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ORIGINAL REPORT

Safety of anthrax vaccine: an expanded review and evaluation of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS)†

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SUMMARY

Purpose To assess the safety of a licensed anthrax vaccine (AVA) given to more than 500 000 US military personnel, through review and medical evaluation of adverse events (AEs) reported to the Vaccine Adverse Event Reporting System (VAERS).

Methods AEs were summarized by person, vaccine lot, type, frequency and impact. A Delphic approach was used to tentatively assess causality in an effort to detect serious AEs (SAEs) or other medically important AEs (OMIAEs) possibly attributable to AVA.

Results The Anthrax Vaccine Expert Committee (AVEC) reviewed 1841 reports describing 3991 AEs (9.4 reports/10 000 doses of AVA) that were submitted to VAERS from 1Q1998 through 4Q2001. One hundred forty-seven reports described an SAE or OMIAE, of which 26 were tentatively rated as possible, probable or certain consequences of vaccination (injection-site reaction [12], 'anaphylactic-like reaction' [5] and eight other systemic AEs [1–2 each]).

Conclusions This review produced no evidence for an unusual rate of any SAE or OMIAE attributable to AVA. It supported an earlier impression that AVA may cause significant local inflammation and should be administered over the deltoid rather than the triceps to avoid direct or compression injury to the ulnar nerve. The subjects of VAERS reports tended to be older than all recipients of AVA. Females generally had and/or reported AEs more often than males, but transient articular reactions were surprisingly more common in males. Variations in the frequency or severity (as judged by hospitalization and/or loss of duty) of reported AEs did not suggest a significant problem with (1) a particular lot of AVA, (2) recurrent AEs after multiple doses or (3) vaccination of persons with a concomitant illness or those given other vaccines or medications. Copyright © 2004 John Wiley & Sons, Ltd.

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

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INTRODUCTION

Recognizing that aerosolized spores of the bacterium *Bacillus anthracis* can be used as a military or terrorist weapon, the Department of Defense (DoD) developed the Anthrax Vaccine Immunization Program (AVIP) to protect active-duty and reserve members of the US military forces, as well as emergency-essential civilians assigned to areas deemed to be at high-risk for anthrax attack.[1] The vaccine used in this program through 2001, designated Anthrax Vaccine Adsorbed (AVA), is an adjuvanted, cell-free filtrate of a *B. anthracis* culture that was licensed by the Food and Drug Administration (FDA) in 1970.[2,3] Initially intended for a relatively small number of veterinarians and persons processing animal hides, who might be at high-risk of infection, only 68 000 doses were distributed between 1974 and 1989.[4] Usage increased sharply in 1991, when an estimated 150 000 American military personnel were given approximately 300 000 doses to protect against the possible use of *B. anthracis* as a biological weapon during the Persian Gulf War.[5]

The AVIP was initiated in March 1998. It went through a series of slowdowns in 2000 and 2001 due to a shortage of FDA-released vaccine, but on 28 June 2002, the DoD announced its resumption for personnel in areas of increased risk.[6] In spite of these delays, more than 500 000 personnel received approximately 2 million doses of AVA over the 4-year period from 1998 through 2001.[7]

In view of the many people already vaccinated, and the prospect that large numbers of service personnel and even civilians may be immunized against anthrax in the future, it is important to monitor vaccinees for evidence of any serious or other medically important AEs possibly attributable to AVA. One means of detecting such events is through ongoing review of reports submitted to the Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system administered jointly by the FDA and the Centers for Disease Control and Prevention (CDC).[8] This has been a prime objective of the Anthrax Vaccine Expert Committee (AVEC), a civilian panel of private-sector physicians and other scientists with expertise in the fields of statistics, epidemiology, infectious diseases, neurology, rheumatology and vaccinology.

In its initial report on the safety of AVA, AVEC summarized and evaluated 1434 AEs described in 602 reports submitted to VAERS during 1998 and 1999.[9] These reports provided no evidence of an elevated incidence or unusual pattern in the occurrence of medically significant AEs. However, this review did suggest that subcutaneous injection of AVA in the region of the triceps might directly traumatize the ulnar nerve or cause delayed-onset compression neuropathy secondary to localized injection-site inflammation. Consequently, AVEC recommended that subcutaneous injection of AVA be positioned over the inferior deltoid to eliminate the risk of such injuries.[9]

This article presents an expanded assessment of the safety of AVA based on the review of 1841 reports describing 3991 AEs, that were submitted to VAERS over a 4-year period from 1Q1998 through 4Q2001. As in our initial report,[9] AEs have been summarized with respect to person, type/location, relative frequency, severity/impact, concomitant illness or receipt of other drugs or vaccines, vaccine dose number and lot, and have been assessed for evidence of unexpected patterns in the occurrence of medically important events that might be attributable to AVA. In addition, this article (1) extends previous observations regarding the effect of gender on the types and frequencies of commonly reported AEs,[9] (2) analyzes the more prevalent AEs for evidence of clustering (including 'multi-symptom syndrome'[9] [MSS] and related symptom complexes) and (3) assesses the responses to further vaccination of vaccinees who had an AE after a previous dose of AVA.

METHODS

The medically qualified members of AVEC reviewed and evaluated on an ongoing basis newly submitted VAERS reports of AEs experienced by recipients of AVA. The AEs were then summarized with respect to several variables, including person (e.g. vaccinee age, gender, service), type/location (e.g. specific event/body system; local injection-site reaction vs a systemic event), relative frequency, severity/impact (e.g. need for medical assistance, loss of duty [LOD], classification as a serious adverse event [SAE] or an other medically important event [OMIAE]), concomitant illness or receipt of other drugs or vaccines, and vaccine lot. AVEC employed a Delphic approach (structured expert consensus) and a scale developed by the World Health Organization (WHO) to tentatively assess the causal relationship between each reported AE and prior receipt of AVA.[10,11] The goal was to use this scale as a tool to screen for potential problems, as opposed to rendering a confirmatory assessment of the relationship between the vaccine and any given event. A detailed account of the data sources and procedures used can be found in the first AVEC report on the safety of AVA.[9]

Vaccine

AVA was initially produced by the State of Michigan in the Michigan Biologic Products Institute (MBPI). This facility, and its operations, were acquired in 1998 by BioPort, a private corporation. In 1999, while reviewing BioPort's license application for a renovated manufacturing facility, the FDA permitted the company to release some lots of vaccine previously manufactured by MBPI. These were used by AVIP to vaccinate military personnel through the end of 2001. Consequently, all of the VAERS reports reviewed by AVEC for this article concern AEs experienced by vaccinees given 'pre-renovation' lots of AVA. In January 2002, the FDA approved BioPort's license application. 'Post-renovation' lots of vaccine produced since that time (made to the same formulation and by the same general process as 'pre-renovation' lots) still carry the generic designation AVA, but also bear the commercial tradename, BioThrax™.[12] 'Post-renovation' lots of AVA may be somewhat more consistent in composition, but there is no reason to believe the profile of AEs associated with these lots will be materially different from that observed in recipients of 'pre-renovation' vaccine.

