booster injections.[6]

The mandate to vaccinate such a large population under AVIP has stimulated questions regarding the safety of AVA. For example, witnesses at a 1999 Congressional hearing expressed concern that recipients of AVA might be at increased risk of incurring medically important adverse events (AEs), including a chronic illness characterized by fatigue, sleep disturbance, neurologic complaints, cognitive dysfunction and other symptoms.[12] Citing data from human clinical studies and post-licensure use, FDA officials have concluded that AVA appears to be safe.[9,13,14]

Several kinds of studies are needed for comprehensive assessment of AVA safety and tolerability. Those involving self-reporting or direct monitoring of injection-site and systemic AEs following injection of AVA in several hundred or thousand vaccinees are useful for estimating the incidence and consequences of relatively common AEs.[9,15–18] However, additional surveillance or structured observational studies of very large numbers of vaccinees will be needed to detect rare AEs or to estimate precisely the incidence of less common AEs. One means of detecting uncommon AEs and gaining at least a qualitative sense as to whether some may be occurring at an unexpected frequency is through ongoing review of reports submitted to the Vaccine Adverse Event Reporting System (VAERS), a passive surveillance program founded in 1990 that is cooperatively implemented by the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC).[19,20,21] While subject to limitations inherent to all systems of passive surveillance (i.e. underreporting as well as incomplete, inaccurate, and biased reporting of events), a review of VAERS reports can at least (1) identify those AEs that healthcare providers or vaccinees feel are important enough to report, (2) generate a signal that some medically important event may be occurring at a higher than expected frequency, or (3) reveal trends in reporting (person, place, time) that may signify a safety problem (e.g. the association of an AE with one or a few lots of vaccine). That information then can be used to direct the development of large prospective or retrospective (case–control) studies capable of generating more precise and less biased estimates of the risk of an uncommon AE and its possible causal relationship to AVA.

The DoD issued a policy directive in April 1998 requiring Service healthcare providers to report to VAERS any event following receipt of AVA that resulted in hospitalization or loss of duty (LOD), as well as events suspected to have resulted from contamination of a vaccine lot.[22] It also encourages providers to report other AEs that appear to be unexpected either in nature or severity, and states that either the patient or a healthcare provider may directly submit a report to VAERS for any possible AE. To help ensure an objective evaluation of these reports, in June 1998 the Surgeon General of the United States Army requested that an independent civilian panel be created to perform ongoing medical assessment of VAERS reports concerning AVA.

The Department of Health and Human Services (DHHS) agreed to organize such a panel and, following a model established by the Canadian Advisory

Committee on Causality Assessment,[23] formed the Anthrax Vaccine Expert Committee (AVEC). Support for the first year of AVEC activity was provided to the Health Resources and Services Administration (HRSA) of the DHHS through an interagency agreement with the National Vaccine Program Office (NVPO), with funding for subsequent years provided through an interagency agreement with the DoD that specifies the HRSA has full independence with respect to the actions and decisions of AVEC.

The membership of AVEC consists of private-sector physicians and other scientists recruited through the Expert Witness Program of the Vaccine Injury Compensation Program of HRSA, who have expertise in the fields of statistics, epidemiology, infectious diseases, neurology, rheumatology, and vaccinology. AVEC has liaison members and support staff from the DHHS and the DoD, including representatives from the FDA/Center for Biologics Evaluation and Research, the CDC/National Immunization Program, the HRSA/National Vaccine Injury Compensation Program, and the Army Surgeon General's Office. The non-medical members of AVEC, liaison governmental members, and other support personnel play no role in assessing the causal relationship between AVA and an AE; that is the sole province of the medically-qualified civilian experts.

AVEC is charged with conducting an ongoing review of VAERS reports that describe AEs occurring after receipt of AVA. One objective of this review is to descriptively profile the reported AEs with regard to person (age, gender, Service), type/location (specific event/body system; local injection site reactions versus systemic events) relative frequency, severity/impact (need for medical assistance, loss of duty, classification of an event as serious), concomitant illness or receipt of other drugs or vaccines, and vaccine lot, and to look for associations that might warrant closer study and evaluation. A second objective is to medically evaluate each reported AE and, subject to limitations imposed by the incomplete information provided in many VAERS reports, to assess the causal relationship between an AE and prior receipt of AVA. While many of these judgements must be considered tentative, the process of assigning causality ratings is integral to one of AVEC's most important functions, i.e. to continually assess whether some serious or other medically important AE that may be causally related to receipt of vaccine seems to be occurring at an elevated frequency and ought to be made the subject of a cautionary use statement and/or a controlled study to estimate more precisely the risks associated with vaccination.

This paper is the first in a planned series of reports from AVEC; it summarizes findings from 602 VAERS reports concerning AVA that were filed in 1998 and 1999 and reviewed over a 1-year period between 7 January 1999 and 6 January 2000.

METHODS

VAERS reports

Each VAERS report has a unique case number. The report form has space in which to record the name, address, and telephone number of the vaccine recipient, the person administering the vaccine and the person reporting the AE, the vaccinee's age and sex, the type, dose number and lot number of each vaccine given, date of vaccination, date of onset and description of the AE (including clinical and laboratory data), information concerning pre-existing illnesses and/or medications, significant consequences of the AE, and the outcome at the time of the report. The VAERS report form does not solicit information concerning race or socioeconomic variables, such as income, profession, or educational level. While virtually all of the reports concerning AVA stem from military personnel, the form does not specifically solicit information concerning branch of service, rank, or active/reserve status. That information can be surmised in some cases from the reporting location and/or other free form text presented by the reporter.

