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Adverse events after anthrax vaccination reported to the Vaccine Adverse Event Reporting System (VAERS), 1990–2007

Manette T. Niu[a,*], Robert Ball[a], Emily Jane Woo[a], Dale R. Burwen[a], Maureen Knippen[b], M. Miles Braun[a], The VAERS Working Group

[a] Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Biostatistics and Epidemiology, Division of Epidemiology, Vaccine Safety Branch, 1401 Rockville Pike, HFM-220, Rockville, MD 20852, United States

[b] Office of Compliance and Biologic Quality+, 1401 Rockville Pike, HFM-220, Rockville, MD 20852, United States

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ABSTRACT

During the period March 1, 1998 to January 14, 2007, approximately 6 million doses of Anthrax vaccine adsorbed (AVA) vaccine were administered. As of January 16, 2007, 4753 reports of adverse events following receipt of AVA vaccination had been submitted to the Vaccine Adverse Event Reporting System (VAERS). Taken together, reports to VAERS did not definitively link any serious unexpected risk to this vaccine, and review of death and serious reports did not show a distinctive pattern indicative of a causal relationship to AVA vaccination. Continued monitoring of VAERS and analysis of potential associations between AVA vaccination and rare, serious events is warranted.

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In recent years, the safety of Anthrax vaccine has been controversial, thus stimulating review panels to reassess the safety and efficacy profile of Anthrax vaccination (e.g., the 6 dose primary immunization schedule and annual booster doses, the cumulative impact of aluminum-adjuvanted vaccines on reactogenicity) [1–6]. In the aftermath of the 2001 anthrax attacks on civilians, public health officials reported that only a minority of persons believed to be at risk for anthrax and who were offered anthrax vaccination opted to receive it [7–11]. Understanding the anthrax vaccine safety profile is important so that the public and health care providers can make an informed decision about the risks and benefits of the vaccine.

Anthrax vaccine adsorbed (AVA) is the only U.S. licensed AVA vaccine approved by the Food and Drug Administration (FDA). Licensed in 1970, AVA is made from cell-free filtrates of microaerophilic cultures of an avirulent, nonencapsulated strain of *Bacillus anthracis* [12]. The primary series is administered at 2, 4, and 6 weeks, followed by 3 additional injections given at 6, 12, and 18 months [6–8]. Subsequent booster doses are recommended annually [5,6,12].

Only mild local and systemic side effects were reported after vaccination in prelicensure clinical trials [13,14]. The Institute of Medicine's review of post-marketing adverse events (AEs) after AVA vaccination found that local reactions (injection site reactions) and systemic events (fever, malaise, myalgia) were similar, in type and rate of occurrence, to events reported after receipt of other adult vaccines [1,15]. The committee found no evidence that vaccine recipients face an elevated risk of developing adverse health effects (life-threatening or permanently disabling) over the immediate or longer term, although data were limited in the latter regard [1]. The Anthrax Vaccine Expert Committee (AVEC), a panel of civilian experts consulting for the Department of Health and Human Services (DHHS), reviewed AEs reported to the Vaccine Adverse Event Reporting System (VAERS). Using an individual case causality assessment approach, they concluded that there was not a "high frequency or unusual pattern" of serious or other medically important AEs, but did identify a few rare events such as aggravation of spondyloarthropathy, anaphylactoid reaction, arthritis, and bronchiolitis obliterans organizing pneumonia as possibly or probably being caused by the vaccine [2,3]. The AVEC also noted that the aluminum-adjuvanted AVA vaccine administered subcutaneously over the triceps could induce swelling sufficient to pinch the ulnar nerve and cause distal paresthesias [2,3]. More recently, the FDA summarized VAERS AVA reports received through August 15, 2005 (including adverse event (AE) reports submitted to Docket No. 1980N-0208) as part of the FDA's final rule

* Corresponding author. Tel.: +1 301 827 6080; fax: +1 301 827 5218.
E-mail address: manette.niu@fda.hhs.gov (M.T. Niu).

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and order on anthrax vaccine safety and effectiveness [4]. This report identified some serious injection site and allergic reactions as being likely related to AVA. It also identified other conditions (arthritis, systemic lupus erythematosus, multisymptom illness, atrial fibrillation, pemphigus vulgaris, diabetes mellitus type 1, optic neuritis, Guillain-Barré Syndrome (GBS), and facial palsy) for which the data were insufficient to establish a causal relationship but for which the VAERS reports were notable in some way and/or had contributed to consideration of the condition for further study [4]. Studies of some of these conditions (e.g., atrial fibrillation, diabetes mellitus, optic neuritis, GBS, connective tissue diseases) have been undertaken (or are planned) by the Centers for Disease Control and Prevention (CDC), Vaccine Analytic Unit [16].

This report updates the previous FDA summary [4] and presents an overview of the case-by-case analysis of serious, positive rechallenge reports and deaths, including results from the VAERS data mining analysis to ensure that higher than expected rates of AVA vaccine-event combinations, if any were to occur, are identified in a timely manner [17–21].

