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Myopericarditis after vaccination, Vaccine Adverse Event Reporting System (VAERS), 1990–2018

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ABSTRACT

Background: Myopericarditis after vaccination has been sporadically reported in the medical literature. Here, we present a thorough descriptive analysis of reports to a national passive vaccine safety surveillance system (VAERS) of myopericarditis after vaccines licensed for use in the United States.
Methods: We identified U.S. reports of myopericarditis received by VAERS during 1990–2018 that met a published case definition for myopericarditis or were physician-diagnosed. We stratified analysis by age group (<19, 19–49, ≥50 years), describing reports by serious/non-serious status, sex, time to symptom onset after vaccination, vaccine(s) administered, and exposure to other known causes of myopericarditis. We used Empirical Bayesian data mining to detect disproportionate reporting of myopericarditis after vaccination.
Results: VAERS received 620,195 reports during 1990–2018: 708 (0.1%) met the case definition or were physician-diagnosed as myopericarditis. Most (79%) myopericarditis reports described males; 69% were serious; 72% had symptom onset ≤ 2 weeks postvaccination. Overall, smallpox (59%) and anthrax (23%) vaccines were most commonly reported. By age, among persons aged < 19 years, *Haemophilus influenzae* type b (22, 22%) and hepatitis B (18, 18%); among persons aged 19–49 years smallpox (387, 79%); among persons aged ≥ 50 years inactivated influenza (31, 36%) and live attenuated zoster (19, 22%) vaccines were most commonly reported. The vaccines most commonly reported remained unchanged when excluding 138 reports describing other known causes of myopericarditis. Data mining revealed disproportionate reporting of myopericarditis only after smallpox vaccine.
Conclusions: Despite the introduction of new vaccines over the years, myopericarditis remains rarely reported after vaccines licensed for use in the United States. In this analysis, myopericarditis was most commonly reported after smallpox vaccine, and less commonly after other vaccines.
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1. Introduction

Myocarditis (inflammation of the myocardium, or heart muscle) and pericarditis (inflammation of the pericardium, or tissue overlying the heart muscle) often occur together (termed myopericarditis), and can range in severity from mild and without symptoms, to severe [1]. Myopericarditis has many causes, including viral infections [1].

Although not establishing causality, myopericarditis has been reported after vaccinations. Myopericarditis is known to occur after administration of smallpox vaccine [2]. Amsel et al., described myocarditis in a male aged 3 months after receiving both combined diphtheria, tetanus, and pertussis (DTP) vaccine, and oral

Abbreviations: AE, adverse event; CDC, Centers for Disease Control and Prevention; DTP, combined diphtheria, tetanus, and whole cell pertussis vaccine; EBGM, Empirical Bayes Geometric Mean; FDA, Food and Drug Administration; HPV, human papillomavirus; IIV, trivalent inactivated influenza vaccine; MedDRA, Medical Dictionary for Regulatory Activities; MGPS, Multi-Item Gamma Poisson Shrinker; MMR, combined measles, mumps, and rubella vaccine; PT, Preferred Term; VAERS, Vaccine Adverse Event Reporting System.

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polio vaccine [3]. de Meester et al. described pericarditis after vaccination with influenza vaccine [4], Peyriere et al. described pericarditis after hepatitis B vaccine [5], and Mei et al. have described recurrent pericarditis after inactivated influenza (IIV) [6]. Except for smallpox vaccine, none of these reports described vaccines licensed for use in the United States.

Myopericarditis after live virus vaccines other than smallpox vaccine has been explored to some degree [7,8]. Reports of myopericarditis after inactivated vaccines have been scant, mostly after IIV [4,9], including a recently published case report attributing myocarditis to adjuvanted inactivated influenza vaccine (Fluad® , Sequirus) [9]. Further, several vaccines that are not IIV – including both live attenuated and inactivated vaccines – have been licensed for use in the United States over the past several years. To better characterize myopericarditis after vaccination, we reviewed and described reports of myopericarditis received by the Vaccine Adverse Event Reporting System (VAERS).