Any person (i.e. the vaccinee, a healthcare provider, or other individual) may initiate a report to VAERS. Thus, some of the VAERS reports concerning AEs following receipt of AVA are sent to the FDA directly from DoD medical channels. These undergo a DoD quality-assurance process to fill in missing demographic information from personnel and immunization databases. Other reports come directly from vaccine recipients or civilian healthcare providers and may provide somewhat less complete information than those channeled through the DoD. Once received by the FDA, the reports are then processed by a private contractor that maintains the system for the agency. Through an agreement with the FDA, that contractor continually forwards to AVEC just those reports concerning AEs experienced by individuals given AVA. To ensure confidentiality, the contractor first redacts individual patient identifiers (name, address (street/city), telephone number and birth date (except for year of birth)) from each report before it is sent to AVEC. If an original report lacks information needed to assess the causal relationship between an AE and prior receipt of AVA, AVEC may ask the VAERS contractor

to request additional information from the original reporter. However, there is no way to ensure a response, and more often than not, the desired information cannot be obtained. VAERS reports reviewed by AVEC are then forwarded to the DoD, where a contractor codes and keys the data into an ACCESS database maintained for use by AVEC (see subsection entitled 'AVEC database').

Serious AEs (SAEs) and other medically important AEs (OMIAEs)

One section of the VAERS report form (item 8) solicits information regarding several events (death, life-threatening illness, hospitalization, prolongation of an existing hospitalization and permanent disability) that are among those the FDA uses to define a 'serious' AE (SAE). In evaluating VAERS reports, AVEC decided to create a supplementary category called 'other medically important AE' (OMIAE). An AE was classified as an OMIAE if the affected individual was judged to have significant risk of chronic disability (i.e. >6 months even though 6 months have not yet elapsed) or major illness, even though one of the previous defining criteria of an SAE was not checked on the VAERS form. Any AE meeting the definitional criteria of an SAE or OMIAE is also considered to be a 'medically important' event.

Flu-like symptoms and 'multi-symptom syndrome'

Two composite symptom sets were created to facilitate a survey of VAERS reports for evidence of constellations of certain kinds of symptoms. The medically-qualified members of AVEC utilized a Delphic approach to achieve an expert consensus with respect to the definition of flu-like symptoms.[24] The term flu-like symptoms was applied to a report involving three or more of the following systemic events: fever (>100.4°F, if specified), chills, headache, photophobia, aching eyes, anorexia, nausea, myalgia, arthralgia, malaise and fatigue but with at most one symptoms referable to either the respiratory or gastrointestinal tract. The aggregate term 'multi-symptom syndrome' was coined to facilitate a review of VAERS reports in response to public concern that AVA might be associated with a chronic illness characterized by fatigue, sleep disturbance, neurologic complaints, cognitive dysfunction, and other symptoms.[12] AVEC operationally defined 'multi-symptom syndrome' as the co-occurrence of at least three of the following events: malaise/fatigue, paresthesia, memory loss, sleep disorder, and altered mentation. Given the incomplete nature of reports made to VAERS, the duration of the symptoms could not always be evaluated, so chronicity *per se* was not part of the definition of this symptom complex.

Medical review of VAERS reports

VAERS reports were studied and abstracted by a civilian AVEC medical reviewer, who developed a preliminary opinion concerning the causal relationship between AVA and the reported AE(s) in each report taking into consideration (1) cumulative information on the consistency of association in different groups, sexes, or ages with inactivated vaccines generally and AVA specifically, (2) the specificity to AVA alone (e.g. did the subject have a concurrent or predisposing illness or did he/she receive other vaccines or medications at the same time as AVA?), (3) the temporal relationship of the AE to receipt of AVA, and (4) biological plausibility (i.e. is there a clear physiological basis for thinking that an AE could have been caused by AVA or have successive doses of vaccine repeatedly induced a particular AE?).

The medical reviewer's initial assessment, along with the original VAERS report and other submitted medical records, was subsequently reviewed by a panel of the medically-qualified civilian members of AVEC. A Delphic approach was again used to achieve expert consensus concerning the causal relationship between each reported AE and AVA.[24] If an original report lacked critical information, AVEC deferred making a final assessment and sought additional medical records through the independent contractor that maintains the VAERS database for the CDC/FDA. When available, such records were evaluated for additional clinical, laboratory, radiographic and pathological information. In most instances, the initial diagnoses were confirmed by this extended review; rarely, new information led to revision of the original diagnosis. When additional medical records were not available, AVEC accepted the diagnosis provided in the initial VAERS report.

A World Health Organization (WHO) scale consisting of the categories: (1) very likely/certain, (2) probable, (3) possible, (4) unlikely, (5) unrelated and (6) unclassifiable was used to classify the causal relationship between an AE and AVA.[23]

AVEC database

Data from the VAERS reports were coded and keyed into an ACCESS database maintained by the Eagle Group under contract to the DoD. This was audited

by the AVEC medical reviewer, who compared critical field database entries with source documents for 100% of the reports involving a SAE or OMIAE plus a 10% sample of the remaining reports randomly selected by civilian AVEC members. All erroneous database entries detected in this audit were corrected.