Definitions

The term 'flu-like symptoms' was applied when a report described three or more of the following events: fever ($>100.4^{\circ}$F, if specified), chills, headache, photophobia, aching eyes, anorexia, nausea, myalgia, malaise and fatigue, but with at most one symptom referable to the respiratory or GI tract. The term MSS was defined as the concomitant occurrence of at least three of the following events: malaise/fatigue, paresthesia, memory loss, sleep disorder and altered mentation. The term 'anaphylactic-like reaction' was assigned to reports describing an event that met the following DoD definition: generalized itching (beyond the injection site) with symptoms of chest tightness, with or without evidence of hives, beginning within 2 hours after administration of AVA. VAERS reports mentioning the administration of epinephrine or certain anti-histamines were also assigned this term because it is not uncommon to give these agents at the first sign of an allergic reaction to preclude progression of symptoms. A report was classified as describing a SAE if any of the following events listed under item number 8 on the VAERS report form were checked as having applied: death, life-threatening illness, permanent disability, hospitalization or prolongation of an existing hospitalization. AVEC classified as an 'other medically important event' (OMIAE) an AE that failed to qualify as an SAE but was thought to place the individual at significant risk of chronic disability (i.e. >6 months even though 6 months had not yet elapsed) or major illness.

Statistical analyses

Reports submitted to a passive surveillance system like VAERS tend to underestimate the true incidence of an event and are often incomplete, inaccurate and/or otherwise biased.[9] Consequently, much of the information derived from such reports is properly restricted to descriptive summarization, formal statistical analyses (e.g. *p*-values, confidence intervals) being appropriate only in selected circumstances where uncertainties concerning the data do not preclude them.

Relationships between vaccine lots and reporting rates were explored via conditional logistic regression models, which were adjusted for gender and calendar time of vaccination and stratified on the location from which the report was filed. We report the odds ratios from these models as descriptive summaries of the data.

For this article, potential clustering of AEs was assessed by ordering patterns of events according to a simple probability model. Specifically, we examined the degree to which the following 10 signs and symptoms occurred in unlikely patterns: the five most commonly reported systemic AEs (i.e. 'flu-like symptoms', malaise/fatigue, arthralgia, headache and rash; each cited in at least 10% of the VAERS reports) and the five most prevalent manifestations of injection-site reactions (i.e. redness/swelling, nodule, local rash, local numbness/tingling, local other; each cited in at least 2% of the VAERS reports).

Assuming these 10 events to be independent, the marginal probabilities of each one occurring in a report (and the complement of not occurring) were calculated and these were used to calculate the probability of each of the $2^{10} = 1024$ potential event patterns. An exact binomial calculation was done of the probability of observing counts at least as high as those observed for each of these patterns and the patterns were ordered accordingly.

RESULTS

Our first report on the safety of AVA assessed 1434 AEs cited in 602 reports submitted to VAERS during 1998 and 1999.[9] This article addresses a substantially larger dataset. Between 1Q1998 and 4Q2001,

approximately 2 million doses of AVA were given to more than 500 000 military personnel.[7] During that time, VAERS received 1841 reports describing 3991 AEs experienced by 1778 vaccinees, a reporting rate of 9.4 reports/10 000 doses of vaccine administered or 1 report/282 vaccinees (each vaccinee given an average of 3.8 doses). Rates for common individual systemic AEs (i.e. those mentioned in at least 1% of the reports) were much lower, 0.09–1.3 reports/10 000 doses or 1 report/2043–28 806 vaccinees. SAEs or OMIAEs were reported at rates of 0.49 reports/10 000 doses (1 report/5404 vaccinees) and 0.26 reports/10 000 doses (1 report/10 172 vaccinees) respectively.

Person, AE type and impact, concomitant vaccination/medication or illness

The expanded set of 1841 VAERS reports was similar with regard to vaccinee age, gender and service affiliation to the first 602 reports reviewed by AVEC.[9] Compared to all recipients of AVA, vaccinees reporting an AE tended to be older (37.5% vs 63.9% at least 30 years of age) and included a disproportionate number of females (10.3% vs 26.4%). Among reports designating a Branch of Service (34.9%), 66.6% concerned vaccinees in the Air Force, although Air Force personnel received only 28.8% of all vaccine doses given.

The proportions of reports citing a local injection-site and/or a systemic AE as well as the proportions noting receipt of another vaccine/medication or a concomitant illness at the time of vaccination with AVA were also similar to those noted in the first AVEC review.[9] Reports of injection-site AEs alone or systemic AEs alone accounted for 27.6% and 50.2% of the total respectively, while 22.0% cited both injection-site and systemic AEs.

A minority of vaccinees reporting an AE had a history of having received one or more other vaccines (13.6%) or medications (21.5%) concomitantly with AVA, or had an existing medical condition (29.3%) when vaccinated. They were slightly more likely to report an AE involving hospitalization and/or LOD than vaccinees to whom these factors did not apply (relative risk [RR]=1.30–1.36).

Overall, 12.8% of all reports described an AE resulting in hospitalization and/or LOD, notably lower than the 25.9% citing such an AE in the initial group of reports reviewed by AVEC.[9] However, the proportions of reports describing any SAE (5.2%), any OMIAE (2.8%), an AE involving a visit to a health care provider (52.9%) or one possibly warranting consultation with a specialist before administering more AVA (42.3%) remained similar to those noted in our first review.[9,13]

Frequently reported AEs

Table 1 lists AEs cited in at least 1% of all reports. The most prevalent category of injection-site AE was inflammation of unspecified magnitude, but an even larger proportion specified inflammation of moderate (>50–120 mm) or large size (>120 mm). While not one of the predefined categories used to classify local injection-site AEs, AVEC became aware of anecdotal accounts that vaccinees sometimes complained of an immediate burning pain on injection. Consequently, all reports describing injection-site pain that (1) had onset within 24 hours, (2) was focused at the injection-site without radiating along a distinct nerve pathway and (3) did not appear to be due to injection-site inflammation, were re-examined. Thirty-one (1.7%) met these criteria, but only seven indicated that onset was immediate or within 1 minute of injection, while another five mentioned onset within 1 hour of injection. Seven of these 12 reports described the pain as burning, stabbing or sharp.

