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Myopericarditis following Smallpox Vaccination

Mark K. Arness[1], Robert E. Eckart[2], Suzanne S. Love[3], J. Edwin Atwood[4], Timothy S. Wells[5], Renata J. M. Engler[6], Limone C. Collins[6], Sharon L. Ludwig[7], James R. Riddle[8], John D. Grabenstein[9], and David N. Tornberg[10] for the Department of Defense Smallpox Vaccination Clinical Evaluation Team

[1] Army Medical Surveillance Activity, Washington, DC.
[2] Brooke Army Medical Center, Fort Sam Houston, TX.
[3] Regional Vaccine Healthcare Center, Naval Medical Center, Portsmouth, VA.
[4] Walter Reed Army Medical Center, Washington, DC.
[5] Naval Health Research Center, San Diego, CA.
[6] Vaccine Healthcare Center Network, Walter Reed Army Medical Center, Washington, DC.
[7] US Coast Guard Health and Safety Directorate, Washington, DC.
[8] Air Force Research Laboratories, Wright-Patterson Air Force Base, OH.
[9] Military Vaccine Agency, US Army Medical Command, Falls Church, VA.
[10] Office of the Assistant Secretary of Defense for Health Affairs, Falls Church, VA.

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Myopericarditis has been a rare or unrecognized event after smallpox vaccinations with the New York City Board of Health strain of vaccinia virus (Dryvax; Wyeth Laboratories, Marietta, Pennsylvania). In this article, the authors report an attributable incidence of at least 140 clinical cases of myopericarditis per million primary smallpox vaccinations with this strain of vaccinia virus. Fifty-eight males and one female aged 21–43 years with confirmed or probable acute myopericarditis were detected following vaccination of 492,730 US Armed Forces personnel from December 15, 2002, through September 30, 2003. The cases were identified through sentinel reporting to military headquarters, active surveillance using the Defense Medical Surveillance System, or reports to the Vaccine Adverse Event Reporting System. The observed incidence (16.11/100,000) of myopericarditis over a 30-day observation window among 347,516 primary vaccinees was nearly 7.5-fold higher than the expected rate of 2.16/100,000 (95% confidence interval: 1.90, 2.34) among nonvaccinated, active-duty military personnel, while the incidence of 2.07/100,000 among 145,155 revaccinees was not statistically different from the expected background rate. The cases were predominantly male (58/59; 98.3%) and White (51/59; 86.4%), both statistically significant associations ($p = 0.0147$ and $p = 0.05$, respectively).

military personnel; myocarditis; pericarditis; smallpox; vaccination; vaccinia virus

Abbreviations: CDC, Centers for Disease Control and Prevention; DMSS, Defense Medical Surveillance System; DoD, US Department of Defense.

The current US Department of Defense (DoD) and US Coast Guard smallpox vaccination program conducted according to Advisory Committee for Immunization Practices guidelines with the licensed smallpox vaccine (Dryvax; Wyeth Laboratories, Marietta, Pennsylvania) was initiated on December 13, 2002, to counter the potential release of variola virus during terrorism or warfare (1). Smallpox vaccinations began at pilot sites: Walter Reed Army Medical Center (Washington, DC), Aberdeen Proving Ground (Maryland), Wilford Hall Air Force Medical Center (San Antonio, Texas), and National Naval Medical Center (Bethesda, Maryland). The first few hundred vaccinations identified certain procedural improvements but validated the approach developed in coordination with the Centers for

Reprint requests to Dr. James R. Riddle, AFRL/HEP, 2729 R Street, Building 837, Wright Patterson, OH 45433-5707 (e-mail: James.Riddle@wpafb.af.mil).

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Disease Control and Prevention (CDC), the Armed Forces Epidemiological Board, and the Advisory Committee on Immunization Practices. Screening forms and educational materials were revised slightly, using feedback from observers who evaluated educational sessions and recorded questions from military service members and families, and smallpox vaccine was distributed and administered in hundreds of immunization clinics around the world, including military forces afloat.

