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Myopericarditis Associated With Smallpox Vaccination Among US Army Personnel – Fort Hood, Texas, 2018

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Original Research

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Abstract

Objective: In March 2018, the US Department of Defense (DOD) added the smallpox vaccination, using ACAM2000, to its routine immunizations, increasing the number of persons receiving the vaccine. The following month, Fort Hood reported a cluster of 5 myopericarditis cases. The Centers for Disease Control and Prevention and the DOD launched an investigation.

Methods: The investigation consisted of a review of medical records, establishment of case definitions, causality assessment, patient interviews, and active surveillance. A 2-sided exact rate ratio test was used to compare myopericarditis incidence rates.

Results: This investigation identified 4 cases of probable myopericarditis and 1 case of suspected myopericarditis. No alternative etiology was identified as a cause. No additional cases were identified. There was no statistically significant difference in incidence rates between the observed cluster (5.23 per 1000 vaccinated individuals, 95% CI: 1.7–12.2) and the ACAM2000 clinical trial outcomes for symptomatic persons, which was 2.29 per 1000 vaccinated individuals (95% CI: 0.3–8.3).

Conclusions: Vaccination with ACAM2000 is the presumptive cause of this cluster. Caution should be exercised before considering vaccination campaigns for smallpox given the clinical morbidity and costs incurred by a case of myopericarditis. Risk of myopericarditis should be carefully weighed with risk of exposure to smallpox.

Introduction

Myopericarditis is a disease characterized by inflammation of cardiac muscle (myocarditis) and the surrounding pericardial sac (pericarditis). Since myocarditis and pericarditis often occur together, albeit with differing intensity, we referred to evidence of 1 or both in the same person as myopericarditis. A heart muscle or pericardial biopsy confirms the diagnosis but cardiac biomarkers, electrocardiogram (ECG), and cardiac imaging can be used to support suspicion for pericardial or myocardial damage in lieu of an invasive biopsy. Clinical diagnosis is often made based on history and signs and symptoms consistent with the disease, after more common illnesses are ruled out. Myopericarditis symptoms can range from asymptomatic to severe chest pain, shortness of breath, and sudden death. It can be caused by both infectious and non-infectious etiologies and present as an acute, subacute, or chronic disorder.[1] The most common viral etiologies in North America include coxsackieviruses, adenoviruses, herpesviruses (eg, cytomegalovirus and Epstein-Barr virus), influenza viruses, hepatitis B and C viruses, varicella-zoster virus, and parvovirus B19.[1]

ACAM2000 (Emergent BioSolutions, Gaithersburg, MD) is a second generation, replication competent smallpox vaccine (SPV) that was licensed by the Food and Drug Administration (FDA) in 2007,[2] at which point, it replaced all previous SPVs in the United States. ACAM2000 contains vaccinia virus derived from the New York City Board of Health strain.[3] In 1990, a decade after eradication of smallpox, the US military discontinued routine vaccinations for smallpox. During 2002, the Department of Defense (DOD) policy was amended briefly. In 2002, in response to concerns about use of smallpox for bioterrorism, vaccinations were reinstituted for a select group of civilian first responders and ~ 39 500 military personnel.

This program peaked by 2003 and, since that time, a smaller number of persons have been vaccinated. Following the 2002 increase, the policy recommended only vaccination to military members deploying to high-risk areas like the Korean Peninsula.[4] On March 5, 2018, the US Army Forces Command (FORSCOM) G-3/5/7 directed that the typhoid, smallpox, and anthrax vaccines be included in the routine adult immunization panel for all active duty soldiers.[5] Myopericarditis is known to occur by an unknown mechanism from live vaccinia virus, which comprises the SPV.[3,4,6-21] In April 2018, a cluster of 5 illnesses consistent with myopericarditis was reported to the DOD Immunization Healthcare Branch (IHB); all affected persons had received SPV within 2 weeks of their symptom onset with ACAM2000 at Fort Hood, Texas.[10]

A joint investigation was launched between an epidemiological consultation team led by the US Army Public Health Center Disease Epidemiology Division and the Centers for Disease Control and Prevention (CDC). Pending the outcomes of the investigation, DOD reverted to their previous policy of only administering SPV to persons deploying to high-risk areas. The aim of our study was to evaluate whether these cases constituted an outbreak of myopericarditis. The objectives of this investigation were to (1) confirm the diagnosis of myopericarditis; (2) review hospital records to describe the scope of the problem (eg, incidence, prevalence, population at risk) and to identify additional cases of myopericarditis among ACAM2000 vaccine recipients at Fort Hood; and (3) make recommendations for prevention and surveillance. To our knowledge, this is the first documented temporal and spatial cluster of SPV-associated myopericarditis cases from ACAM2000. We describe the results of the investigation.