'Flu-like symptoms', rash, malaise, arthralgia and headache remained the most prevalent systemic AEs reported to VAERS (each event cited in at least 10% of all reports), followed by myalgia, paresthesia and dizziness (each mentioned in at least 5% of the reports) (Table 1). With the exception of rash, this spectrum of common systemic AEs resembles that reported by British service personnel following receipt of another anthrax vaccine quite similar in composition to AVA.[14]

Further review of the 301 systemic dermatologic events reported to VAERS showed that 168 were nonspecific rashes, but 64 were urticarial (5 accompanied by shortness of breath or wheezing). Urticaria occurred within 1 day of vaccination in 37 (57.8%) of the 64 cases. There were 13 cases of recurrent urticaria after another dose of AVA (eight were more severe or had more involvement than the initial event), suggesting a possible allergic reaction to some component of the vaccine. Among the other rash reports, 14 involved pruritus without rash, 8 were angioedema and 15 were oral lesions including a case of pemphigus vulgaris and a case of toxic epidermal necrolysis (TENS). There were also individual or small numbers of many different kinds of dermatologic events including idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, petechiae with aplastic anemia, lichen planus, atopic dermatitis and eczema, contact dermatitis, psoriasis, herpes zoster, acne, cellulitis and cysts.

Table 1. Summary by body system of commonly reported adverse events (AEs) (cited in ≥1% of VAERS reports)

AEs by body system	Percentage (*n*) of VAERS reports [*n* = 1841]
Local (injection site)	
SC nodule	7.3 (134)
Inflammation (redness/swelling)	
<30 mm	1.7 (31)
30–50 mm	2.1 (39)
>50–120 mm	10.4 (191)
>120 mm	10.8 (199)
Size unspecified	15.9 (292)
Local numbness/tingling	3.1 (57)
Rash	2.3 (42)
Other event(s) at injection site	3.2 (58)
Body as a whole	
'Flu-like symptoms'	13.8 (254)
Malaise/fatigue	12.8 (236)
Fever	4.0 (73)
Pain, not otherwise specified	3.0 (54)
Diaphoresis	1.2 (23)
Chills	1.2 (21)
Weakness	1.2 (23)
Syncope	1.1 (20)
Cardiovascular system	
Heart rate/rhythm abnormality	1.7 (31)
Digestive system	
Nausea	4.2 (78)
Diarrhea	2.1 (38)
Vomiting	1.7 (32)
Oral symptom	1.7 (32)
Other gastrointestinal symptom(s)	2.7 (50)
Hematologic/lymphatic system	
Swollen lymph nodes	1.0 (18)
Integumentary system	
Rash	13.6 (251)
Pruritis	1.1 (21)
Other skin symptom(s)	2.4 (45)
Musculoskeletal system	
Arthralgia	12.4 (229)
Myalgia	5.3 (99)
Chest tightness	1.0 (19)
Chest pain	1.7 (31)
Arthritis	1.1 (20)
Other musculoskeletal symptom(s)	2.5 (44)
Nervous system	
Headache	10.6 (196)
Paresthesia	6.9 (127)
Dizziness	6.5 (120)
Altered mentation	2.5 (46)
Memory loss	2.4 (44)
Sleep disorder	2.0 (37)
Other neurologic symptom(s)	1.7 (32)
Respiratory system	
Dyspnea	1.6 (29)
Throat symptom	1.1 (21)
Other respiratory symptom(s)	3.5 (64)
Special senses	
Tinnitus	2.6 (48)
Eye symptom(s)	3.0 (56)

Serious and other medically important AEs

While AVEC reviewed and evaluated all reported AEs, particular attention was given to those meeting the definition of an SAE or OMIAE. Table 2 lists the 96 SAEs and 51 OMIAEs identified in the set of 1841 VAERS reports, together with a tentative assessment of their causal relationship to AVA. Many SAEs (35.4%) were so classified only because they involved a hospitalization, while an additional 2.1% were judged to result in prolongation of an existing hospitalization. Check boxes under item number 8 on the VAERS report form identified permanent disability and life threatening illness as the 'worst outcome' defining basis for 38.5% and 17.7% of the SAEs respectively, although many reports provided little or no support for these outcomes. Table 3 presents an account of the six SAEs (6.2%) that terminated in death. None appeared to be attributable to vaccination with AVA.

Of the 96 SAEs, 19 (19.8%) were assessed as possibly, probably or certainly related to receipt of AVA. Twelve of these were injection-site reactions; 11 were judged very likely/certain consequences of vaccination, while one was rated as having a possible relationship to vaccine because the report provided insufficient information concerning the exact location, extent and time of onset of the inflammatory response. All 12 were classified as SAEs only because they involved a hospitalization (1–10 days, median 1 day). Nine cases were treated with IV antibiotics. Reports indicated that ten individuals had recovered, while the recovery status of two others was not specified.

Seven systemic SAEs ('anaphylactic-like reaction' [2], bronchiolitis obliterans organizing pneumonia [BOOP], ulnar nerve neuropathy, urticaria, rash, muscle spasms) and seven systemic OMIAEs ('anaphylactic-like reaction' [3], arthritis [2], aggravation of spondyloarthropathy and HLA B-27+ arthropathy) were judged to be possible, probable, or very likely/certain consequences of vaccination with AVA (Table 2).

The five vaccinees (four males and one female) reporting an 'anaphylactic-like reaction' (two SAEs and three OMIAEs, one previously described as an 'anaphylactoid reaction'[9]) ranged in age from 19 to 32 years. Four had reactions that occurred within 20 minutes of vaccination, while the fifth developed diffuse angioedema with onset of pruritis 6 hours post-vaccination followed by generalized urticaria 4 hours later. None appeared to have experienced true anaphylaxis (i.e. a life-threatening airway and/or vascular collapse). All recovered after treatment with

Table 2. Number of reported serious adverse events (**SAEs**) and other medically important adverse events (*OMIAEs*) by body system

