

REF. 17

**Review of VAERS Anthrax Vaccine Reports Received Through 8/15/05,
and Adverse Event Reports Submitted to Docket No. 1980N-0208**

12/13/05

This document provides a summary of FDA's review of VAERS anthrax vaccine reports received through 8/15/05, and adverse event reports submitted to Docket No. 1980N-0208. To provide context, we have included some general information about FDA's approach to post-licensure vaccine safety monitoring of anthrax vaccine. This general information and conclusions from the adverse event review will also be described in the final order entitled "Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review; Anthrax Vaccine Adsorbed" which will be published in the Federal Register.

**FDA'S APPROACH TO POST-LICENSE VACCINE SAFETY MONITORING OF
ANTHRAX VACCINE**

For any drug or biological product, rare adverse events not observed during pre-licensure clinical studies may occur post-licensure. The need to understand the relationship between vaccination and adverse events that occur after licensure, and the limitations of clinical trials, have led to the use of other methods to detect and evaluate the link between vaccination and rare events. Post-marketing monitoring of vaccine safety involves the identification of possible adverse effects of vaccination, followed in some cases by evaluation of these "signals" for a possible causal link to the vaccine. The most common method of signal generation is through the evaluation of spontaneous reports of cases of adverse events reported to manufacturers or government-sponsored systems such as the Vaccine Adverse Event Reporting System (VAERS). The identification of "signals" and their prioritization for evaluation involves qualitative and

quantitative aspects, along with medical and epidemiological judgment. Evaluation of signals can involve literature review and clinical, laboratory, and epidemiological studies.

Surveillance for Adverse Events

Surveillance for adverse events after vaccination is undertaken using VAERS, which is jointly managed by FDA and CDC. Uses of VAERS include detecting unrecognized adverse events, monitoring known reactions, identifying possible risk factors, and vaccine lot surveillance. Established in 1990, VAERS receives approximately 15,000 adverse event reports annually for all vaccines. Reports are submitted by vaccine manufacturers, vaccine providers, other health care givers, vaccine recipients and their relatives, vaccine manufacturers, attorneys, and other interested parties. While vaccine manufacturers are responsible for investigating and evaluating reports made to them, FDA and CDC also follow up reports from other parties of deaths and adverse events resulting in life-threatening illness, hospitalization, prolongation of hospitalization, persistent or significant disability, or congenital anomaly/birth defect, 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 limitations. Vaccine-associated adverse events will inevitably be underreported to an unknown extent. Moreover, adverse events reported in association with vaccination may or may not be caused by vaccination. For example, some adverse events might be expected to occur by coincidence after vaccination. Temporal associations often are reported with little data to evaluate whether any causal connection with the vaccine exists. Given these limitations, while safety signals may be detected, incidence rates cannot be determined from VAERS

data. A particularly important limitation on the usefulness of VAERS reports as a means of investigating the possible causal relationship between an event and a vaccination generally is the lack of a direct, concurrent and unbiased comparison group from which to determine the incidence of the same type of adverse events among people who have not been vaccinated.

Another important limitation is the lack of standardization of diagnoses in VAERS reports. Reporting of unconfirmed diagnoses is common VAERS reports. On follow-up, initially reported diagnoses are sometimes found to be inaccurate. 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 database. 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 in which a physician documents joint swelling and tenderness. As a result, coding terms must be interpreted very cautiously.

Because of the limitations of passive surveillance data, it is usually not possible to assess whether a vaccine caused the reported adverse event, except for conditions such as injection site reactions, some hypersensitivity conditions (e.g., anaphylaxis occurring shortly after vaccination), and illnesses consistent with the naturally occurring disease where vaccine components can be recovered from tissue specimens (e.g., recovery of live attenuated vaccine virus from vaccine-associated paralytic polio).

Analysis of VAERS data focuses on describing clinical and demographic characteristics of reports and looking for patterns to detect “signals” of adverse events plausibly linked to a vaccine. In its guidance document on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, the FDA defines a safety signal as a concern about an excess of adverse events compared to what would be expected to be associated with a product’s use. This guidance document also details approaches for signal evaluation. Evidence of a signal in case reports and in case series of spontaneous reports includes unexpected patterns in clinical conditions by such factors as age, gender, time to onset, and dose. Three reports of an event can be used as the minimum number for case series analysis of rare conditions. Positive rechallenge is defined as the same event occurring after more than one dose of the same vaccine in the same subject and may also be considered evidence of a signal. Signals detected through analysis of VAERS data do not necessarily represent a causal relationship with the vaccine and almost always require confirmation through additional study.

In addition to the approach combining descriptive epidemiology with medical judgment, described above, several quantitative approaches, sometimes referred to as “data mining” methods, have been proposed. A common feature of data mining methods is that they identify patterns in the data that consist of a condition or group of conditions that are reported as a higher proportion of all adverse events after a particular vaccine or combination of vaccines than after other vaccines.

Calculations of reporting rates (number of adverse events reported/number of doses of vaccine distributed) and reporting rate ratios (ratio of reporting rate in the vaccine of interest to the reporting rate in the comparison vaccine(s)) of adverse events

have been used to generate signals. Comparison of reporting rates with background incidence rates for an adverse event is also sometimes advocated. Biases in reporting, inadequate denominator data, uncertainty of the risk interval (the interval after vaccination during which a person might be at risk for the adverse event under study), and lack of background incidence rates from an appropriate comparison population for some conditions limit the utility of the reporting rate approach.

Regardless of the method used, interpretation of vaccine-adverse event combinations that are identified as possible signals with any quantitative method must use medical knowledge about the disorders and take into account biases in reporting, misclassification of reports that occur with adverse event coding systems, and other limitations of passive surveillance systems previously discussed. Signals generated through such quantitative analysis need to be subject to the same clinical, descriptive epidemiological, and other analysis as for case reports and case series of spontaneous reports. Elevated reporting rate ratios or proportional reporting ratios or similar scores from data mining should not by themselves be interpreted as establishing a causal relationship between an adverse event and a vaccine, but almost always require independent confirmation through additional study.

In spite of these limitations, use of VAERS data has provided initial reports that upon further evaluation have raised suspicions, later confirmed, about rare reactions to vaccines (e.g., intussusception after rotavirus vaccine). VAERS data also have suggested the need for further study of other adverse events (e.g., myopericarditis after smallpox vaccine).

Signal Evaluation

Many possible signals* can be generated with these methods and prioritization for further evaluation is required. Because information submitted to VAERS is often incomplete, it is sometimes necessary to do enhanced follow-up of reports to systematically collect information as the first stage in the signal evaluation process. Objective factors such as seriousness and “newness” of the adverse event, size of the population potentially affected, ability to prevent the adverse event, and ability to study the question, influence priority for further evaluation.

VAERS reports are not the only source of information used to evaluate the safety of a vaccine. Evaluation of signals usually requires a literature review followed by epidemiological studies, sometimes combined with clinical and laboratory analysis. To evaluate specific hypotheses it is sometimes necessary to conduct cohort, population-based case series, case-control or other epidemiological studies using large administrative databases with medical record review. For example, the Vaccine Analytic Unit (VAU) was formed as a collaboration between the Department of Defense (DoD) and CDC to study the safety of anthrax vaccine, applying this approach to the data from the Defense Medical Surveillance System. FDA worked with this group to develop a list of adverse

* Safety signals that may warrant further investigation may include, but are not limited to, the following: (1) new unlabeled adverse events, especially if serious; (2) an apparent increase in the severity of a labeled event; (3) occurrence of serious events thought to be extremely rare in the general population; (4) new product-product, product-device, product-food, or product-dietary supplement interactions; (5) identification of a previously unrecognized at-risk population (e.g., populations with specific racial or genetic predispositions or co-morbidities); (6) confusion about a product's name, labeling, packaging, or use; (7) concerns arising from the way a product is used (e.g., adverse events seen at higher than labeled doses or in populations not recommended for treatment); (8) concerns arising from potential inadequacies of a currently implemented risk minimization action plan (e.g., reports of serious adverse events that appear to reflect failure of a risk minimization action plan goal); and (9) other concerns identified by the sponsor or FDA. (“Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoeconomic Assessment,” March 2005.)

events for further study based on VAERS and other data sources. In 2004, VAU participants and a workgroup of the National Vaccine Advisory Committee (NVAC) agreed the VAU's research agenda would include five topics for initial study: systemic lupus erythematosus, optic neuritis, arthritis, erythema multiforme, and multiple, near-concurrent vaccinations. Description of the VAU and the topic selection process are available at <http://www.cdc.gov/nip/webutil/about/annual-rpts/ar2005/2005annual-rpt.htm#online> (click on "Leadership in Vaccine Safety") and http://cdc.confex.com/cdc/nic2004/techprogram/session_787.htm.

Systematic Methods for Evaluating Vaccine Safety Concerns

If a clinical trial with sufficient statistical power to evaluate the adverse event of interest has not been conducted, assessing the potential causal link between a vaccine and an adverse event often requires integration of different types and quality of information (e.g., laboratory studies, case reports, epidemiological studies, and clinical trials). Causal inference criteria, patterned after those proposed by A. Bradford Hill in 1965, and adapted by others, and formal risk assessment have been applied to vaccine safety assessments. In a study of pertussis and rubella vaccines in the early 1990s, the Institute of Medicine (IOM) used the strength of association, the nature of the dose-response relation, the existence of a temporally correct association, consistency of association, specificity of the association, and the biological plausibility of the association for assessing whether evidence indicates a causal relationship between an adverse event and vaccine exposure. These criteria were also used in other more recent vaccine safety reviews performed by the IOM in 2001 through 2004.