1. Methods

VAERS is the U.S. passive surveillance system to which vaccine manufacturers, health professionals, and the public report clinical events temporally associated with vaccination. VAERS is jointly administered by the FDA and CDC and receives over 14,000 reports annually since its inception in 1990. VAERS solicits reports of any event temporally related to immunization [22]. The causal relationship between vaccination and a reported event cannot generally be inferred solely from VAERS data [22].

We reviewed AEs after AVA received by VAERS from August 16, 2005 to January 16, 2007. Serious AEs from this time period were pooled with all other reports of the specific AE found in the entire VAERS database (January 1, 1990 to January 16, 2007) before completing a case-by-case review. Duplicate reports were excluded. We searched for AE patterns according to AE coding terms (Coding Symbols for a Thesaurus of Adverse Reaction Terms [COSTART]), vaccination date, age, sex, and time from vaccination to symptom onset. Non-fatal serious, death, and positive rechallenge reports that included the dates of vaccination and time from vaccination to symptom onset were reviewed on a case-by-case basis. Non-serious reports were reviewed in the aggregate. The Code of Federal Regulations [21CFR600.80] defines serious AEs as those that are reported as resulting in death, life-threatening adverse experience, hospitalization, prolongation of hospitalization, persistent or significant disability, congenital anomaly/birth defect, or any event that, based on appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of these outcomes [23]. Positive re-challenge is defined as an AE that occurs after receipt of a vaccine, and re-occurs after subsequent exposure to the same vaccine. Cases of multisymptom illness were defined as having l or more symptom from at least 2 of 3 categories (fatigue, mood-cognition, and musculoskeletal) without regard for the duration of symptoms as a simpler way of identifying such conditions given the limitations of VAERS data (e.g., missing data on duration of symptoms); this definition differs from those published by Fukuda [19] (i.e., time requirement for duration of chronic illness), and Sever [2,3].

All serious events and positive rechallenge VAERS reports after AVA vaccination received during the period January 1, 1990 to January 16, 2007 were reviewed on a case-by-case basis by physicians. Serious and death reports received during the period August 16, 2005 to January 16, 2007 (i.e., reports received after a previous FDA review was completed) are a focus of this review [4].

1.1. Reporting rates and Empirical Bayesian data mining

Crude reporting rates were calculated as follows: the number of reports of specific AEs was divided by the number of vaccination doses that were administered according to data obtained from the Department of Defense (DoD), Military Vaccine Agency (MILVAX), for the time period March 1, 1998 to January 14, 2007, and March 1, 1998 to May 7, 2007 (for the gender analysis), and compared with background rates. For these calculations we focused on the period after 1998 because relatively few doses of AVA were used by the military before 1998.

We used data mining statistics employing previously described Empirical Bayesian approaches controlling for age and sex to screen for AEs potentially associated with AVA [20–24]. The comparison group included all VAERS reports not involving AVA vaccine for vaccinees 18 years and older for the period January 1, 1990 to January 16, 2007. We selected for further review VAERS reports with higher than expected reported AVA vaccination-event combinations. Our study used the Empirical Bayesian Geometric Mean (EBGM) threshold of at least 2 to screen for reports to review further (potential signal) [17,20]. Individual case reports were reviewed to assess reports with data mining scores above threshold. Data were managed and analyzed with Business Objects software (Business Objects Americas, San Jose), and WebVDME (Lincoln Technologies) data mining software.

2. Results

2.1. Update since FDA report [4]: summary of AE Reports from August 16, 2005 to January 16, 2007

There were 518 AEs after AVA reported to VAERS, of which 394 were non-serious (76%), 119 non-fatal serious (23%), and 5 (1%) death reports. The 119 non-fatal serious events reported to VAERS occurred in 14 (12%) females and 102 (88%) males, the median age of the patients was 38 years (range = 18–62 years), the median number of days from vaccination to symptom onset was 13 (range = 0–2144 days), and the median number of AVA doses received was 3 (range = 1–9 doses). The most commonly reported conditions (COSTARTs, not mutually exclusive) were: myalgia (39%), arthralgia (35%), pain (29%), headache (28%), depression (26%), asthenia (25%), rash, anxiety and insomnia (24%), and back pain (20%).

Seventy-two (61%) serious reports included both the dates of vaccination and symptom onset and were not attributed to concomitant administration of another vaccine (e.g., myocarditis or perimyocarditis after smallpox vaccination). Thirty (42%) reported a medical diagnosis made between 3 months and 5 years after vaccination.

The most common COSTARTs in non-serious reports were: arthralgia, headache, pain, myalgia, rash, asthenia, pruritus, insomnia, amnesia, paresthesia, back pain, and dizziness.