A three-pronged approach was implemented for postvaccination surveillance and patient safety. This program assessed the screening process, health events shortly after vaccination, and events months or years after vaccination. Previously established Vaccine Healthcare Centers at Walter Reed Army Medical Center and Portsmouth Naval Hospital (Portsmouth, Virginia; a collaborative effort with the CDC) were utilized for specialist consultation and evaluation of complex cases. A national registry was established for women given the vaccine before they recognized that they were pregnant. An independent safety monitoring panel, formed jointly by the Armed Forces Epidemiological Board and the Advisory Committee for Immunization Practices, received weekly updates on safety experiences (2). Early lessons from the program were shared regularly with the CDC and state health departments. For quality control of the vaccination procedure, DoD clinics tracked the vaccination response rates (i.e., "take rates") of the first 25–100 people vaccinated by each vaccinator. All clinics and hospitals performed process and root-cause analyses of "misses" and "near misses" regarding vaccination of those with contraindications.

On the basis of historical experience, myocarditis and pericarditis were not expected with use of the US-licensed strain of smallpox vaccine; however, early in the program, they were found to occur at a statistically elevated rate above baseline (3). To our knowledge, only five cases of postvaccinial myopericarditis associated with use of the US-licensed strain of smallpox vaccine were reported in the medical literature between 1955 and 1986 (4–11). Postvaccination myocarditis and pericarditis have been reported more commonly with other vaccinia virus strains (12–20), may be associated with other adverse events postvaccination (5), and may be asymptomatic (13, 21–23). In 1968, Price and Alpers (17) noted that minor cardiac complications after smallpox vaccination may be more common than is generally suspected. MacAdam and Whitaker (24) reported three cases of cardiac complications 5–14 days following smallpox vaccination and suggested that cardiac complications had previously been overlooked. In 1983, the incidence of postvaccination myocarditis among Finnish military conscripts hospitalized with mild myocarditis following vaccination with the Finnish strain of smallpox was estimated to be as high as 1 per 10,000 (25).

Between December 2002 and August 2004, DoD immunized more than 630,000 personnel against smallpox. From December 15, 2002, through September 30, 2003, the DoD and US Coast Guard identified 57 probable and two confirmed cases of postvaccinial myopericarditis among 492,671 otherwise healthy, adult personnel vaccinated with the licensed smallpox vaccine (Dryvax). In this article, we report epidemiologic analysis of the cumulative case series detected among persons vaccinated through September 30, 2003, 18 of which correspond to a series first reported by Halsell et al. (3).

MATERIALS AND METHODS

The DoD and US Coast Guard smallpox vaccination program included a comprehensive educational and postvaccination adverse-event surveillance effort (1). Clinical reports through medical channels were actively solicited. Guidelines were published to alert providers to the occurrence of adverse events following smallpox vaccination and to encourage reporting the clinical encounter through the Vaccine Adverse Event Reporting System using established guidelines. The Vaccine Adverse Event Reporting System is a cooperative program for vaccine safety of the CDC and the US Food and Drug Administration. This postmarketing safety surveillance program collects information about adverse events (possible side effects) that occur after US-licensed vaccines are administered (refer to the following website: http://www.vaers.org/). To enhance this system of spontaneous reporting, clinicians were provided extensive education and vaccinees were informed verbally and in writing to heighten awareness of potential adverse events, including cardiac events. An Internet site providing access to a comprehensive array of materials and ongoing program status was established (http://www.smallpox.army.mil/).

Each DoD hospital and clinic established bandage- and site-evaluation stations to monitor health-care workers' vaccination sites and promote effective bandaging. Scrupulous hand hygiene was encouraged. For other vaccinated personnel (i.e., employees not involved in health care), the infection-control practices of bandage use (usually simple adhesive bandages), wearing of long shirt sleeves to cover the vaccination site, and hand washing were repeatedly taught. Extensive documentation recorded screening results, vaccination delivery, vaccination response assessment (i.e., "take check"), and adverse-event management, if any. To disseminate scientific principles and vaccination procedures worldwide to thousands of medical units and tens of thousands of care providers, the Army Surgeon General conducted a 4-day training conference in October 2002 on smallpox preparedness for health-care providers and planners for each of the armed services. The training emphasized epidemic investigations and vaccination delivery. This conference was videotaped and then transformed into a multimedia presentation, which was posted on the Internet. For ships and other sites with limited Internet access, the training curriculum was provided on compact discs. Typically, installation medical directors completed 8 hours of training, other physicians and supervising nurses completed 6 hours, and vaccinating nurses and medics completed 3 hours.

