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Ischemic Cardiac Events and Other Adverse Events following ACAM2000® Smallpox Vaccine in the Vaccine Adverse Event Reporting System

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Abstract

Background—The Vaccine Adverse Event Reporting System (VAERS) is a passive reporting system, used for monitoring the safety of all US licensed vaccines. In March 2008, ACAM2000® replaced Dryvax® as the only licensed smallpox vaccine and is administered to all persons entering military service and certain civilian researchers. In 2011, routine data mining of VAERS identified a vaccine safety concern resulting in acute ischemic cardiac events (ICE) following ACAM2000®.

Methods—During March 1, 2008 through June 30, 2013, we reviewed all serious reports received following ACAM2000®and classified them by diagnostic category. We identified possible ICE cases by searching the Medical Dictionary for Regulatory Affairs (MedDRA) terms for “myocardial ischaemia,” “acute myocardial infarction,” “myocardial infarction,” and “ischaemia,” and applied standardized surveillance case definitions.

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The views, findings and conclusions in this report are those of the authors and do not reflect the official policy or position of the Centers for Disease Control and Prevention, the Departments of the Army/Navy/Air Force, Department of Defense, nor the US Government. Use of trade names and commercial sources is for identification only and does not imply endorsement by the Centers for Disease Control and Prevention, the US Department of Health and Human Services, the Departments of the Army/Navy/Air Force, the Department of Defense, or the US Government. Mention of a product or company name does not constitute endorsement by the CDC. None of the authors have conflicts of interest to declare. Because VAERS is a routine surveillance program that does not meet the definition of research, it is not subject to institutional review board review and informed consent requirements.

Results—VAERS received 1,149 reports following ACAM2000® administration; 169 (14.7%) were serious (resulting in permanent disability, hospitalization, life-threatening illnesses or death), including one death. The two most frequent diagnostic categories for serious reports were cardiovascular and other infectious conditions. The MedDRA search found 31 reports of possible ICE after receipt of ACAM2000® vaccine. Of a total 30 possible ICE cases with demographic information, all but one was male; the age range was 20–45 years (median 32) and median interval to onset of symptoms was 12 days. On clinical review there were 16 cases of myocarditis/pericarditis and 15 ICE cases.

Conclusions—Our review of the data mining signal did not substantiate the concerns about ICE after ACAM2000®. Our study also suggests that with current pre-vaccination screening, cardiac morbidity in generally healthy vaccinated populations remains uncommon.

Keywords

ACAM2000®; ischemic cardiac events; myocarditis; pericarditis; myo/pericarditis

INTRODUCTION

In June 2001, the Advisory Committee on Immunization Practices (ACIP) made recommendations for using smallpox vaccine to protect persons working with orthopox viruses and to prepare for a possible terrorist attack.[1] In December 2002, the US Department of Defense (DOD) began vaccination as part of the national program of preparedness.[2] On January 24, 2003, the US Department of Health and Human Services (DHHS) authorized voluntary smallpox vaccination of civilians, including healthcare workers and members of smallpox teams identified by state or local health departments, who might be called on to monitor or treat persons exposed to smallpox.[3] These programs used the first generation calf lymph vaccinia vaccine (Dryvax®, Wyeth) and focused exclusively on healthy adults.

As part of these military and civilian smallpox vaccination programs, DOD and the Centers for Disease Control and Prevention (CDC) conducted enhanced vaccine safety monitoring for possible adverse events (AEs).[4] Enhanced VAERS monitoring involves performing clinical review of medical records or available documentation (e.g., diagnostic tests) for selected medical adverse events that are reported to VAERS). These programs reported a previously underappreciated relationship between smallpox vaccine and acute cardiac AEs.[5–10] Although reports of myo/pericarditis (MPC) predominated, possible ischemic cardiac events (ICE) were also identified.[11–14] The civilian program was severely curtailed after 10 months with contributing factors for the relatively low turnout of volunteers for immunization including a concern about possible rare vaccine adverse events combined with the failure to find Iraqi bioweapons which seemed to diminish the threat; however, a very limited civilian program vaccinating mainly high risk laboratory/research personnel is ongoing with smallpox vaccine supplied by CDC. In contrast, the military program has continued to the present.[15] On August 31, 2007, the new second generation, clonal, Vero cell cultured vaccinia vaccine ACAM2000® (Sanofi Pasteur Biologics Co.) was approved by the FDA for use in the US.[16] On February 29, 2008, a notice was published informing providers that ACAM2000® vaccine was replacing the calf lymph vaccinia vaccine (Dryvax®) and that all lots of Dryvax® expired on that date.[17]