2.2. Summary of AE Reports, January 1, 1990 to January 16, 2007

As of January 16, 2007, there were 4753 reports filed after receipt of AVA vaccination to VAERS, of which there were 4273 (90%) non-serious, 455 (9.6%) serious, and 25 death (0.5%) reports (Fig. 1). During March 1, 1998 to May 7, 2007, approximately 6 million AVA doses were administered to military personnel (DoD, MILVAX, unpublished data) (Fig. 1). There were 163 VAERS reports of

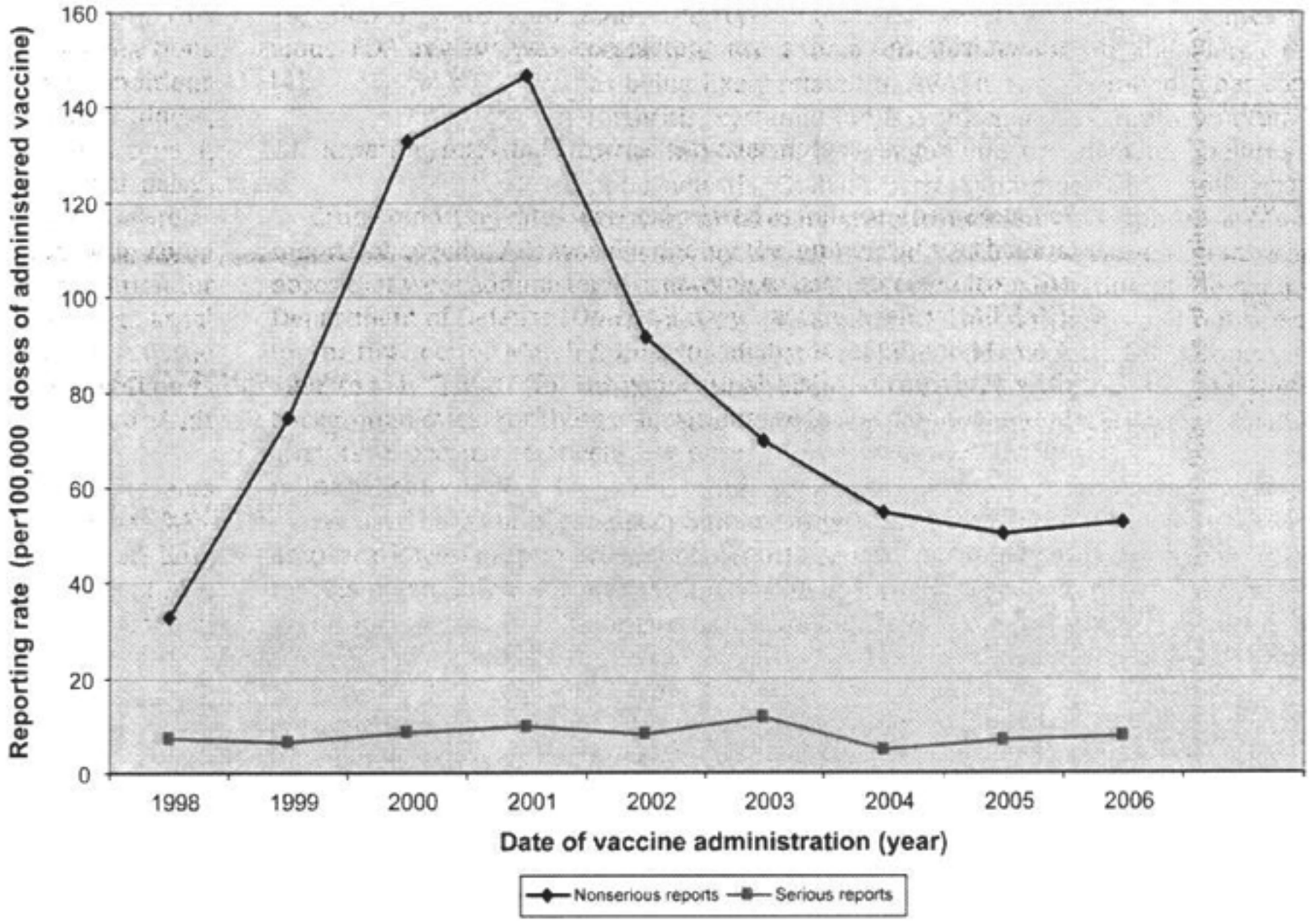

Fig. 1. Reporting rates for serious and nonserious adverse events (per 100,000 doses of administered Anthrax vaccine), VAERS, by year of vaccine administration (March 1, 1998-December 31, 2006).

injection site reactions (105 (64%) males, 56 (34%) females). The crude reporting rate for injection site reactions in males was 1.9 per 100,000 doses of administered AVA, compared with 8.3 per 100,000 doses in female recipients.

2.3. Summary of death reports, January 1, 1990 to January 16, 2007

There were 25 deaths (0.5% of reports) after AVA reported to VAERS. The causes of death and demographic characteristics are shown in Table 1. Of 5 deaths due to myocardial infarction, 4 persons had either a history of previous myocardial infarction, or were found to have severe atherosclerosis at autopsy. The other patient, a 37-year-old African-American male reportedly died of myocardial infarction; follow-up information was unavailable.