A central website was established for on-demand distribution of primary source documents and references. To communicate smallpox information clearly to service members and their families, DoD developed hierarchical message maps, with increasing levels of technical detail, informational brochures, and lecture slides. Communications staff were available to respond to questions asked via telephone (877-

TABLE 1. Definitions of postvaccinial myopericarditis cases following surveillance for adverse events related to vaccination, United States, December 15, 2002–September 30, 2003

Confirmed postvaccinial myopericarditis	Acute myocarditis* with or without pericarditis, with onset 4–30 days after vaccinia exposure, and
	Absence of another causal infection, disease, or toxic etiology, and
	Histopathologic evidence of myocardial inflammation found at endomyocardial biopsy or autopsy and/or pericardial inflammation evident from pericardial tissue obtained at surgery or autopsy
Probable postvaccinial myopericarditis	Acute myocarditis* with or without pericarditis,* with onset 4–30 days after vaccinia exposure, and
	Absence of another causal infection, disease, or toxic etiology

* For surveillance purposes, a suspected diagnosis of myocarditis is classified as probable by detection of elevated serum levels of creatine kinase (MB isoenzyme), troponin I, and troponin T, usually in the presence of electrocardiogram (ECG) abnormalities beyond normal variants and/or evidence of focal or diffuse depressed left-ventricular function of indeterminate age identified by an imaging study, not documented previously or an abnormal result of cardiac radionuclide imaging. A suspected diagnosis of pericarditis is classified as probable by detection of a pericardial rub, or ECG with diffuse ST-segment elevations or PR depressions without reciprocal ST depressions not previously documented, or echocardiogram indicating the presence of an abnormal collection of pericardial fluid (27).

† Whether postvaccinial myopericarditis is a direct viral cytopathogenic effect or an immune-mediated disease remains unclear.

GET-VACC), e-mail (vaccines@amedd.army.mil), and the Internet (http://www.smallpox.mil).

The cases reported here were detected through both active and spontaneous surveillance methods, to include sentinel reporting to military headquarters and/or to the Vaccine Adverse Event Reporting System, or through Defense Medical Surveillance System (DMSS) diagnostic surveillance of vaccinees at military treatment facilities using *International Classification of Diseases*, Ninth Revision–coded diagnoses (420.90, 420.99, unspecified and other acute pericarditis; 422.90, 422.91, acute unspecified and idiopathic myocarditis; and 429.0, unspecified acute myocarditis) (26). This system integrates data from sources worldwide in an expanding relational database of military and medical experiences of personnel throughout their careers. It allows prompt morbidity assessments of those who share common characteristics such as vaccinations. DMSS personnel data are obtained from the Defense Manpower Data Center (Monterey Bay, California), including demographic information (age, gender, race) and service-related data (e.g., date of entry into military service, date of separation from military service, and occupation). Once cases were identified and records were assembled, a committee of cardiology, internal medicine, and immunology specialists classified the cases on the basis of clinical records review according to myocarditis and pericarditis surveillance case definitions developed by a joint workgroup of the DoD's Armed Forces Epidemiological Board and the CDC's Advisory Committee for Immunization Practices (27).

Only confirmed or probable cases were included in this analysis. Criteria for inclusion were as follows: vaccinated under the auspices of the DoD and US Coast Guard smallpox vaccination program; presentation for medical care within 30 days of vaccination; and clinical diagnosis of, or consistent with, myopericarditis, defined as an elevation of cardiac enzymes and/or abnormal electrocardiogram and/or echocardiogram findings consistent with myopericarditis upon presentation (table 1). Possible or suspect cases based on subjective symptoms but without objective clinical evidence were excluded from this analysis. Revaccinee status was determined at the time of vaccination by documented immunization, presence of a characteristic scar, date of birth, and/or date of entry into military service. Concomitant vaccinations, defined as vaccination within 1 week before or after receiving smallpox vaccine, were determined by use of data records from the DMSS, review of individual patient records, and patient self-reporting.

These 59 cases were compared with all other smallpox vaccinees to describe univariate differences in sex, vaccination status (primary or revaccinee), ethnicity (Hispanic, non-Hispanic), race (White, African American, other), and service (Army, Navy, Marine Corps, Air Force, and Coast Guard, which included one Merchant Marine). Additionally, demographic variation in home of record location, unit of assignment location, and history of concomitant vaccine administration was compared with that of the total primary vaccinee population. Home of record location and unit of assignment location were included in the univariate analysis to explore a possible association with local epidemic viral disease that could cause myopericarditis. The number of smallpox vaccinees by military service, sex, race, and primary/revaccinee status was derived from data reported by the military services to the Military Vaccine Agency as of November 19, 2003. Univariate statistics for demographic data were computed by using Pearson chi-square tests (28).