Primary event by body system[a]	*n*	AVEC causality assessment
Injection site reactions[b,c]	**12**	**Very likely (11), possible (1)**
Systemic AEs		
Body as a whole		
Fatigue	*2*	*Unlikely (1), unrelated (1)*
Febrile illness	**1**	**Unrelated**
'Multisymptom syndrome'	**2**	**Unclassifiable**
'Multisymptom syndrome'	*17*	*Unlikely (2), unrelated (4), unclassifiable (11)*
Syncope	**4**	**Unlikely (1), unrelated (1), unclassifiable (2)**
'Flu-like symptoms'	**2**	**Unrelated**
Suicide (died)	**1**	**Unrelated**
Cardiovascular system		
Acute MI (died)	**1**	**Unrelated**
Arteritis (died)	**1**	**Unrelated**
Atrial fibrillation	**3**	**Unlikely**
Cardiac arrest (died)	**1**	**Unrelated**
Endocarditis	**1**	**Unrelated**
Myocarditis	**1**	**Unrelated**
PACs	**1**	**Unrelated**
Pericardial cyst	**1**	**Unrelated**
Pericarditis	**1**	**Unlikely**
PVCs and bigeminy	*1*	*Unrelated*
Tachycardia/chest pain	*1*	*Unclassifiable*
Endocrine system		
Diabetes mellitus (type II)	**2**	**Unrelated**
Grave's disease	**1**	**Unclassifiable**
Hashimoto's thyroiditis[d]	*2*	*Unclassifiable*
Hypothyroidism	**1**	**Unclassifiable**
Hypothyroidism	*2*	*Unclassifiable*
Events attributable to infection		
Inflammation over olecranon process	**1**	**Unrelated**
Liver abscess, *E. coli* septicemia	**1**	**Unrelated**
Nonbacterial meningitis	**3**	**Unrelated (2), unclassifiable (1)**
Exocrine system		
Breast cancer	**1**	**Unrelated**
Gastrointestinal system		
Crohn's disease	**1**	**Unlikely**
Hematologic/lymphatic system		
Aplastic anemia (died)	**1**	**Unclassifiable**
Chronic lymphocytic leukemia	**1**	**Unrelated**
Idiopathic thrombocytopenic purpura	**1**	**Unclassifiable**
Large B-cell lymphoma involving CNS (died)	**1**	**Unrelated**
Neutropenia	**1**	**Unclassifiable**
Neutropenia	*1*	*Unclassifiable*
Thrombotic thrombocytopenic purpura	**1**	**Unrelated**
Von Willebrand's disease, type I	*1*	*Unrelated*
Immune system		
'Anaphylactic-like reaction'	**2**	**Very likely**
Anaphylactic-like reaction	*3*	*Very likely (1), probable (2)*
Angioedema	**1**	**Unrelated**
Rheumatoid arthritis	**1**	**Unrelated**
Systemic lupus erythematosus	**1**	**Unlikely**
TENS[e]	**1**	**Unrelated**
Urticaria	**1**	**Probable**
Integumentary system		
Extensive atopic dermatitis	*1*	*Unclassifiable*
Pemphigus vulgaris	**1**	**Unlikely**
Rash	**2**	**Possible (1), unrelated (1)**
Musculoskeletal system		
Abdominal pain [f]	**1**	**Unrelated**
Arm weakness	*1*	*Unclassifiable*
Arthralgia	**3**	**Possible (1), unrelated (1), unclassifiable (1)**
Arthralgia	*2*	*Unlikely (1), unclassifiable (1)*

Continues

Table 2. Continued

Primary event by body system[a]	*n*	AVEC causality assessment
Arthritis	*8*	*Possible (2), unrelated (3), unclassifiable (3)*
Arthropathy (HLA B-27+)	*1*	*Possible*
Chest pain	**1**	**Unclassifiable**
Fibromyalgia	**1**	**Unclassifiable**
Muscle spasms	**1**	**Possible**
Spondyloarthropathy aggravation	*1*	*Possible*
Nervous system		
Acute encephalitis	**1**	**Unrelated**
Ataxia/cervical myelitis	*1*	*Unclassifiable*
Bipolar disorder	**1**	**Unclassifiable**
Dizziness	**1**	**Unrelated**
Dysesthesias from T1 down	**1**	**Unclassifiable**
Dystonia movements of left side	*1*	*Unclassifiable*
Guillain Barré syndrome	**4**	**Unrelated (1), unclassifiable (3)**
Memory loss	**2**	**Unclassifiable**
Multiple sclerosis	**3**	**Unlikely (2), unclassifiable (1)**
Neurological symptoms	**1**	**Unlikely**
Optic neuritis	**1**	**Unclassifiable**
Optic neuritis	*1*	*Unclassifiable*
Peripheral neuropathy	*1*	*Unclassifiable*
Pervasive developmental disorder in offspring	**1**	**Unclassifiable**
Seizure	**2**	**Unrelated**
Tension/migraine headache	**1**	**Unrelated**
Transverse myelitis	**1**	**Unlikely**
Undiagnosed progressive paralytic neurologic disease	**1**	**Unrelated**
Ulnar nerve neuropathy	**1**	**Very likely**
Reproductive system		
Spontaneous abortion	*2*	*Unclassifiable*
Trisomy 13	*1*	*Unlikely*
Respiratory system		
Respiratory illness	**1**	**Unrelated**
Bronchospasms	**2**	**Unlikely (1), unclassifiable (1)**
BOOP[g]	**1**	**Probable**
Special senses		
Bilateral scleritis	**1**	**Unrelated**
Hearing loss in left ear	**1**	**Unrelated**
Loss of vision in right eye	**1**	**Unclassifiable**
Totals		
SAEs	**96**	
OMIAEs	*51*	

[a]Events are listed in this table according to the signs or symptoms that first allowed the reported experience to be classified as an SAE or OMIAE. Reports from several vaccinees described other symptoms with later onset that in the absence of the initial symptoms might have been classified as a different SAE or OMIAE (see subsequent footnotes).

[b]One vaccinee initially hospitalized for an injection-site reaction following AVA dose 5, 2 days later (while still hospitalized) developed numbness, paresthesias, weakness and facial drop involving the left arm, left leg and left face. He was hospitalized for a total of 6 days. The neurologic diagnosis, duration of symptoms and recovery status were not specified. AVEC requested additional medical records, but none was received. The causal relationship of AVA to the neurological symptoms was rated as unclassifiable.

[c]A second vaccinee initially hospitalized for an injection-site reaction also complained of extreme fatigue and had an extended 10 day course of hospitalization. AVEC requested additional medical records but none was received. The VAERS report provided no details regarding either the injection-site reaction (causality rated as possible) or the complaint of fatigue (causality rated as unclassifiable).

[d]One vaccinee reporting Hashimoto's thyroiditis also self reported pernicious anemia (causality rated as unclassifiable) but provided no details regarding these conditions. Other complaints noted were upper respiratory symptoms, otitis media, 'vertigo', fatigue, arthralgias, intermittent dizziness, intermittent headaches and numbness in the arm after each vaccination. This subject was ANA positive. AVEC requested additional medical records, but none was received.

[e]TENS = toxic epidermal necrolysis.

[f]This vaccinee reported postprandial abdominal pain, nausea, vomiting and diarrhea within 1 day after receiving the second dose of AVA, symptoms that were still occurring more than a year later. A subsequent report stated this vaccinee had additional symptoms following the third dose of AVA, including chronic fatigue, recurrent blepharitis, arthralgia, esophagitis due to candida, memory loss, lack of concentration, weight loss, headaches and leukopenia that continued for more than a year, emm follow; AVEC assessed the causal relationship of the G.I. symptoms as well as the subsequent blepharitis and weight loss as unrelated, while the chronic fatigue, arthralgia, memory loss, lack of concentration, headaches and leukopenia were rated as unclassifiable. AVEC requested but did not receive additional medical records.

[g]BOOP = bronchiolitis obliterans organizing pneumonia.