When abstracting VAERS reports, the AVEC reviewer applied codes for aggregate classes of local and systemic reactions defined in a DoD document entitled 'Clinical Practice Guidelines for Managing Adverse Events after Vaccination',[25] but did not code every individual sign or symptom. To facilitate the summarization of reported events in a useful and manageable way but with more specificity than allowed by these aggregate classes of local and systemic reactions, AVEC created a simplified symptom set with 96 categories.[†] First, the ACCESS database was merged with a data extract provided by the FDA containing COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) codes for all reported signs and symptoms in the set of VAERS reports concerning AVA.[26] Then, the hundreds of individual COSTART terms were assigned to 96 simplified symptom groupings that reflected a mixture of anatomic (e.g. nasal), physiologic (e.g. bronchospasm), and diagnostic (e.g. Guillain-Barré syndrome, thyroid disease) constructs. Synonymous medical symptoms such as itching and pruritus were combined in a single category, whereas important medical events of particular interest to the committee (e.g. multiple sclerosis, arthritis) were each assigned to distinct categories. Following review and approval by the full committee, this simplified symptom set was used to create the summary listings of AEs presented in this paper.

DMSS database

Denominator data were obtained from the Defense Medical Surveillance System (DMSS), which contains one record for every dose of AVA given during the reference period. A coded individual identification field enables linking multiple vaccinations to the same person. Duplicate records were eliminated by reference to date of vaccination, and typographical variants or errors regarding the lot of vaccine received were corrected to a uniform two-digit data field. To ensure confidentiality, no linkage was made between individual data in this database and the VAERS reports reviewed by AVEC.

[†]A listing of these symptom categories will be provided on request by the senior author.

Data summaries and statistical analyses

Reports made to VAERS represent an unknown fraction of all events that actually occur, and the frequency of reporting can be influenced by a variety of unknown external factors. Thus, formal hypothesis testing and other statistical assessments (e.g. *p*-values, confidence intervals) were generally not applied to the univariate and bivariate data summaries in this paper. Instead, the paper provides descriptive summaries of the reported AEs with regard to such variables as person, type/location, relative frequency, severity/impact, concomitant illness or receipt of other drugs or vaccines, and vaccine lot.

Most summaries of numerator data are based on the number of reports. This slightly exceeds the number of vaccinees reporting one or more AEs because a few individuals filed reports following each of two or more different doses of vaccine. Summarizing at the report level captures information regarding the variety and circumstances of the AEs that might be lost in a summary focused on persons. The paper also includes AE summaries at the medical event level, since some reports cited multiple signs or symptoms.

To explore lot-to-lot variations in the reporting frequency for any AE or one involving hospitalization and/or LOD, data were analyzed via conditional logistic regression models. Two models were fit using the numerator data from the VAERS reports plus denominator data from the DMSS database. In the first, the approximate odds of an immunization leading to a VAERS report were modeled. In the second, the event of interest was a VAERS report that also had an associated hospitalization and/or LOD, i.e. a more severe (and perhaps more objective) version of the event in the first model. In both models, the data were restricted to the 12 lots that had been used for more than 50 000 immunizations each. These lots were represented by 11 dummy variables, with odds ratios comparing lots calculated by exponentiating differences between their coefficients. Also included were dummy variables to account for gender and calendar time of immunization. Odds ratios >2 were considered to be of potential clinical interest. Geographic variation in frequencies was accounted for by stratifying these conditional logistic models on the locations (states or countries) from which the reports came, an approach that has been used successfully in other research on vaccine safety.[27]

Special assessment of selected AEs

Beyond its routine review of all VAERS reports, AVEC occasionally assigns to one of its members

having appropriate expertise the responsibility of further evaluating an AE of special interest. This might be done if the reporting frequency of a certain AE seems unexpectedly high or has an unusual distribution with respect to person, place or time, if there is emerging evidence for a causal relationship between a particular AE and other vaccines, or if there has been considerable public interest expressed in the possibility of such a relationship. In the set of VAERS reports summarized in this paper, cases of paresthesia following vaccination elicited special interest and so were assigned to the neurologist-member of AVEC (A. D. G.) for more detailed review and evaluation.

RESULTS

Distribution of reported AEs by person, dose number, type, concomitant illness or treatment, severity and conceivable causality

Table 1 shows that the subjects of VAERS reports tended to be older and were more often female than all vaccinees given AVA. Although many reports lacked information regarding Service affiliation, from those which did, it appears that vaccinees in the Air Force (including those in the Air Force reserve, data not shown) were more likely than those in other Services to report an AE. At the time of this study, 79% of AVA injections given through AVIP represented first, second, or third doses of the primary vaccination series (Table 1). A similar proportion of the reports submitted to VAERS (82.5%) concerned AEs following one of the first three doses of AVA. An observational comparison of the number of reports submitted versus total doses given suggests that the likelyhood of a report was a greatest following the first dose and tended to decrease with subsequent doses.

Table 1. Age, gender, Service affiliation, and dose number for VAERS reports and individual immunizations

Characteristic	% (Number) of VAERS reports ($N = 597$)*	% (Number) of all AVA doses ($N = 1\,349\,327$)†
Age (years)		
<20	2.2% (13)	7.8% (105 139)
20–29	32.5% (194)	55.2% (745 260)
30–39	37.5% (224)	28.4% (383 861)
≥40	24.5% (146)	8.5% (114 220)
Not specified	3.4% (20)	<0.1% (847)
Gender		
Male	72.0% (430)	90.1% (1 215 970)
Female	26.6% (159)	9.8% (132 510)
Not specified	1.3% (8)	<0.1% (847)
Service		
Army	10.9% (65)	34.4% (464 415)
Navy	5.2% (31)	17.9% (240 943)
Marine Corps	3.4% (20)	17.6% (237 245)
Air Force	25.5% (152)	29.9% (403 766)
Coast Guard	0.2% (1)	<0.1% (851)
Not specified	55.9% (328)	0.2% (2107)
Service component		
Active	31.2% (186)	93.0% (1 245 261)
Reserve	11.1% (66)	6.9% (92 959)
Not specified	57.8.% (345)	0.2% (2107)
Dose number		
1	38.9% (232)	29.2% (393 462)
2	25.5% (152)	26.3% (355 122)
3	18.1% (108)	23.4% (315 430)
4	8.5% (51)	14.6% (196 712)
5	6.0% (36)	5.1% (69 192)
6	0.8% (5)	1.2% (15 538)
>6	0% (0)	0.3% (3871)
Not specified	2.2% (13)	0% (0)‡