There were 3 reports of fatal amyotrophic lateral sclerosis (ALS). The first report involved a 44-year-old male who 3 days after receiving his first dose of AVA tripped while playing baseball and could not stand. Ten months after vaccination he was diagnosed with "non-typical ALS," and died 1(1/2) years later. The second report described a 28-year-old female, who 4 weeks after receiving AVA #3 developed twitching in her middle finger that ultimately resolved. Several weeks after receiving AVA #4 she developed progressive weakness. She was diagnosed with ALS a year after receiving her 3rd dose of AVA and died nearly two years later. The third patient was a 38-year-old male who nearly 2 years after receiving his AVA vaccination developed fatigue, headaches, irritable bowel syndrome, and muscle twitching. He was diagnosed with ALS nearly 7 years post-vaccination, and died several months after the diagnosis was made.

Two patients who developed pulmonary emboli after AVA vaccination died of their disease. A 39-year-old male who had pulmonary embolus and deep venous thrombosis received his first dose of AVA 32 days before his death from pulmonary embolus. He was later found to be positive for Factor V Leiden mutation R506Q (heterozygous mutant associated with a three- to six-fold increase in the risk for vein thrombosis). The second death was reported in a 49-year-old male who 4 years after receipt of AVA #2 died from pulmonary embolus, cytomegalovirus pneumonitis, focal segmental glomerulosclerosis, end-stage renal disease, and multi-organ failure.

A 22-year-old African-American female developed chest pain, dyspnea, and anorexia 2 days after AVA and other vaccines. Nine days afterwards she became febrile with myalgias and dizziness, and was treated for acute pharyngitis. Sixteen days after vaccination the patient was hospitalized for treatment of pneumonitis. She eventually developed pneumonia, sepsis, left pleural effusion, and anemia. She died 33 days post-vaccination. Post-mortem examination indicated that the immediate cause of death was anoxic encephalopathy, adult respiratory distress syndrome, active epicarditis, and lupus-like autoimmune disorder associated with recent smallpox and AVA vaccination. Results of immune studies on stored frozen serum obtained from the patient before she received AVA and smallpox vaccination were positive for Anti-nuclear antibody (ANA) at 1:640 (speckled pattern), she had an extended ANA titer of 1:5120, and an elevated SSA antibody. This patient's past medical history was significant for diffuse arthralgia and malar rash that occurred several months prior to an Army physical examination.

There were 3 deaths due to malignant tumors after AVA vaccination: Non-Hodgkin's diffuse large cell B lymphoma (1), primary synovial sarcoma of the heart (1), and cancer of the bile duct (1) (Tables 1 and 2). There were 3 cases of lymphoma after AVA in the VAERS database. Two cases were diagnosed as Non-Hodgkin's Diffuse Large Cell B lymphoma (NHL) including the one death report, and one case was Stage 2A Hodgkin's Lymphoma. Review of the VAERS database did not reveal other cases of sarcoma or bile duct cancer after AVA vaccination.

There were 4 reports of suicide, all in men. One man was known to have a history of Post-Traumatic Stress Syndrome since his mili-

Table 1
Deaths after anthrax vaccination reported to VAERS, 1990–2007 ($n = 25$).

Age	Sex	No. AVA doses	Lot no.	Concurrent vaccine	State	No. of days after vaccination	Initial symptoms	Cause of death	Autopsy yes (Y)/no (N)
57	M	22	FAV044	N.A.	MD	11	Sudden death	Acute myocardial infarction (MI)	N
52	M	4	FAV044	N.A.	MD	8	Sudden death	Cardiorespiratory arrest, S/P MI	N
47	M	1	FAV078	N.A.	NC	2	Sudden death	Severe coronary artery disease (CAD), S/P MI	Y
42	M	–	–	N.A.	Kuwait	3	Sudden death	CAD, S/P MI	Y
37	M	–	–	N.A.	DE	–	–	MI	N
53	M	6	–	FLU	CO	303	Suicide	Suicide	N
27	M	4	FAV073	FLU	MI	1	Suicide	Suicide	N
36	M	3	FAV044?	N.A.	KS	1115	Suicide	Suicide	Y
–	M	2	–	N.A.	CA	–	Heart failure, seizure, depression, paresthesia, anxiety, arthalgia, myalgia, diplopia	Suicide	N
47	M	1	FAV066	N.A.	CA	1	Sudden death	Cardiac arrythmia, sepsis	Y
61	M	11	FAV047	N.A.	MI	30	Fatigue, arthralgia, arthritis	Polyarteritis nodosa	Y
32	F	1	FAV031	N.A.	WA	25	Fatigue, petechiae, pancytopenia	Aplastic anemia, invasive aspergillosis	Y
22	F	1	–	TYP	IL	4	Dypsnea, fever, myalgia, vomiting	Adult respiratory distress syndrome, epicarditis Lupus-like autoimmune disease	Y
22	M	2	FAV064	TYP, OPV, SMALL, TD, MMR, HEP, FLU	TX	1	Drug overdose	Drug overdose (accidental)	Y
39	M	1	–	N.A.	NY	1	Sudden death	Pulmonary emboli, deep venous thrombosis	Y
45	M	2	–	N.A.	CA	4	Proteinuria	Pulmonary embolus, cytomegalovirus pneumonitis End-stage renal disease	Y
30	M	–	–	N.A.	NC	–	–	Bile duct (liver) cancer	N
33	M	6	FAV047	N.A.	MD?	14	Flu-like syndrome, fatigue	Lymphoma of the brain	Y
23	M	1	–	HEPA, TYP	AZ	0	Chest pain, dizziness, hemorrhagic Pericarditis, cardiac tamponade	Primary cardiac sarcoma	Y
21	M	4	FAV075	HEP, TYP	Iraq	166	Heat-related illness	Heat-related death	Y
40	M	2	–	N.A.	VA	180	Burn	Burn, sepsis	Y
–	M	3	–	N.A.	–	180	Rash, seizures	Seizures	N
28	F	4	–	N.A.	PA	28	Twitching, weakness	Amyotropic lateral sclerosis (ALS)	N
44	M	3	FAV030?	N.A.	VA	3	Weakness	ALS	N
38	M	3	FAV017	N.A.	FL	646	Fatigue, headache, eye ache, irritable bowel syndrome, twitching	ALS	N