The DOD smallpox vaccination program utilizes a pre-vaccination screening algorithm based on CDC Advisory Committee on Immunization Practices (ACIP) recommendations to identify and defer the administration of smallpox vaccine to persons with known underlying heart disease, with or without symptoms, or who have three or more known major cardiac risk factors (i.e., hypertension, diabetes, hypercholesterolemia, heart disease at age 50 years in a first-degree relative, and smoking).[18] The ACIP did not recommend special medical follow-up for persons with cardiovascular risk factors who have been vaccinated but advised that persons with risk factors or known atherosclerotic coronary artery disease should be routinely cared for by their physicians.

Under a post marketing commitment (PMC), the DOD, FDA, CDC and the vaccine manufacturer are gathering additional safety information on AEs following administration of ACAM2000® utilizing the Vaccine Adverse Event Reporting System (VAERS).[19] On March 25, 2011, the Medical Dictionary for Regulatory Activities (MedDRA®) coding term “acute myocardial infarction” and ACAM2000® exceeded a predetermined data mining threshold in the VAERS database, which warranted further investigation (see Methods - FDA Data Mining). To better understand the possible association of ICE and ACAM2000®, we conducted an in-depth clinical review of VAERS data to confirm reports of ICE following ACAM2000® and included all data through June 30, 2013.

METHODS

VAERS database

VAERS, co-administered by CDC and the Food and Drug Administration (FDA), is a national passive surveillance system that accepts reports from healthcare and vaccine providers, manufacturers, and vaccine recipients or their caregivers.[20] Information on age, gender, medical history, vaccines and AEs are collected on the VAERS form, and signs and symptoms of AEs are coded by trained personnel using the MedDRA terms.[21] Reports are coded as serious, as defined by the Code of Federal Regulations, if at least one of the following was reported: death, life-threatening illness, hospitalization or prolonged hospitalization, or permanent disability.[22] As part of the routine surveillance activities, medical records are requested only for serious reports submitted by vaccinees or healthcare providers.

Review of ACAM2000® VAERS reports

We identified and reviewed US VAERS reports received by June 30, 2013 for persons vaccinated with ACAM2000® smallpox vaccine from March 1, 2008 through June 30, 2013 (including those with missing vaccination dates). Two medical officers conducted independent clinical review of all VAERS reports, and the primary AEs reported were categorized into one of the following diagnostic categories; [23] allergic (including anaphylaxis), cardiovascular (including cerebrovascular accident), ENT (ears, nose, throat), gastrointestinal, local reaction, musculoskeletal, neurologic (including GBS, narcolepsy and seizures), pregnancy-specific events, psychiatric, respiratory (including influenza-like illness, pneumonia, and non-infectious upper/lower respiratory conditions), other infectious, other non-infectious (e.g., diabetes, thrombocytopenia, dermatologic conditions), and death.

Known serious smallpox vaccine AEs eczema vaccinatum, generalized vaccinia, progressive vaccinia, and inadvertent inoculation of vaccinia virus (e.g., autoinoculation, contact transmission) were classified under “other infectious” category.[4] Reports without any AE per se, that were submitted to VAERS as a result of administering the vaccine at an inappropriate site, schedule or dosage or to a person of inappropriate age or with contraindication to smallpox vaccine (excluding pregnancy) were classified as a vaccination error. A review of medical records, if available, of VAERS reports was conducted to verify the diagnosis. If no medical record was available, the CDC Medical Officer determined a possible diagnosis to classify reports by diagnostic category. Reports suggestive of anaphylaxis were verified using the Brighton Criteria[24] or if medical records included physician diagnosis of anaphylaxis. Cause of death was verified by autopsy report or death certificate.