*Based on numerator database excluding five reports from civilians not affiliated with the DoD.
†From the DMSS database.
‡Obtained by counting numbers of doses reported for each individual in the DMSS database, so none missing.

Table 2 further classifies the 602 VAERS reports with respect to (1) the type or location of the AE, (2) concomitant administration of another vaccine, concurrent use of medication, and existence of a preceding/concomitant medical condition when AVA was given, (3) the severity or impact of the AE, and (4) AVEC's assessment as to whether the AE may have been causally related to receipt of AVA. Each of these factors is considered in greater detail below.

Most frequently reported local and systemic AEs

Nearly half of the VAERS reports cited a local (injection-site) AE, and more than three-quarters described a systemic AE, most without a concomitant local AE (Table 2). The most common local AE was inflammation (redness/swelling) of unspecified degree (18.4%), but nearly as large a proportion (16.6%) cited a moderate (>50–120 mm) or large (>120 mm) degree of inflammation (Table 3). The systemic AEs covered a broad spectrum, with 34 types cited in the reports at a frequency ≥1% (Table 3). By far the most common of these were flu-like symptoms, malaise, rash, arthralgia, and headache (frequency of each ≥10%).

Serious/other medically important AEs

Thirty-four (5.6%) of the 602 VAERS reports described a SAE (Tables 2 and 4). A majority (58.8%) were so classified simply because they involved a hospitalization. There were no deaths reported in this group. AVEC also identified 13 reports that met the defining criteria of an OMIAE (Table 4).

Table 2. AE frequencies by type, concurrent treatment or medical condition, severity, and causal relationship to AVA

	% (Number) of VAERS reports ($N = 602$)
Type of AE	
Local (injection site) only	22.1% (133)
Systemic only	55.5% (334)
Local and systemic	22.3% (134)
Unclassifiable	<0.1% (1)
Concomitant vaccination, medication or medical condition	
Other vaccine(s) administered same day as AVA	12.6% (76)
Concurrent medication(s)	20.9% (126)
Preceding/concomitant medical condition	29.9% (176)
Severity of AE	
Serious AE (SAE)	5.6% (34)
Other medically important AE (OMIAE)	2.2% (13)
Hospitalization and/or loss of duty (LOD) ≥ 1 day*	25.9% (156)
Involved a health care visit	49.2% (296)
Might warrant consultation with specialist before giving an additional dose of AVA†	43.0% (259)
AVEC assessment of causality ($N = 1434$)‡	
Very likely/certain	27.1% (388)
Probable	10.8% (155)
Possible	17.1% (245)
Unlikely	5.3% (76)
Unrelated	8.6% (124)
Unclassifiable	31.0% (445)
Not indicated	<0.1% (1)

*This category includes some individuals in the SAE category, since hospitalization is one of the defining criteria of a SAE.

†The AVEC medical reviewers classified all VAERS reports with respect to a set of aggregate classes of local and systemic reactions originally created by the DoD to help providers make decisions about medical management of patients and the administration of additional doses of vaccine.[25] DoD recommendations suggest that a provider consult a specialist before giving additional doses of vaccine if an AE falls in a certain three of the eight local reaction classifications (including redness $\geq$50 mm with/without other complications) or 10 of the 16 systemic event classes (arthritis, severe and/or prolonged 'flu'-like illness; tinnitus and/or persistent dizziness; generalized pruritic or non-pruritic skin reaction; diffuse blistering dermatitis and/or mucositis; anaphylaxis or generalized allergic reaction; angioedema/swelling diffuse or distant from injection site within 2 weeks of vaccination; severe neurologic disease; focal neurologic disease; prolonged fatigue >60 days).

‡In contrast to other measures summarized in the table, this summary of AVEC's causality assessment is with regard to all reported events ($N = 1434$) rather than reports ($N = 602$).

AEs probably or very likely caused by AVA

AVEC considered that more than one-third of the events cited in the 602 VAERS reports had a probable or very likely/certain causal relationship to AVA. Since AVA is administered by injection, it is not surprising that almost all (92.0%) of the 316 local