SUMMARY OF POST-LICENSURE VACCINE SAFETY MONITORING OF ANTHRAX VACCINE ADSORBED (AVA)

Global Summary of FDA analysis of VAERS data

Data from VAERS cannot generally be used to determine if a vaccine causes an adverse event, but VAERS data can be useful for signal detection and hypothesis generation. As noted in the AVA labeling, a report of an adverse event following vaccination is not proof that the vaccine caused the event.

Approximately 1.3 million military personnel received 5.3 million doses of AVA from 1990 through March 31, 2005. During this period, we received 4,279 VAERS reports of adverse events following AVA and have evaluated them using a combination of the techniques described above (e.g., pattern assessment using frequency calculations, identification and descriptive analysis of case series, assessment of reporting rates for certain clinical conditions in the context of available information about background incidence rates and risk intervals, and data mining). Unrelated to vaccination, some of these 1.3 million persons would be expected to develop transient or chronic illnesses, some serious. In the absence of studies that determine the incidence of certain adverse events among vaccinees and compare them to a concurrent unvaccinated control group, good estimates of the background incidence of various illnesses in unvaccinated individuals may sometimes be useful for preliminary comparisons with what has been observed in vaccine recipients. Ideally, the background incidence rates used for such a comparison should be from recent studies and obtained from the military or similar populations in terms of demographics such as age, sex, race and ethnicity and prior health risk profile (such as other medical conditions). However, such information is frequently

unavailable, or the appropriate risk interval (i.e., time period after vaccination) for comparison is unclear. Additionally, reporting rates (number of adverse events reported/number of doses of vaccine distributed) to VAERS are not necessarily the same as the actual incidence (e.g., total number of people vaccinated who develop the adverse events/total number of people vaccinated during a given time period) of the adverse event. The amount of underreporting to VAERS, when it occurs, may vary by clinical condition, and the way conditions are described in VAERS reports may differ from the definitions used in available studies of background incidence rates. For these reasons, we have limited our comparison with background incidence rates to those events for which we feel adequate information is available to allow reasonable preliminary comparisons with the rates observed in the vaccinated population.

Based on this review, we cannot conclude that there is a causal relationship between serious adverse events (other than some injection site reactions and some reports of allergic reactions) or deaths and the administration of AVA. However, as with any medical product, FDA cannot rule out that some rare adverse events could be caused by AVA. As described above, VAERS data were used, along with other data, to develop a list of certain adverse events that were considered for further study by the Vaccine Analytic Unit to determine whether AVA has a causal role. FDA continues to perform surveillance and periodic evaluations of adverse event reports, and will review post-marketing data from any studies that become available to FDA.

For the period 4/1/05 to 8/15/05 there were 91 additional VAERS reports, of which 23 were serious. Taking these reports into account does not change the above conclusion because the reported events were clinically diverse, not materially different

from previously reported conditions, and did not form any unusual patterns in clinical or demographic characteristics.

In the next section of this document, we provide further details of the reported adverse events.

ADVERSE EVENTS FOLLOWING ANTHRAX VACCINE REPORTED TO THE
VACCINE ADVERSE EVENT REPORTING SYSTEM FROM JULY 1990
THROUGH MARCH 2005

We summarize all reports of adverse events following administration of anthrax vaccine received by VAERS since its inception in July 1990 through March 2005 and highlight serious[†] adverse events.

VAERS received 4,279 reports; of these, 390 (9.1%) were listed as serious.

MOST FREQUENTLY REPORTED ADVERSE EVENTS AMONG 4279 REPORTS*

	COSTART	Number of Reports With the Indicated COSTART
1	Hypersensitivity injection site reaction	914
2	Edema injection site reaction	743
3	Vasodilation	690
4	Pain	684
5	Pruritis	675
6	Headache	628
7	Rash	619
8	Asthenia	556
9	Arthralgia	501
10	Pain injection site reaction	487
11	Myalgia	480
12	Mass injection site reaction	465
13	Fever	425
14	Edema	394
15	Paresthesia	359

* Each report may be assigned multiple COSTARTs (Coding Symbols for Thesaurus of Adverse Reaction Terms)

[†] Serious reports are defined as events that resulted in death, life-threatening illness, hospitalization, prolongation of hospitalization, persistent or significant disability, or congenital anomaly/birth defect.

MOST FREQUENTLY REPORTED ADVERSE EVENTS AMONG 390 SERIOUS REPORTS AS CODED IN THE VAERS DATABASE*

	COSTART	Number of Reports With the Indicated COSTART
1	Asthenia	91
2	Headache	83
3	Fever	76
4	Myalgia	69
5	Chest Pain	64
6	Rash	56
7	Arthralgia	55
8	Dyspnea	54
9	Pain	54
10	Paresthesia	49
11	Nausea	38
12	Vasodilation	37
13	Dizziness	36
14	Amnesia**	29
15	Edema	29

* Each report may be assigned multiple COSTARTs

** Coding term for forgetfulness or memory disturbance

CATEGORIZATION OF REPORTED ADVERSE EVENTS BY BODY SYSTEM AMONG 390 SERIOUS REPORTS AS CODED IN THE VAERS DATABASE

	BODY SYSTEM		Number of Adverse Events*
1	BODY	Body as a Whole or Nonspecific	729
2	CV	Cardiovascular	246
3	DIG	Digestive	172
4	ENDO	Endocrine	20
5	HAL	Heme and Lymphatic	42
6	MAN	Metabolic and Nutritional	98
7	MS	Musculoskeletal	196
8	NER	Nervous	451
9	RES	Respiratory	179
10	SKIN	Skin	187
11	SS	Special Senses (Eye and Ear)	76
12	UG	Urogenital	52

* Total 2448 COSTARTS Among 390 Reports

FATALITY REPORTS

	Year of Death	Age/ Sex	Summary	Anthrax vaccine dose number	Other Vaccines?	Days since vaccination
1	2000	32F	Aplastic anemia and invasive aspergillosis	6		92
2	2000	61M	MI, coronary arteritis c/w polyarteritis nodosa	11		85
3	2000	52M	Out-of-hospital cardiopulmonary arrest	4		18
4	2000	57M	Out-of-hospital cardiopulmonary arrest	~21		11
5	2001	53M	Suicide	2		875
6	2001	33M	Central nervous system lymphoma	6		391
7	2002	30M	Suicide	3		~1150
8	2003	22M	Overdose; multiple drug ingestion; accidental	1	SPV, other	5
9	2003	47M	Arrhythmia	1		2
10	2003	22F	ARDS, SLE	1	SPV, other	33
11	2003	39M	Pulmonary emboli, DVT	1 or 2	SPV	32
12	2003	47M	Atherosclerotic cardiovascular disease	1	SPV, other	2
13	2003	27M	Suicide	4		1
14	2004	23M	Cardiac sarcoma	1		182
15	2004	42M	Atherosclerotic cardiovascular disease	3		3
16	2004	39M	Unintentional burn injury	3	SPV	573
17	2004	45M	End stage renal disease, pulmonary embolus, CMV pneumonitis, possible SLE	2		1510
18	2001	27F	ALS vs multifocal motor neuropathy	4		692
19	2003	21M	Heat-related death; Accidental	3		166

Abbreviations: ALS, amyotrophic lateral sclerosis; ARDS, acute respiratory distress syndrome; CMV, cytomegalovirus; DVT, deep venous thrombosis; SLE, systemic lupus erythematosus; SPV, smallpox vaccine.

At the time of the initial report, patient 18 was alive; follow-up information indicated the patient later died. The report about patient 19 initially focused on another vaccine, but follow-up information indicated that anthrax vaccine was administered closer in time (4 months prior) to the death than the other vaccine.

The reported deaths were clinically diverse, had widely varying times from the time of vaccination to death, and did not form any unusual patterns in clinical or demographic characteristics. These deaths, as a group, were not considered suggestive of causation by the anthrax vaccine. Some clinical topics are discussed further below.

ANTHRAX VACCINE: SERIOUS EVENTS AND REPORTS OF POSITIVE RECHALLENGE FROM JULY 1990 THROUGH MARCH 2005

INDIVIDUAL CASE REPORT SUMMARIES

All serious events and reports of positive rechallenge reported from July 1990 through March 2005 were reviewed. The case report summaries below generally focus on serious events with three or more reports. In addition, for selected clinical topics where additional reports would better inform our analysis, we include descriptions of some clinically significant reports that were not coded as serious (i.e., the reporter did not code the event in a manner that automatically classified it as serious).

ALLERGIC EVENTS

Possible anaphylactic reactions

There were a total of 10 reports (including 7 serious and 3 other clinically significant reports) with signs or symptoms compatible with anaphylaxis. In five of these reports, the physician diagnosed anaphylaxis following anthrax vaccination; onset of symptoms was within 15 minutes following vaccination. Other vaccines were administered simultaneously with anthrax in only two of these cases: oral polio vaccine in one case and typhoid, meningococcal and yellow fever in another. One of these

reports disclosed similar anaphylaxis-like reactions following prior anthrax vaccinations that worsened after each vaccination (positive rechallenge). In another report, the interval of vaccination to onset was 2 days but the laboratory analysis disclosed IgE-mediated anthrax vaccine allergy.