FDA data mining

Empirical Bayesian data mining techniques are routinely used with the VAERS database to assess disproportionate reporting of AEs for all US licensed vaccines, including smallpox vaccine.[25, 26] To identify vaccine-event pairs for further evaluation, we applied the criteria suggested by Szarfman et al.[26]

Identification of possible ICE cases

To better understand the possible association between ACAM2000®and ICE, we identified possible ICE cases from 1/1/2008 through 7/31/2013 by searching the VAERS database using the Medical Dictionary for Regulatory Affairs (MedDRA) terms for “myocardial ischaemia,” “acute myocardial infarction,” “myocardial infarction,” and “ischaemia” for reports of persons vaccinated with smallpox vaccine since 2008. We reviewed possible ICE cases and applied standardized surveillance case definitions. For our review of possible ICE cases, we classified all cardiovascular AEs based on information from the VAERS form and medical records, death certificates and autopsy reports (when available) according to the following categories: acute myocarditis (suspected, probable, and confirmed) and acute pericarditis (suspected, probable, and confirmed).[27] For ICE cases, we used a modified definition from Swerdlow et al.:[14] a primary clinician diagnosis of symptoms consistent with myocardial infarction (MI) or angina pectoris supported by evidence of ischemia by electrocardiogram (ECG), serial cardiac enzyme testing, cardiac catheterization or autopsy.

RESULTS

ACAM2000® VAERS review

During March 1, 2008 to June 30, 2013, approximately 832,035 ACAM2000® smallpox vaccinations were administered to DOD personnel (DOD Military Vaccines Agency, personal communication), and 2,430 to civilians (2,113 laboratory/research personnel, 201 Laboratory Response Network personnel, 17 first responders, and 99 not specified) (CDC Drug Services, personal communication). Of the total 1,149 reports submitted to VAERS, 169 (14.7%) were serious; the proportion of serious reports was similar among service personnel (164/1118; 14.7%) and civilians (5/31; 16.1%). There were 1,118 AEs after ACAM2000® reported to VAERS from DOD, resulting in an overall reporting rate of 13.4

per 10,000 (0.13%) individuals vaccinated. In the civilian population, there were 31 AEs reported and 2,430 individuals vaccinated for a rate of 128 per 10,000 (1.3%) persons vaccinated. Thus, the overall rate of AE reporting in the civilian population was approximately10-fold higher than in the military population. The reporting rate of serious reports for both populations combined was 20.25 per 100,000 (0.02%) doses of ACAM2000® vaccine administered. No AEs were noted in 62 (5.4%) reports. Of these reports without AEs per se, 21 (33.9%) were vaccination errors, and 28 (45.2%) were reports in pregnant women. Characteristics of the reports are shown in Table 1. The most common vaccines given concomitantly with ACAM2000® were anthrax vaccine adsorbed (AVA) in 163 (14.2%), and AVA and typhoid in 173 (15.0%). The youngest reported case was a child with a parent who received ACAM2000®; 11 days later, the child was exposed to a used dressing from the parent's vaccination site, and two days later, developed a "pimple-like reaction above the left eyebrow."

Among the 31 pregnant women who received ACAM2000®, two (6.5%) had a spontaneous abortion (in both, the gestational age was unknown) and one (3.2%) had a voluntary termination of the pregnancy at 11.5 weeks gestation. Ages of these women were 18, 22, and 26 years; pregnancies ended 19 days after vaccination in two of the cases and 22 days in one case.

Of the serious reports, a diagnosis was verified in 138 (81.7%) cases. The most frequent diagnostic categories for serious reports were cardiac (92, 54.4%) and "other infectious" conditions (29, 17.2%) (Figure 1). Myo/pericarditis (37, 40.2%), myocarditis (33, 35.9%), and pericarditis (13, 14.1%) were the most common serious cardiac diagnoses. Other infectious conditions included five cases of autoinoculation, four cases of contact transmission, and AEs such as generalized vaccinia following exposure to vaccinia virus (Table 2). One serious report, shown in Table 2, involved a 20-year-old male military vaccinee who was diagnosed with progressive vaccinia approximately one month after commencing induction chemotherapy for acute myelogenous leukemia during evaluation of neutropenic fever and 42 days after vaccination. He recovered following specific antiviral therapy and treatment for complications of sepsis and multi-organ failure.[28]