Methods

Epidemiological Investigation

All of the patients were recognized as having recently received the SPV and were consequently suspected to have myopericarditis. We conducted extensive reviews of all available medical records related to the myopericarditis events. We evaluated all physical exams, laboratory results, and diagnostic imaging; pertinent results are documented in Table 1. Diagnostic testing for individual patients included a subset of the following: cardiac enzymes (ie, troponin I) level, ECGs, echocardiograms, cardiac magnetic resonance imaging, cardiac catheterizations, and computed tomography angiography scans.

We defined suspected, probable, and confirmed cases of myopericarditis as follows[4,11]:

Suspected myopericarditis: Symptoms consistent with myocarditis and/or pericarditis (eg, chest pain, dyspnea, or palpitations) and no evidence for an alternative diagnosis in a service member stationed at Fort Hood, TX, who was vaccinated with ACAM2000 within 4 weeks of symptom onset.

Probable myopericarditis: (1) Illness that met criteria for suspected myopericarditis and (2) illness met one of the following: elevated levels of troponin I OR new onset of depressed left ventricular function by imaging OR abnormal imaging consistent with myocarditis OR nonspecific ECG findings supportive of myopericarditis (eg, localized ST elevations and T-wave inversions and widespread ST elevations and ST depression in specific leads).

Confirmed myopericarditis: Histopathologic evidence of myopericarditis by endomyocardial biopsy.

Interviews were conducted with persons who met the case definition to capture information that was not recorded in the medical records. A standardized questionnaire including 21 open-ended and yes/no questions was developed and administered through interviews conducted by a Carl R. Darnall Medical Center (CRDAMC) nurse case manager (see supplemental material).

We conducted active case findings by querying laboratory reports of patients with elevated troponin levels and through patient interviews. The laboratory database was searched for patients with elevated troponins ages 17–30 years who presented to CRDAMC during January 1–May 2, 2018. We reviewed medical records of these persons for evidence of SPV within the 30 days prior to their elevated troponin levels. During patient interviews, we asked whether they knew of any other service member with similar symptoms to theirs. The number of SPVs given over the previous year (May 2017 to April 2018) was enumerated.

Laboratory Assessment

SPV as the cause of myopericarditis was evaluated using a previously published algorithm developed for vaccine adverse event assessment.[22] Myopericarditis can be caused by many infectious etiologies, and attributing it to SPV is a diagnosis of exclusion. The DOD's diagnosis and treatment standardized algorithm was used for all patients to rule out other pathogens in order to conclude that the true cause of myopericarditis was SPV.[23] A commercial laboratory completed initial serologic testing, including influenza A/B (rapid antigen test), coxsackievirus A7, A9, A16, A24 (IgG, IgM), coxsackievirus B1, B2, B3, B4, B5, B6 (Ab), parvovirus B19 (IgG, IgM), herpes simplex virus (HSV)-1 (IgG), HSV-2 (IgG), Epstein-Barr virus (capsid Ab IgG, IgM, heterophile Ab, early Ab IgG, nuclear Ab IgG), adenovirus (Ab), cytomegalovirus (PCR), and viral culture. The CDC's laboratory performed testing for enterovirus and parechovirus testing on additional serum and stool samples from all 5 patients.

Comparison of Incidence Rates

We compared estimated rates of symptomatic myopericarditis from ACAM2000 clinical trials with observed incidence rates for all cases of myopericarditis at Fort Hood during April.[2,24] We calculated the rate of symptomatic myopericarditis using data from clinical trials. The denominator for the Fort Hood incidence rate estimate was obtained from administrative records of the number of service members vaccinated. These records did not adjust for first-time recipients of SPV compared with soldiers who had previously received the vaccine. A 2-sided exact rate ratio test was conducted (using the uniformly most powerful unbiased test, significance cutoff $P < 0.05$) assuming 2 Poisson counts in the package "rateratio.test" in R 3.3.1.[25,26] Exact confidence intervals were calculated for both estimates and for the rate ratio itself.

Ethics Determination

The CDC's human subjects research experts reviewed this investigation and provided a non-research determination. Informed consent was obtained prior to interviews and sample collection.