In four of the 10 reports anaphylaxis was not explicitly stated as the diagnosis, but the signs or symptoms described were of possible anaphylaxis (dermatologic and respiratory signs or symptoms, and the patient was treated with epinephrine, and/or parenterally administered antihistamines and corticosteroids).

Angioedema

Two reports of angioedema were coded as serious. The first report is of mild left jaw swelling in a 24-year-old male. This occurred after dose 1 and dose 2. The first time it was treated as a dental infection. The second time it was treated as angioedema with antihistamines and parenteral steroids. The second report is of a 44-year-old male who developed periorbital angioedema and generalized hives 1 day after receiving anthrax, influenza, hepatitis, meningococcal and typhoid vaccines. He was treated with prednisone, fexofenadine and diphenhydramine. Another 16 reports were not coded as serious.

Urticaria

There are eight serious reports of urticaria. In 3 reports, urticaria is part of a description of an allergic reaction. One report also mentions paresthesia and asthenia. Another report, also involved angioedema and is included in that section. A sixth report

mentions rash, swelling, joint stiffness and urticaria 409 days after anthrax vaccine dose

3. One person developed urticaria and dyspnea on the day after vaccination. He was later diagnosed with bronchiolitis obliterans organizing pneumonia. One additional report is included in the vasculitis section. Numerous reports not coded as serious also mentioned urticaria.

The clinical descriptions of the allergic events (anaphylaxis, angioedema, and urticaria), the relatively short times to onset of at least some of the events, and the biological plausibility of allergic reactions to a component of the anthrax vaccine provide evidence that the anthrax vaccine is the likely cause of at least some of the reports of allergic events.

CANCER

There are six cases of different malignant tumors. A 53-year-old male was diagnosed with chronic lymphocytic leukemia. He noticed an enlarged gland following his second dose of anthrax vaccine and was diagnosed with chronic lymphocytic leukemia about 18 months later. A 45-year-old male was diagnosed with multiple myeloma about 3 years after his fifth dose of anthrax vaccine. A 40-year-old male was diagnosed with a left seminoma about 2 months after his third anthrax vaccination. A 57-year-old female was diagnosed with extensive intraductal breast cancer in 2000 about 3 months after her third dose of anthrax vaccine. She had had a negative mammogram 18 months previously. A 23-year-old male developed a cardiac sarcoma and died 182 days after his first dose of anthrax vaccine and a 33-year-old male developed a cerebral B cell

lymphoma and died 391 days after the sixth dose of anthrax vaccine. The reports of malignant tumor are each very different in terms of type and site of origin and do not provide significant support for causality by the anthrax vaccine.

CARDIOVASCULAR EVENTS

Chest Pain

There were 27 serious reports of chest pain occurring after anthrax vaccine. Since chest pain can be associated with myopericarditis, and myopericarditis is associated with smallpox vaccine, we separated the smallpox vaccine-associated reports from those that received anthrax vaccine without smallpox vaccine (though other vaccines may have been administered in these cases).

Table: Serious Reports of Chest Pain after Anthrax Vaccine Separated by Concomitant Smallpox Vaccination Status

Clinical Category	With Smallpox Vaccine	Without Smallpox Vaccine
Rhythm disturbance	1	1
Multisystem Complaints	1	6
Allergic Response		1
Pleuritic CP/Pneumonia		2
Coronary Artery Disease	2	
Cardiomyopathy	1	
Myocardial Infarction	2	
Noncardiac CP		1
Myopericarditis	4	2
Possible myopericarditis	3	

Of the 27 reports, 14 were associated with the administration of both smallpox vaccine and anthrax vaccine. In four of the smallpox vaccine-associated cases, the diagnosis of myopericarditis was provided in the report, and an additional three <38-year-old males had a clinical picture consistent with myopericarditis, consisting of chest pain and abnormal EKG and/or elevated troponin within the first 10 days after vaccination, but myopericarditis was not mentioned on the report. Among the other smallpox vaccine-associated reports, there were two cases of myocardial infarction (see below) and two of

coronary artery disease diagnosed by cardiac catheterization. There was one case with chest pain 5-8 days after vaccination, and cardiomyopathy diagnosed 5 months later (discussed below), and one case of ventricular tachycardia occurring 10 days after vaccination.

There were 13 reports not associated with administration of smallpox vaccine. Two of these were of myopericarditis 29 and 583 days post-vaccination (see below for details). One report stated that the diagnosis was “noncardiac chest pain”. Two had pleuritic chest pain and/or pneumonia. One patient had difficulty breathing and chest pain immediately after vaccination with multiple vaccines, including anthrax, a response consistent with anaphylaxis.

Finally, there was one case of chest pain lasting for 20 minutes following the first dose of anthrax vaccine, followed by premature atrial contractions one day after vaccination with the third dose of anthrax vaccine. Six of the non-smallpox vaccine associated reports had multisystem complaints (see below).

There were seven reports with chest pain as one component of multi-system complaints; six after anthrax without smallpox vaccine, and one after anthrax with smallpox and other vaccines. These reports were of symptoms referable to at least three organ systems including cardiovascular, respiratory, gastrointestinal, and/or neurological. There was not a consistent clinical pattern among the group as a whole and thus these reports do not provide significant support for causality by the anthrax vaccine.

Cardiomyopathy

There were three serious reports of cardiomyopathy following anthrax and smallpox vaccines. One report was of a 37-year-old male with dilated cardiomyopathy (DCM) 5 months after vaccination with both anthrax vaccine dose 1 and smallpox vaccine, who had chest pain 5-8 days after vaccination. Another described DCM in a 42-year-old male 1 month after receiving both anthrax vaccine dose 3 and smallpox vaccine. The third describes a 34-year-old male with cough starting 4 months after anthrax vaccine dose 3, and 3 months after smallpox vaccine. He was admitted to the hospital with DCM 4 months after onset of cough and 4 days after anthrax vaccine dose 4. There were three serious cases of DCM after anthrax vaccine and without smallpox vaccine. The first was a 24-year-old male who presented approximately 6 weeks after vaccination with atrial fibrillation and probable myocarditis as well as DCM. The second was a 36-year-old male with coughing and wheezing 1 day after anthrax vaccine dose 3, diagnosed 4 days later with cardiomyopathy on echocardiogram. The third was a fatality report of a 47-year-old male, the cause of death being arrhythmia, with aspiration pneumonia 2 days after vaccination. Findings of cardiomegaly and myocardial fibrosis on autopsy suggested preexisting cardiomyopathy. For 2 of those reports of cardiomyopathy after anthrax vaccine alone, the short time interval between vaccination and event onset does not support causality by the anthrax vaccine. For those reports after anthrax and smallpox vaccine, it is plausible that smallpox vaccine could have caused or contributed to these cases because smallpox vaccine is known to cause myopericarditis which in other settings can be an antecedent to cardiomyopathy. However, the relationship between smallpox vaccine and cardiomyopathy, if any, is uncertain.

Myocardial infarction (non-fatal)

Four reports of non-fatal myocardial infarction involved two 54-year-old males, a 39-year-old female, and a 23-year-old male. These were diagnosed 19 days, 8 months, 3 months, or 4 months, respectively, after vaccination. All had one or more risk factors for coronary artery disease such as hyperlipidemia, hypertension, or tobacco smoking. These reports lack a clear pattern in demographics and onset interval. Also, the background occurrence of myocardial infarction in the general population is relatively common (increasing with age). Given these factors, these reports do not provide significant support for causality by the anthrax vaccine.

Myopericarditis

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 four serious reports of myopericarditis following anthrax vaccine without smallpox vaccine. One presented 29 days after the third dose of anthrax vaccine with pneumonia and myocarditis (with cardiac enzyme elevation and EKG abnormalities), one presented 2 days after the first dose of anthrax vaccine 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. One report described a 21-year-old male who developed recurrent pericarditis 18 months after his fifth dose of anthrax vaccine. The widely varying intervals between vaccination and onset of myopericarditis do not provide significant support for causality by the anthrax vaccine.

Atrial fibrillation

Five serious reports and two other clinically significant reports not coded as serious of atrial fibrillation following anthrax vaccination have been reported to VAERS. All occurred in males, ages 19 to 38.

Five reports involved atrial fibrillation and related symptoms as the central event. All involved anthrax vaccine alone, and occurred 0 to 17 days after the first, third or fourth dose of anthrax vaccine (interval unknown for one). As part of the diagnostic work-up, one patient had an echocardiogram showing cardiomyopathy with left ventricular ejection fraction of 40%. A second patient also had an echocardiogram showing an ejection fraction of approximately 40% and was thought to have probable myocarditis and dilated cardiomyopathy. This patient had a multiple uptake gated acquisition scan 6 days later showing an ejection fraction of 53%. The third patient reported that the atrial fibrillation persisted and was jeopardizing his career. He also reported having atrial fibrillation previously after an anthrax vaccine dose, but based on the dates, ages, and symptom text reported, it is unclear whether he is reporting a positive rechallenge or the same episode. The fourth patient had a syncopal episode about 10 hours after receiving the anthrax vaccine. He went to the emergency room by ambulance and was found to be in atrial fibrillation with a ventricular rate of about 145. The fifth patient reported episodes of rapid heart rate starting after his first dose of anthrax vaccine. After the fourth dose, he had an episode lasting 4 hours and presented to an emergency room. He was subsequently evaluated by cardiologists and diagnosed with atrial fibrillation.