One reported death occurred in an 18-year-old male soldier with a history of glucose-6-phosphate dehydrogenase deficiency within 30 days of receiving ACAM2000®, anthrax and typhoid Vi polysaccharide vaccines. He collapsed during a 5-mile run 8 days after vaccination. He was noted to have CK-MB of >20,000 ng/ml after administration of adenosine and cardioversion, and a temperature of 103°F. His presumptive diagnosis on hospital admission was rhabdomyolysis. During the course of hospitalization, he developed hepatitis and severe liver injury, renal failure, thrombocytopenia, and disseminated intravascular coagulation. On the fifth day of hospitalization, he became bradycardic during dialysis and ultimately expired. The cause of death on autopsy was reported as myocarditis (dilated cardiomyopathy), infarction/necrosis of the liver and hemorrhage/necrosis of the right adrenal gland.

Among the non-serious reports, the most frequent diagnostic categories were cardiac (31%) and allergic outcomes (22.4%) (Figure 1). Although medical records are not routinely

requested for non-serious reports, we reviewed 59 (6.0%) of the 980 non-serious reports which had records submitted; and the most common categories among those with verified diagnosis were other infectious [16], allergy [15] and cardiac [14]). Among 220 reports of allergy, three were reported as anaphylaxis; one met the Brighton criteria level 1 and two met the Brighton criteria level 2. To advance the science of immunization safety the Brighton Collaboration has developed standardized case definitions and guidelines for data collection, analysis and presentation.[29] Of the 304 cardiac cases, myo/pericarditis (54, 17.8%), pericarditis (44, 14.5%) and myocarditis (41, 13.5%) were the most common diagnoses. There were also 15 cases of myocardial/subendocardial infarction among the non-serious reports.

2011 FDA data mining signal

In March 2011, FDA data mining detected a signal for acute myocardial infarction (AMI) after ACAM2000® (EB05=2.46, n=7). A meeting in April 2011 conducted by FDA with DOD and the manufacturer, led to the identification of an additional nine reports; nine reports were coded with the MedDRA® term “acute myocardial infarction” and seven reports were coded with the term “myocardial infarction” (two were identified as duplicates). These reports are highlighted in Table 3 (Cases 1–15).

Identification and review of possible ICE cases

Our review of the VAERS database for reports received through June 30, 2013, using updated MedDRA terms identified an additional 16 possible ICE cases (Table 3, Cases 16–31). Of a total 30 possible ICE cases with demographic information, all were service personnel, all but one was male, the age range was 20–45 years (median 32), and median interval from vaccination to onset of symptoms was 12 days. On clinical review there were 16 cases of myo/pericarditis and 15 ICE (includes Cases 18 and 31; although no medical history was available for these patients, both were reported with a diagnosis of acute subendocardial infarction after ACAM2000®).

Of the myocarditis cases, medical record was unavailable for one case. Fourteen (88%) reported chest pain. ECG was performed in 15 (94%) cases, and in 13 cases this was reported as abnormal (ST elevation/ST waves/diffuse ST [9 cases], subendocardial/inferior septal infarct [2], left ventricular hypertrophy [1], slight PR elevation [1]), and in two cases it was reported as normal. One or more scans (echocardiogram, MRI, or CT) were performed in 12 (75%) cases (reported as normal in six cases, and the abnormal findings included: ventricular enlargement [1], inferior wall abnormality [1], decreased left ventricular ejection fraction [1], myo- and pericardial enlargement [1], pericardial effusion [1] and mild aortic stenosis and pericardial enhancement of lateral wall [1]). A serum cardiac enzyme test(s) (serum troponin I, creatinine kinase and creatinine kinase-MB) was performed in 13 cases (reported as abnormal/elevated in 12 cases, and normal in one). Cardiac angiography was performed in eight cases (in three cases this was reported as negative/normal/no coronary artery disease; abnormalities included single coronary artery [1], left ventricular ejection fraction reduced (50%) [1], no coronary artery disease but myocardial bridge in left anterior descending coronary artery non flow-limiting [1], “inflammation around the heart” [1], and minimal coronary artery disease [1]).