The 2002 background incidence of myopericarditis among 1,390,352 active-duty service members was 2.16 (95 percent confidence interval: 1.90, 2.34; Poisson distribution) per 100,000 over any given 30-day period (*International Classification of Diseases*, Ninth Revision–coded diagnoses 420.90, 420.99, unspecified and other acute pericarditis; 422.90, 422.91, acute unspecified and idiopathic myocarditis; and 429.0, unspecified acute myocarditis). This background incidence rate was used to estimate vaccinees' crude relative risk of myopericarditis. To assess seasonality associated with baseline myopericarditis rates, DMSS provided monthly myopericarditis counts, by service, for January 2001–September 2003. These counts included all

cases diagnosed within both the outpatient and the inpatient DoD medical care system, including referrals to civilian health-care agencies. To determine whether observed changes in myopericarditis incidence after December 2002 were attributable to seasonal differences, myopericarditis incidence rates were calculated for three 10-month calendar periods: December 1, 2002–September 30, 2003; February 1, 2002–November 30, 2002; and December 1, 2001–September 30, 2002. Poisson regression was used to calculate unadjusted chi-square tests and p values for the comparison between these three calendar periods. The US active-duty military population totals for the midpoint of each period were used as the denominator.

A multivariable Poisson regression model was developed by using the information from the 59 cases (29). These cases were stratified by age at diagnosis (≤22, 23–26, 27–29, ≥30 years), race (White, all other races), service (Army, Air Force, Navy/Marine Corps, Coast Guard/Merchant Marine), and calendar period of diagnosis (prior to March 25, 2003; March 25, 2003–June 30, 2003; and July 1, 2003–September 30, 2003). Calendar period of diagnosis was added to determine whether observed associations were influenced by the March 25, 2003, CDC notification. Adjusted Cox estimates of the cumulative and discrete probability of hospitalization from vaccination to diagnoses were graphed to evaluate temporal trends in risk following smallpox vaccination (30, 31). Statistical analysis was performed by using SAS, version 9.0 and/or JMP Professional 5.0.1 software (SAS Institute, Inc., Cary, North Carolina). All reported p values were two sided and were considered statistically significant when they were less than 0.05 (32).

RESULTS

Fifty-nine cases of probable and confirmed postvaccinial myopericarditis were reported among 492,671 total vaccinees after the DoD smallpox vaccination program was introduced on December 15, 2002, through September 20, 2003. Characteristic of the myopericarditis cases was the widespread geographic distribution across 21 states as well as military facilities in both Europe and southwest Asia. Cases primarily occurred in states with large military populations preparing for deployment in support of Operation Iraqi Freedom or homeland security operations. No geographic pattern was apparent for either home of record or unit of assignment (data not shown).

Myopericarditis cases occurring during this time period were not evenly distributed among the services (figure 1). Sixty percent of all Air Force postvaccinal cases were diagnosed prior to March 25, 2003, compared with the Army (40.0 percent), Navy and Marine Corps (0 percent), and Coast Guard (16.7 percent) (Fisher's exact test, $p = 0.015$). Myopericarditis cases were predominantly male (58/59 vs. 433,383/492,671; Pearson chi-square = 5.96; $p = 0.015$), non-Hispanic (58/59 vs. 446,737/492,671; Pearson chi-square = 4.06; $p = 0.044$), White (51/59 vs. 356,703/492,671; Pearson chi-square = 6.01; $p = 0.05$), and members of the US Army (22/59 vs. 221,700/492,671; Pearson chi-square = 137.9; $p < 0.001$) (table 2). For both cases and noncases, revaccinee status was determined and documented

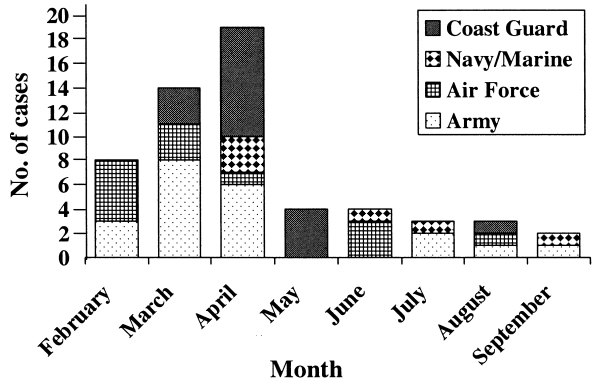

FIGURE 1. Cases of postvaccinial myopericarditis by month and branch of US military service, December 15, 2002–September 30, 2003. The Coast Guard category includes one Merchant Marine.

as part of the electronic records at the time of vaccination, as described above. Primary vaccinees were statistically significantly more likely to develop myopericarditis than were revaccinees (56/59 vs. 347,516/492,671; Pearson chi-square = 16.9; $p < 0.001$). There was no significant difference between the mean age of cases (27.2; standard deviation, 5.3 years) and all vaccinees (29.3; standard deviation, 8.4 years). The average age of all active-duty military personnel in 2002 was 27.8 years (data from the DMSS).