The sixth patient (not coded as serious) had a seizure disorder and neurocardiogenic syncope starting 3 months after the second dose of anthrax vaccine, with development of atrial fibrillation following a seizure. The seventh patient had “episodic atrial fibrillation” among other events including three syncopal episodes, fatigue, headache, impaired memory, personality change, poor balance, and episodes of disorientation with abnormal EEG, with no clear diagnosis indicated; this patient had received several other vaccines (influenza, hepatitis B, Japanese encephalitis virus, typhoid) concomitantly with the anthrax vaccine.

An additional serious report describes a 61-year-old female with onset of palpitations 6 days after her second smallpox vaccine, and 19 days after her first smallpox and fourth anthrax vaccine. She was subsequently diagnosed with atrial fibrillation and heart failure. The evidence is insufficient to establish a causal relationship between anthrax vaccine and atrial fibrillation. This condition was reviewed as part of the Vaccine Analytic Unit's research agenda setting, but was not selected for initial study.

Hypertension

There were six serious reports of hypertension 20 minutes to 1 month after anthrax vaccine, in individuals 23 to 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. One report involved elevated blood pressure (159/62) 5 days after anthrax vaccine dose 2, in a 23-year-old experiencing pain and edema at injection site. One report describes a 39-year-old male

with multiple symptoms including hypertension, arthralgia, dyspnea, and tachycardia. 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. Although it is possible that anxiety about vaccination or pain from the injection could cause transient elevations of blood pressure, these reports do not provide significant support for causality of chronic hypertension by the anthrax vaccine in part because hypertension is common in the US adult population so it is likely some cases of hypertension would occur in temporal association with anthrax vaccination by coincidence.

Syncope

Two persons, age 19 or 23, had syncope hours after vaccination. Both had vomiting and one had severe headache. The latter also reported subsequent "black-outs", dizziness and urinary incontinence. Five other persons reporting syncope are listed under other categories. Syncope may be due to a variety of diagnoses, and these reports do not suggest a single or dominant diagnosis. Vasovagal syncope occurring within a short time of vaccination is a well known phenomenon, but these reports do not provide significant support for causality of recurrent syncope by the anthrax vaccine.

Deep Venous Thrombosis (DVT)

There were five reports of deep venous thrombosis occurring 0 to 27 days after anthrax vaccine and other vaccines. One report described fatal pulmonary embolism in a 39-year-old male with Factor V Leiden mutation. Factor V Leiden mutation was also

mentioned in one report of DVT without pulmonary embolism. One report described the development of cellulitis and DVT in the extremity that had received anthrax vaccine. 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. A causal relationship between anthrax vaccine and DVT in persons with genetic risk factors cannot be determined from these reports. The presence of genetic risk factors alone is not sufficient evidence of a causal relationship between vaccine and DVT in people with those risk factors, since one might expect a high proportion of reports of DVT would include a genetic risk factor regardless of what other factors might have contributed to the DVT. These reports are further confounded by other risk factors such as dehydration and prolonged immobility, as well as simultaneous administration of multiple vaccines in some cases. Because of these issues, these reports do not provide significant support for causality by the anthrax vaccine.

DERMATOLOGICAL EVENTS

Injection site reactions and cellulitis

There were a total of 18 serious reports in which injection site reactions were the central complaints. In most of these reports, onset or presentation for medical care was within 5 days. Eleven of these reports specifically described severe, extensive, or whole limb reactions. One report of extensive swelling and redness also described neck swelling and difficulty breathing (the patient was treated with epinephrine). Four reports described numbness, paresthesias or other signs compatible with polyneuritis or

peripheral neuropathy, and one described cellulitis complicated with deep venous thrombosis. Injection site reactions are clearly linked to the vaccine, and extensive reactions have been reported after anthrax and other vaccines.

Lymphadenopathy

There were nine serious reports that included lymphadenopathy without a specific etiology described. One report is a case of a 53-year-old male who developed lymphadenopathy, amnesia, arthralgia, tinnitus, weight loss and other complaints after his fourth dose of anthrax vaccine. He later committed suicide. The other eight cases included five males and three females. The onset time is 0 to 9 days. Three cases also received smallpox vaccine. Two reports describe lymphadenopathy in the neck area; one in the axilla and one in the hand. In five cases the location is not specified. Smallpox vaccine is known to cause lymphadenopathy in some cases and may be the cause in those cases where it is co-administered with anthrax vaccine. Among reports involving anthrax vaccine alone, varying levels of detail are provided about the site of lymphadenopathy and signs or symptoms of infection or injection site inflammation, so these reports do not provide significant support for causality by the anthrax vaccine.

Stevens Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)

Two serious reports and two other clinically significant reports that were not coded as serious of SJS/TEN following anthrax vaccine were received. These involved males, ages 18 to 27 years, who had onset 2, 5, 20 or 38 days after receipt of anthrax vaccine. The number of doses received prior to symptom onset was 2, 1, unknown, and

3, respectively. One reported painful oral lesions after the first dose of anthrax vaccine, with flares occurring within 48 hours after the second and third doses. Three patients received concomitant vaccines. For one, the reporter attributed the SJS to smallpox vaccine, though no rationale is provided. Two of the four patients reported taking other medications, either at the time of vaccination or the day prior to onset of rash and mucosal symptoms. Two were hospitalized. Follow-up information indicated that one patient had chronic eye problems continuing a year later due to cicatricial changes (scarring), two patients recovered, and unknown for one. Medications and infections are two of the most common causes of SJS/TEN, and the condition has been reported after smallpox and other vaccines. The presence of some of these exposures in the cases reported to VAERS leads us to conclude that the evidence is insufficient to establish a causal relationship between anthrax vaccine and SJS/TEN, but SJS/TEN was selected for further study by the Vaccine Analytic Unit as part of the Erythema Multiforme diagnosis.

Pemphigus Vulgaris

Two serious reports and two other clinically significant reports that were not coded as serious of pemphigus vulgaris (PV) following anthrax vaccine were received. These involved three persons diagnosed after anthrax vaccination and one diagnosed prior to anthrax vaccination who experienced a flare following vaccination. All were males, ages 33 to 46 years. One patient reported symptom onset sometime after receiving one dose of anthrax vaccine, initially with an abnormal feeling in his throat as if something was stuck, followed by mouth sores and blistering, and lesions on his chest and head. He was diagnosed with PV approximately 16 months after vaccination.

Another patient reported symptom onset several hours after the first dose of anthrax vaccine, starting with soreness in mouth and throat and some sloughing of mucosa. Throat and mouth symptoms reportedly worsened several hours after the second dose of anthrax vaccine, but did not worsen after the third dose. He was subsequently diagnosed with PV. Another patient developed mouth lesions and conjunctival erythema approximately 2 months after his third dose of anthrax vaccine, and was diagnosed with PV approximately 4 months after the third dose with supportive results from biopsy, serum staining, and HLA typing. The fourth patient, who was diagnosed with PV prior to receiving any anthrax vaccinations, reported a flare within 3 to 4 days after receiving anthrax and three other vaccines. The evidence is insufficient to establish a causal relationship between anthrax vaccine and PV. This condition was reviewed as part of the Vaccine Analytic Unit's research agenda setting, but was not selected for initial study.

Rash

There were 13 serious reports of rash not elsewhere classified. The rashes began 0-14 days after various doses of anthrax vaccine, and five of the vaccinees had received smallpox vaccine on the same day. The longest reported duration of a rash was 3 weeks. Rashes are a common medical event independent of vaccination, with a wide range of causes. In many cases, the description of the rashes in the reports was not sufficient to determine the exact type of rash or the possible exposures, other than anthrax vaccine, that might have contributed to them. Thus, these reports do not provide significant support for causality by the anthrax vaccine.

MULTI-SYSTEM SYNDROMES

There were 41 serious, non-fatal reports of signs/symptoms in at least two of the following three areas: (1) musculoskeletal complaints, (2) fatigue, and (3) changes in mood or cognition. The information submitted to VAERS often does not contain sufficient detail to determine the duration of certain symptoms. Notwithstanding, we identified 20 reports of symptom duration of at least 6 months in at least one of the three categories. The onset of symptoms ranged from immediately after anthrax vaccine to 3 years after vaccination and nine onset values are missing. These conditions are complex and have multiple etiologies so that VAERS data are insufficient to establish a causal relationship between anthrax vaccine and multi-system syndromes. Multi-system syndromes were reviewed as part of the Vaccine Analytic Unit's research agenda setting, but were not selected for initial study.

MUSCULOSKELETAL EVENTS

Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is reported in three serious reports and one other clinically significant report (that was not coded as serious). A 22-year-old female died with SLE and acute respiratory distress syndrome (ARDS) 33 days after receiving anthrax (first dose), smallpox, typhoid, hepatitis B, and measles-mumps-rubella vaccines. Symptoms of chest pain and shortness of breath began within 1-2 days after vaccination. This case was reviewed by two Federal Government committees. The CDC's Advisory Committee on Immunization Practices and DoD's Armed Forces Epidemiology Board said the evidence "strongly favors" the theory that vaccination led to the death. Three

members of a Health Resources and Services Administration committee said it was “possible” vaccination caused the death, and two members said it was “probable”. Because multiple vaccines were administered simultaneously, attribution was not made to a specific vaccine. A 29-year-old female was diagnosed with systemic lupus erythematosus and nephritis with symptom onset 12 days after her second dose of anthrax vaccine. A 45-year-old male was noted to have asymptomatic proteinuria approximately 4 days after his second dose of anthrax vaccine. A urinalysis 9 years prior was normal, with none available in between. Kidney biopsy showed focal segmental glomerulosclerosis and mild nephrosclerosis. Approximately 2 years after vaccination, his creatinine began to increase. Later notes indicate his rheumatologist believed he had a variant of lupus. He was also found to be lupus anticoagulant positive. He died 4 years after vaccination with end stage renal disease, pulmonary embolus, and CMV pneumonitis. A 44-year-old male developed fatigue and right knee pain within 24 hours after his fourth dose of anthrax vaccine. These symptoms persisted at about the same level for over a year. Approximately 12 months after vaccination, he awoke with chest pain and was diagnosed with pericarditis. Approximately 19 months after vaccination he was diagnosed with SLE. The evidence is insufficient to establish a causal relationship between anthrax vaccine and SLE, but SLE was selected for further study by the Vaccine Analytic Unit.

