

Adverse Events Following Anthrax Vaccine Reported to the Vaccine Adverse Event Reporting System

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Introduction

For any drug or biologic product, rare events or associations with other health problems that were not seen during pre-licensure clinical trials may occur post-licensure. As one approach to monitoring the number and type of adverse events following vaccination we analyzed reports of adverse events following anthrax vaccination submitted to the federal Vaccine Adverse Event Reporting System (VAERS).

Established in 1990 and operated collaboratively by the FDA and the CDC, VAERS receives approximately 15,000 adverse event reports annually. Reports are submitted by vaccine providers, other health care givers, vaccine recipients and relatives of recipients, vaccine manufacturers, attorneys, and other interested parties. Deaths and serious reports (operationally defined as an event that resulted in life-threatening illness, hospitalization, prolongation of hospitalization, persistent or significant disability, and congenital anomaly/birth defect) are followed up by telephone to obtain additional information about the event and the patient's prior medical history.

Passive surveillance systems such as VAERS are subject to many limitations. True associations will inevitably be underreported, to an unknown extent. Other adverse events might be expected to occur coincidentally after vaccination. It is problematic that temporal associations will be reported, often with little data to evaluate any causal connection with the vaccine. This inability to obtain precise numerators coupled with inadequate denominator data means that incidence rates cannot be determined. Although

the number of doses distributed is available to the FDA we do not know the number of doses actually administered or the demographic distribution of those receiving the vaccine. Reporting of unconfirmed diagnoses is common, and on follow-up initially reported diagnoses are not uncommonly found to be inaccurate. For purposes of evaluating the possible causal relationship between an event and a vaccination, a particularly important limitation is the lack of a direct and unbiased comparison group from which to determine the incidence of the same type of adverse events among people who have not been vaccinated.

Because of these and other limitations, it is usually not possible to determine whether causal associations exist between vaccines and adverse events from VAERS reports, unless the event is a well-recognized reaction (e.g. injection site reaction) or confirmatory laboratory results are included (e.g. vaccine strain virus detected in paralytic polio case). Signals of possible causally-linked adverse events are identified by finding unexpected patterns in age, gender, dose number, and time to onset, or by finding substantial numbers of “positive rechallenge” reports. Positive rechallenge is defined as the same event occurring after more than one dose of the same vaccine. Additional elements such as biological plausibility, the presence of pre-existing conditions, and concomitant illnesses, medication usage, or other exposures need to be examined to further determine the plausibility of an association between a vaccine and an adverse event. Adverse events identified as possibly linked to the vaccine almost always require confirmation using an adequately controlled epidemiological or other (e.g. laboratory) study.

An important additional limitation of VAERS is the lack of standardization of diagnoses. Reports are coded by non-physicians, without the benefit of standardized case definitions, using the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) to describe the adverse event in a computerized data base. Report coding depends on the reporter's use of certain words or phrases. This results in the use of the same COSTART term for reports with different degrees of diagnostic precision. For example, a report may simply say, "I developed arthritis after I received the vaccine", without any other supporting medical information. Such a report would likely be coded as "arthritis", as would a report that included a complete medical record documenting joint swelling and tenderness by a physician examination. As a result, coding terms must be interpreted very cautiously.

In spite of these limitations, use of VAERS data has provided initial reports that upon further evaluation have allowed for the identification of previously unrecognized or rare reactions to vaccines (e.g. intussusception after rotavirus vaccine) and has suggested the need for further study of other adverse events (e.g. hair loss after routine immunizations). We summarize all reports of adverse events following administration of anthrax vaccine received by VAERS since its inception in July 1990 through November 2004 and briefly highlight serious adverse events with 3 or more reports not mentioned in the label dated January 2002 (appendix 1).

Anthrax Vaccine: VAERS Reports from July 1990 through November 2004

VAERS received 4136 reports of these, 347 (8.4%) were listed as serious.

Most frequently reported adverse events (All reports)

	Costart	Number of Reports (n=4136)
1	Hypersensitivity injection site reaction	895
2	Edema injection site reaction	727
3	Vasodilation	666
4	Pain	654
5	Pruritis	652
6	Rash	597
7	Headache	594
8	Asthenia	521
9	Pain injection site reaction	478
10	Arthralgia	470
11	Mass injection site reaction	452
12	Myalgia	450
13	Fever	409
14	Edema	383
15	Parasthesia	334

Most frequently reported adverse events (SERIOUS reports)

	Costart	Number of Reports (n=347)
1	Asthenia	81
2	Headache	70
3	Fever	69
4	Chest Pain	63
5	Myalgia	61
6	Rash	50
7	Pain	49
8	Dyspnea	49
9	Arthralgia	44
10	Paresthesia	42
11	Vasodilation	35
12	Dizziness	35
13	Nausea	33
14	Edema	29
15	Chills	27