tary assignment in Southeast Asia, while another man had a history of depression and suicidal ideation since divorcing his wife the year before his death. The time interval between vaccination and suicide was 1303, and 1115 days (this information was not available from one case).

There was 1 death reported in a 61-year-old male who developed nausea, joint swelling and arthralgia 4 weeks after his 11th dose of AVA (Tables 1 and 2). The cause of his death at autopsy was multifocal coronary arteritis consistent with polyarteritis nodosa.

2.4. Serious adverse events after AVA vaccination, VAERS, January 1, 1990 to January 16, 2007

Table 2 summarizes serious AEs reported to VAERS that include both dates of vaccination and onset of symptoms. In some cases, symptoms preceded vaccination but worsened after AVA. For some AEs, such as Multiple Sclerosis and ALS, the diagnosis was made many months or even years after AVA. There were 2 patients with previous rheumatologic disorders who reported exacerbation of their symptoms. A 31-year-old male developed "worsening ankylosing spondylitis" 24 h after receiving AVA #1. A 51-year-old female reported exacerbation of "severe symptoms of rheumatoid arthritis" the day after receiving each of her AVA doses #1–3 (e.g., new arthralgia and/or swelling).

2.5. Summary of multisystem illness reports, January 1, 1990 to January 16, 2007

There were 30 (0.6%) reports of multisystem illness after AVA vaccination that included the dates of vaccination and symptom onset (Table 2). The cases occurred in 27 males and 3 females, median age of the patients was 43 years (range = 21–62 years), and

Table 2
Demographic characteristics of selected serious adverse events after anthrax vaccination, VAERS, January 1, 1990 to January 16, 2007.

Diagnosis	No. (%)	Age (years)		Gender		Doses		Interval from vaccination to onset of symptoms (days)		Interval to diagnosis median (range)
		Median	Range	Female	Male	Median	Range	Median	Range	
Multiple sclerosis	11 (0.2)	26	21–39	2	9	4	1–5	9	0–51	15 months (3 months to 13 years)
Transverse myelitis	3 (0.06)	42	35–57	1	2	3	3–5	76	12–156	5 months (3–6 months)
Amyotrophic lateral sclerosis[a]	3 (0.06)	38	28–44	1	2	3	1–4	30	3–674	1 year (10 months to 7 years)
Psoriasis[b]	4 (0.08)	38	20–50	0	4	4	3–5	7	3–15	
Psoriatic arthritis	1 (0.02)	48		0	1	3		6		
Polyarteritis nodosa[c]	1 (0.02)	61		0	1	11		28		
Rheumatoid arthritis	15 (0.3)	35	23–50	6	9	3	1–6	21	0–2069	6 months (3 weeks to 7 years)
Systemic lupus erythematosis	4 (0.08)	29	22–44	3	1	3	1–4	18	0–39	71 days (33 days to 1 (1/2) years)
Myocardial infarction	5 (0.1)	47	37–57	0	5	4	1–21	6	2–11	
Pulmonary emboli[d]	4 (0.08)	47	39–49	0	4	3	1–6	713	32–1495	
Aplastic anemia[e]	2 (0.04)	26	19–32	1	1	5	5	23	21–25	
Lymphoma	3 (0.06)	33	32–42	1	2	6	1–7	355	53–2192	
Multi-symptom illness	30 (0.6)	43	21–62	3	27	3	1–9	67	0–1075	

[a] All 3 cases were fatal.
[b] Includes 1 case of Psoriatic arthritis.
[c] Patient died 3 months after AVA #11.
[d] 2 cases were fatal.
[e] No. of doses available for one individual.

the symptom onset occurred between 0 and 1075 days (median = 67 days) after vaccination. The median number of doses received was 3 (range 1–9 doses). Fourteen (47%) patients had neurological symptoms (i.e., neuropathy, paresthesias, headache, dizziness, vertigo, myoclonus, Bell's palsy, "black-outs") in addition to their multi-system illness, 12 (86%) of them were male. The number of days from vaccination to onset of symptoms ranged from 0 to 1075 days (median = 178 days).