Rheumatoid Arthritis

Five serious reports and five other clinically significant reports that were not coded as serious indicated a diagnosis of rheumatoid arthritis. The serious reports

involved a 31-year-old male who developed urticaria, arthralgia, and arthrosis about 3 days after his seventh anthrax vaccination. He was hospitalized with a differential diagnosis of rheumatic fever, vasculitis and non-specific autoimmune disease and eventually diagnosed with rheumatoid arthritis. Other reports include a 50-year-old male with symptom onset approximately 3 weeks after the first dose of anthrax vaccine and smallpox vaccines; a 35-year-old male who developed pain in multiple joints approximately 8 months after the fourth dose of anthrax vaccine; a 36-year-old male with onset of symptoms approximately 5.5 years after one dose of anthrax vaccine. The fourth report involves a 23-year-old male who reported multiple symptoms and conditions during the 2 years after vaccination with anthrax vaccine (first dose) and other vaccines, including rheumatoid arthritis, sleep apnea, chemical sensitivities, and hospitalization with *Mycoplasma pneumoniae*.

The other reports (not coded as serious) of rheumatoid arthritis involve a 41-year-old male with onset of hand swelling and pain a few weeks after starting the anthrax vaccine series; a 28-year-old male with onset of joint symptoms approximately 6 weeks after anthrax vaccine dose 4; a 43-year-old male with arthralgias of knees and hands starting 5 days after anthrax vaccine dose 1, worsening after each of the next two doses, including additional joint involvement after the third dose and subsequently diagnosed with rheumatoid arthritis; a 42-year-old male with bilateral hip osteoarthritis and concern noted about possible rheumatoid arthritis, but negative rheumatoid factor, anti-nuclear antibody and erythrocyte sedimentation rate. Another report is listed under arthritis flare reports below. The evidence is insufficient to establish a causal relationship between

anthrax vaccine and arthritis, but arthritis was selected for further study by the Vaccine Analytic Unit.

Arthritis Exacerbation or Flare

Three reports involving arthritis flares after anthrax vaccine are as follows (not coded as serious). A 51-year-old female with a pre-existing history of rheumatoid arthritis had pain in multiple joints within 24 hours after anthrax vaccine doses 1, 2 and 3. A 41-year-old male developed inflammatory arthritis with onset after the fifth dose, and a flare after the sixth dose lasting 3 to 4 weeks. A 36-year-old male with a pre-existing history of spondyloarthropathy had flares after the first and third doses, the latter involving back and peripheral joint pain. Reports involving arthritis flares after anthrax vaccine can be difficult to interpret because the natural history of arthritis is often a waxing and waning course. The evidence is insufficient to establish a causal relationship between anthrax vaccine and arthritis flares, but as noted above, arthritis was selected for further study by the Vaccine Analytic Unit.

Other Connective Tissue Disease

Three serious reports and at least three other clinically significant reports that were not coded as serious noted other connective tissue disorders; these involved one report each of dermatomyositis, connective tissue disease (not otherwise specified), and localized scleroderma. One report was of a 57-year-old male admitted to the hospital approximately 3 or 4 weeks after anthrax vaccine dose 3 and diagnosed with dermatomyositis and nephrotic syndrome. A 25-year-old male had onset of connective

tissue disease approximately 2 weeks after anthrax vaccine dose 3. A 27-year-old male had onset of multiple symptoms including headaches, dizziness, depression beginning 39 days after anthrax vaccine (unknown dose number). He was later diagnosed with multiple lipomas, localized scleroderma and multiple sclerosis.

A report not coded as serious described a 41-year-old male who was diagnosed with an inflammatory arthritis with symptom onset 6 days after his fifth dose of vaccine. A 38-year-old female was diagnosed with a connective tissue disorder and urticaria after anthrax vaccine (unknown dose number, and onset interval unclear). After a subsequent anthrax vaccination, medical records indicate that the skin lesions markedly worsened. A 31-year-old male with history of ankylosing spondylitis had “severe worsening” of his underlying illness within 24 hours after his first dose of anthrax vaccine, with no change in treatment. These conditions are clinically diverse with diverse times to onset. The evidence is insufficient to establish a causal relationship between anthrax vaccine and these connective tissue disorders, but as noted above, arthritis was selected for further study by the Vaccine Analytic Unit.

Fibromyalgia

Three reports described multiple symptoms cases for which fibromyalgia was one of the potential diagnoses. All three cases required hospitalization. Antiphospholipid antibodies were identified in one case. The interval from vaccination to onset was ≤ 1 day in one report, 16 days in a second, and was reported as over 3 years in a third. The main signs and symptoms described included in the first report anxiety, insomnia, loss of appetite, fatigue and attempted suicide, in the second report obstructive sleep apnea,

memory loss, hyperesthesia, exhaustion, diarrhea, palpitations, and in the third report thrombocytopenia, cough, acute pulmonary embolism, vasculitis, dyspepsia, cough, wheezing, vertigo, allergic rhinitis, memory loss and chronic fatigue. These conditions are clinically diverse with diverse times to onset and do not provide significant support for causality by the anthrax vaccine.

Rhabdomyolysis

There were five reports of rhabdomyolysis 1-4 days after anthrax vaccine. All five individuals were male. Available laboratory results included the following creatine phosphokinase (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 four men. A fifth report was of a 21-year-old male with myalgia starting the same day as anthrax vaccine dose 5. He was admitted to the hospital where a maximum CPK of 2012 IU/L was noted 2 days later. Possible contributing factors described in these reports included restricted oral hydration because the water was non-potable in one case, and heavy exercise that preceded the onset of muscle pain in three cases. Because these are sometimes factors in causing rhabdomyolysis in unvaccinated individuals, these reports do not provide significant support for causality by the anthrax vaccine.

NEUROLOGICAL EVENTS

Facial Palsy

Fifteen reports of facial palsy, including three possible positive rechallenge reports (not coded as serious) and three serious reports have been received. Thirteen of

the reports involved anthrax vaccine alone; two reports indicated concomitant vaccines were administered.

The three reports of possible positive rechallenge are as follows:

A 41-year-old male had peripheral 7th cranial nerve palsy occurring within 2 days after the second dose, and again within 2 to 3 days after the fourth dose of anthrax vaccine. Tests for Lyme disease, RPR, and a brain MRI with gadolinium were reported to be negative or normal. A 32-year-old female had Bell's palsy occurring approximately 3 months after third dose, and left facial numbness, tingling and weakness occurring 7 days after the fourth dose. These two reports did not mention whether the facial palsy had resolved completely prior to the next dose. A 24-year-old male had left-sided facial weakness consistent with Bell's palsy after his first dose of anthrax vaccine, resolving after 2.5 weeks, and again 3 days after a subsequent dose of the vaccine (unknown dose number).

Eleven other persons had facial palsy that was reported as Bell's palsy, facial nerve palsy, 7th cranial nerve palsy, or unilateral facial paralysis. Three were reported as serious; one with encephalitis, one with positive Lyme titer, and one with recurring episodes of facial paralysis reported as permanent disability. The interval between anthrax vaccine and onset was 2-15 days for six persons, 70 days for one person, 17 months for one person, and unknown for three persons. Two reports indicated other concomitant vaccines were administered. One person had a throat culture positive for beta Streptococcus, one had otitis media, and one had a positive Lyme titer. One person reported Bell's palsy after his second dose of anthrax vaccine (onset interval unknown), and had right face twitching and numbness that started on the same day as his third dose,

but no mention of weakness. One person was diagnosed with mild encephalitis with concomitant arm and leg weakness, photophobia and headache, with onset 8 days after receiving anthrax, smallpox and other vaccines. Another report did not mention Bell's or facial nerve palsy, but indicated left facial numbness with right facial weakness, lip numbness, and loss of taste starting 1 day after the second dose of anthrax vaccine.

The background rate for Bell's palsy in the military is 42.7 per 100,000 person years, according to an analysis of the DoD's Defense Medical Surveillance System¹, corresponding to a rate of 0.8 per 100,000 person weeks. In this analysis, cases of Bell's palsy were ascertained using diagnostic codes without medical record validation. If we assume approximately 1.3 million military personnel have received 5.3 million doses of anthrax vaccine, the 10 VAERS reports of facial palsy occurring from 1 to 15 days after anthrax vaccination represents a reporting rate of about 0.19 per 100,000 doses. If the additional three reports with unknown onset date are included the rate increases to about 0.25 per 100,000 doses. This range of reporting rates (0.19-0.25/100,000 doses) should be compared with the estimated background rate of 1.6 cases every 2 weeks per 100,000 persons, although this background rate is likely to be an overestimate because it is based on unvalidated ICD-9 codes. The evidence is insufficient to establish a causal relationship between anthrax vaccine and facial palsy. Although the reporting rate does not exceed the background rate, we note the likelihood of underreporting reducing the reporting rate, the use of unvalidated administrative data increasing the background rate, and the presence of three positive rechallenge reports.