Table 3. Summary by body system of AEs cited in $\geq$1% of VAERS reports

AE	% (Number) of VAERS reports ($N = 602$)
Local (injection site)	
SC nodule	5.3% (32)
Inflammation (redness/swelling)	
<30 mm	2.3% (14)
30–50 mm	2.0% (12)
>50–120 mm	5.6% (34)
>120 mm	11.0% (66)
Size unspecified	18.4% (111)
Rash	2.3% (14)
Other event(s) at injection site	2.5% (15)
Body as a whole	
Flu-like symptoms	20.8% (125)
Malaise/fatigue	13.3% (80)
Pain, not otherwise specified	5.8% (35)
Fever	4.3% (26)
Diaphoresis	2.3% (14)
Syncope	1.5% (9)
Chills	1.5% (9)
Weakness	1.0% (6)
Digestive system	
Nausea	4.8% (29)
Diarrhea	4.6% (28)
Vomiting	2.0% (12)
Oral symptom	1.8% (11)
Other gastrointestinal symptom(s)	1.0% (6)
Respiratory system	
Dyspnea	3.0% (18)
Throat symptom	1.8% (11)
Other respiratory symptom(s)	1.0% (6)
Nervous system	
Headache	10.1% (61)
Dizziness	7.3% (44)
Paresthesia	7.0% (42)
Memory loss	3.0% (18)
Sleep disorder	2.8% (17)
Altered mentation	2.0% (12)
Other neurologic symptom(s)	1.3% (8)
Integumentary system	
Rash	14.2% (88)
Skin other	2.2% (13)
Pruritus	1.8% (11)
Musculoskeletal system	
Arthralgia	12.0% (72)
Myalgia	5.5% (33)
Chest tightness	1.7% (10)
Chest pain	1.2% (7)
Special senses	
Tinnitus	4.2% (25)
Eye symptom(s)	3.2% (19)
Urogenital system	
Any genitourinary symptom(s)	1.5% (9)
Cardiovascular system	
Heart rate/rhythm abnormality	1.3% (8)

Table 4. Reports of SAEs* and OMIAEs by body system

AE	Number	AVEC causality assessment
Injection site reaction*	6	Very likely/certain
Body as a whole		
'Multi-symptom syndrome'	4[†]	Unlikely (1), unclassifiable (3)
Syncope*	2	Unlikely (1), unrelated (1)
Flu-like symptoms*	1	Unrelated
Respiratory system		
Respiratory illness*	1	Unrelated
Bronchospasms*	1	Unlikely
Sleep apnea*	1	Unrelated
BOOP*[‡]	1	Probable
Nervous system		
Guillain-Barré syndrome*	3	Unrelated (2), unclassifiable (1)
Bipolar disorder*	1	Unclassifiable
Seizure*	1	Unrelated
Dysesthesias from T1 down*	1	Unclassifiable
Multiple sclerosis*	1	Unlikely
Special senses		
Loss of vision in right eye*	1	Unclassifiable
Cardiovascular system		
Atrial fibrillation*	2	Unlikely (1), unclassifiable (1)
Endocarditis*	1	Unrelated
PVCs and bigeminy		Unrelated
Endocrine system		
Diabetes mellitus (Type II)*	1	Unrelated
Hypothyroidism	1	Unlikely
Immune system		
Systemic lupus erythematosus*	1	Unlikely
Neutropenia*	1	Unclassifiable
Angioedema*	1	Unrelated
TENS*[§]	1	Unrelated
Anaphylactoid reaction	1	Possible
Musculoskeletal system		
Arthritis	2	Possible
Spondyloarthropathy aggravation	2	Possible
Chest pain*	1	Unclassifiable
Hematologic system		
Neutropenia and RBC decrease	1	Unclassifiable
Reproductive system		
Spontaneous abortion	1	Unrelated
Events attributable to infection		
Non-bacterial meningitis*	2	Unrelated (1), unclassifiable (1)
Liver abscess, *E. coli* septicemia*	1	Unrelated

*Event classified as a SAE.
[†]While there were five cases of 'multi-symptom syndrome', only four had persistent symptoms for $\geq$6 months and thus were classifiable as OMIAEs.
[‡]BOOP, bronchiolitis obliterans organizing pneumonia.
[§]TENS, toxic epidermal necrolysis.

reactions could be judged as very likely/certain consequences of AVA, while another 3.2% were rated as probably caused by AVA. The causality of systemic AEs is much harder to judge; for the 1110 systemic AEs, AVEC assessed the causal relationship to AVA as very likely/certain for 8.8% and probable for another 13.1%.

The causal relationship of AVA to SAEs and OMIAEs was an issue of particular interest. Only seven SAEs and no OMIAE were categorized as probably or certainly caused by AVA (Table 4). Six SAEs were local reactions; all were so classified because the affected vaccinees were hospitalized due to the large size of the local reaction and in most cases were treated with i.v. medication. All of the hospitalizations were for a single day, and all patients recovered without difficulty. These local reactions had onset between 8 hours to 5 days following the

administration of AVA and involved swelling and erythema of the upper arm and forearm, and in one case of the hand. In all these cases, systemic symptoms were only mild or absent. AVEC classified the causal relationship between these SAEs and receipt of AVA as very likely/certain. This classification was based on the compatibility of the interval from vaccination to onset, the absence of any other known potential cause, the association of the reaction with the injection site, and the known pattern of local reactions occurring after administration of AVA.

A single systemic illness meeting the definition of a SAE (bronchiolitis obliterans organizing pneumonia (BOOP) was considered probably related to vaccination. This report, submitted by a treating physician and allergist, stated that an apparently healthy 39-year-old male, who had developed an injection-site reaction and an unspecified diffuse rash that resolved following an initial dose of AVA, also had an injection-site reaction after the second dose of vaccine. One day after receiving the second dose he developed urticaria on the extremities and trunk and cough and dyspnea that persisted. A chest examination and radiograph done 1 week later were normal, and he was treated for an allergic reaction with diphenhydramine, methylprednisolone, and ranitadine. The urticaria resolved, but 2 weeks after the second dose he had dyspnea on exertion, an interstitial process affecting diffusion on pulmonary function testing, and negative AVA and glycerine skin tests. He continued to improve on therapy. A CT chest scan done approximately 6 weeks after the second dose showed nodular ground glass opacities mainly in the upper lobes. Transbronchial biopsies revealed uniform interstitial fibrosis with occasional plugs of immature fibroblastic tissue and poorly formed granulomata in alveolar spaces. Biopsy findings were interpreted as suggestive of idiopathic bronchiolitis obliterans organizing pneumonia (BOOP) in the absence of evidence for hypersensitivity pneumonitis or pulmonary embolism. The subject had negative bacterial and fungal bronchial cultures and negative serologic assays for rubella, adenovirus, mycoplasma, rheumatoid factor (RF), antinuclear antibody (ANA), and antineutrophil cytoplasmic antibody (ANCA). With steroid therapy, his dyspnea resolved and his pulmonary function tests returned to normal.