2. Methods

2.1. Data source

VAERS is a national spontaneous reporting system for monitoring AEs after vaccination [10]. Reports of AEs following vaccines licensed for use in the United States are accepted from healthcare providers, vaccine manufacturers, vaccine recipients and other persons and entities, including the military. Reported signs and symptoms are coded using Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) [11]. MedDRA PTs are not necessarily medically confirmed diagnoses, and a VAERS report can be assigned multiple MedDRA PTs. The Code of Federal Regulations defines a report as serious if at least one of the following conditions is reported: death, life-threatening illness, hospitalization or prolongation of existing hospitalization, permanent disability, or a congenital anomaly or birth defect [12]. An AE might therefore present as an acutely severe condition, but not be classified as a serious report. For non-manufacturer serious reports, medical records are routinely requested and made available to VAERS personnel. Due to regulatory processes [13], vaccine manufacturers will request and review medical records before reporting a serious report to VAERS: as a result, serious reports from vaccine manufacturers typically do not contain medical records that VAERS personnel can review.

2.2. Descriptive analysis

We searched the VAERS database for reports of myocarditis, pericarditis, myopericarditis, and perimyocarditis following vaccination received by VAERS during January 1, 1990 through December 31, 2018 (among U.S. reports processed by CDC through May 31, 2019). We searched for reports containing PTs that included the words "myocarditis", "coxsackie carditis", "pericarditis", and "pericardial effusion"; a complete list of PTs searched is available in the Supplemental Materials. Our search included PTs from past versions of the MedDRA browser, to capture reports using these older PTs. All identified reports were reviewed for signs and symptoms that met case definitions previously used for surveillance of myopericarditis after smallpox vaccine [14]; we also included for review reports where there was a diagnosis by a physician, regardless of if the reported case met the published case definition. Reports of cases that either met the definition for myocarditis or pericarditis, or were diagnosed by a physician, were stratified by age group (<19 years, 19–49 years, ≥50 years), in part because of age differences in recommended vaccination schedules [15,16], and the known association between smallpox vaccine, administered routinely to selected populations, and myopericarditis [2,14]. For each age group, we analyzed cases by seriousness of report (death, serious, or non-serious), sex, and time from vaccination to onset of symptoms. In addition, we analyzed by whether vaccines were given alone or concomitantly with other vaccines. Because myopericarditis is commonly viral in origin in the community [1], we conducted a secondary analysis that excluded reports in which patients exhibited signs or symptoms of influenza-like illness (including fever, malaise, upper or lower respiratory symptoms, gastrointestinal symptoms like nausea or vomiting) or had a history of such symptoms within 42 days of symptom onset for myopericarditis [14].

2.3. Estimated reporting rates

Data on doses of vaccine that were distributed or administered are difficult to obtain. Estimating reporting rates of AEs after vaccination using data from VAERS is therefore challenging. For smallpox vaccine, doses administered data were unavailable, but doses distributed data were available. We were able to estimate crude reporting rates of myopericarditis after smallpox vaccine using reports received during 2014 through 2018 as the numerator, divided by doses distributed during the corresponding time period (which included disbursements to the U.S. military) (Centers for Disease Control and Prevention, Division of State and Local Readiness, personal communication) as the denominator; rates were estimated as reports per 1,000 doses distributed. For influenza vaccine, vaccine coverage data were available, and could be used to estimate doses administered. We therefore estimated annual crude reporting rates for influenza vaccine (all types), with reports received during 2014 through 2018 as the numerator, with population estimates and vaccine coverage for the corresponding year multiplied as the denominator [18,19]; rates for 2 age groups (1–17 years, ≥18 years) were estimated. From these annual crude reporting rates, median rates of reports per million doses administered were estimated for 2014 through 2018.

2.4. Disproportionality analysis

Empirical Bayesian data mining techniques [17] were used to identify MedDRA PTs related to myopericarditis that occurred among U.S. reports more often than expected following each individual U.S. licensed vaccine: AEs after a given vaccine were compared to AEs reported for all vaccines, with adjustment for age, sex, and year of report receipt. The statistic calculated for this data mining analysis was the Empirical Bayes Geometric Mean (EBGM) and its associated 90% confidence interval (EB05, EB95). An EB05 $\geq$ 2.0 indicates a vaccine-event pair occurs at least twice as often as expected, assuming that vaccine-event pairs are random, and is the commonly used threshold for considering an AE as a potential signal [18]; we thus used an EB05 $\geq$ 2.0. Disproportionality analyses are intended to assess potential associations between a vaccine and an AE, but do not imply causality between the vaccine-event pair.