Results

Setting and Routine Procedures

Fort Hood is a US military installation located in Killeen, Texas. Based on personnel reports, approximately 34 500 assigned

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Table 1. Case classifications, clinical parameters leading to case classification and laboratory results for the 5 patients presenting to Fort Hood's emergency department in April 2018

Patient	1	2	3	4	5
Gender	Male	Male	Male	Male	Female
Age	27	22	19	25	23
Case classification	Probable myopericarditis	Probable myopericarditis	Probable myopericarditis	Probable myopericarditis	Suspected myopericarditis
Reasons for classification	Chest pain, elevated troponin, ECG showed diffuse ST-segment elevation, PR interval depression, and diffuse T wave abnormalities with no pericardial effusion	Chest pain, elevated troponin, bradycardia, ECG results were non-ischemic, concave-upward ST-segment elevation and PR-segment depression	Chest pain, elevated troponin, echo results showed systolic dysfunction without heart failure	Chest pain, elevated troponin, ECG showed a mild ST-segment depression and an ST drop in the augmented Vector Left (aVL) lead with mild PR interval depression and with a concave form of ST elevation	Chest pain, normal troponin
Sample Collection Date	22-May-18	1-May-18	27-Apr-18	8-May-18	4-May-18
Troponin 1 normal range: (0-0.03)	0.25	2.12	0.83	2.24	–
Flu A/B (Rapid Ag)	–	Negative	Negative	–	Negative
Coxsackie A7, A9, A16, A24 (IgG/IgM)	**IgG +/ IgM +**	–	IgG +/ IgM -	IgG +/ IgM-	A-9 /A-24 IgG+/ IgM-
Coxsackievirus Ab B1, B2, B3, B4, B5, B6	–	B2 Positive	–	–	–
Parvo B19 (IgG/IgM)	**IgG +/ IgM +**	IgG +/ IgM -	IgG +/ IgM -	IgG-/IgM-	IgG +/ IgM -
HSV 1 (Glycoprotein G Ab IgG)	**Positive**	**Positive**	**Positive**	**Positive**	–
HSV 2 (IgG)	Negative	Negative	Negative	Negative	–
Epstein interpretation	Past infection	Unable to determine	Unable to determine	Past infection	Past infection
Epstein Barr Virus Capsid Ab IgG	**Positive**	–	–	**Positive**	**Positive**
Epstein Barr Virus Ab	Negative	–	Negative	Negative	Negative
Epstein-Barr Virus Capsid Ab IgM	Negative	Negative	Negative	Negative	Negative
Epstein-Barr Virus Early Ab IgG	Negative	Negative	–	Negative	Negative
Epstein-Barr Virus Nuclear Ab IgG	**Positive**	Negative	–	**Positive**	**Positive**
Adenovirus Ab[a]	**Positive**	Negative	Negative	Negative	Negative
Cytomegalovirus DNA PCR	Negative	–	–	Negative	Negative
Viral Culture	Not done	Negative	Negative	Not done	Negative
Enterovirus	Negative	Negative	Negative	Negative	Negative
Parechovirus	Negative	Negative	Negative	Negative	Negative

Notes: All cases were classified as vaccinia associated myopericarditis in the absence of an alternative diagnosis. Dashes indicate that the corresponding test was not conducted for that patient. Positive results are bolded for emphasis.
[a]Adenovirus 4/7 vaccination is routinely given during basic training.