All other systemic SAEs were rated either as unrelated or unclassifiable based on the WHO causality scale.[23] Five OMIAEs (i.e. anaphylactoid reaction, arthritis (two reports), aggravation of spondyloarthropathy (two reports)) were judged possibly related to receipt of AVA, while all the others were rated as unlikely, unrelated or unclassifiable.

'Multi-symptom syndrome'

Since there has been public concern that AVA might be associated with a chronic illness characterized by fatigue, sleep disturbance, neurologic complaints, cognitive dysfunction, and other symptoms,[12] AVEC reviewed the VAERS reports for such a complex of symptoms. Only five reports described cases of a 'multi-symptom syndrome' (see Methods for case definition); each had four but none had all five of the events defining this syndrome. These reports indicated that symptoms had persisted for at least 6 months in four of the five cases and so were classified as OMIAEs. In no case was AVA judged to be a probable or certain cause of this symptom complex (Table 4).

Paresthesia

There were 18 cases of sensory symptoms occurring ipsilateral and distal to the site of injection, 14 of which included significant injection-site inflammation. Few reports provided descriptions of the exact neurologic distribution of symptoms (e.g. ulnar nerve or its cutaneous distribution). However, implementation plans of the military medical services indicate that AVA should be injected subcutaneously in the triceps region of the arm,[28,29] which is close to the ulnar nerve. While information on duration was not given in every report, symptoms persisted for at least 1 week in nine cases and 1 month or longer in five cases.

Concomitant vaccination, medication or illness

A systemic AE (e.g. headache) could possibly be due to AVA, but it might also be caused or made worse by another inciting factor. Thus, AVEC examined AEs resulting in hospitalization and/or LOD and found that this outcome was not more frequent in the minority of vaccinees receiving other vaccines (12.6%), taking medications (20.9%), or having a preceding/concomitant medical condition (29.9%) when given AVA (data not shown).

Other measures of impact: LOD, healthcare visit, need for consultation with a specialist

Most SAEs or OMIAEs required medical assistance or consultation, and many may have resulted in LOD, but an even broader spectrum of AEs appear to have these kinds of impact. One-quarter of all VAERS reports reviewed by AVEC noted hospitalization and/or LOD, half cited a healthcare visit and more

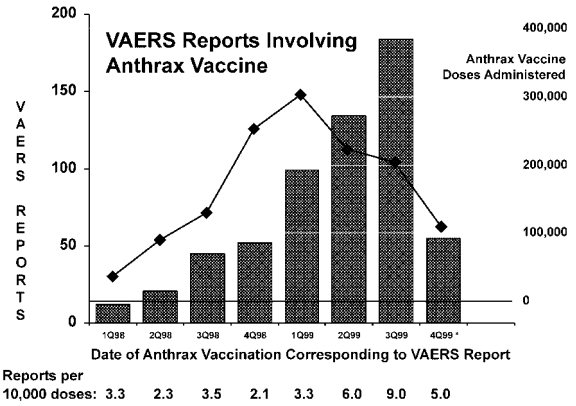

Figure 1. Temporal distribution of AVA doses administered and reports to VAERS of AEs involving AVA. The segmented line shows the number of doses of AVA administered each quarter, while each vertical bar shows the number of reports submitted to VAERS with vaccination dates corresponding to that quarter. *This quarter only includes doses given and VAERS reports with vaccination dates through 11/17/99

than 40% described symptoms that might have warranted consultation with a medical specialist (Table 2).

Clustering of AEs

The VAERS reports were also reviewed for evidence of temporal or geographic clustering. Most of the reports were submitted in 1999, but some (21.6%) had been filed in 1998. Figure 1 shows by quarter for the interval from January 1998 through November 1999 (1Q98–4Q99) the number of VAERS reports (based on vaccination date) and the number of doses administered. The number of doses increased each quarter through 1Q99 but then decreased over the remainder of 1999. The frequency at which AEs were reported to VAERS during this period ranged from 2.1–9.0 reports/10 000 doses of vaccine. It reached a maximum of 9.0 in 3Q99, then fell to 5.0 in 4Q99.

The DMSS database showed that vaccine from 19 lots of AVA was administered during the period covered by this study, with >50 000 doses derived from each of the 12 most extensively used lots. That database was also queried to identify the geographic locations at which the various lots of AVA had been used. Based on the 582 VAERS that contained information on geographic location, it was estimated that 0.04% of all AVA vaccinations resulted in an AE report, but there was wide variation among locations. The largest number of reports came from Delaware (86), followed by California (41) and Korea (39). Among locations generating five or more reports, the highest reporting rates were in Michigan (3.9% of 283 vaccinations), Oregon (4.6% of 520 vaccinations), and Delaware (1.8% of 4863 vaccinations), while it was very low in California (0.008% of 494 351 vaccinations). There was substantial geographic variation in the proportion of reports describing an AE involving hospitalization and/or LOD (e.g. 14% in Delaware, 49% in California, 42% in Korea), and the actual mix of AEs reported also varied. For example, reports from Delaware cited injection-site reactions, flu-like symptoms and rash at relatively low frequencies but malaise, arthralgia, paresthesia, dizziness, tinnitus, memory loss and heart rate/rhythm abnormality at relatively high frequencies compared to reports from other locations.