Of the ICE cases, medical records were unavailable for two. Three (20%) cases were reported with chest pain. ECG was performed in 11 (73%) cases (this was reported as abnormal in nine [82%] cases and normal in two [18%] cases). A scan(s) (echocardiogram, MRI, CT) was performed in 8 (53%) cases (this was reported as normal in five [63%] cases and abnormal in three [37%] cases). Serum cardiac enzymes (serum troponin I, creatinine kinase, or creatinine kinase-MB) were reported as abnormal/elevated in 10 (67%) cases. Cardiac angiography was performed in two cases (one case underwent thrombectomy/stent insertion and the second had two vessel coronary disease [one vessel with 98% occlusion] and required stent insertion).

One death was reported among the ICE cases, a 44-year-old male (Case 19) died 36 days after receiving smallpox vaccine (no brand name) and two other inactivated vaccines. From this patient's vaccination date (July 31, 2008) it is reasonable to infer that this smallpox vaccine was ACAM2000®. This patient's past medical history included bee sting allergy, prior cigarette smoking and hypercholesterolemia. Twenty-five days after receiving ACAM2000® he presented to the Emergency Department with a generalized pruritic rash and was prescribed cefalexin, Benadryl® and topical hydrocortisone cream. Ten days later following a several mile run he collapsed and suffered a cardiac arrest and cardiopulmonary resuscitation was unsuccessful. At autopsy the cause of death was reported as ICE with hypertension and hypercholesterolemia as contributing conditions.

DISCUSSION

This systematic evaluation of reports to VAERS following ACAM2000® was prompted by a March 2011 signal for "acute myocardial infarction" found in the VAERS post-marketing data of ACAM2000® on routine data mining. Upon review of VAERS reports screened as possible ICE, the diagnosis of myo/pericarditis was identified in 16 cases, and 15 had ICE. The 31 possible ICE cases showed a marked male predominance which may reflect the gender distribution of personnel receiving the vaccine. The results of our investigation are consistent with ACAM2000® labeling which states that ICEs have been reported after smallpox vaccination but the relationship of these events, if any, to vaccination has not been established.[30] Our study also suggests that with current pre-vaccination screening, cardiac morbidity in generally healthy vaccinated populations remains uncommon.

In addition to review of cardiac AEs, we reviewed all other serious and non-serious VAERS reports following ACAM2000®. We found the two most frequent diagnostic categories for serious reports were cardiac and "other infectious" conditions; myo/pericarditis, myocarditis and pericarditis were the most common cardiac diagnoses. Among the non-serious reports, the most frequent categories were cardiac and allergic outcomes and again myo/pericarditis, pericarditis and myocarditis were also the most common cardiac diagnoses.

The overall reporting rate for all AEs after ACAM2000® was approximately 10-fold higher in the civilian population than the military rate which is consistent with the earlier findings of McMahon et al.[31] These authors compared military and civilian reporting rates to VAERS following Dryvax® and hypothesized the following factors responsible for the higher civilian reporting rate: 1) civilian reporters may have a lower "threshold" for reporting AEs; 2)

civilians have more ready access to assistance reporting AEs compared to servicemen deployed overseas after vaccination, and 3) military vaccinees potentially readying for deployment are likely healthier than working civilian vaccinees (i.e., “healthy warrior effect”). [30]

A limitation to our analysis of potential ICE cases is that cases may have been underreported and case definitions are difficult to apply to VAERS data due to the lack of consistent clinical information in the reports (e.g., incomplete data).[32] There are also important differences between the population in the present study (younger, male predominance, and screened to exclude individuals with cardiac and other conditions) and the general population. Therefore, these findings may not be generalizable to the broader population which may have a higher prevalence of cardiac conditions. Data from NHANES 2009–2010 reveal that overall, 7.2% of American adults 20 years of age and older self-reported some type of cardiovascular disease (3.2 % coronary artery disease, 2.7% stroke and 2.0% congestive heart failure).[33] Nevertheless, our findings provide additional insight for this rare but potentially serious adverse outcome reported following administration of this new smallpox vaccine.