NB: Each report may be assigned multiple COSTARTs

Most frequently reported adverse events (SERIOUS reports)

	Body System		Number of Adverse Events (N=2220 COSTARTS among 347 reports)
1	BODY	Body as a Whole	640
2	CV	Cardiovascular	218
3	DIG	Digestive	140
4	ENDO	Endocrine	16
5	HAL	Heme and Lymphatic	37
6	MAN	Metabolic and Nutritional	101
7	MS	Musculoskeletal	167
8	NER	Nervous	430
9	RES	Respiratory	173
10	SKIN	Skin	168
11	SS	Special Senses (Eye and Ear)	73
12	UG	Urogenital	57

NB: Each report may be assigned multiple COSTARTs

Fatality Reports

	Year of Death	Age/ Sex	Summary	Anthrax vaccine dose number	Other Vaccines?	Interval since vaccination
1	2000	32F	Aplastic anemia and invasive aspergillosis	6		3 months
2	2000	61M	MI, coronary arteritis c/w polyarteritis nodosa	11		3 months
3	2000	52M	Out-of-hospital cardiopulmonary arrest	4		18 days
4	2000	57M	Out-of-hospital cardiopulmonary arrest	~21		11 days
5	2001	53M	Suicide	2		29 months
6	2001	33M	Central nervous system lymphoma	6		13 months
7	2002	30M	Suicide	3		37 months
8	2003	22M	Overdose; multiple drug ingestion; accidental	1	SP, other	5 days
9	2003	47M	Arrhythmia	1		2 days
10	2003	22F	ARDS, SLE	1	SP, other	33 days
11	2003	39M	Pulmonary emboli, DVT	1 or 2	SP	32 days
12	2003	47M	Atherosclerotic cardiovascular disease	1	SP, other	2 days
13	2003	27M	Suicide	4		1 day

14	2004	23M	Cardiac sarcoma	1		6 months
15	2004	42M	Atherosclerotic cardiovascular disease	3		3 days
16	2004	39M	Unintentional burn injury	3	SP	19 months

Anthrax Vaccine: Update of Serious Events and Reports of Positive Rechallenge from October 2001 through November 2004

Case Summaries

All serious events and reports of positive rechallenge reported from October 2001 through November 2004 were reviewed in detail. Serious events with 3 or more reports not mentioned in the label dated January 2002 are summarized here.

Deep Venous Thrombosis (DVT) - There were 5 reports of deep venous thrombosis occurring 0-27 days after AVA and other vaccines. One report described fatal pulmonary embolism (PE) in a 39-yo male with Factor V Leiden mutation. Factor V Leiden mutation was also mentioned in one report of DVT without PE. One report described the development of cellulitis and DVT in the extremity that had received AVA. A fourth report described a possible protein S deficiency. Another report described the development of DVT after a long airplane ride, in a person with a possible deficiency of protein S. Both protein S deficiency and Factor V Leiden mutation are known genetic risk factors for DVT.

Rhabdomyolysis – There were 4 reports of rhabdomyolysis 1-4 days after AVA. All 4 individuals were male. One man reported restricted oral hydration because the water in his barracks was non-potable. The other three reports described heavy exercise that had preceded the onset of muscle pain. Available laboratory results included the following CPK levels (and reference range, U/L): >8000 (0-193); 12,175 (55-170); 27,549 (42-209); or 111,909 (22-269), respectively, for each of the 4 men.

Pneumonia - There were 7 reports of pneumonia 0 days to two months after AVA. One report described *Mycoplasma pneumoniae*. Another report described aspiration pneumonia, arrhythmia, and cardiomegaly, but the time sequence with respect to AVA is unclear. A third report described pneumonia as a complication of acute disseminated encephalomyelitis (ADEM). One report described pneumonia, headache, and myasthenia. Three reports described pneumonia that accompanied myo/pericarditis.

Type 1 diabetes mellitus - There were 2 reports consistent with type 1 diabetes mellitus in 25 year old males who had onset of frequent urination and thirst approximately 2-3 days or 5 days, respectively, after their 1st dose of AVA. One was hospitalized. Both indicated that they were prescribed insulin and other medications. A 21 year old female had an abnormal glucose tolerance test approximately 3 months after her 3rd dose of AVA. An endocrinologist diagnosed her with impaired glucose tolerance, indicated concern that she might be developing Type 1 diabetes, and recommended close monitoring.

Hypothyroidism - There were 3 reports of hypothyroidism that developed 0 days to 5 months after AVA, including a report of Hashimoto's thyroiditis. One of the hypothyroidism reports also described Addison's disease.

Hypertension - There were 3 serious reports of hypertension 20 minutes to 1 month after AVA, in individuals 34-53 years old. One report described elevated systolic blood pressure (190) 20 minutes after anthrax dose #2 and the person was later diagnosed with chronic hypertension and non-cardiac chest pain. The other reports described hypertension accompanied by fatigue, memory loss, and multiple chronic symptoms relating to fatigue and decreased ability to function. One of these reports also described obstructive sleep apnea.