Paresthesias

There was a total of 37 serious reports in which paresthesias were described. Fifteen had a known medical illness that could explain the paresthesias, including two acute disseminated encephalomyelitis, three Guillain Barre syndrome, three allergic reactions, one meningismus, one rheumatoid arthritis, three multiple sclerosis, and two transverse myelitis reports. Of the remaining 22, seven had paresthesias associated with swelling or cellulitis in the injected arm and 15 had neuropathies without specific reported diagnoses. Paresthesias can be symptoms of a variety of diverse diagnoses. No single diagnosis was suggested by these reports, but subsets of the reports had some clinical similarities (e.g., injected arm). The evidence is insufficient to establish a causal relationship between anthrax vaccine and paresthesia. This condition was reviewed as part of the Vaccine Analytic Unit's research agenda setting, but was not selected for initial study.

Guillain Barre Syndrome (GBS)

The eight serious reports and one other clinically significant report that was not coded as serious of GBS involved symptom onset 0, 0, 0, 1, 7, 14, 17, 21 or 137 days following receipt of anthrax vaccine. An interval of 0 indicates that symptoms started after vaccination on the same date as vaccination. The dose number after which symptoms started varied. Specifically, symptoms occurred after dose number 1 (3 persons with onset on day 0, 7, or 14), 2 (1 person with onset on day 0), 3 (3 persons with onset on day 0, 1, or 137), 5 (1 person with onset on day 17), or 6 (1 person with onset on day 21). The patient with onset 137 days after vaccination had a mild sinus infection prior to onset. One patient reported no recent illness (six unknown). One patient received

concomitant influenza vaccine, and another received concomitant hepatitis A vaccine and received influenza vaccine 5 days later. The latter patient had symptom onset 17 days after the anthrax vaccine.

The one report not coded as serious involved a 52-year-old male with a childhood history of vaccine-associated poliomyelitis. He reported mild numbness and weakness in the lower extremities after the first anthrax vaccine dose, which increased following the second and third doses and was subsequently thought to be a post-vaccine syndrome or subacute GBS.

The reporting rate for GBS (excluding the report involving onset 137 days after vaccination since this is outside the time window [e.g., 6 weeks, based on some studies linking certain other vaccines and GBS] post vaccination during which GBS might be considered related to vaccination), based on 8 GBS reports from approximately 1.3 million persons vaccinated with 5.3 million doses (0.62 per 100,000 persons), is 0.16 per 100,000 doses administered. Estimates of the annual background incidence of GBS vary from 0.4 to 4 per 100,000 persons²; if 6 weeks is selected as the risk window, this annual rate corresponds to a background rate of 0.05 to 0.46 per 100,000 in a 6 week period. The reporting rate for GBS is similar to previously reported background rates and does not provide clear evidence of a causal relationship between anthrax vaccine and GBS. The evidence is insufficient to establish a causal relationship between anthrax vaccine and GBS. This condition was reviewed as part of the Vaccine Analytic Unit's research agenda setting, but was not selected for initial study.

Demyelinating conditions

The 15 serious reports of demyelinating conditions involving the central nervous system included seven persons with multiple sclerosis, three with acute disseminated encephalomyelitis, five with optic neuritis (including one with multiple sclerosis and one with acute disseminated encephalomyelitis [ADEM]), one with transverse myelitis, and one with an inflammatory demyelinating central nervous system disease that was not otherwise specified. All occurred in persons age 21 to 50 years. The conditions were reported following one to six doses of anthrax vaccine (two reports did not state the number of previous doses). Onset interval ranged from 0-76 days (three intervals were not reported). Persons with shorter onset intervals did not necessarily have more prior doses of anthrax vaccine. For example, three of the persons with 0 or 1 day onset intervals had not received any previous doses of the vaccine.

A total of three serious reports described ADEM following anthrax vaccination. The intervals from vaccination to onset were 34, 5, and 2 days, respectively. Two of the reports indicated that the patient required hospitalization. In two reports, anthrax was the only vaccine administered. In the remaining report the patient had received a total of six vaccines (including anthrax) on the same day.

The three reports of optic neuritis that did not report multiple sclerosis or ADEM involved symptom onset within 1 day (2 persons) of vaccine receipt, or during same month but interval unknown (1 person). Symptom onset occurred after the 1st (2 persons) or 4th (1 person) dose of anthrax vaccine, respectively. None reported receiving concomitant vaccines. The evidence is insufficient to establish a causal relationship between anthrax vaccine and optic neuritis. Optic neuritis was selected for further study by the Vaccine Analytic Unit.

The other demyelinating conditions in this case series are clinically diverse with multiple known and unknown causes and these reports do not provide significant support for causality by the anthrax vaccine.

Encephalitis

A total of four serious reports described encephalitis following anthrax vaccination. All required hospitalization. Of them, two had also received smallpox vaccination and were reported as vaccinia encephalitis. Of the remaining two, one, with onset 1 month after anthrax vaccination, had also received influenza vaccination. The other, with symptoms onset 10 days after vaccination, was diagnosed as herpes simplex encephalitis. Other causes of encephalitis were identified in the reports and/or long intervals between vaccination and onset were reported, thus these reports do not provide significant support for causality by the anthrax vaccine.

Aseptic meningitis

The four reports of aseptic or viral meningitis occurred in males, ages 25 to 33 years, with onset 1, 9 or 18 days after the first, third, or fourth dose of anthrax vaccine. With these varied onset times and dose number, these reports do not provide significant support for causality by the anthrax vaccine.

Headache

There were a total of four serious reports in which headache was a central complaint. In none of them was there an indication that another vaccine had been

administered concomitantly with anthrax vaccine. In two of them the interval vaccination-onset was <1 day. One indicated that the diagnosis was viral meningitis. In one report, the interval vaccination-onset was not indicated, and periodic episodes of headache and chills were described. The remaining report described a case of chronic tension headache. Headaches, including recurrent headaches, are a very common event independent of vaccination. At least one report identified an alternative etiology. Transient headache has been described as an occasional event after anthrax or other vaccines in some clinical trials, though studies may be uncontrolled. These reports do not provide significant support for causality of chronic headache by the anthrax vaccine.

Seizure

There were four serious reports of seizure after anthrax vaccine. The first was of a 21-year-old male who developed seizures 4 months after his first anthrax vaccine. He had a normal head CT, MRI, and lumbar puncture, and EEG showed “minute amount of neural activity not focused”. He also had multisystem complaints, and developed a positive ANA within the next 2 years. The second was of a 53-year-old female with multisystem complaints following the second dose of anthrax vaccine, including blackouts. Seizure was a diagnosis on the medical record. The third was of a 20-year-old male described as having a viral syndrome and seizure 3 days after the third dose of anthrax vaccine. Lumbar puncture was “consistent with viral meningitis”. The fourth was of a 19-year-old male who had new onset seizures one month after receiving smallpox and anthrax vaccines (unknown dose number). These conditions are clinically

diverse with diverse times to onset and do not provide significant support for causality by the anthrax vaccine.

OTHER EVENTS WITH POSSIBLE AUTOIMMUNE BASES

Thrombocytopenia

There were four serious reports of thrombocytopenia after anthrax vaccine. The first two reports were of idiopathic thrombocytopenic purpura (ITP). A 25-year-old male developed ITP 4 weeks after the third dose of anthrax vaccine. A 36-year-old male was hospitalized 10 days after vaccination with anthrax dose 1 with a platelet count of 0, and was diagnosed with ITP. There was one serious case of thrombotic thrombocytopenic purpura (TTP) in a 40-year-old female 4 months after anthrax vaccine (unknown dose#), treated with plasmapheresis and splenectomy. Finally, there was a case of aplastic anemia of unknown etiology with thrombocytopenia in a 19-year-old male 1 month after he received anthrax dose 1. Thrombocytopenia has been reported after other vaccines, but a clear causal relationship has not been established except for thrombocytopenia after live attenuated measles mumps rubella virus vaccine. These reports are clinically diverse, and do not provide significant support for causality by the anthrax vaccine.

Type 1 diabetes mellitus

There were five reports consistent with type 1 diabetes mellitus, two of which involved 25-year-old males who had onset of frequent urination and thirst approximately 2 to 3 days or 5 days, respectively, after their first dose of anthrax vaccine. One was hospitalized. Two reports described patients with frequent urination, thirst and ketonuria

who were later diagnosed with insulin dependent diabetes mellitus after the fifth dose anthrax vaccine: a 23-year-old male and a 38-year-old male, with onset of symptoms at 0 and 9 days after vaccination, respectively. One report described a 29-year-old male who developed diabetic ketoacidosis and was diagnosed with Type 1 diabetes mellitus, 2 years after his third dose of anthrax vaccine. In addition to these 5 reports, a 21-year-old female had an abnormal glucose tolerance test approximately 3 months after her third dose of anthrax vaccine. An endocrinologist diagnosed her with impaired glucose tolerance, and indicated concern that she might be developing Type 1 diabetes. The evidence is insufficient to establish a causal relationship between anthrax vaccine and diabetes mellitus. This condition was reviewed as part of the Vaccine Analytic Unit's research agenda setting, but was not selected for initial study.