The data in this analysis resulted from routine public health surveillance activities. U.S. federal law specifies that these activities do not constitute research. This analysis was therefore exempt from institutional review.

3. Results

3.1. Descriptive analysis

During the analytic period, VAERS received a total of 620,195 reports. Of these reports, 708 (0.1%) either met the published case

definition for myopericarditis [14] or were diagnosed by a physician as myopericarditis (Table 1). Most reports described males (79%), and most reports were classified as serious (69%), with a reported time to symptom onset of 14 days or less (72%). Median reported age was 24 years (range: 0 to 90 years): among people ≤ 18 years of age, median age was 8 years (range: 0 to 18 years); among people 19 to 49 years of age, median age was 25 years (range: 19 to 49 years), with 75% of reports among people 19 to 31 years of age; among people ≥ 50 years, median age was 64 years (range: 50 to 90 years). We observed notable differences by age group: most reports (69%) were among persons 19 to 49 years of age, most of whom (90%) were males, and most of whom reported a time to symptom onset of 8 to 14 days after vaccination (whereas for other age groups, the greatest proportion of reported persons had symptom onset within 7 days of vaccination). Also, in over half of reports among persons 18 years of age and younger, the patient died. When excluding reports after smallpox vaccine, most reports still described males, were classified as serious, reported time to symptom onset of 14 days or less, with similar median ages and distribution of sex by age (data not shown).

Considering all vaccines (regardless if administered with other vaccines, or alone), the most frequently reported vaccines were smallpox (59%), anthrax (23%), and typhoid (13%) vaccines; IIV was also frequently reported (11%) (Table 2). Among persons 18 years of age and younger, the most frequently reported vaccines were *Haemophilus influenzae* type b (22%) and hepatitis B (18%) vaccines; among persons 19 to 49 years of age, smallpox vaccine

Table 1
Reported cases of myopericarditis, general characteristics by age group, 1990–2018.

	0 to 18 years n = 99 (%)	19 to 49 years n = 490 (%)	50 + years n = 85 (%)	Unreported n = 34 (%)	Total N = 708 (%)
Sex					
Male	55 (56)	439 (90)	42 (49)	23 (68)	559 (79)
Female	44 (44)	51 (10)	43 (51)	7 (21)	145 (20)
Unreported	0 (0)	0 (0)	0 (0)	4 (12)	4 (1)
Seriousness*					
Non-serious	5 (5)	184 (38)	13 (15)	19 (56)	221 (31)
Serious, non-death	40 (40)	294 (60)	63 (74)	15 (44)	412 (58)
Serious, death	54 (55)	12 (2)	9 (11)	0 (0)	75 (11)
Diagnosis**					
Both MMWR definition and MD	54 (55)	293 (60)	39 (46)	8 (24)	394 (56)
MMWR only	20 (20)	45 (9)	21 (25)	4 (12)	90 (13)
MD only	25 (25)	152 (31)	25 (29)	22 (65)	224 (32)
Time to onset, days					
≤7	46 (46)	111 (23)	49 (58)	3 (9)	209 (30)
8 to 14	15 (15)	263 (54)	8 (9)	14 (41)	300 (42)
15 to 29	8 (8)	62 (13)	13 (15)	1 (3)	84 (12)
≥30	14 (14)	20 (4)	4 (5)	1 (3)	39 (6)
unreported	16 (16)	34 (7)	11 (13)	15 (44)	76 (11)

* Serious defined as death, life-threatening illness, hospitalization or prolongation of existing hospitalization, permanent disability, or a congenital anomaly or birth defect. [12].
** Case definition from published analysis [ref]; MD = clinical diagnosis by a physician.

Table 2
Most frequently reported vaccines among myopericarditis reports, by age.