There was no statistically significant association for concomitant administration of smallpox vaccine with other vaccines among these myopericarditis cases when compared with noncase vaccine recipients; 41 percent of myopericarditis cases received other concomitant vaccines compared with 43 percent of all other smallpox vaccinees. Concomitant vaccines administered with vaccinia to these 59 cases included anthrax, typhoid, hepatitis A, hepatitis B, influenza, meningococcal, measles-mumps-rubella, poliovirus, and yellow fever.

All 59 myopericarditis cases were diagnosed between 2 and 29 days postvaccination, with all but 10 (83 percent) clustered within a 6-day period (20 percent of the 30-day period) (figure 2). During the postvaccination period, the mean number of days to diagnosis was significantly shorter for non-Whites versus Whites—8.0 days versus 11.4 days, respectively (two-tailed t test, unequal variance, $p = 0.027$). The cumulative distribution of myopericarditis risk by day postvaccination was calculated by using Cox proportional hazards regression. Daily risks were adjusted by calendar period of diagnosis, race, branch of service, age, and concomitant vaccinations, and they graphically illustrated an approximate 3.4-fold increase in myopericarditis risk during the 9–12-day postvaccination period (figure 3).

The 56 cases among 347,572 primary vaccinees represent an incidence of 16.11 per 100,000 over a 30-day observation window during December 15, 2002–September 30, 2003. This incidence provides an unadjusted relative risk of 7.46 (95 percent confidence interval: 6.89, 8.48; Poisson distribu-

TABLE 2. Characteristics of myopericarditis cases diagnosed among smallpox vaccinees, United States, December 15, 2002–September 30, 2003

Characteristic	Myopericarditis				*p* value
	Yes		No		
	No.	%	No.	%	
Sex					
Male	58	98.3	433,383	88.0	0.015
Female	1	1.7	59,288	12.0	
Vaccination status					
Primary	56	94.9	347,516	70.5	<0.001
Revaccinee	3	5.1	145,155	29.5	
Ethnicity					
Hispanic	1	1.7	45,934	9.3	0.044
Non-Hispanic*	58	98.3	446,737	90.7	
Race					
White	51	86.4	356,703	72.4	0.05
African American	6	10.2	87,652	17.8	
Other	2	3.4	48,316	9.8	
Service					
Army	22	37.3	221,700	45.0	<0.001
Navy	5	8.5	106,550	21.6	
Marine Corps	1	1.7	63,642	12.9	
Air Force	13	22.0	83,858	17.0	
Coast Guard†	18	30.5	16,921	3.5	
Total	59	100.0	492,671	100.0	

* Includes 16,294 subjects whose ethnicity was unspecified.
† Includes one Merchant Marine.

tion) compared with the calendar year 2002 background rate of 2.16 (95 percent confidence interval: 1.90, 2.34) per 100,000 over a 30-day observation window. Three cases among 145,155 revaccinees represents a 30-day incidence of 2.07 per 100,000 previously vaccinated recipients. This incidence provides an unadjusted relative risk of myopericarditis in revaccinees of 0.96 (95 percent confidence interval: 0.89, 1.09; Poisson distribution). Univariate Poisson models were developed to calculate the baseline risk of myopericarditis across all services irrespective of smallpox vaccination status to assess seasonal trends in myopericarditis risk. The baseline incidence rate for the study period (December 1, 2002–September 30, 2003) was compared with the myopericarditis incidence during the previous 10-month period (February 1, 2002–November 30, 2002) and the same period from the prior year (December 1, 2001–September 30, 2002) (table 3). The 10-month incidence rate for December 1, 2002–September 30, 2003, was 24.6 per 100,000. Similarly, the 10-month incidence rates for February 1, 2002–November 30, 2002, and December 1, 2001–September 30, 2002, were 22.0 per 100,000 and 24.3 per 100,000, respectively, and these differences were not statistically significant.