Table 3. SAEs resulting in death

Number	Age and sex	AVA vaccine Hx (time prior to death [PTD])	Medical Hx	Presentation	Diagnoses/treatment/outcome	AVEC causality assessment
1	32-year-old female	Dose 4 (14 months PTD); dose 5 (9 months PTD); dose 6 (3 months PTD)	Remote Hx of carpal tunnel syndrome. Medications: paroxetine (Paxil™) until ~1 month and buproprion (Wellbutrin™) for 3 days before presentation	**Presentation (3 months PTD)**—skin rash, heavy menses and sore left hand and thumb at site of a kitchen knife injury several days earlier (initially thought to be a cellulitis); also related a 1 mo. Hx of increasing fatigue and mild dyspnea	**Diagnosis**—aplastic anemia. Patient was hospitalized for almost 2.5 months before death; she was given antibiotic therapy and prophylaxis, high-dose prednisone, anti-thymocyte globulin, cyclosporine and GM-CSF, she expired in mid-2000	Unclassifiable
				Laboratory findings—pancytopenia (WBC 1–5, PMN 0.0, Hgb 9.5, Plts 7000); bone marrow biopsy—hypocellularity with fatty infiltration; serologies for HIV, parvovirus, HBV and HCV all negative; serologies for CMV (IgG) and anti-HBs positive; episode of bacteremia in hospital (VRE, *K. pneumoniae*)	**Autopsy**—invasive aspergillosis involving lungs, GI tract (typhlitis) and anoxic brain damage	
2	61-year-old male	0.5 dose 11 (4 months PTD); 0.5 dose 11 (2 weeks after first half-dose)	Elevated BP and remote Hx of carpal tunnel syndrome; burn to chest wall and hernia repair	**Presentation (3 months PTD)**—because of prior severe reactions to AVA (swelling and pain in arms) dose 11 was split, but patient still developed swelling of upper extremities (elbows, wrists, hands) ~1 month after 2nd half dose associated with diffuse arthralgias and fatigue that was unresponsive to celecoxib (Celebrex™) or diphenhydramine	**Ante-mortem diagnosis**—presentation initially thought to be an 'allergic reaction', but patient was subsequently found unresponsive at home in mid-2000	Unclassifiable
				Anti-mortem laboratory findings-↑total complement (173 U—normal 63–145 U); ↑ESR (20–42 mm/hour—normal range 0–15 mm/hour); normal C3 and C4; low positive anti-smooth muscle Ab (1:20); ↓lymphocytes (10.3%—normal range 14–41%)	**Autopsy**—pancarditis with focal coronary arteritis; fusion of the aortic cusps; inflammation involving AV and SA nodes; extensive lateral and posterior wall infarction, diffuse vasculitis involving prostatic, testicular and periduodenal arteries	
				Post-mortem laboratory findings—ASO titer positive (>200—normal range 1–10); parvovirus IgM (negative), IgG (positive)/serum c-ANCA and p-ANCA negative	**Post-mortem diagnosis**—healing phase of polyarteritis nodosa; extensive fibrointimal proliferation; possibly secondary to parvovirus B19 infection; differential diagnosis—rheumatic carditis/vasculitis	

3	53-year-old male	Dose 1 (29 months PTD); dose 2 (28.5 months PTD); dose 3 (28 months PTD); dose 4 (22 months PTD); dose 5 (16 months PTD); dose 6 (9 months PTD)	Very few details available (VAERS form only) but multiple prior complaints following receipt of AVA, including arthralgias, bradycardia, syncope, staring spells, weight loss, tinnitus, dizziness, mood swings, memory loss, lymphadenopathy, night sweats and splinter hemorrhages	**Presentation (early 2001)**—suicide	**Diagnosis**—suicide	Unrelated
4	53-year-old male	Dose 3 (6 months PTD); dose 4 (1 month PTD)	Significant for a myocardial infarct 6 years PTD with significant coronary artery disease (RCA, LAD), hypertension, peripheral vascular disease, gout and elevated cholesterol. His medications included metoprolol (Atenolol™), simvastatine (Zocor™), cilostazol (Pletal™), allopurinol and coated aspirin. His history was also significant for participation in several experimental vaccination protocols (e.g. WEE, EEE, VEE—last dose ~2 weeks PTD)	**Presentation (10 days PTD)**—he was found unresponsive on desk at work; CPR was initiated and he was transported to the hospital where he developed a quasi-stable rhythm after a 60 minute resuscitation effort **Laboratory findings**—echocardiogram-35% ejection fraction with inferior and inferolateral hypokinesis; slightly elevated cardiac enzymes (no values given in reports)	**Diagnosis**—probable myocardial infarction. Patient never regained consciousness and died 10 days later in late-2000 **Autopsy**—no autopsy performed	Unrelated

Continues

Table 3. Continued

Number	Age and sex	AVA vaccine Hx (time prior to death [PTD])	Medical Hx	Presentation	Diagnoses/treatment/outcome	AVEC causality assessment
5	57-year-old male	Primary AVA series—1983-annual boosters thereafter; most recent AVA booster (same month as death); other vaccines:-smallpox 5 months PTD; —botulinum toxin 2 months PTD	Few details available, but he had a history of coronary artery disease, as well as a remote history of PVCs and Hashimoto's thyroiditis. Both parents had died of myocardial infarctions	**Presentation (late 2000)**—he was found unresponsive (no details provided)	**Diagnosis**—presume myocardial infarction (no records)	Unrelated
					Autopsy—no autopsy performed	Unrelated
6	33-year-old male	Dose 1 (33 months PTD); dose 2 (32.5 months PTD); dose 3 (32 months PTD); dose 4 (27 months PTD); dose 5 (20 months PTD); dose 6 (12 months PTD)	No significant medical Hx. He was taking no medications and had reported no reactions to the first five doses of AVA	**Presentation (∼11 months PTD)**—approximately 2 weeks after AVA dose 6 he had a relatively mild flu-like illness that lasted 1 day. Approximately 11 months PTD, he began to experience intermittent diplopia. His neurologic presentation evolved over the next 12 months with right-side paresthesias (∼7 months PTD) and aphasia (∼5 months PTD)	**Ante-mortem diagnosis.** He was initially diagnosed as having multiple sclerosis and was treated with repeated courses of high-dose steroid therapy, IVIG, interferon, and finally mitoxantrone, none of which had any lasting effect on his condition. He died in mid-2001	
				Ante-mortem laboratory findings—during a 12 month period of neurologic deterioration, multiple lumbar punctures, CT scans, MRI-spectroscopic and MRI-thallium studies, and a brain biopsy (∼5 months PTD) failed to provide a final diagnosis. Serologic tests demonstrated no HIV or syphilis infection	**Autopsy**—limited autopsy led to the diagnosis of diffuse, large-cell B cell lymphoma	

parenteral (i.m.) anti-histaminics, nasal O_2 and IV hydration (three also received s.c. ephinephrine). There was no apparent association between these reactions and any particular vaccine lot or geographic location at the time of vaccination. Two reactions occurred after the first dose of AVA, two others followed the second dose and one had onset after the third dose. Three of the reactions were rated as very likely/certain and two were rated as probable consequences of vaccination.