	Age group, years (%)				
Vaccine*	0-18 n = 99	19–49 n = 490	≥50 n = 85	Not reported n = 34	Total N = 708
Smallpox	6 (6)	387 (79)	4 (5)	19 (56)	416 (59)
Anthrax	5 (5)	151 (31)	1 (1)	6 (18)	163 (23)
Typhoid	3 (3)	83 (17)	2 (2)	2 (6)	90 (13)
Influenza, inactivated	11 (11)	33 (7)	31 (36)	2 (6)	77 (11)
Hepatitis B	18 (18)	17 (3)	3 (4)	3 (9)	41 (6)
Influenza, not specified	3 (3)	22 (4)	13 (15)	2 (6)	40 (6)
Tdap**	9 (9)	17 (3)	3 (4)	1 (3)	30 (4)
Influenza, live attenuated	3 (3)	22 (4)	0 (0)	3 (9)	28 (4)
Hepatitis A	12 (12)	9 (2)	1 (1)	3 (9)	25 (4)
Varicella	16 (16)	6 (1)	0 (0)	2 (6)	24 (3)
Haemophilus influenzae type b	22 (22)	0 (0)	0 (0)	0 (0)	22 (3)
Zoster, live attenuated	0 (0)	0 (0)	19 (22)	2 (6)	21 (3)
MMR**	13 (13)	7 (1)	0 (0)	0 (0)	20 (3)
4-valent HPV**	16 (16)	3 (1)	0 (0)	0 (0)	19 (3)
DTaP**	14 (14)	2 (0)	1 (1)	1 (3)	18 (3)
Meningococcal conjugate	14 (14)	2 (0)	0 (0)	2 (6)	18 (3)
Polio, inactivated	11 (11)	4 (1)	0 (0)	1 (3)	16 (2)
Pneumococcal polysaccharide	1 (1)	8 (2)	4 (5)	0 (0)	13 (2)
Pneumococcal conjugate, 7-valent	12 (12)	0 (0)	0 (0)	0 (0)	12 (2)
Pneumococcal conjugate, 13-valent	7 (7)	1 (0)	3 (4)	1 (3)	12 (2)

* Counts not mutually exclusive; in descending order of overall reports.
** Tdap = combined tetanus and diphtheria toxoid, acellular pertussis vaccine MMR = combined measles, mumps, and rubella vaccine; HPV = human papillomavirus vaccine; DTaP = combined diphtheria and tetanus toxoid, acellular pertussis vaccine.

(79%) was most frequently reported; and among persons 50 years of age and older IIV (36%) and live attenuated zoster (22%) vaccines were most frequently reported.

Of vaccines administered alone, the most frequently reported vaccines were smallpox (53%) and IIV (12%) vaccines (Table 3). By age, among persons 18 years of age and younger, the most frequently reported vaccines were 4-valent human papillomavirus (HPV) (25%) and hepatitis B (13%) vaccines; among persons 19 to 49 years of age, smallpox vaccine (71%) was most frequently reported; and among persons 50 years of age and older IIV (38%) and live attenuated zoster (23%) vaccines were most frequently reported.

Of the 708 identified reports of myopericarditis, 138 (19%) described signs or symptoms of influenza-like illness up to 42 days prior to symptom onset for myopericarditis. Reported median age was 24 years (range: 0 to 90 years); 101 (73%) reported persons were male, and 37 (27%) were female. Of these 138 reports, 129 reports were serious, including 31 (24%) reports where the patient died; 21 (68%) of these reported deaths had histologic evidence of myopericarditis on autopsy. Reported median time to symptom onset was 8 days after vaccination (range: 0 to 1,025 days). When excluding these 138 reports from consideration, the most frequently reported vaccines – both administered with other vaccines and administered alone – the order of vaccines most commonly reported did not change appreciably (Tables 4 and 5).

We identified 75 reports of myopericarditis in which the patient died. Median reported age was 7 years (range: 0 to 80 years); 40 reported patients were male, and 35 were female. Median time to onset of myopericarditis was 6 days after vaccination (range: 0 to 571 days). In 60 (80%) reports, myopericarditis could be attributed to other known causes (e.g., viral infection, disseminated bacterial infection, systemic lupus erythematosus), including 45 of 54 (83%) reported deaths among patients aged 0 to 18 years (Table 1). Of the remaining 15 reports, the reported vaccines reflected recommended vaccines for the patient's age: among 5 reports describing patients < 1 year of age, 4 received vaccines containing diphtheria and tetanus toxoids, and acellular pertussis antigen , and 3 received pneumococcal conjugate vaccines (2 received the

Table 3
Most frequently reported vaccines administered alone among myopericarditis reports, by age.