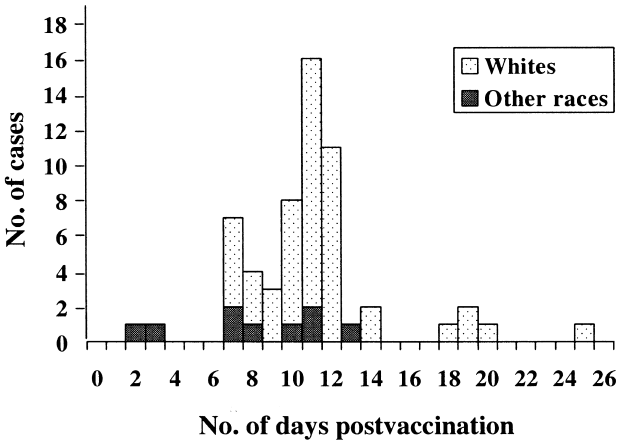

FIGURE 2. Cases of postvaccinial myopericarditis by number of days from vaccination until diagnosis and by race, United States, December 15, 2002–September 30, 2003.

There were no statistically significant findings when data on the 59 cases were entered into a multivariable Poisson regression model for simple case counts (table 4). In the adjusted model, cases with the highest risk were less than 22 years of age and were White; when compared with the Army, members of the Coast Guard and Air Force had

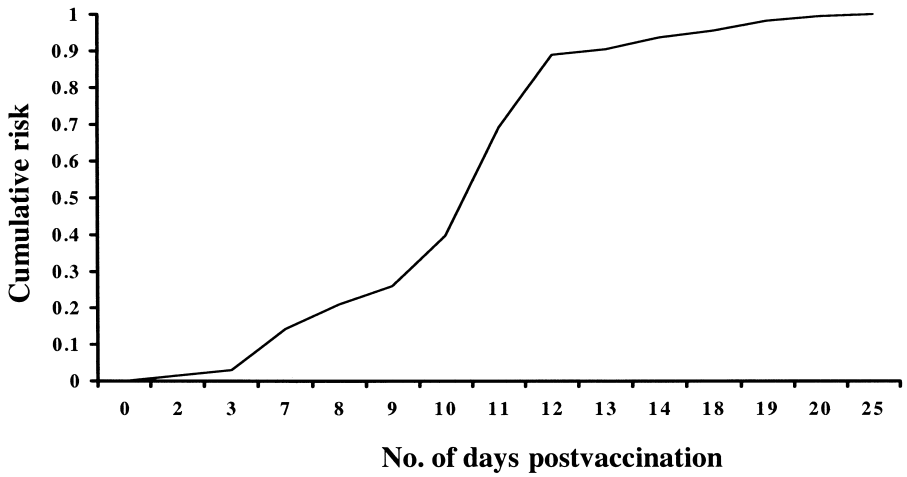

FIGURE 3. Cumulative distribution of risk (adjusted for calendar time, race, military service, age, and concomitant vaccinations) of postvaccinial myopericarditis by number of days from vaccination until diagnosis, United States, December 15, 2002–September 30, 2003. No. of days postvaccination refers to days on which cases were diagnosed.

higher risks. The risk of myopericarditis was not evenly distributed either by calendar time or during the postvaccination period. When 15 days or more following vaccination was compared with the 8–14-day postvaccination window regarding cases of myopericarditis that developed, the latter period presented the highest risk for these 59 cases. It is also likely that the March 25, 2003, CDC notification of a possible association between smallpox vaccination and myopericarditis may have increased the risk of diagnosis after this announcement (relative risk = 1.22, 95 percent confidence interval: 0.65, 2.31; Poisson distribution).

There was no apparent difference in case severity when cardiac enzyme levels were used as a surrogate among cases diagnosed early in the program and those diagnosed later. Most patients presented initially with chest pain or substernal pressure (56/59; 94.9 percent). The majority (54/59, 91.5 percent) also noted prodromal symptoms including fever and chills (32/59; 54.2 percent) as well as myalgias and arthralgias (15/59; 25.4 percent). Headache, diaphoresis, and fatigue were also commonly reported. Catheterization with coronary angiography was performed in 22 (37.3 percent) patients, none of whom were reported to have obstructive coronary artery disease. Of the two instances in which myocardial tissue could be studied, there was no evidence of vaccinia virus by culture or DNA detection methodology. Although variably performed, extensive serologic and culture testing for other infectious etiologies was universally unremarkable (2).