The case of BOOP, tentatively rated as probably related to AVA, was described in our previous report.[9] This event was recently reviewed in another article, whose authors suggested it may have resulted from a hypersensitivity reaction to the aluminum hydroxide adjuvant in AVA.[15]

The case of ulnar nerve neuropathy involved a 41-year-old male vaccinee, who reported 'neuropathic pain' with loss of strength, motion and dexterity involving the three outer fingers, palm of the hand and the arm from the bottom to the mid-triceps area immediately after receiving the fourth dose of AVA. He suggested the injection had been misplaced so as to involve the ulnar and subcutaneous nerves, triggering an immune response against both nerves, and reported an EMG showed 'ulnar & submuscular nerve involvement'. Symptoms persisted 11 months later and the vaccinee indicated he had been permanently disabled. AVEC requested original medical records, but the patient declined to release them. AVEC assessed the causality of this SAE as very likely/certain.

The rash classified as an SAE concerned a 29-year-old male, who presented with a systemic pruritic rash 11 hours after the first dose of AVA. He was hospitalized for 1 day (reason not specified) and was off duty for 3 weeks but recovered. The VAERS report gave no other information regarding the nature or duration of his symptoms. AVEC requested additional medical information but none was received. AVEC rated this SAE as possibly caused by AVA because the timing of the rash made a relationship to vaccination biologically plausible. A second dermatologic SAE, urticaria, involved a male vaccinee (age redacted in error from the VAERS report), who developed recurring, generalized urticaria about 14 hours after receiving the fourth and fifth doses of AVA. He also complained of fatigue, recurring headaches and a 50% loss of feeling in his toes. Symptoms persisted 1½ years later; he was unable to fly and was only able to work part time. AVEC assessed the causal relationship of the urticaria to AVA as probable. Other symptoms were rated as unclassifiable because there is no evidence linking AVA with such events and they may occur for many reasons.

The last SAE rated as possibly caused by AVA involved a 34-year-old male, who developed muscle spasms 1 day after the second dose of AVA. The spasms were described as severe, occurring daily, exacerbated by physical activity and worse after the third dose of AVA. They were reported as still occurring after 5 months. AVEC requested additional medical records, but none was received.

The remaining four systemic OMIAEs involving articular complaints (arthritis [2], HLA B-27+ arthropathy and aggravation of spondyloarthropathy), all rated as possibly attributable to AVA, were noted previously in the first AVEC report.[9]

Positive rechallenge

A positive rechallenge (i.e. recurrence of a particular AE following multiple, especially successive, exposures to an agent) is considered strong evidence for a possible causal relationship between receipt of a pharmaceutical or vaccine and a subsequent AE. Two hundred forty-eight (13.5%) of the VAERS reports described recurrent AEs. Injection-site reactions comprised the most common type of recurrent AE, accounting for 44.4% (110) of these reports, followed by 'flu-like symptoms' (16.1% [40]), rash (12.1% [30]), arthritis or arthralgia (9.7% [24]) and malaise/fatigue (8.9% [22]).

Practically all the recurrent injection-site reactions were considered possible (0.9%), probable (5.4%) or very likely/certain (92.7%) consequences of vaccination with AVA. Given the relatively large number of these reports (110), AVEC tried to gauge whether injection-site reactions tended to increase in severity with successive doses of vaccine. One hundred two (92.7%) of these reports specified dose numbers, with 65.7% stating that the first injection-site reaction occurred after the first dose; 90% specified that recurrent reactions occurred after two or more (range 2–5 doses) successive doses of AVA. It was not possible to detect a trend in severity because most reports with quantitative information on the extent of local reaction (e.g. longest dimension of inflammation $<$30 mm, 30–50 mm, 50–120 mm etc.) did not present this in a dose number-specific way.

All 40 reports of 'flu-like symptoms' noted recurrence following two or more successive doses of vaccine (range 2–5 doses), with 75% indicating that the first episode of this AE occurred after the first dose. All but one case of recurrent 'flu-like symptoms' were judged to be possible (25.0%), probable (40.0%) or very likely/certain (32.5%) responses to vaccination. Of the 30 reports of recurrent rash, 19 (63.3%) involved

the first dose in combination with one or more through the sixth dose of AVA. Twenty-four (80%) of the rash reports were assessed as at least possibly associated with vaccination. The 24 reports of recurrent arthritis/arthralgia were widely distributed without any specific pattern of dose association; 6 (25%) were assessed as at least possible rechallenge events. In general, the 22 reports of recurrent malaise/fatigue involved the first dose, with 7 (31.8%) reported as recurring after the first and second doses and another 4 after the first, second and third doses. Ten (45.5%) of the malaise/fatigue reports were assessed as at least possibly associated with AVA.

In general, information in the VAERS reports was too limited to either identify or rule out a trend in the severity of recurrent systemic AEs. However, eight positive rechallenge reports of urticarial rash indicated greater severity or more extensive involvement after subsequent doses of AVA. An analysis of all AEs involving hospitalization and/or LOD suggested no marked increase in the severity of recurrent events. The relative risk of hospitalization and/or LOD was nearly the same for vaccinees reporting a recurrent event as for those reporting the event for the first time (RR = 1.09).

Concomitant occurrence of multiple AEs

Both unrelated illnesses and some reactions attributable to vaccination may be marked by a particular complex of signs or symptoms. However, similar complexes could also occur through chance association of individual AEs. The distribution of multiple signs and symptoms cited in the VAERS reports was first explored by calculating (under a model assuming independent occurrence of all events) probabilities of the observed frequencies for all 1024 potential event patterns involving one or more of the five most commonly reported systemic AEs ('flu-like symptoms', malaise/fatigue, arthralgia, headache, rash) and the five most common injection-site AEs (redness/swelling, nodule, local rash, burning/other sensations, local other). There was a clear break in this distribution at the point of the 13 most unlikely patterns, which had probabilities at least tenfold smaller than the fourteenth pattern. Eight of these patterns were unusual in that only one of the 10 most commonly reported AEs was mentioned (only malaise/fatigue, and the injection-site category, local (other), did not occur more often than expected as isolated events). Systemic rash was especially notable, with 162 reports of this AE as an isolated event (65 expected). Of the other five patterns, malaise/fatigue + arthralgia (41 observed, 18 expected) was the most prevalent, followed by malaise/fatigue+arthralgia+headache (13 observed, 4 expected). The other three highly unlikely patterns were noted in only three or fewer reports.

A second analysis probed the relationship between each of the five most commonly reported systemic AEs and the severity of injection-site inflammation as defined by five ordered categories of local redness and/or swelling: <30 mm (in the longest dimension), 30–50 mm, >50–120 mm (but not extending below the elbow), >120 mm without complications, >120 mm with complications or extending below the elbow.[13] For reports citing an injection-site AE falling into one of these categories, the proportions in each group that occurred concomitantly with each of the 5 most common systemic AEs were calculated. The analysis found no consistent relationship between the severity of a reported injection-site AE and the concomitant occurrence of these systemic AEs.