2.6. Summary of positive re-challenge reports, January 1, 1990 to January 16, 2007

There were 147 (3%) reports of positive rechallenge after AVA vaccination. The most commonly reported events were injection site reaction (35%), headache (19%), fatigue (16%), arthralgia (12%), myalgia (11%), fever (11%), rash (10%), diarrhea (9%), nausea (8%), and flu-like symptoms (8%). Urticaria (5%), facial edema (2%), angioedema (1%) were reported at less common frequencies.

Of 13 reports of arthralgia with positive re-challenge, 12 (92%) involved males. Most cases developed after each of 2–4 doses of AVA. Four cases reported arthralgia in addition to multiple other symptoms including: myalgia, diarrhea, headache, shortness of breath, fever, dizziness, vomiting, chills, earache, stomatitis, or recurrent rash. There were 3 reports of alopecia with positive re-challenge occurring 7–14 days after 2–4 doses of vaccination.

2.7. Data mining

Data mining results with EBGMs of at least 2 were found for several AEs (Table 3). Headache is listed as a known side effect of AVA vaccination [12], hypercholesterolemia, unintended pregnancy (persons who had inadvertent administration of AVA vaccine during pregnancy), attention and sleep disorders, gastroesophageal reflux disease, and gastritis are common conditions, some with multiple possible etiologies.

There were 18 (0.37%) reports of hypothyroidism after AVA vaccination with symptom onset between 0 and 1891 days (median = 21 days) after vaccination. These cases occurred in 11 males and 7 females, and the median age of the patients was 35 years (range = 21–46 years). The median number of doses received was 3 (range 1–5 doses). Two hypothyroid patients were diagnosed with Addison's disease 103 days and more than 2 years after AVA vaccination.

There were 33 (0.68%) reports of alopecia after AVA vaccination with the onset of symptoms between 0 and 87 days (median = 12 days) after vaccination. These cases occurred in 16 males and

Table 3
Data mining analysis: AVA-vaccination-adverse event combinations for adult vaccinations, Empirical Bayesian Geometric Mean (EBGM) signal scores of at least 2, VAERS (January 1, 1990 to January 16, 2007).

Event	*N*
Gastroespohageal reflux disease	45
Blood cholesterol increased	41
Alopecia	55
Memory impairment	60
Vaginal hemorrhage	8
Dry skin	30
Hypothyroidism	22
Sleep disorder	65
Disturbance in attention	67
Positive rechallenge	61
Migraine	76
Unintended pregnancy	30
Cyst	35
Gastritis	23

17 females, and the median age of the patients was 36 years (range = 21–53 years). The median number of doses received was 3 (range 1–7 doses). Eight (24%) patients who developed alopecia had other medical conditions: SLE (1), hypothyroidism (2), panhypopituitarism (1), Henoch-Schonlein purpura and chronic steroid dependence (1), dissecting cellulitis (2) or folliculitis of the scalp (1), and transverse myelitis (1). There were 4 cases of alopecia areata, of which 2 cases were positive rechallenges which occurred between 1 and 2 weeks after AVA #1 and #2, and AVA #2 and #3.

There were 8 reports of uterine hemorrhage after AVA with different etiologies (i.e., abnormal PAP, post-menopausal bleeding, miscarriage, fibroids, menses (2), pregnancy, and spotting). The 30 VAERS reports of cyst formation after AVA also showed different characteristics (i.e., pericardial cyst, recurring cysts, sebaceous cysts, multiple cysts, cystic rash, macular cyst, ovarian cyst (2), injection site cyst, epididymal cyst, dissecting cellulitis, cyst (12), pilinodal cyst, bone cyst, ganglionic cyst, baker's cyst, epidermal inclusion cyst, and mucous retention cyst (2)). There were 23 reports of gastritis in association with multiple symptom complaints.