DISCUSSION

Viral myopericarditis is an inflammatory disorder of the myocardium characterized by injury of myocytes with associated inflammatory infiltrate (27, 33). Often, pericarditis and myocarditis are observed in tandem, hence the term *myopericarditis* (34). Vaccinia virus has long been associated with rare cases of myopericarditis but was an unrecognized sequelae following vaccination with the New York City Board of Health strain (33–35). Most of the cases of this disorder in this series occurred in otherwise healthy, young,

TABLE 3. Baseline rates of myopericarditis among US military service members during three time periods, December 1, 2001–September 30, 2003

Period	No. of cases	Population	Incidence*	*p* value
December 2002–September 2003	346	1,407,061	24.6	N/A†
February 2002–November 2002	309	1,402,244	22.0	0.161
December 2001–September 2002	337	1,386,555	24.3	0.879

* Ten-month rate per 100,000 service members.

† N/A, not applicable.

TABLE 4. Multivariable Poisson regression analysis of myopericarditis cases, United States, December 15, 2002–September 30, 2003

Characteristic	Cases		RR*	95% CI*
	No.	%		
Age (years)				
≤22	17	28.8	1.38	0.67, 2.83
23–26	16	27.1	0.92	0.43, 1.98
27–29	11	18.6	1.14	0.48, 2.72
≥30	15	25.5		
Service				
Air Force	15	25.4	1.22	0.60, 2.49
Coast Guard†	18	30.5	1.38	0.71, 2.68
Navy and Marine Corps	6	10.2	0.94	0.37, 2.41
Army	20	33.9		
Race				
White	51	86.4	1.10	0.46, 2.61
Non-White	8	13.6		
Postvaccination window (no. of days)				
0–7	10	25.0	1.20	0.36, 4.00
8–14	25	62.5	1.90	0.71, 5.09
>15	5	12.5		
Calendar period of diagnosis (2003)				
After June 30	7	17.5	0.77	0.30, 1.98
March 25–June 30	19	47.5	1.22	0.65, 2.31
Before March 25	14	35.0		

* RR, relative risk; CI, confidence interval.
† Includes one Merchant Marine.

adult, White males among a broader population screened for conditions that preclude vaccination. The higher rate of diagnosis following the initial reporting of our first 18 cases (7.8/100,000 vs. 16.11/100,000) is not unexpected given the initial relative lack of clinical suspicion of myopericarditis following vaccination with the New York City Board of Health strain of vaccinia virus and cardiac disease in a population of healthy, young military personnel (2). All 59 cases included in this analysis had a moderate-to-severe initial clinical presentation and met a strict case definition requiring objective clinical findings.

The finding of only one female case among 59 vaccinees with myopericarditis compared with the expected proportion of all female vaccinees is unlikely to be due to chance alone. This case had a fatal outcome 33 days following deployment vaccination against smallpox, anthrax, measles-mumps-rubella, hepatitis B, and typhoid. Objective findings of carditis were noted 29 days postvaccination but were negative when assessed earlier. The possibility of an association with vaccination was reviewed by two independent groups of medical experts; although the fatality was ruled likely to be associated with the vaccination experience, a definitive link to smallpox or any other specific vaccine could not be established. The clinical course in this case was considered more consistent with lupus-induced serositis, associated with low-grade pericarditis, than a symptom of the postvaccinial myopericarditis syndrome (1, 2, 36–38).

The March 25, 2002, CDC notification subsequently changed the criteria for prevaccination risk screening, leading to establishment of the DoD case-management guidelines for myopericarditis associated with smallpox vaccine and publication of the original case series of 18 by Halsell et al. (2, 27, 39, 40). Prior to the CDC notification, members of the Air Force were significantly more likely to be diagnosed than were members of the other services. These findings cannot be explained alone by differences in age distribution among the services (Pearson chi-square = 9.28, $p = 0.412$) because one would expect older members with cardiovascular syndromes to receive a more rigorous diagnostic examination. Because of these differences in case recognition, the observed incidence of myopericarditis is likely an underestimate resulting from variability in case ascertainment and case detection bias. The inconsistent distribution of cases among the military services suggests that many clinically mild or inapparent cases were undiagnosed, perhaps because of situational differences in access to

medical and diagnostic resources. For example, most Navy and Marine Corps personnel were vaccinated afloat, where availability of laboratory diagnostics is limited, as opposed to US Coast Guard personnel who were evaluated primarily in civilian facilities located in the United States. The index of suspicion for cardiac testing of patients reporting to a civilian emergency room with chest pain or substernal pressure is also likely higher than in comparable military healthcare facilities.