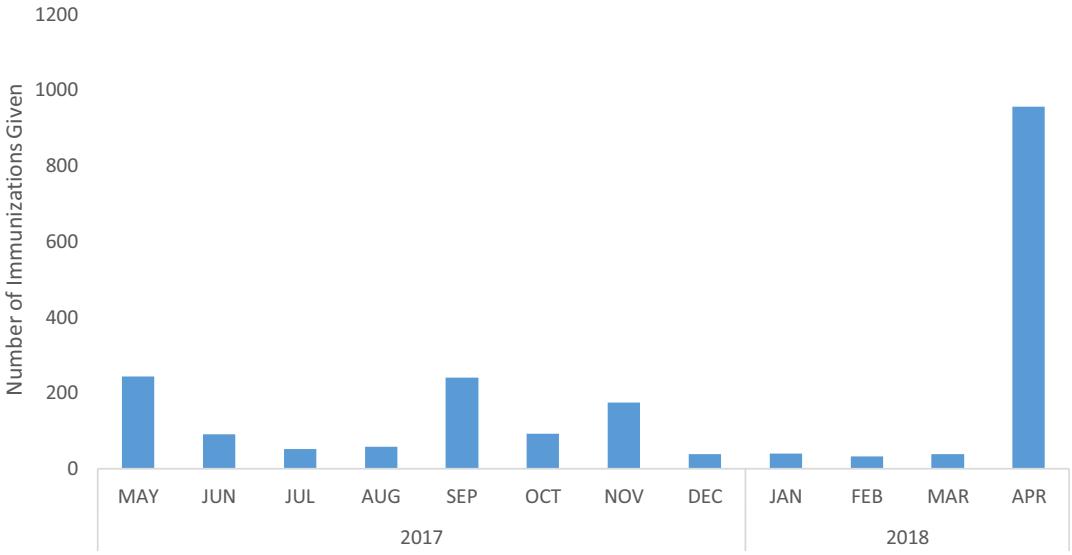

Figure 1. Smallpox immunizations given by month in 2017 and 2018 – Fort Hood, Texas.

soldiers and 13 500 civilian employees were at Fort Hood at the time of this investigation.

All SPVs were conducted at a single clinic location for service members and/or Department of the Army civilian employees who required the vaccine. Counseling for SPV was conducted in a group setting using a standardized script. Medical personnel discussed risk of transmission to contacts, and potential adverse events, including myopericarditis. All soldiers were instructed to seek immediate medical care if they suspected an adverse reaction. Trained medical providers screened soldiers for SPV contraindications individually, using a standardized template.[27] Individuals who did not have any identified contraindications were vaccinated percutaneously with 2.5 – 12.5 x 105 plaque forming units live vaccinia virus, which is the standard recommended dose. Trained medical personnel instructed on proper care of the vaccination site and gave out supplies for site care that included gloves, bandages, and alcohol-based hand sanitizer. Vaccinees were instructed to return after 7 days, at which time, the vaccination site was assessed for the robustness of the cutaneous reaction, also known as a "take," and health care providers inquired about adverse events.[28] Soldiers were told that if they should develop symptoms consistent with adverse events, they should report directly to CRDAMC Emergency Department (ED), which is at the Fort Hood base.

Fort Hood CRDAMC staff increased the amount of SPV administered from 38 soldiers in March to 956 in April (Figure 1). The difference in vaccination numbers was attributed to a policy change on March 5, 2018, when FORSCOM G-3/5/7 directed that the typhoid, smallpox, and anthrax vaccines be included in the routine adult immunization panel for all soldiers.[5]

Epidemiological Investigation

Of the 5 cases, 1 was a suspected case and 4 were probable cases (see Table 1). Illness onset of the cases was during April 14 to April 27, 2018. None of the patients had a heart biopsy; therefore, they could not be classified as confirmed. The first 4 cases have been previously described.[10] Briefly, the 5 cases were all vaccinated during April 3–18 with ACAM2000 from the same lot number but different vials. All 5 were ages 19–27 years, Caucasian, and healthy; 4 were male, and 1 was female. All were first-time recipients of the SPV. The time from vaccination to illness onset ranged from 8–11 days, with an average of 9.4 days. All of the patients presented to the ED as first-time vaccinees with an acute onset of chest pain but without complaints of recent body aches, fever, or respiratory symptoms that might have suggested an influenza-like illness. Other clinical signs at presentation included shortness of breath, diaphoresis, dizziness, chills, and fever. Four patients were admitted from the CRDAMC ED to 3 different hospitals in the surrounding area. One patient had milder symptoms and was treated as an outpatient. Inpatient hospital stays ranged from 2–5 days. All of the patients received follow-up care with a cardiologist for 6 months and serial cardiac imaging. All were placed on limited duty with no exercise for 6 weeks and a non-deployable status for at least 6 months. Three of the patients experienced continued intermittent chest pain for as long as 4 weeks following hospital discharge. One patient was re-admitted for continued chest pain 3 weeks after the initial admission and was released after 24 hours. All patients were followed by a cardiologist until complete recovery for between 3 and 9 months.