	Age group, years (%)				
Vaccine*	0-18 n = 40	19-49 n = 307	≥50 n = 77	Not reported n = 25	Total n = 449
Smallpox	2 (5)	219 (71)	4 (5)	13 (52)	238 (53)
Influenza, inactivated	4 (10)	19 (6)	29 (38)	0 (0)	52 (12)
Zoster, live attenuated	0 (0)	0 (0)	18 (23)	2 (8)	20 (4)
Anthrax	1 (3)	16 (5)	1 (1)	0 (0)	18 (4)
Influenza, not specified	1 (3)	4 (1)	10 (13)	2 (8)	17 (4)
Tdap**	1 (3)	12 (4)	2 (3)	1 (4)	16 (4)
Hepatitis B	5 (13)	6 (2)	2 (3)	0 (0)	13 (3)
4-valent HPV**	10 (25)	1 (0)	0 (0)	0 (0)	11 (2)
Influenza, live attenuated	1 (3)	7 (2)	0 (0)	1 (4)	9 (2)
Hepatitis A	1 (3)	3 (1)	1 (1)	1 (4)	6 (1)
Meningococcal conjugate	4 (10)	1 (0)	0 (0)	1 (4)	6 (1)
Varicella, live attenuated	3 (8)	2 (1)	0 (0)	1 (4)	6 (1)
MMR**	3 (8)	2 (1)	0 (0)	0 (0)	5 (1)
Pneumococcal conjugate, 13-valent	0 (0)	1 (0)	3 (4)	1 (4)	5 (1)

* Counts in descending order of overall reports.
** Tdap = combined tetanus and diphtheria toxoid, acellular pertussis vaccine; HPV = human papillomavirus vaccine; MMR = combined measles, mumps, and rubella vaccine.

Table 4
Most frequently reported vaccines among myopericarditis reports, excluding recent illness, by age.

	Age group, years (%)				
Vaccine*	0-18 n = 63	19-49 n = 409	≥50 n = 63	Not reported n = 35	Total n = 570
Smallpox	5 (8)	345 (84)	4 (6)	18 (51)	372 (65)
Anthrax	3 (5)	117 (29)	1 (2)	6 (17)	127 (22)
Typhoid	2 (3)	71 (17)	1 (2)	2 (6)	76 (13)
Influenza, inactivated	7 (11)	23 (6)	26 (41)	1 (3)	57 (10)
Influenza, not specified	0 (0)	18 (4)	7 (11)	6 (17)	31 (5)
Hepatitis B	11 (18)	12 (3)	2 (3)	2 (6)	27 (5)
Tdap**	8 (13)	6 (2)	3 (5)	4 (11)	21 (4)
Influenza, live attenuated	1 (2)	15 (4)	0 (0)	2 (6)	18 (3)
Hepatitis A	8 (13)	6 (2)	1 (2)	2 (6)	17 (3)
Zoster, live attenuated	0 (0)	0 (0)	14 (22)	2 (6)	16 (3)
4-valent HPV**	12 (19)	3 (1)	0 (0)	0 (0)	15 (3)
MMR**	8 (13)	6 (2)	0 (0)	0 (0)	14 (3)
Haemophilus influenzae type b	13 (21)	0 (0)	0 (0)	0 (0)	13 (2)
Meningococcal conjugate	10 (16)	2 (1)	0 (0)	1 (3)	13 (2)
DTaP**	9 (14)	0 (0)	0 (0)	3 (9)	12 (2)

* Counts not mutually exclusive; in descending order of overall reports; excludes reports describing people with documented flu-like symptoms (including gastrointestinal symptoms) prior to vaccination, and within 30 days of symptom onset.
** Tdap = combined tetanus and diphtheria toxoid, acellular pertussis vaccine HPV = human papillomavirus vaccine; MMR = combined measles, mumps, and rubella vaccine; DTaP = combined diphtheria and tetanus toxoid, acellular pertussis vaccine.

Table 5
Most frequently reported vaccines administered alone among myopericarditis reports, excluding recent illness, by age.