3. Discussion

The Institute of Medicine's Committee to Assess the Safety and Efficacy of the Anthrax Vaccine found no evidence that people face an increased risk of experiencing life-threatening or permanently disabling adverse events immediately after receiving AVA, when compared with the general population, nor did it find any convincing evidence that people face an elevated risk of developing adverse health effects over the longer term, although data are limited in this regard (as they are for all vaccines) [1]. The FDA's review of VAERS AVA reports received through August 15, 2005 found no causal relationship between deaths and other serious adverse events (other than some injection site reactions and some reports of allergic reactions) and the administration of AVA, but recommended some conditions (e.g., systemic lupus erythematosus, optic neuritis, arthritis) for further study [4]. The AVEC review of VAERS reports following AVA vaccine concluded that there was not a "high frequency or unusual pattern" of serious adverse events or other medically important AEs, but the Committee did identify a few rare events (e.g., aggravation of spondyloarthropathy, anaphylactoid reaction, arthritis, and bronchiolitis obliterans organizing pneumonia) as possibly or probably being caused by the vaccine [2,3]. Cases involving a wide range of adverse events (e.g., pemphigus vulgaris, rheumatoid arthritis, lymphocytic vasculitis, optic neuritis, polyarteritis nodosa, aggravation of spondyloarthropathy, arthritis, bronchiolitis obliterans organizing pneumonia) temporally associated with AVA vaccination are reported in the medical literature [4,25–30]. The results of our review confirm previous findings—we did not find any unexpected serious adverse event that could be definitively linked to AVA vaccination, however, given VAERS methodologic limitations, continuous monitoring by other studies with the ability to test specific hypotheses, is warranted [22].

DoD policy requires submission of a VAERS report for post-vaccination health events that result in hospitalization or loss of time from duty of more than 24 h [1]. The number of events reported to VAERS may be influenced by increased media coverage regarding a particular vaccine (i.e., "stimulated" reporting) [20]. Media coverage of AVA vaccine-related events occurred during the years 1998–2002, including the well-publicized concerns about the safety of AVA vaccination at Dover Air Force Base, the recommendations of Advisory Committee on Immunization Practices published in the MMWR, and reports on the safety and/or efficacy of AVA vaccine from the Department of Health and Human Services (DHSS), Anthrax Vaccine Expert Committee (AVEC), and the Institute of Medicine [1–3,5,6,9,31]. The highest VAERS reporting rates occurred during or shortly after this time period (Fig. 1).

The number of reports presented in this report is less than the sum of the recent reports and the number reported in an earlier FDA report [4] due to continual updates in the VAERS data (e.g., additional information received about existing reports, consolidation of some reports, and/or quality checks on the database). A number of conditions that were addressed in the earlier FDA report are not mentioned because no new serious VAERS reports of these conditions were received during the recent period (and included dates to determine onset interval), or some reports were received but they did not substantively change the conclusions indicated in the earlier FDA document (e.g., optic neuritis, GBS, diabetes mellitus, erythema multiforme, anaphylactoid reaction, bronchiolitis, pemphigus vulgaris, vasculitis, facial palsy, atrial fibrillation) [4].

Approximately 3.6–34% of vaccine recipients experience local injection site reactions within days of AVA vaccination, while < 1% experience systemic events (fever, chills, malaise) (12, 13, 32–34); these reactions occur at rates comparable to those observed with other vaccines [1,34]. In our VAERS review, injection site reactions, myalgia, arthralgia, headache, and fatigue were common complaints of AVA recipients who filed reports with VAERS regardless of the severity of the report (non-serious, serious). The crude reporting rate of injection site reactions was higher in females than males (female: 8.3 per 100,000 administered doses, male: 1.9 per 100,000 administered doses). Female susceptibility to develop local reactions after vaccinations has been noted by multiple authors [1,4,32–34]. McNeil et al. estimate that women have at least twice the risk of having an injection site reaction compared to men (2.78 age-adjusted relative risk, 95% Confidence Interval: 2.29, 3.38) for multiple vaccines [33]. The exact factors accounting for these sex differences are not known but may be a function of differences in muscle mass, dose per unit of body mass, physiologic factors, or differences in healthcare-seeking behavior [1,32–34].

The mean annual incidence rate of ALS is 0.8–2.0 per 100,000 persons [35–43]. Horner et al reports the overall occurrence of ALS is 0.43 per 100,000 military personnel per year [39]. An increased incidence of ALS among Gulf War veterans [39,40] and an increased death rate from ALS in military personnel compared to those who did not serve has been reported [41], however these studies did not specifically evaluate AVA vaccination as a risk factor for ALS [39–42]. In VAERS, there were 3 reports of ALS, all of which were fatality reports, for a crude reporting rate of 0.05 per 100,000 administered doses. Although the median age of ALS at the time of onset ranges from 56 to 67.5 years [35–37,43], the median age of AVA vaccinees with ALS in reports to VAERS was 38 years (range = 28–44 years). The median age of persons submitting VAERS reports after AVA vaccination was older than the mean age of active duty military personnel (38 years vs. 28 years). Case review of the ALS fatalities reported to VAERS did not provide significant support for a direct, causal link between ALS and AVA vaccine.