Finally, the VAERS reports were surveyed for evidence of a symptom complex designated in the first AVEC report as MSS (operationally defined as the concomitant occurrence of at least three of the following: malaise/fatigue, paresthesia, memory loss, sleep disorder and altered mentation).[9] Twenty-five (1.4%) described symptoms consistent with MSS. However, the definition of MSS did not include musculoskeletal symptoms, a category of AE found to be very prevalent among Gulf War veterans reporting a chronic multi-symptom illness,[16,17] so the reports were also surveyed to identify multiple symptom complexes including arthralgia (the most common musculoskeletal AE reported by recipients of AVA) plus at least two of the symptoms previously used to define MSS. Forty-four (2.4%) described such a symptom complex. In addition to the 19 newly identified reports, arthralgia was cited in 13 (52%) of the 25 reports that met the original definition of MSS. As noted previously for all 1841 VAERS reports, the prevalence of arthralgia + malaise/fatigue in these 32 reports was also far greater than expected. However, none of the other four symptom categories (i.e. paresthesia, memory loss, sleep disturbance and altered mentation) was mentioned in the 26 reports citing arthralgia + malaise/fatigue more often than in the set of all 44 reports noting at least three concomitant symptoms or the subset of 18 reports not citing arthralgia-malaise/fatigue.

Effect of gender

Most of the doses of AVA were given to male vaccinees (M/F ratio 8.7:1), so if males and females were at equal

risk both of having an AE and of reporting it to VAERS a similar ratio would be expected for the set of all reports. In fact, this M/F ratio was only 2.7:1, indicating that females were three times more likely than males either to have and/or report an AE. The 1827 reports specifying gender were examined to determine the M/F ratio for (1) the most commonly reported systemic AEs (i.e. AEs cited in at least 10% of all reports), (2) injection-site reactions and (3) AEs having substantial impact (i.e. SAEs, OMIAEs, those resulting in hospitalization and/or LOD).

The M/F ratio for reports of 'flu-like symptoms' was 2.8:1, similar to that for all reports. Females were less prevalent among vaccinees reporting malaise/fatigue (M/F ratio 3.8:1), but accounted for relatively more reports of headache (M/F ratio 2.2:1) and rash (M/F ratio 2.3:1). The M/F ratio for arthralgia, 5.7:1, was strikingly different from that for other common systemic complaints, pointing to a marked prevalence of this complaint among male vaccinees. As many disorders involving articular inflammation are more common in women than men,[18–20] this finding prompted the rheumatologist member of AVEC (A.B.) to further review every report of arthralgia and other articular complaints. A preliminary summary of that review has appeared in abstract form.[21] Vaccinees reporting an articular complaint were older than those reporting other AEs. Most articular reactions began within 3 days of vaccination but resolved within 30 days and generally were not associated with an injection-site reaction. As noted previously, arthralgia was associated with fatigue/malaise or with fatigue/malaise+headache more often than predicted by chance alone, but there was scant evidence for reactive arthropathy following vaccination with AVA.

Compared to all AE reports, females accounted for larger proportions of reports citing any injection-site AE (M/F ratio 2.0:1) and those detailing either moderate (>50–120 mm) or extensive (>120 mm) inflammation at the injection site (M/F ratio 1.9:1).

AEs reported by female vaccinees were not more likely to involve hospitalization and/or LOD than those reported by male vaccinees (M/F ratio 2.7:1). Female vaccinees accounted for a somewhat smaller proportion of reports defining a SAE (M/F ratio 3.3:1), but a larger fraction of reports describing events classified as OMIAEs (M/F ratio 2.1:1).

Distribution of AE reports by time, location and vaccine lot

During 1998, when AVIP was first initiated, AEs were reported to VAERS at rates of 2.8–5.5 reports/10 000 doses of AVA. This increased progressively, from 4.5 reports/10 000 doses in 1Q1999 to 17.9 reports/10 000 doses in 2Q2000, then declined somewhat to 8.2–14.7 reports/10 000 doses between 3Q2000 and 2Q2001. By the end of 2Q2001, 99.9% of the AVA doses covered by this report had been given. A shortage of FDA-released vaccine substantially reduced vaccination under AVIP until 2Q02;[6] only 1231 doses were given during 3Q2001 and 4Q2001, and four AE reports were submitted to VAERS during that period.

As for all AEs, reporting rates for those having greater impact (e.g. hospitalization and/or LOD) varied substantially over time, but the proportion of reports describing such an AE tended to decrease as the overall reporting rate increased. During 1998, when the AE reporting rate was 4.0 reports/10 000 doses, 22.4% of the 205 reports submitted described AEs involving hospitalization and/or LOD. By contrast, during a subsequent 4 quarter period (3Q1999-2Q2000), when the reporting rate reached 14.1 reports/10 000 doses, AEs involving hospitalization and/or LOD accounted for only 10.0% of 1119 reports.

The geographic trends noted in our initial review of 602 VAERS reports were essentially unchanged in the expanded set of 1841 reports.[9] Locations yielding the largest number of reports remained Delaware (180), California (131) and Korea (88). Delaware had the highest rate (248 reports/10 000 doses), followed by Michigan (164 reports/10 000 doses) and Oregon (141 reports/10 000), while the reporting rates were much lower in California (1.9 reports/10 000 doses) and Korea (4.6 reports/10 000 doses).

The 15 vaccine lots that had each been used for more than 50 000 doses were used in the conditional logistic regression models of reporting rates. In a model to estimate the odds of reporting an AE using lot FAV020 as the reference lot (the lot associated with the lowest reporting rate), the highest odds of reporting were associated with lots FAV031 (5.2:1) and FAV041 (4.2:1). The median relative odds for all lots was 3.1:1. Using a different model to estimate the odds of reporting an AE that involved hospitalization and/or LOD, lot FAV044 had the highest odds (3.2:1), followed by lot FAV024 (2.3:1) and lot FAV047 (2.3:1). In this case, the median relative odds for all of the lots was 1.6:1. Additional models that restricted the analysis to a substantially smaller subset of reports containing information on Service and status (active vs reserve) did not reduce lot-to-lot variability in the odds of reporting an AE to VAERS, but did identify somewhat different sets of lots as being associated with the highest odds. Finally, a model used to estimate the relative odds of reporting to VAERS an AE

involving moderate to severe inflammation (>50 mm) at the injection site showed that lot FAV033 had the highest odds (3.4:1) followed by lot FAV038 (3.0:1) and lot FAV041 (2.8:1).