	Age group, years (%)				
Vaccine*	0-18 n = 25	19-49 n = 262	≥50 n = 58	Not reported n = 26	Total, n = 371
Smallpox	2 (8)	208 (79)	4 (7)	12 (46)	226 (61)
Influenza, inactivated	2 (8)	12 (6)	23 (40)	0 (0)	37 (10)
Zoster, live attenuated	0 (0)	0 (0)	13 (22)	2 (8)	15 (4)
Anthrax	0 (0)	11 (4)	1 (2)	0 (0)	12 (3)
Influenza, not specified	0 (0)	1 (0)	6 (10)	5 (19)	12 (3)
4-valent HPV**	9 (36)	1 (0)	0 (0)	0 (0)	10 (3)
Tdap	1 (4)	4 (2)	2 (3)	3 (12)	10 (3)
Hepatitis B	2 (8)	5 (2)	2 (3)	0 (0)	9 (2)
Influenza, live attenuated	0 (0)	4 (2)	0 (0)	1 (4)	5 (1)
Hepatitis A	1 (4)	2 (1)	1 (2)	0 (0)	4 (1)
Meningococcal conjugate	2 (8)	1 (0)	0 (0)	1 (4)	4 (1)

* Counts in descending order of overall reports.
** HPV = human papillomavirus vaccine.

13-valent vaccine, 1 received the 7-valent vaccine); among 4 reports describing patients 12 to 18 years of age, 2 received meningococcal conjugate vaccines, 1 received 4-valent HPV vaccine, and another received monovalent mumps vaccine; among 6 reports describing patients 19 years of age and older, 2 received smallpox vaccine, 2 received influenza vaccine (not specified), 1 received IIV, and 1 received live attenuated zoster vaccine.

3.2. Estimated reporting rates

During 2014 through 2018, myopericarditis after smallpox vaccine was reported to VAERS at an estimated rate of 4.0 per 1,000 doses distributed. Regardless of age group, estimated median reporting rates of myopericarditis during 2014 through 2018 after influenza vaccine (all types) was < 0.1 per 1,000,000 doses administered.

3.3. Disproportionality analysis

Disproportionality analysis identified an elevated EB05 (≥2.0) for smallpox vaccine and the myopericarditis-related PTs of "Myocarditis", "Pericardial disease", "Pericardial effusion", and "Pericarditis". An EB05 ≥ 2.0 was found for anthrax vaccine and the PTs "Myocarditis", "Pericardial disease", and "Pericarditis"; most patients (95%) received a concomitant smallpox vaccine. An EB05 ≥ 2.0 was also identified for typhoid vaccine and the PT "Pericardial disease"; review of these typhoid vaccine reports revealed that all patients received smallpox vaccine concomitantly with typhoid vaccine. No other product-specific vaccine had an EB05 ≥ 2.0 for any myopericarditis-related PT.

4. Discussion

We performed a comprehensive review of post-licensure vaccine surveillance data on myopericarditis, using both a published case definition [14] and review of medical records to identify such reports. Smallpox vaccine remained the most commonly reported vaccine, while other reported vaccines were consistent with vaccine types recommended for the given age group of the patient and therefore might reflect relative frequencies of vaccine exposures per recommended schedules for vaccination [17,18]. Myopericarditis remained a rarely reported AE after vaccines (0.1% of reported AEs during the analytic period), and this analysis revealed no new or unexpected safety concerns.

Distribution of reports by sex was similar to previous case series among hospitalized pediatric and adult patients (Table 1). A case series describing myocarditis among children and adolescents 18 years of age and younger found a comparable proportion (57%) of cases among males [19], but a case series among adults hospitalized in a group of Finnish hospitals found a preponderance of cases among males<55 years of age [20]. A potential explanation for these differences by sex and age remains elusive, although findings in studies with BALB/c mouse models of acute coxsackievirus-induced myocarditis suggest possible biologic mechanisms [21,22]. The patients in both case series would be considered serious by definition (due to hospitalization); likewise, a large proportion of serious reports were observed in the VAERS data.