Interviews with the 5 patients were reviewed to evaluate SPV processes on Fort Hood and generate hypotheses for potential risk factors and other etiologies for myopericarditis. Interviews determined that one of the patients should not have received SPV because his spouse, with whom he lives, was pregnant. At the 7-day follow-up appointment, only 1 patient was asked about chest pain, shortness of breath, fever, abdominal pain, or joint pain. The others were not asked whether they were experiencing these symptoms; at the 7-day checkup visit, patients' vaccination sites were simply evaluated for a major cutaneous reaction. One patient did not have a 7-day check. The only cardiac risk factor that was identified for any patient in the cluster was past or current tobacco use among 3 patients. One patient reported using preworkout and post-workout supplements. No one described heavy alcohol usage; 1 patient reported having a glass of wine less than weekly. The patients were not aware of any respiratory illness among their units or close friends. When asked about family history of autoimmune disease, 2 patients reported autoimmune disease among parents, including thyroid disease, multiple sclerosis, and type 1 diabetes.

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Table 2. Comparison of estimated incidence rates from ACAM2000 clinical trial and Fort Hood cluster

Sample Population	x	(N)	Rate Per 1000	(95% CI)			
ACAM2000 clinical trial[a]	5	(873)	5.7	(1.9-13.3)			
Symptomatic Cases					Rate Ratio	(95% CI)	*P*
ACAM2000 clinical trial	2	(873)	2.29	(0.3-8.3)	0.4	(0.04-2.7)	0.53
Fort Hood	5	(955)	5.23	(1.7-12.2)			

Notes: The "x" in the table indicates the number of cases identified in each of the two situations.
[a]Estimate includes both asymptomatic cases and symptomatic cases.

Active case findings were made through searching the laboratory database for individuals with elevated troponins and patient interviews. These investigations identified 59 individuals with elevated troponin levels and 1 additional person with chest pain. However, medical records indicated none had recent SPV, and the treating clinicians attributed the elevated troponin levels and chest pain to alternative diagnoses. These were not cases.

Laboratory Assessment

Extensive testing for infectious illnesses on the differential diagnosis was completed (see Table 1). Non-infectious etiologies were not evaluated. No single alternative etiology was identified that could explain this temporal-spatial cluster.

Comparison of Incidence Rates

Clinical trials data included 3 asymptomatic cases of myopericarditis. We removed these from the numerator of the clinical trial estimate so that the newly calculated rate reflected only symptomatic persons and could be compared to the rate of illness we observed at Fort Hood. The estimated rate for symptomatic myopericarditis from clinical trials evaluating ACAM2000, therefore, was 2.29 per 1000 vaccinated individuals (95% CI: 0.3–8.3),[2,24] only slightly lower than observed rates at Fort Hood (5.23, 95% CI: 1.7–12.2) (Table 2). There was no significant difference between the ACAM2000 clinical trial rate and the observed rate at Fort Hood in April 2018 at the 0.05 level (RR = 0.4, 95% CI: 0.04–2.7, $P = 0.53$).

Discussion

Guidelines for the management of vaccinia-associated myopericarditis have been outlined by the DOD's IHB.[23] Management and limited duty recommendations for soldiers include a referral to cardiology for evaluation, which includes an ECG and exercise stress testing and recommendation to abstain from strenuous activity until a 6- to 12-week follow-up. Myopericarditis may result in medical non-deployability for 3–6 months or longer. The potential for long-term sequelae of myopericarditis is currently unknown.[3] The inability of a soldier to deploy negatively impacts unit readiness by decreasing the available workforce, and further imposes costs to the military through frequent follow-up visits to medical specialists.

The ACAM2000 package insert (https://www.fda.gov/media/75792/download) estimates the risk of myocarditis and/or pericarditis in symptomatic and asymptomatic patients as 5.7/1000 (95% CI: 1.9–13.3), which roughly equates to 1 in 200 vaccine recipients. No significant difference was observed between the rate seen at Fort Hood and published rates that occurred during the clinical trials. The available evidence suggests that this was not an outbreak (unexpected elevation in the rate of a disease or condition) but rather a predictable number of myopericarditis cases proportional to the increased number of vaccinations performed at Fort Hood during a short period of time. This observed rate is what should be expected under continued SPV use.