Alopecia - Six cases of alopecia were reported after anthrax vaccine, 5 after anthrax vaccine alone. Four male and 2 female individuals aged 21 – 53 years had alopecia after anthrax vaccination. A 41 year old male, developed alopecia 2.2 years after 6th dose and had concomitant endocrine disorders. A 21 year old man, 6 days after anthrax vaccination (previous dose unknown), had concomitant cellulitis; A 21 year old man, approximately 4 months after 1st dose of anthrax had concomitant vasculitis.

Paresthesias - There were a total of 15 serious reports in which paresthesias were described. Six, including one acute disseminated encephalomyelitis, one Guillain Barre syndrome, two allergic reactions, one meningismus, and one rheumatoid arthritis, had a diagnosis that could explain the paresthesias. Of the remaining nine, three had paresthesias associated with swelling or cellulitis in the injected arm. The remaining six had neuropathies without specific reported diagnoses.

Sleep Apnea - Three reports indicated sleep apnea. These involved males, age 23-34 years. Two mentioned treatment with continuous positive airway pressure. A fourth report mentioned possible sleep apnea in a 21 year old male.

Myocardial infarction (non-fatal) - Three reports of non-fatal myocardial infarction involved two 54 year old males, and a 39 year old female. These were diagnosed 19 days, 8 months, or 3 months, respectively, after vaccination.

Myopericarditis- Myocarditis alone is mentioned in the anthrax vaccine label. There were 13 serious reports of myopericarditis following smallpox and anthrax vaccine, but most of these are presumed to be associated with smallpox vaccine, a known risk factor for myopericarditis. There were 3 serious reports of myopericarditis following anthrax vaccine without smallpox vaccine. One presented 29 days after vaccination with pneumonia and myocarditis (with cardiac enzyme elevation and EKG abnormalities), one presented 2 days after vaccination with pneumonia and mildly elevated cardiac enzymes, and one presented 67 days after the third dose of anthrax vaccine with multisystem failure and cardiac tamponade thought to be secondary to pericarditis.

Appendix 1- Excerpt from 31 JAN 2002 Anthrax Vaccine Label

Post Licensure Adverse Event Surveillance

Data regarding potential adverse events following anthrax vaccination are available from the Vaccine Adverse Event Reporting System (VAERS).⁸ The report of an adverse event to VAERS is not proof that a vaccine caused the event. Because of the limitations of spontaneous reporting systems, determining causality for specific types of adverse events, with the exception of injection-site reactions, is often not possible using VAERS data alone. The following four paragraphs describe spontaneous reports of adverse events, without regard to causality.

From 1990 to October 2001, over 2 million doses of BioThrax have been administered in the United States. Through October 2001, VAERS received approximately 1850 spontaneous reports of adverse events. The most frequently reported adverse events were erythema, headache, arthralgia, fatigue, fever, peripheral swelling, pruritus, nausea, injection site edema, pain/tenderness and dizziness.

Approximately 6% of the reported events were listed as serious. Serious adverse events include those that result in death, hospitalization, permanent disability or are life-threatening. The serious adverse events most frequently reported were in the following body system categories: general disorders and administration site conditions, nervous system disorders, skin and subcutaneous tissue disorders, and musculoskeletal, connective tissue and bone disorders. Anaphylaxis and/or other generalized hypersensitivity reactions, as well as serious local reactions, were reported to occur occasionally following administration of BioThrax. None of these hypersensitivity reactions have been fatal.

Other infrequently reported serious adverse events that have occurred in persons who have received BioThrax have included: cellulitis, cysts, pemphigus vulgaris, endocarditis, sepsis, angioedema and other hypersensitivity reactions, asthma, aplastic anemia, neutropenia, idiopathic thrombocytopenia purpura, lymphoma, leukemia, collagen vascular disease, systemic lupus erythematosus, multiple sclerosis, polyarteritis nodosa, inflammatory arthritis, transverse myelitis, Guillain-Barré Syndrome, immune deficiency, seizure, mental status changes, psychiatric disorders, tremors, cerebrovascular accident (CVA), facial palsy, hearing and visual disorders, aseptic meningitis, encephalitis, myocarditis, cardiomyopathy, atrial fibrillation, syncope, glomerulonephritis, renal failure, spontaneous abortion and liver abscess. Infrequent reports were also received of multisystem disorders defined as chronic symptoms involving at least two of the following three categories: fatigue, mood-cognition, musculoskeletal system.

Reports of fatalities included sudden cardiac arrest (2), myocardial infarction with polyarteritis nodosa (1), aplastic anemia (1), suicide (1) and central nervous system (CNS) lymphoma (1).