Reported case fatality after acute myocarditis among pediatric patients has been reported around 8% to 12% [23,24]. The high proportion of deaths reported among persons 18 years of age and younger in this analysis (Table 1) would seem unusual. However, biased reporting to VAERS can occur, and deaths after vaccination among otherwise healthy young people might be more prone to report compared to deaths among older or less healthy populations [10]. Conversely, younger persons (such as children) who experience mild myopericarditis might not be reported to VAERS; such lack of reporting would skew the proportion of reported deaths among this population. These and other limitations of VAERS will be discussed shortly.

The high proportion of reported myopericarditis after smallpox vaccine (Tables 2 and 3) likely reflects the known association between myopericarditis and smallpox vaccine [2,14], which is also reflected in the disproportionality analysis results. The preponderance of myopericarditis after smallpox vaccine reported among people 19 to 31 years of age (predominately male) in this analysis is consistent with smallpox vaccination among selected military personnel [25]. Indeed, during the analytic period, the military conducted active surveillance (and subsequent reporting to VAERS) of myopericarditis after smallpox vaccine [26]. Despite this potential simulated reporting, the most frequently reported vaccines, by age range, would not vary after discounting smallpox vaccine (Tables 3 and 4) (except among people 19–49 years of age). Disproportionate reporting of anthrax and typhoid vaccines and myopericarditis-related PTs likely reflect coadministration with smallpox vaccine, as was common practice in the military during the analytic period [26].

During 2008–2018, ACAM2000® was the smallpox vaccine in use (prior to 2008, Dryvax® was the smallpox vaccine used). Myopericarditis after ACAM2000 has been reported at rate of 5.7 per 1,000 doses administered [27]. A rate of 6.9 per 1,000 doses administered has been reported among people receiving their first dose of ACAM2000 [28]. The estimated reporting rate of myopericarditis we observed after smallpox vaccine during 2014–2018 (4.0 per 1,000 doses distributed) is comparable to these rates.

Other vaccines after which myopericarditis was reported largely reflect recommended vaccination schedules for people in the corresponding age groups [15,16]. Myopericarditis has not been described previously after hepatitis B, *Haemophilus influenzae* type b, 9-valent HPV, or live attenuated zoster vaccines that were licensed for use in the United States, and only sparse case reports describe myocarditis after inactivated influenza and diphtheria, tetanus, and inactivated polio vaccines [9,29,30]. Myopericarditis has been reported after 4-valent HPV vaccine [31]. Of interest, myopericarditis is commonly caused by viral infections, [1] including varicella zoster virus [32]. Discounting smallpox vaccine, myopericarditis after live attenuated viral vaccines was reported infrequently (Tables 2 and 3), a result consistent with a past report describing no increased risk of myopericarditis after live attenuated virus vaccines (except smallpox vaccine) [7]. Together, these observations suggest that – aside from smallpox vaccine – myopericarditis after vaccines licensed for use in the United States is rare. As noted in the below paragraph, these reports do not establish a causal relationship between vaccines and myopericarditis.

VAERS is a passive surveillance system that gathers reports from across the United States, and can detect rare events [10], like myopericarditis, after vaccination. VAERS also shares the limitations of passive surveillance systems: under-reporting, reporting biases, inconsistent data quality and completeness, changes in reporting over time, and lack of an unvaccinated comparison group [10,13]. These limitations generally do not allow VAERS data to determine if a vaccine caused a particular adverse event, including myopericarditis or death. Also, because doses administered data were not available, we used doses distributed as the denominator in estimating reporting rates after smallpox vaccine. That our estimates (4.0 per 1,000 doses distributed) are comparable to known rates of myopericarditis after smallpox vaccine (5.7 per 1,000 doses administered) is reassuring. Also reassuring is the confirmation of the known association between smallpox vaccine and cardiac-related PTs on disproportionality analysis (EB05 > 2).

Given that smallpox vaccine continues to be administered to selected military and civilian personnel [25,33] and that new vaccines continue to be approved for use, continuing surveillance for myopericarditis after vaccination is warranted. However, this analysis revealed no unexpected safety concerns, and reports of myopericarditis after vaccines remain rare.

5. Note

This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

6. Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC), or the US Food and Drug Administration (FDA). Mention of a product or company name does not constitute endorsement by the CDC or FDA.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.12.046.

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