Temporal or geographic clustering of AE reports could be a result of many factors, but a question of particular interest is whether clustering might be due to variation in reactogenicity across vaccine lots. We assessed this question by fitting conditional logistic regression models that accounted for gender, calendar time of vaccination, and geographic location. One analysis modeled the approximate odds of an immunization being reported using 465 reports that cited both a reporting location and one of the 12 most extensively utilized lots of AVA (>50 000 doses/lot). Thus, it covered 1.04 million (77.0%) of the total 1.35 million doses administered. The approximate odds of reporting an AE to VAERS was found to be lowest for lot FAV038 (followed closely by lot FAV020), and greatest for lot FAV041. The odds ratio comparing lot FAV041 to lot FAV038 was 3.3, followed by 3.0 and 2.7 for lot FAV044 and lot FAV030, respectively (with a median odds ratio of 1.6 among the 11 comparisons to lot FAV038).

A second analysis approximated the odds of reporting an AE that involved hospitalization and/or LOD; there were 124 such cases. The odds were greatest for lot FAV044 and least for lot FAV020, with an odds ratio comparing the two of 19.0, followed by 6.9 for lot FAV037 and 6.3 for lot FAV041 (with a median odds ratio of 2.9). Fifteen (37.5%) of the AEs associated with lot FAV044 resulted in hospitalization and/or LOD, but only the two (5.0%) that involved hospitalization were classed as SAEs. Most (80%) mentioned at least one of the following events: injection-site reaction, flu-like symptoms, dizziness, malaise, or headache. Further examination of reports from Delaware focused on lot FAV030 and lot FAV041, which accounted for 53% of the doses given in and 66% of the AE reports submitted from that state. Excluding Delaware from the analysis, the odds ratio for lot FAV030 decreased slightly, with an

increase for lot FAV041. However, the proportion of lot FAV041-associated AEs involving hospitalization and/or LOD was actually lower than with most other lots.

DISCUSSION

Safety of AVA

A question of paramount interest was whether a review of this initial set of 602 VAERS reports would find an excessive number of medically important AEs (SAEs or OMIAEs) attributable to AVA. That was not the case. There were no deaths among these reports and only seven of 34 reported SAEs were judged to fit the WHO causality categories of probable or very likely/certain.[23] Six were local injection-site AEs, all of which involved a period of hospitalization but resolved completely. They were rated as very likely/certain consequences of vaccination with AVA. A tentative causality rating of probable was assigned to a single systemic SAE, a case of bronchiolitis obliterans organizing pneumonia (BOOP) following the second dose of AVA in a vaccinee who had negative bacterial and fungal bronchial cultures and negative serologic assays for rubella, adenovirus, mycoplasma, RF, ANA and ANCA, but who had experienced an injection-site reaction and an unspecified diffuse rash after the first dose of vaccine. No OMIAE appeared to have either a probable or very likely/certain relationship to AVA, but the vaccine was considered to be at least a possible factor in the occurrence of five of 13 systemic AEs meeting the definition of an OMIAE (i.e. aggravation of spondyloarthopathy (2), anaphylactoid reaction, and arthritis (2)). While these events were clearly very significant to the individuals involved, their aggregate numbers do not yet suggest an unexpectedly high occurrence of any AVA-attributable SAE or OMIAE.

The review of VAERS reports confirmed findings of previous surveys that injection-site reactions, muscle or joint aches, headache, and fatigue are among the most common complaints cited by recipients of AVA.[18] Furthermore, it appears that the local reactogenicity of this vaccine can be quite substantial, since nearly half of the VAERS reports cited some degree of local reaction and more than one-third of those described a moderate to large degree of inflammation. A particularly significant finding is that some vaccinees with injection-site inflammation also experienced distal paresthesia. AVEC concludes that in some cases administration of AVA as a subcutaneous injection in the region of the triceps apparently resulted in direct trauma to the underlying ulnar nerve or delayed-onset compression neuropathy due to localized inflammation. Subcutaneous injection of AVA over the inferior deltoid could eliminate the risk of such injuries and is recommended. In fact, the DoD has now changed its instructions to indicate that the deltoid area instead of the triceps should be used for the subcutaneous inoculation of AVA.

A focused survey of the reports, carried out in response to concern that AVA might be associated with increased risk of a chronic illness characterized by fatigue, sleep disturbance, neurologic complaints, cognitive dysfunction, and other symptoms,[12] found only five that described such a 'multi-symptom syndrome', and none of these appeared to be causally related to vaccination. However, the phenomenon deserves further inquiry. The outcome of a survey for multiple symptom complexes can be very sensitive to variations in the way the complex is defined, one incorporating very common or broadly defined events being expected to result in more 'hits' than one using a more restrictive definition. For example, one study found that a very large proportion of Air Force Veterans reported having symptoms of a chronic multi-symptom illness (45% of those who served in the Gulf War compared to 14.7% of those not so deployed), but this survey employed a highly nonspecific definition of chronic multi-symptom illness (i.e. chronic persistence ($\geq$6 months) of events falling in at least two of three very broadly defined categories of complaint, including fatigue, mood and cognition, musculoskeletal).[30] While such a definition can provide a sensitive first probe, it almost certainly fails to define a discrete condition. As AVEC continues its review of reports submitted to VAERS, it plans to study how variations in the definition of 'multi-symptom syndrome' affect the prevalence of this condition and to further assess which events have the strongest tendency to occur together, to see if this might help identify a real, specific illness.