While there is clear evidence and biologic plausibility to indicate a causal relationship between myo/pericarditis and live attenuated vaccinia immunization, there is no supportive evidence of a similar association for ICE. In 2005, Poland et al. reported 24 ICE cases following Dryvax® vaccine among 730,580 DOD vaccinees (13 had a myocardial infarction [one fatal], five had angina and six had atherosclerotic disease [two fatal]).[34] These authors concluded that “the available data do not support a causal association between ischemic cardiac events and receipt of smallpox vaccine; however, this possibility cannot be excluded.” [34]

On January 24, 2003, the DHHS civilian program began vaccinating health care and public health workers who volunteered for smallpox response teams. Reports of post vaccination myo/pericarditis and ICE began in February and March 2003, respectively.[12] The civilian program which was halted in late 2003 reported ICE in 10 of 37,901 vaccinees (six cases of myocardial infarction [two resulting in sudden death], and four cases of angina).[14] The observed number of myocardial infarctions exceeded estimated expectations (5 vs. 2) but remained within the 95% predictive interval (PI) (0.6–5.4). After the establishment of a policy to defer vaccination among persons with >3 risk factors or known cardiac disease, no ICE were reported among an additional 6,638 vaccinees.[14] A follow-up safety summary by DOD in May 2007, after >1 million vaccines had been administered, reported a total of 16 patients with ICE temporally related to smallpox vaccination.[35] However, the incidence of ischemic complications in vaccinees was similar to that of age-matched unvaccinated personnel.[36] These investigators found implementation of pre-vaccination cardiac risk factor screening was not associated with a reduction of cardiac events.

Clinical myocarditis can mimic myocardial infarction and is suspected in patients with clinical and ECG evidence of acute coronary syndrome along with a normal coronary angiogram; this is true particularly in younger patients.[37–41] Chest pain or heart failure symptoms after smallpox vaccination should be taken seriously and addressed with a

diagnostic work up and treated appropriately. The cases should be reported to VAERS. Despite current pre-vaccination screening procedures, rare cases of cardiac morbidity (myocarditis and/or ICE) can occur following ACAM2000®.

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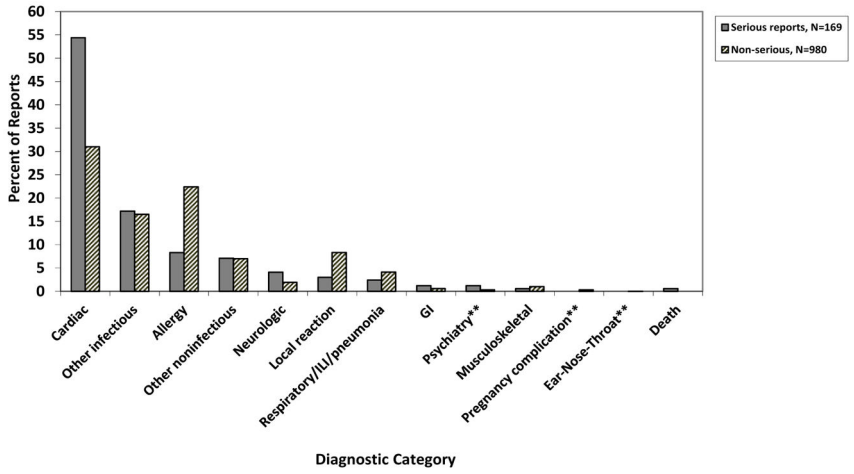

Figure 1.

Distribution of diagnostic categories for serious and non-serious reports to the Vaccine Adverse Events Reporting (VAERS) followingACAM2000®*

*Vaccination and report dates from March 1, 2008 through June 30, 2013

**Non-serious: Psychiatry, 0.3%; Pregnancy complication, 0.3%; Ear-Nose-Throat, 0.1%

Table 1

Characteristics of reports to the Vaccine Adverse Events Reporting (VAERS) following ACAM2000®, March 1, 2008 June, 30, 2013, United States