Hypothyroidism

There were three reports of hypothyroidism involving symptom onset 0 days, 5 months, or 3 years after anthrax vaccine, including a report of Hashimoto's thyroiditis. One of the hypothyroidism reports also described Addison's disease. Hypothyroidism is a common condition with numerous causes. The reported cases had diverse times to onset, and do not provide significant support for causality by the anthrax vaccine.

Alopecia

Eight cases of alopecia were reported after anthrax vaccine in reports coded as serious, 6 after anthrax vaccine alone. Four male and 4 female individuals aged 21 to 53 years had alopecia after anthrax vaccination. A 29-year-old female, developed alopecia

12 days after her second dose of anthrax vaccine, and was later diagnosed with Systemic Lupus Erythematosus. A 41-year-old male, developed alopecia 2.2 years after his sixth dose and had concomitant endocrine disorders. A 21-year-old male developed alopecia and cellulitis 6 days after anthrax vaccination (previous doses unknown). Two reports involved alopecia onset after the fourth dose of anthrax vaccine: a 22-year-old male and a 23-year-old male developed alopecia at 0 and 10 days, respectively, after vaccination. A 35-year-old female developed transverse myelitis 76 days after the 3rd dose of anthrax vaccine. She developed a rash and alopecia (onset not specified). A 21-year-old female developed type 1 diabetes after the first dose of anthrax vaccine, and alopecia and fatigue at an unknown interval after the third dose. A 53-year-old female experienced alopecia, fatigue, pain, and syncopal episodes 1 month after the second dose of anthrax vaccine. These anthrax vaccine reports have varying underlying conditions that may contribute to alopecia, onset intervals, and dose numbers, and do not provide significant support for causality by the vaccine. Of note, alopecia has been reported after other vaccines such as hepatitis B and the hypothesized link between other vaccines and alopecia is under study.

Vasculitis

Two serious reports and four other clinically significant reports that were not coded as serious mention vasculitis. A 21-year-old male developed nose bleeds, fatigue, alopecia and weight loss 3 months after anthrax vaccine dose 1. Fatigue continued over the next months and 18 months later also developed hematuria. He then proceeded to renal failure and began dialysis. He was diagnosed with glomerulonephritis and vasculitis polynodosa. A 61-year-old male died suddenly 85 days after his eleventh dose

of anthrax vaccine. Coronary arteritis consistent with polyarteritis nodosa was found at autopsy. The reports not coded as serious included a 53-year-old male who presented with erythematous rash on leg and feet 11 days after anthrax vaccine dose 5. He also had low-grade fever and chills. He developed edema progressing to 3+ in entire lower extremities. Punch biopsy showed "leukocytic vasculitis" that resolved over a few months. A 27-year-old female was reported to have vasculitis at injection site, with onset 10 days after anthrax vaccine dose 3. She received hepatitis B vaccine concomitantly. No other details were provided. A 21-year-old male developed an itchy, erythematous, urticaria-like rash on the upper torso approximately 4 days after anthrax vaccine dose 3. Differential diagnosis based on punch biopsy findings included vasculitis, drug reaction, and fungal infection. The vasculitides are a diverse group of conditions with different etiologies. These reports do not suggest a single or dominant type of vasculitis and do not provide significant support for causality by the anthrax vaccine.

PREGNANCY-RELATED MEDICAL CONDITIONS

There were six reports of women who received anthrax vaccine during pregnancy. Two reports described spontaneous abortion (one had concomitant oral typhoid vaccine), one report described a 25-year-old woman with HELLP[†] syndrome and renal failure (also received influenza vaccine and gave birth to a baby with premature lungs), and three reports described children with medical problems born to mothers who received anthrax vaccine during pregnancy (one with recurrent infections since age of 2 months, one with pervasive developmental disorder, and one with multiple systemic complaints including

[†] HELLP syndrome is a group of symptoms that occur in pregnant women who have:
H – hemolysis, EL -- elevated liver enzymes, LP -- low platelet count.

infections, alopecia areata, stuttering). There were an additional 29 clinically significant reports of anthrax vaccination during pregnancy including 22 reports with unknown pregnancy outcome, two reports described spontaneous abortion (one confirmed and one probable), one report described elective abortion, one report described birth of a normal baby, one report described a child with birth defect, one report described a child with autism, and one report described fetal demise with trisomy 13 and multiple congenital anomalies. The pregnancy-related conditions reported to VAERS are diverse and these reports do not provide significant support for causality by the anthrax vaccine. The number of pregnant women who received anthrax vaccine is not known. Preliminary results of a recent unpublished retrospective study of infants born to women in the U.S. military service worldwide in 1998 and 1999 suggest the vaccine may be linked with an increase in the number of birth defects when given during pregnancy. DOD has undertaken to verify these preliminary results. We will review those results, when available, and we will continue to review adverse events.

PSYCHIATRIC EVENTS

Affective Disorders

There were three reports of bipolar disorder after anthrax vaccination. Age reported ranged from 27 to 32 years. In one report of bipolar disorder the condition was diagnosed after second dose of anthrax vaccine. In another report the individual also received smallpox vaccine. There were 13 reports of depression after anthrax vaccination (doses ranging from first to sixth) among individuals aged 19 to 44 years. In eleven reports, depression was part of multiple systemic complaints (including three individuals

who had prior history of depression). The remaining two reports described a 30-year-old man with depression and a 29-year-old female with depression and migraine/anxiety. There was another report of a 29-year-old female who developed anxiety and depression after her first dose of anthrax vaccine. The affective disorders occur commonly independent of vaccination and these reports do not provide significant support for causality by the anthrax vaccine.

RESPIRATORY EVENTS

Asthma

There were three serious reports after anthrax vaccination of individuals without preexisting asthma, developing wheezing after anthrax vaccine. A 36-year-old man developed coughing and wheezing 1 day after vaccination with anthrax vaccine (unknown dose #), and atrial fibrillation with cardiomyopathy was diagnosed 4 days later. Another 34-year-old male developed decreased oxygenation and shortness of breath 5 days after vaccination with anthrax vaccine dose 5 and was diagnosed with reactive airway disease. A 41-year-old female had fever, diarrhea, and vomiting for several days following anthrax vaccination (unknown dose #), followed by chest tightness and cough, later diagnosed with asthma. There was a fourth report of a 41-year-old female with preexisting asthma who developed bronchitis and asthmatic exacerbation 10 days after anthrax vaccine (dose #1). It is possible that individuals without asthma may develop acute transient allergic reactions to the vaccine that may involve wheezing. Asthma is relatively common in the US adult population so it is likely some cases of asthma would occur in temporal association with anthrax vaccination by coincidence. Also, among

persons with asthma attacks, certain triggers may be difficult to ascertain such as viral infections or environmental allergens. These reports do not provide significant support for causality of asthma by the anthrax vaccine.

Pneumonia

There were seven serious reports of pneumonia 0 days to 2 months after anthrax vaccine. One report described pneumonia in a 33-year-old male diagnosed with Common Variable Immunodeficiency. One report described mycoplasma pneumonia. Another report described aspiration pneumonia, arrhythmia, and cardiomegaly, but the time sequence with respect to anthrax vaccine is unclear. Another report described pneumonia as a complication of acute disseminated encephalomyelitis (ADEM). A fourth report described pneumonia, headache, and myasthenia. Three reports described pneumonia that accompanied myo/pericarditis. These conditions are clinically diverse, with diverse times to onset, multiple other etiologies, and do not provide significant support for causality by the anthrax vaccine.

Sleep Apnea

Three serious reports indicated sleep apnea along with other conditions. These involved males, ages 23 to 34 years. Two mentioned treatment with continuous positive airway pressure. A fourth serious report mentioned possible sleep apnea in a 21-year-old male. These conditions are clinically diverse, with diverse times to onset, multiple other etiologies, and do not provide significant support for causality by the anthrax vaccine.

REFERENCES

1. MSMR. May/June 2000;6:10-12.
2. J Infect Diseases 1997;176(Suppl 2):S92-8.

12/13/05

Review of Adverse Event Reports Submitted to Docket No. 1980N-0208

The comments submitted to Docket No. 1980N-0208 (69 FR 78281, December 29, 2004 – Bacterial Vaccines & Toxoids Efficacy Review Proposal) described adverse events after Anthrax Vaccine Adsorbed (AVA) in approximately 111 individuals. Multiple submissions were received for some individuals. To facilitate analysis of this information and to compare the comment reports with other VAERS reports, we entered into VAERS the adverse events reported in comments to the extent possible based on the information provided. Comments to the docket that reported only non-specific adverse events such as became “ill” or had a “bad reaction” were not entered into VAERS because of the lack of adequate specificity. Also, submissions that described groups of persons, adverse event statistics, or otherwise lacked key individual-level details used in VAERS, were not entered into VAERS, but were considered.

More than one source (e.g., health care provider, patient, manufacturer) might submit to VAERS information concerning a single individual’s adverse events following a particular vaccination date, resulting in multiple reports. Routine report processing in VAERS includes steps aimed at identifying and linking such related reports. Using these processes, we found that 48 (43%) of the 111 individuals described in these adverse event reports submitted in comments to the docket were the subjects of reports previously entered into VAERS.

The Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) is routinely used as a part of VAERS report processing to describe adverse events in a computerized database. The distribution of adverse event coding terms by body system and most frequently reported adverse events by coding term are shown in the tables below. We categorized 106 of the 111 reports as serious, including 6 deaths. Most described one or more chronic symptoms or illnesses, though the duration was not always evident.