DISCUSSION

Our review found no evidence that any SAE or OMIAE potentially attributable to AVA occurred at an unexpectedly high rate. Of the 26 SAEs or OMIAEs considered possible, probable or very likely/certain consequences of vaccination, 12 were injection-site reactions that led to a brief period of hospitalization but no extended disability. Nearly half of all reports cited some kind of injection-site AE, so it was not surprising to find 12 that met the minimal definition of an SAE (i.e. hospitalization). Since the term 'anaphylactic-like reaction' was defined and applied in a very broad way (see 'Definitions' under 'Methods') and none of the five vaccinees reporting this AE experienced true anaphylaxis (i.e. life-threatening airway and/or vascular collapse), AVEC concluded that these reports did not signal a significant safety problem. The other reports of AVA-related SAEs or OMIAEs described only 1–2 cases of eight other kinds of systemic AEs. None of the six deaths reported to VAERS appeared to be related to AVA.

AVEC found no evidence to support anecdotal accounts that vaccinees often experience sharp or burning pain immediately or shortly after injection of AVA, but the finding of 56 reports of paresthesia in the arm distal to the site of injection, most likely representing trauma to the underlying ulnar nerve, further reinforces our recommendation that s.c. injections of AVA should be given over the inferior deltoid instead of the triceps to avoid compression injury to this nerve.[9] In fact, with the resumption of AVIP in 2002 the DoD has instructed providers to inject AVA over the deltoid area.[22]

A survey of the VAERS reports for evidence of MSS or other related symptom complexes similar to those reported by a number of veterans returning from service in the Gulf War,[16,17,23,24] found that only 2.4% cited the concomitant occurrence of at least three of the following six types of AE: arthralgia, malaise/fatigue, paresthesia, memory loss, sleep disorder and altered mentation. Arthralgia + malaise/fatigue was more prevalent than expected by chance alone if the two events occurred independently, but this association is not surprising as multiple studies of patients with various rheumatoid illnesses have found fatigue to be a very common complaint. [25–28] By itself, the combination of arthralgia + malaise/fatigue does not define a specific illness and none of the other four symptom categories (paresthesia, memory loss, sleep disturbance and altered mentation) occurred in conjunction with this pair of symptoms more often than expected by chance. We cannot exclude the possibility that some recipients of AVA may be at increased risk of a chronic, multiple symptom illness that includes cognitive and/or neurologic elements, but the available VAERS reports provide no evidence of a specific illness warranting detailed study.

The frequency of reported AEs was not markedly influenced by (1) concomitant receipt of another vaccine or medication, (2) concomitant illness, (3) recurrence of an AE following multiple doses of vaccine or (4) vaccine lot. The proportion of AEs resulting in hospitalization and/or LOD was slightly higher among personnel with a pre-existing illness or those given other vaccines or medications concomitantly with AVA. The risk of hospitalization and/or LOD was nearly the same among vaccinees reporting a recurrent AE compared to those reporting an AE for the first time, although there was some evidence for slight increases in the severity or extent of urticarial rash after multiple doses of AVA. Finally, there was no consistency in the vaccine lots most often associated with reports of (1) any AE, (2) AEs involving hospitalization and/or LOD and (3) moderate to severe inflammation (>50 mm) at the injection site, so no lot could be clearly identified as more reactogenic than others.

Our review did find relatively strong associations between the frequencies and/or types of reported AEs and (1) vaccinee age, (2) vaccinee gender, (3) service affiliation, (4) the calendar time of vaccination and (5) the geographic origin of the AE reports. Female vaccinees were three times more likely than males to either experience and/or report an AE to VAERS (especially headache, rash and injection-site reactions involving moderate to severe local inflammation), a finding consistent with results from prior military studies in which female Service personnel reported higher rates of reaction to AVA than male Service personnel.[29–31] However, male vaccinees accounted for a surprisingly large proportion of reports of arthralgia, a finding that will be the subject of a separate article. AVEC concludes that the most common articular complaint, transient arthralgia (especially occurring in conjunction with fatigue/malaise, rash or headache) might be indicative of a systemic allergic reaction rather than a reactive arthropathy.

Variations previously noted in the rate of reporting to VAERS by Service, by calendar time of vaccination

and by geographic location,[9] were again seen in this review. Vaccinees in the Air Force appeared to report AEs at a substantially higher rate than members of other Services, but it was noted the Air Force has a much higher proportion of reservists than other Services, and further review showed that the reporting rate by vaccinees on reserve status was nearly threefold greater than by those on active duty. Consequently, duty status (reserve vs active) might be more important than Service in explaining variations in reporting rate. Vaccination of reserve personnel was only 1.5 times more likely to generate a report of an AE involving hospitalization and/or LOD, so perhaps reservists are more likely than active duty personnel to report less severe AEs.

Variations in reporting rate by calendar time of vaccination and by geographic location may in part reflect temporal or local variations in the emphasis given to submitting reports of less serious AEs. The DoD has directed Service healthcare personnel to report to VAERS any event following receipt of AVA that resulted in hospitalization and/or LOD, as well as events suspected to have resulted from contamination of a vaccine lot.[32] The policy encourages but doesn't require patients or healthcare providers to report less serious AEs. It might have been expected that some time would be needed to fully implement AE reporting after AVIP was initiated, and that the earliest reports would be enriched in AEs having greater impact. Indeed, the overall rate of reporting to VAERS increased several-fold during the first 3 years of AVIP, but the proportion of reports describing an AE involving hospitalization and/or LOD declined during this period. Perhaps persistent variation in reporting rates reflects geographic differences in the emphasis given to identifying and reporting less serious AEs.

It is important to emphasize that the apparent relationships between reporting rates and characteristics of person, place or time are subject to standard caveats that apply to any analysis of data derived from a passive surveillance system like VAERS (i.e. underreporting as well as incomplete, inaccurate and biased reporting of events). Even in a military context, there may be wide variation in the propensity to report an AE, according to situation-specific confounding variables about which we have no data. Consequently, the relationships described in this report have value primarily for hypothesis generation and should not be viewed as definitive conclusions.

In summary, our assessment of AE reports submitted to VAERS over a 4-year period from among more than 500 000 recipients of AVA found no evidence of a significant safety problem. The DoD restarted AVIP in 2002 with the objective of vaccinating personnel in areas of increased risk for anthrax and there is a possibility that vaccine could be widely administered to civilians in an emergency. These vaccinees will receive 'post-renovation' lots of AVA (BioThrax™) made under the establishment license granted to the manufacturer in 2002 (see 'Vaccine' under 'Methods'). This vaccine is made to the same formulation and by the same general process as the 'pre-renovation' lots assessed in our review. Newly produced lots of AVA may have a narrower range of variability, but there is no reason to believe that the AE profile associated with these lots will be different than those reported here. The CDC and the FDA will continue to monitor the safety of AVA, and the DoD plans to use the Defense Medical Surveillance System (DMSS) database to analyze and compare the safety profiles of 'pre-renovation' and post-renovation' lots of AVA given through AVIP.

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