Characteristics	Number	%
Reports	1,149	
Military	1,118	97.3
Civilian	31	2.7
Serious reports	169	14.7
Death	1	0.1
Life-threatening illness	22	1.9
Hospitalization	143	12.4
Extended hospital stay	2	0.2
Permanent disability	1	0.1
Non-serious reports	980	85.3
Male	901	78.4
Median age (range), years	24	1.3—65
Median onset interval (range), days	10	0—351
ACAM2000® given alone	638	55.5
Reported by:		
Provider	329	28.6
Manufacturer	308	26.8
Patient	62	5.4
Other*	450	39.2

*This category includes e.g., state vaccine safety coordinators

Table 2

Primary diagnosis of serious infectious conditions

Diagnosis	N
Generalized vaccinatum	5
Eczema vaccinatum	1
Progressive vaccinia	1
Autoinoculation	5
Contact transmission	4
Cellulitis, abscess	5
Meningitis	4
Herpes zoster	1
Viral illness	2
Infection of unclear etiology	1
Total reports	29

Table 3

Relevant clinical findings of 31 primary vaccinee cases with suspected ICE following smallpox vaccination among DOD personnel

Case	Age (yr) /Sex	Medical history/family history (FM)	Onset after vaccination (days)	Vaccines	Chest pain	ECG findings	ECHO findings	Cardiac enzymes	Cardiac catheterization (CC)	Diagnosis/Outcome
1	21M	Flu symptoms	11	ACAM2000® Only	Midsternal	Diffuse ST waves	Normal Normal MRI	Troponin + CK-MB 20 CK281	No CC	Myopericarditis Treated for HTN
2	22M	Smoker	2–3	ACAM2000®	Sharp substernal, SOB	ST elevation	NR	Troponin peak 17.3 CK-MB 60	Single coronary artery	Myopericarditis Congenital CAD
3	41M	NR	13	ACAM2000® AVA (2 days earlier)	Acute precordial	ST elevation	NR	NR	No CAD	Acute myopericarditis
4	33M	NR	9	ACAM2000® Typhim Vi AVA	Intermittent	Abnormal	NR	NR	Thrombectomy and stent insertion mid-circumflex	Acute MI due to hypercoagulability (released from active duty)
5	20M	No cardiac risk factors Dyspnea, Headaches	12	ACAM2000® AVA (14 days earlier) Influenza	Substernal pressure	ST elevation	Normal	Troponin peak 19	Negative	Myopericarditis
6	26M	No significant PMH	11	ACAM2000® AVA	NR	Abnormal	NR	Troponin 0.45	Normal	Acute MI
7	39M	Syncopal episodes	12	ACAM2000® AVA Influenza (1 week earlier) Typhim Vi (1 week earlier)	NR	Possible ST elevation	Ventricular cavity enlargement/normal	CK elevated Troponin 24.11	LV-EF 50%	Vaccine induced myopericarditis
8	39M	HTN, MI, hypercholesterolemia, asthma, smoking for 10 yrs FH of MI in mother and paternal grandfather	13	ACAM2000®	NR	Normal	Normal	Troponin peak 9.16	2 vessel CAD 98% occlusion in one; MI, stent insertion	Non Q wave subendocardial MI
9	37M	NR	11	ACAM2000® only	Pressure	Abnormal mild ST elevation	Normal	Troponin peak 2.68	No CAD, myocardial bridge in LAD non-flow limiting	Myocarditis s/p smallpox vaccination
10	28M	FH positive for CAD	12	ACAM2000® AVA	Aching substernal pain	ST elevation	Inferior wall abnormality	Troponin peak 5.72 CK-MB peak 16.8	No CC	Myocarditis