None of the other patterns found in this review of VAERS reports (i.e. a tendency for vaccinees reporting an AE to more often be female, older, or in the Air Force than all personnel given AVA, as well as temporal, geographic, dose-to-dose and lot-to-lot variations in the rate at which AEs were reported to VAERS) suggest that AVA is unsuitable for members of certain subpopulations or that any particular lot of the vaccine is unsafe. Although definitive explanations cannot yet be offered for many of the observed variations, they warrant further evaluation. A better understanding of their origins might point to measures that could improve the safety and tolerability of vaccination with AVA.

The relative predominance of females among vaccinees reporting an AE to VAERS is consistent with findings of prior military studies that female Service personnel reported higher rates of reaction to AVA than male Service personnel.[18] Perhaps this difference has an immunological or anatomical basis, or there might be a difference between females and males in willingness to report a given event. An apparent decline in reporting rate with successive doses of AVA could also be due to several factors, such as increasing familiarity with the vaccine or possibly deferral or exemption of some vaccinees from the population given subsequent doses because of reactions to previous doses. It is possible, but unproven, that temporal or geographic variations in media attention to the issue of AVA safety could have influenced the threshold for reporting an AE to VAERS. Finally, since AVA is produced from the sterile filtrate of a microaerophilic culture of attenuated *B. anthracis* without fixed criteria concerning the identity and quantity of bacterial antigens in each lot, there could be a real biological basis for lot-to-lot differences in reactogenicity. Ongoing surveillance of reported AEs is needed to ascertain if a given lot is ever associated with an excessive number of medically important AEs. In the current study, lots consistently associated with an elevated reporting frequency (e.g. lot FAV041 and lot FAV044) did not differ from others in regard to the clinical profile of the AEs or to the rates at which SAEs or OMIAEs were reported. Lot FAV044 was cited in an FDA notice.[31] This notice, however, concerned only a labeling error that has been corrected.

Future studies

It is important that providers and recipients alike have access to reliable information concerning the frequencies and consequences of AEs commonly associated with vaccination. A number of studies, each involving self-reporting or direct monitoring of injection-site and systemic AEs in several hundred or thousand vaccinees given AVA have been undertaken.[9,15–18] These have served to identify a number of fairly common postvaccination complaints (e.g. inflammation at the injection site, malaise, muscle or joint aches, headache, fatigue), but there have been substantial variations between studies in the types, frequencies, and severity of reported AEs. Most of the studies have lacked at least one of the design features (i.e. randomization, blinding, use of a placebo control, uniform active surveillance of subjects given vaccine and placebo) needed to make precise, unbiased estimates of the types and frequencies of AEs associated with AVA, and to decide which systemic events may be causally related to vaccination. Thus, additional well-designed, prospective studies are still needed to better define the more common AEs associated with receipt of AVA. Prospective studies with active follow-up of all vaccinees could also determine whether the frequency or severity of AEs following receipt of AVA is similar to that associated with other commonly used vaccines such as tetanus toxoid or influenza and whether frequency or severity increases with successive doses of AVA.

These needs will be addressed at least in part through a new CDC/DoD study based on results from a preliminary study of 173 adults suggesting that intramuscular as opposed to subcutaneous injection of AVA is associated with lower rates of local injection-site reactions and that a reduced number of doses given by either route may induce a similar level of antibody as the current regimen.[32] The CDC and DoD plan to further assess these findings in a randomized, controlled study involving approximately 1600 adult male and female vaccinees. Slated to begin soon, initial study results should be available in 2003 (N. Marano, DVM, CDC).

Conclusions regarding the safety of AVA that can be drawn from VAERS reports alone will necessarily be restricted by limitations inherent in all passive surveillance systems (i.e. under-reporting as well as incomplete, inaccurate, and biased reporting of events). However, as shown by its role in detecting an excess incidence of intussusception among vaccinated infants that led to the subsequent withdrawal of a live, tetravalent, rhesus-based rotavirus vaccine (RRV-TV) from the market,[33–35] VAERS has the capacity to generate a warning signal if some medically important AE is occurring at a greater than expected frequency or to reveal trends in reporting (e.g. person, place, time) that might signify a safety problem (e.g. association of a particular AE with one or a few lots of vaccine).

AVEC will continue to review VAERS reports concerning recipients of AVA, giving especially close attention to SAEs and OMIAEs. Should this effort detect a signal that an uncommon medically important AE may be occurring at an elevated rate, then a large controlled study with complete ascertainment will be needed to make an informed, unbiased estimate of the actual level of risk and its causal relationship to AVA. Sources of data for such a study could include the Defense Medical Surveillance System (DMSS), coordinated by the Army Medical Surveillance Activity in Washington, DC, that maintains an ongoing collection

of electronic records of hospitalizations, outpatient medical visits, personnel records, and deaths. Another source could be The Naval Health Research Center (NHRC) in San Diego, which conducts research based on medical records and also coordinates the DoD Birth Defect Registry. In fact, DMSS and NHRC analyses are currently being carried out by the DoD to assess the relative risk for hospitalization, ambulatory visits, and other health outcomes (using the *International Classification of Diseases*, 9th edition, Clinical Modification (ICD9-CM) at the 3- and 4-digit level) among service members who have or have not received AVA (J. Grabenstein, AVIP, DoD, personal communication).

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