As part of our investigation, we made several recommendations. We recommended that because of the severity of myopericarditis, the risk of administering SPV should be weighed against the actual risk of exposure to smallpox and that caution be used in re-instituting a vaccination policy that results in a large number of people being vaccinated. We observed that some patients were not asked about chest pain during their 7-day follow-up appointment. We recommended that the DOD increase surveillance efforts by ensuring the soldiers are explicitly asked about symptoms consistent with adverse events from ACAM2000 (eg, chest pain) during the 7-day "take" appointment. This timepoint is a critical opportunity to explicitly remind the SPV recipient that he/she is nearing the "window" in which symptoms of myocarditis and/or pericarditis may develop. The DOD may consider making soldier educational materials that adequately depict the adverse effects, specifically describing the risk for and symptoms of myopericarditis. All service members should be screened using a standard form prior to vaccination and at the "take" check, and all screening materials should be included in the service member's medical records. We stressed the importance of accurately capturing disqualifying factors so that soldiers with a contraindication to vaccination (eg, a pregnant spouse at home as occurred with one of the patients in this investigation) are not vaccinated. Medical providers, in the case of this cluster, were aware of the risk of myopericarditis following SPV. Providers outside of military hospital networks should know to take an immunization history for any service member presenting with chest pain and difficulty breathing. All suspected cases of myopericarditis following SPV should be reported to the Vaccine Adverse Event Reporting System. In an effort to continue active case finding, IHB may consider routinely searching the Defense Medical Surveillance System for ICD-10 codes consistent with myopericarditis to identify new clusters.

Several limitations should be noted when interpreting the results from this investigation. First, no confirmatory myopericarditis testing was completed, as definitive confirmation of these conditions requires a heart biopsy, an invasive procedure.[4,11] Secondly, active surveillance (ie, monitoring ECGs and troponin levels) was not possible for all recipients of SPV at Fort Hood due to resources associated with such intensive monitoring. While active surveillance was done during the clinical trials, it is not done routinely by the DOD. Therefore, the observed incidence rate and the comparison incidence rates (derived from randomized clinical trials) were estimated using vastly different methods. As only those patients presenting with symptoms of myopericarditis were identified in this setting, it is likely that asymptomatic cases went undetected among SPV recipients at Fort Hood. Of the 5 total cases in

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the clinical trial, 3 were asymptomatic. This under-detection suggests more cases of myopericarditis than were brought to medical attention. Finally, completing rule-out testing for myopericarditis can be challenging. Collecting the correct sample types at the right time is rarely done. Ideally, a nasopharyngeal swab would be collected during the prodromal phase of infection in a person with a systemic febrile illness or upper respiratory tract infection.[19-21] Unfortunately, nasopharyngeal swabs were not collected from these patients.

An alternative to ACAM2000 became licensed in September 2019. MVA-BN is a novel third generation, non-replicating SPV with an improved safety profile.[29] Safety studies specifically addressing cardiac adverse events have been conducted, and no cases of myopericarditis (symptomatic or asymptomatic) have been reported.[30] A study examining ECGs following SPV with MVA-BN did not find any significant ECG abnormalities that could be attributed to vaccination.[31] MVA-BN has been studied in populations that are not able to receive first and second generation vaccinations, such as those with atopic dermatitis, HIV, or history of stem cell transplant.[32-34] MVA-BN may be considered by the DOD as a pre-exposure vaccination for a wide variety of populations across the military in lieu of ACAM2000. However, planning for adverse events that could occur from MVA-BN should be considered before such a campaign is launched. To our knowledge, no additional clusters have been identified since our investigation at Fort Hood or other military installations. SPX vaccinations, since the recognition of this cluster, have remained limited to soldiers deploying to high-risk areas. We noted that smoking, vaping, or use of smokeless tobacco occurred in 3 of 5 of the patients, but whether this was an incidental or in some way contributed to the incidence of severity of myopericarditis is not known; if an uptick in myopericarditis cases occurs in the future, in addition to evaluating for SPV, investigators may consider evaluating whether these habits occurred among the affected persons.

Conclusions

We conclude that 4 cases of probable myopericarditis and 1 case of suspected myopericarditis were associated with administration of SPV, ACAM2000. The known association between SPV and myopericarditis, lack of evidence for other causes, and onset occurring within the 30-day window of increased risk support this conclusion.[22] Myocarditis and pericarditis are known possible adverse events associated with ACAM2000, the only SPV product used by the DOD.[3,4,6-21] Due to the potential severity of myopericarditis, the risk of administering SPV should be weighed against the actual risk of exposure to smallpox. The risk of smallpox infection should be informed by available threat intelligence and should be evaluated against the known risks of SPV. This risk assessment should be conducted on a regular, recurring basis and as information changes to continuously inform decisions about which populations should receive SPV.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/dmp.2020.478

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