Case	Age (yr) /Sex	Medical history/family history (FM)	Onset after vaccination (days)	Vaccines	Chest pain	ECG findings	ECHO findings	Cardiac enzymes	Cardiac catheterization (CC)	Diagnosis/Outcome
11	22M	Asthma, smoker	10	ACAM2000® Typhoid Vi AVA	NR	Provisional diagnosis subendocar dial infarction	NR	NR	CC performed “inflammation around heart”	Myopericarditis
12	25M	None	9	ACAM2000® LAIV AVA	Substernal superficial radiating to back	LVH, NSR	WNL	Troponin peak 0.12 CK-MB undetectable	No CC	Myopericarditis/Acute MI,
13	21M	Obesity	10	ACAM2000®	Substernal crushing squeezing	Normal	Slightly decreased LVEF	Troponin peak 14.00 CK 600s CK-MB 22	No CC	Myopericarditis
14	21M	None FH alcoholism	12	ACAM2000® AVA	Upper chest pain worse on inspiration	Normal	Unavailable CT normal)	Troponin peak 0.58	No CC	Myopericarditis
15	41M	NR	10	ACAM2000®	Midsternal	Diffuse ST	NLVEF Thickened pericardium Cardiac MRI mid-myocardial enhancement consistent with myocarditis	Troponin 18.00	Minimal CAD	Myopericarditis
16	37 M	Sickle cell trait, Rheumatoid arthritis, Episodic syncope, HTN, Heart murmur, Arrhythmia, FH of CVA, HTN, DM and SLE	1	ACAM2000® AVA	Chest pain	Abnormal	Normal	Troponin x3 normal	No CC	Myopericarditis
17	31M	Hypercholesterolemia	13	ACAM2000® (3 weeks earlier AVA, Hep B Typhoid Vi),	NR	Abnormal	Normal	Troponin 0.52	No CC	Subendocardial infarction
18	NR	NR	NR	ACAM2000®	NR	NR	NR	NR	NR	Acute MI, subendocardial infarction
19	44M	Smoker, Hypercholesterolemia Allergic to bee sting	36	ACAM2000®	Pruritic rash on D25 then C/ arrest on PT	NR	NR	NR	NR	Autopsy probable COD ICE (RFs)
20	36M	HTN, psychiatric illness	18	ACAM2000®	NR	Normal	Normal	Troponin 1.19	NR	Subendocardial infarction
21	21M	NR	11	ACAM2000® AVA	Chest pain	Abnormal - acute ST elevation	Abnormal	Troponin 16.2	NR	Acute MI
22	38M	Hyperlipidemia, no allergies	8	ACAM2000®	Chest pain intermittent SOB	Slight PR elevation	Pericardial effusion	Troponin 1.02	NR	Myopericarditis
23	42M	Drug allergy Hyperlipidemia	13	ACAM2000®	Chest pain atypical + itchy rash	ST elevated Atrial Fib	Mild aortic stenosis, chest CT normal, MRI - pericardial enhancement of lateral wall	Troponin 7.05 CK-MB 23	Normal	Myopericarditis

Case	Age (yr) /Sex	Medical history/family history (FM)	Onset after vaccination (days)	Vaccines	Chest pain	ECG findings	ECHO findings	Cardiac enzymes	Cardiac catheterization (CC)	Diagnosis/Outcome
24	27M	None	11	ACAM2000® AVA Typhim Vi	Chest pain	Abnormal	Unavailable	Troponin 0.57	NR	Subendocardial infarction
25	42M	NR	13	ACAM2000® Prev AVA TdaP	NR	NR	NR	NR	NR	Acute MI inferolateral wall
26	23M	Headaches only	6	ACAM2000®	NR	Abnormal	Normal	Troponin 0.18	NR	Acute subendocardial infarction
27	27M	None	11	ACAM2000®	Chest pain	Unavailable	Unavailable	Unavailable	Unavailable	Myopericarditis
28	44M	HTN, Hypercholesterolemia	13	ACAM2000® AVA Influenza TdaP	NR	Abnormal	Normal	Troponin 0.13	NR	Subendocardial inarction
29	27M	None	14	ACAM2000®	NR	Abnormal	Abnormal	Troponin 16.75	NR	Acute MI/myocarditis
30	41F	HTN	6	ACAM2000® Typhim Vi AVA LAIV	NR	Abnormal	Abnormal	Troponin 52.04	NR	Acute MI
31	45M	Unavailable	27	ACAM2000® AVA Hepatitis B	Unavailable	Unavailable	Unavailable	Unavailable	NR	Acute subendocardial infarction

NR No record; PMH Past medical history; MI Myocardial infarction; CAD Coronary artery disease; HTN Hypertension; DM Diabetes mellitus; SLE Systemic lupus erythematosus; Atrial Fib Atrial fibrillation; NLVEF Normal left ventricular ejection fraction. The order of listing the cases is the order in which they have been reported.