That nearly all of the cases were White males is difficult to explain. In the military health system, it is unlikely that the level of diagnostic attention regarding myopericarditis differed to any significant degree for women and minorities compared with White men. Among the 59 cases, there were no statistically significant differences in the distribution of race by age, service, or postvaccination window of diagnosis. Of interest is the finding that male minorities had a statistically significantly shorter interval between vaccination and diagnosis. This finding is based on a limited number of minority cases and may in fact either represent a spurious finding or perhaps indicate genetic differences in the risk of developing myopericarditis.

The observed narrow clustering of all cases postvaccination combined with the wide geographic and temporal distribution during the vaccination program, and the increasing trend in diagnosis (along with the lack of alternative diagnoses), when taken together provide strong epidemiologic evidence of a relation between vaccinia inoculation and myopericarditis. The observed myopericarditis incidence, nearly 7.5-fold higher among primary vaccinees (vs. nonvaccinees), is even more powerful evidence of an association. The finding that the estimated incidence of myopericarditis in revaccinees was equivalent to the expected background rate further supports a causal association with primary vaccination, especially because baseline myopericarditis rates do not appear to be influenced by seasonality. To accurately determine the true incidence of postvaccinia myopericarditis, a prospective study is needed.

Study limitations

A unique strength of this study is the large number of patients vaccinated and the comprehensive nature of adverse-event reporting. Potential bias existed for both under- and overreporting of cases (2). Although extensive efforts were made to identify all cases, underreporting may have resulted from incomplete ascertainment, especially of cases with mild-to-moderate acute presentation and rapid recovery. Alternatively, clinicians may have created a diagnostic suspicion bias if they were aware of the possible causal association between vaccine and myopericarditis. Adherence to strict case definitions and case inclusion criteria helped control this bias (27).

Potential for differential exposure bias existed in ascertainment of concomitant administration of smallpox vaccine with other vaccines. Exposure of myopericarditis cases was determined from electronic DMSS records, review of available medical and vaccination records, and self-report. Exposure among all other vaccinees was determined from electronic DMSS records only. Note that this potential for differential exposure bias in ascertainment of concomitant vaccinations would most probably bias results toward finding an association, so the lack of an association is even more convincing.

The generalizability of these findings is limited (2). Cases were detected in a prescreened population of personnel, primarily those deployed in support of military operations. Additionally, the results of the multivariable Cox and Poisson models for these 59 cases are subject to the biases inherent in detecting these cases. Further investigation is ongoing to better define the occurrence, potential risk factors, and long-term clinical outcomes of postvaccinial myopericarditis. Continued monitoring of longer-term morbidity, including enrollment of cases in the central DoD smallpox myopericarditis registry, is also ongoing. It will be important to monitor closely the longer-term health of these patients, because studies have indicated that viral myocarditis may result in long-term or permanent damage to the heart (35, 41–45).

Implications

These findings are relevant to current policies and guidelines for vaccinating people against smallpox. A smallpox vaccination program should allow for education, screening, and appropriate clinical follow-up to ensure evaluation, diagnosis, and treatment of suspected postvaccinial myopericarditis cases. Our findings suggest that postvaccinial myopericarditis is an expected adverse event, with a minimum attributable morbidity estimate of at least 140 clinical myopericarditis cases per million primary vaccinees in comparable adult populations. If it is assumed that the rate among US Coast Guard vaccinees more closely approximates the true incidence of postsmallpox vaccination myopericarditis, the minimum expected rate would be approximately 600 per million vaccinations. Postvaccinial myopericarditis should be considered in the differential diagnosis of patients with chest pain onset within 30 days of smallpox vaccination. Disease can usually be expected to be mild and self-limited, but the complete clinical significance will not be known until potential longer-term consequences are evaluated (45, 46).

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The Department of Defense Smallpox Vaccination Clinical Evaluation Team: Dr. Jeffrey S. Halsell (The University of Virginia, Charlottesville, Virginia); Dr. Roger L. Gibson (Office of the Assistant Secretary of Defense for Health Affairs, Washington, DC); Dr. John F. Brundage, Karen E. Campbell, Barbara Nagaraj, and Gabriella Andreotti (Army Medical Surveillance Activity, Washington, DC); Drs.

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