Some adverse events reported in comments are not listed in the AVA labeling. There was no pattern among the adverse events reported that clearly and conclusively suggested an association with AVA. These included amyotrophic lateral sclerosis, central nervous system vasculitis, fibromyalgia, intervertebral disc protrusion or herniation, degenerative bone disease, tendon tear, antiphospholipid syndrome, colon polyps, colorectal cancer, ulcerative colitis, Crohn's disease, irritable bowel syndrome, abdominal pain, gastroesophageal reflux disease, multiple myeloma, sleep apnea, pneumonia, obstructive lung disease, sinus polyps, vision problem, hypogonadotropic hypogonadism, thyroiditis, endometriosis, parotid gland disorder, weight gain, rash, seborrheic dermatitis, lipoma, and hair loss.

Additional information about the adverse event reports submitted to the docket is summarized below.

**MOST FREQUENTLY REPORTED ADVERSE EVENTS AMONG 111
INDIVIDUALS FOR WHOM DOCKET REPORTS WERE SUBMITTED***

	COSTART	Number of Individuals With the Indicated COSTART
1	Arthralgia	37
2	Asthenia	37
3	Amnesia**	25
4	Immune system disorder	21
5	Myalgia	20
6	Dizziness	17
7	Pain	16
8	Paresthesia	14
9	Thinking abnormality	14
10	Headache	13
11	Dyspnea	12
12	Syncope	11

* Each report may be assigned multiple COSTARTs

** Coding term for forgetfulness or memory disturbance

**CATEGORIZATION OF REPORTED ADVERSE EVENTS BY BODY SYSTEM
AMONG 111 INDIVIDUALS FOR WHOM DOCKET REPORTS WERE SUBMITTED**

	Body System		Number of Adverse Events*
1	BODY	Body as a Whole or Nonspecific	186 (26%)
2	CV	Cardiovascular	56 (8%)
3	DIG	Digestive	49 (7%)
4	ENDO	Endocrine	4 (<1%)
5	HAL	Heme and Lymphatic	7 (<1%)
6	MAN	Metabolic and Nutritional	16 (2%)
7	MS	Musculoskeletal	96 (13%)
8	NER	Nervous	195 (27%)
9	RES	Respiratory	38 (5%)
10	SKIN	Skin	45 (6%)
11	SS	Special Senses (Eye and Ear)	21 (3%)
12	UG	Urogenital	13 (2%)

* Total 726 COSTARTS Among 111 Individuals.

FATALITY REPORTS

	Year of Death	Age/ Sex	Summary	Anthrax vaccine dose number	Other Vaccines?	Interval since vaccination
1	2001	27F	Amyotrophic lateral sclerosis (ALS) vs multifocal motor neuropathy	4		~23 months
2	2004	45M	End stage renal disease, pulmonary embolus, CMV pneumonitis, possible SLE	2		49 months
3	2003	M*	Seizure	3		Unknown
4	2000	37M	Heart attack	Unknown		Unknown
5	2000	44M	"Rapid onset ALS"	Unknown		~10 months
6	2002	30M	Bile duct cancer	Unknown		Unknown

* Age unknown

VAERS reports had previously been received for patients 1 and 2. The report about patient 1 was initially submitted as non-fatal serious; follow-up information indicated the patient later died. The report about patient 2 was submitted to VAERS in January 2005. Patient 3 is listed under fatalities based on inference from a statement in the docket submission.

Amyotrophic Lateral Sclerosis

Two comments to the docket reported amyotrophic lateral sclerosis (ALS) following administration of AVA. This brings to a total of three patient reports to VAERS of a diagnosis of ALS following administration of AVA. The reports involved 1 female and 2 males, ages 27, 44, or 50 years old. Initial symptoms and interval relative to vaccination were reported as follows. One patient had right hand twitching 1-2 months

after her third dose of anthrax vaccine, and right upper extremity weakness approximately 1 month after her fourth dose. Another patient had an episode of being unable to stand after falling 3 days after his first dose of anthrax vaccine, and inability to stand on tiptoes. The third patient developed diarrhea, headaches, memory loss, low back pain, and foot drop, with symptoms beginning the same Spring as his fourth dose of anthrax vaccine. He developed bilateral lower extremity weakness approximately 22 months after his fourth dose. In these 3 ALS reports, the onset interval between vaccination and signs attributable to ALS varied or is difficult to assess. Also, the number of doses prior to onset varied. The reporting rate for ALS, based on 3 reports from approximately 1.3 million persons vaccinated with 5.3 million doses, is 0.23 per 100,000 persons or 0.057 per 100,000 doses. Estimates of the annual background incidence of ALS vary from 0.6 to 2.4 per 100,000 persons (J Neurol Neurosurg Psychiatry 1992;55:1106-1115.). The incidence among Gulf War veterans has been reported as 0.43 per 100,000 persons per year and varied by deployment status (Neurology 2003;61:742-749). Background incidence rates per year are useful, but the optimal comparison period is not known and may be less than a year such as weeks or months. Considering all these factors and uncertainties, these reports of ALS do not provide significant support for causality by the anthrax vaccine.

Summary of comments describing adverse events in groups of people

Another docket submission lists 81 persons who apparently died, but for whom insufficient information was provided to construct an individual report. The information provided is generally the name, date (which we presume is the date of death), age,

city/state, and condition (which we presume is the cause of death). No details about anthrax vaccination for these individuals were provided. The age range is 18 to 55 years. The conditions listed are as follows (among 81 persons): heart attack or suspect heart attack or “heart” (17), collapsed (5), not breathing (4), pulmonary embolism or blood clot in lung (3), pneumonia (3), self-inflicted gunshot (2), cardiac arrest (2), diabetic complication (1), heat stroke (1), cancer (1), blood clots after emergency intestinal surgery (1), not stated (41).

Other comments reported multiple persons with adverse events, but did not provide sufficient information to construct an individual report. Two comments reported that half a brigade developed pneumonia. One reported knowing one person who “lost use of his arm”, one who was hospitalized and almost died with heart problems, and one with severe asthma. Another person reported that in a unit with approximately 150 vaccinated persons, eight had pneumonia, one polio-like symptoms, one multiple sclerosis, one rheumatoid arthritis, one brain lesions, one toxic shock syndrome, one suicide, one lupus and infections, one “CFS & fibro and other disabling injuries.” One person reported that in a squadron of approximately 120 persons, 20 had rashes, four had arthritis and two others were being evaluated, two had pneumonia, one had “autoimmune system shutdown” and almost died, one had extreme fatigue, and one had gastrointestinal problems and headache. One person reported that several others told him they had aches, pains, or joint and muscle pain lasting months. One submission reported a number of persons at Dover AFB with a variety of adverse events including myocarditis, heart failure, vertigo, “blackouts”, “grayouts”, joint pain, arthritis, fever, injection site nodule, headache, tinnitus, chronic fatigue, rash, thyroiditis,

hypothyroidism, elevated rheumatoid factor, memory loss, diabetes, impaired gross motor ability, and/or “tissue lesions.” Another person reported that “dozens” of persons had a variety of conditions including burning sensation, thinking problems, depression, and fatigue. Another person indicated that the adverse effects in some people include “paralysis, hospitalization, organ shutdown.” Another person indicated that some servicemen have developed anti-squalene antibodies after vaccination and “many friends” have Gulf War syndrome symptoms described as migraine headaches, chronic fatigue, and aching joints. One person reported pemphigus vulgaris after multiple vaccinations, but the specific vaccines were unknown. A news article reported several persons with deep vein thrombosis, pulmonary embolus, myocardial infarction or stroke. (For some, a corresponding report is in VAERS.)

Another group of comments reported persons who had adverse events, but the comments lacked specificity. These comments to the docket indicated that there were 38 soldiers with “adverse medical reactions”, relatives who became “ill” or had a “bad reaction”, a relative who received the vaccine and “it almost killed him”, vaccine recipients who are “disabled”, a relative with “100% disability”, a vaccine recipient who indicated that the injection “almost killed me” and was taken to a hospital, patients with “moderate to severe reactions”, friends who had become “ill” or had “a strong reaction”, a friend who “has a susceptibility” to the vaccine, a friend who “experienced significant health problems”, a vaccine recipient who was “harmed” and requires daily medications.

Some comments described general or non-specific concerns about adverse events. These included one person who indicated changes in her life including no longer working in her previous position, another comment stating that many soldiers (exact number not

specified) prefer to avoid the “horrendous side effects of the vaccine”, another reporting that 16 of 32 pilots chose to leave a guard unit due to safety concerns about the vaccine, and another concerned possible overcounting of vaccinees and underestimation of adverse event rates due to commanding officers who “look the other way” if a serviceman refuses the vaccine.

Summary of Adverse Event Reports Submitted to the Docket

The adverse event reports submitted to the docket did not provide substantially different information about possible new safety signals than the previous reports to VAERS. The previous reports to VAERS, together with the reports to the docket, do not establish a causal relationship between serious adverse events (other than some injection site reactions and some reports of allergic reactions) or deaths and AVA. We have entered into the VAERS database the conditions described in comments to the docket. These conditions will be considered along with all other adverse event reports received through continuing surveillance and incorporated into the periodic evaluations of these reports.

Robert Ball 12/13/05

Robert Ball, MD, MPH, ScM

Date

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