Vaccine-associated autoimmune disease has been reported within several weeks after vaccination [44–46]. Schonberger et al. (1979) reported an increased risk in the development of Guillain Barre Syndrome (GBS) within the 5–10 week period after receipt of the 1976 "swine flu" influenza vaccine [45]. Others have reported thrombocytopenic purpura after vaccination [46–50]. In VAERS there were a few case reports with onset or exacerbation of immune-related symptoms within several weeks of AVA vaccination (e.g., rheumatoid arthritis with radiologic changes consistent with disease, psoriasis, transverse myelitis, ALS, and a patient who died with autoimmune disease symptoms who was found to be ANA-positive with SSA antibodies prior to her receiving AVA). It is

unclear whether AVA played a role in their disease development or progression or whether the relationship to AVA vaccination is simply temporal; however, these events were not reported with high frequency nor did the clinical symptoms (e.g., interval between vaccine and onset of symptoms) follow a consistent pattern. Nearly 6 million doses of AVA have been administered during the past 9 years, and the crude reporting rates for the selected serious AEs (i.e., multiple sclerosis, transverse myelitis, ALS, rheumatoid arthritis, polyarteritis nodosa and psoriasis) evaluated in our study appears to be below the background rate in the general population [35–38,51–62]; however, because the appropriate risk interval for comparison is unclear, the optimal comparisons could not be made. VAERS reporting rates must not be interpreted as incidence rates primarily because of limitations of VAERS (e.g., under-reporting and unconfirmed diagnoses); it is possible that the AE might have occurred by chance after vaccination [22]. Despite this limitation, VAERS was able to identify a safety signal by detecting an excess incidence of intussusception among infants who received a live, tetravalent, rhesus-based rotavirus vaccine; this finding led to voluntary withdrawal of the vaccine from the market [63–66].

There were 30 serious reports of multisystem illness (MSI) [2,3,24]. In all but 2 cases, information submitted to VAERS did not contain sufficient information to determine the duration of the multi-system disease or of its symptoms. Compared to cases of MSI without neurological symptoms (e.g., paresthesias, headache), patients who developed neurological symptoms were younger (median age = 37 years vs. 46 years), and the interval from vaccination to symptom onset was longer (median interval = 178 days vs. 46 days). Whether the longer interval from vaccination to symptom onset reflects a longer latency period before the development of neurological findings, or is an artifact indicative of only a temporal association could be investigated in future studies. The data reported to VAERS regarding MSI after AVA vaccination is at this time insufficient to establish a causal relationship between AVA and MSI [2,3,24].

We reviewed reports of suicide after AVA and found no pattern with regard to vaccine dose number or time interval between vaccination and death. Eaton et al. reports the suicide rate among military personnel to be lower than among civilians of the same age, but these rates are not specific to personnel who received AVA vaccine [67]. Whether personnel who receive AVA are more likely than other military personnel to experience depression and suicidal ideation may deserve further exploration, although such study would need to adequately control for possible confounders (e.g., stress associated with deployment) and likely be methodologically challenging.

VAERS has methodological limitations inherent to passive surveillance systems such as under-reporting, reporter-bias, incomplete reporting, lack of consistent diagnostic criteria, lack of a control group, and lack of data as to the precise number of doses of vaccine administered to the population; however, VAERS has strengths that make it essential to the U.S. vaccine safety monitoring system [22]. It is the only vaccine surveillance system that covers the entire U.S. population and is the largest U.S. repository of case reports of events temporally associated with vaccination. Other strengths include the timely availability of data from a geographically diverse population, the ability to detect possible new, unusual or rare adverse events and to generate hypotheses that may be tested in other databases [22]. Spontaneous report-based surveillance programs can perform an important function by generating signals of potential problems that may warrant further investigation.

Our review of VAERS reports did not definitively link any unexpected serious adverse event to AVA vaccination, other than injection site and some allergic reactions. Review of serious and death reports did not show a distinctive pattern indicative of a causal relationship to vaccination (e.g., consistent time interval between vaccination and onset of symptoms, positive re-challenge). Additionally, our study included review of reports highlighted by data mining screening of VAERS which did not reveal specific events with a consistent clinical pattern. If crude reporting rates of AEs approached or exceeded the background rate for those conditions, concern about a possible association between AVA and that condition would be raised. While we did not observe any such elevation, our reassurance must be tempered by the acknowledged limitation of under-reporting. Nevertheless, the varied approaches we used to evaluate VAERS led to the same conclusion.

Like many vaccines, AVA can cause local injection site and allergic reactions [1,5,6,12–15,32–34]. In this regard, the CDC's Vaccine Analytic Unit, DoD, the FDA, and the National Vaccine Advisory Committee collaborated on a research agenda with the objective of analyzing unusual AEs using the DoD's longitudinal system for tracking vaccinations and medical events in military personnel, the Defense Medical Surveillance System (DMSS), including: idiopathic optic neuritis [29], and AEs possibly associated with concurrent multiple vaccination administration [68]. Other study topics include AVA vaccine and diabetes mellitus, atrial fibrillation, connective tissue diseases, GBS, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis [4,68,69]. Results from a clinical trial of a reduced AVA vaccination schedule are pending [32]. As with any medical product, we cannot rule out that some rare adverse events could be caused by AVA. Continued monitoring of VAERS and analyses of potential associations between AVA vaccination and rare, serious events is warranted.

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