HHS Public Access

Author manuscript

Vaccine. Author manuscript; available in PMC 2022 February 25.

Published in final edited form as:

Vaccine. 2018 July 05; 36(29): 4369–4374. doi:10.1016/j.vaccine.2018.04.038.

Adverse events following vaccination with an inactivated, Vero cell culture-derived Japanese encephalitis vaccine in the United States, 2012–2016

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Abstract

Background: In March 2009, the U.S. Food and Drug Administration licensed an inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC [IXIARO®]) for use in persons aged ≥17 years. In 2013, licensure was extended to include children aged ≥2 months. A previous analysis reviewed adverse events reported to the U.S. Vaccine Adverse Event Reporting System (VAERS) from May 2009 through April 2012.

Methods: We reviewed adverse events reported to VAERS following JE-VC administered from May 1, 2012 through April 30, 2016. Adverse event reporting rates were calculated using 802,229 doses distributed.

Results: During the 4-year period, 119 adverse event reports were received for a reporting rate of 14.8 per 100,000 doses distributed. Nine (8%) adverse events were classified as serious for a reporting rate of 1.1 per 100,000 distributed. The most commonly reported event was hypersensitivity (n=24; 20%) for a rate of 3.0 per 100,000 doses distributed; 1 anaphylaxis event was reported. Ten (8%) neurologic events were reported for a rate of 1.2 per 100,000 doses distributed; 2 events were classified as seizures. Sixty-three (53%) adverse events occurred after a first dose of JE-VC. Eighty (67%) adverse events occurred after administration of JE-VC with other vaccines. Eleven (9%) adverse events were reported in children; 1 was considered serious.

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Contributions

WLW and IBR participated in study design, data acquisition and analysis, interpretation of findings, and manuscript preparation. ERM participated in data acquisition and manuscript preparation. SLH and MF participated in interpretation of findings and manuscript preparation. All authors have approved the final version of the manuscript for journal submission.

Authorship statement

All authors attest they meet the ICMJE criteria for authorship.

Conflict of interest

Declarations of interest: none.

Conclusions: These data continue to support the generally favorable safety profile of JE-VC. Reporting rates of adverse events were similar to those of the previous analysis. Although reporting rates of adverse events in children could not be calculated, there were low numbers of reported events in this age group. Post-licensure adverse event surveillance for this relatively new vaccine continues to be important to monitor adverse event reporting rates and identify possible rare serious events.

Keywords

Adverse event; children; Japanese encephalitis; vaccine; VAERS

1. Introduction

Japanese encephalitis (JE) virus, a mosquito-borne flavivirus, is the most common cause of vaccine-preventable encephalitis in Asia [1]. Less than 1% of persons infected with JE virus develop encephalitis. However, among patients with encephalitis, 20–30% die and 30–50% of survivors have persistent neurologic or psychiatric sequelae [1,2]. For most travelers to endemic areas, the risk for JE is very low but varies depending on destination, duration, season, and activities [3]. Therefore, recommendations for use of JE vaccine are targeted to travelers at increased risk of exposure based on their planned travel itinerary [4,5].

In March 2009, the U.S. Food and Drug Administration (FDA) licensed an inactivated Vero cell culture-derived vaccine (JE-VC [IXIARO®]) for use in adults aged ≥17 years [6]. In May 2013, FDA extended the licensure to include children aged 2 months through 16 years [5]. JE-VC is given in a two-dose primary series administered 28 days apart. For adults aged ≥17 years, a booster dose may be given if the primary series was administered >1 year earlier [7].

JE-VC has had a generally favorable safety profile [8–13]. From 2009–2012, a total of 42 adverse events were reported to the U.S. Vaccine Adverse Events Reporting System (VAERS) following administration of JE-VC in adults aged ≥17 years [13]. Five of the reports were classified as serious. There were 12 reported hypersensitivity events but none were anaphylaxis. The rate of neurologic events was higher than that reported for the previously available mouse brain-derived JE vaccine (JE-MB), and authors advised continued monitoring in particular for this type of adverse event [13,14]. At the time of the earlier VAERS analysis, JE-VC was not licensed for use in children. To date, limited safety data from pediatric clinical trials and surveillance have shown a generally good safety profile [5,10,11,15]. We analyzed adverse events reported to VAERS following administration of JE-VC during the 4 years since the previous analysis, including the 3 years following licensure in children.

2. Methods

2.1. VAERS

VAERS is a national passive surveillance system for monitoring adverse events following immunization (AEFI) [16,17]. VAERS is co-administered by the U.S. Centers for Disease

Control and Prevention (CDC) and FDA. Vaccine manufacturers, healthcare providers, and vaccine recipients submit reports using a standardized form that includes data on patient demographics, vaccination(s), and adverse events. VAERS administrators assign Medical Dictionary for Regulatory Activities (MedDRA) codes to the reported adverse events and obtain medical records for any event reported as serious. For individual VAERS reports, the causal relationship between vaccination and reported events cannot usually be determined.

2.2. Case definitions and classifications

We reviewed adverse events reported following JE-VC administered from May 1, 2012 through April 30, 2016, either in the United States or to U.S. military personnel. We included reports received by VAERS as of April 30, 2017. Onset interval was calculated from the time of JE-VC administration to onset of the first adverse event symptom. Events were excluded if the onset interval was >60 days (n=1, a report of aplastic anemia occurring 81 days after administration), a local reaction occurred in the arm contralateral to the site of JE-VC administration (n=10), a report was submitted but no adverse event occurred (n=6), or symptoms were clearly related and unique to another vaccine (n=1).

A serious adverse event was defined according to the FDA regulatory definition (21 CFR 600.80) as life-threatening or resulting in death, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability, a congenital anomaly, or another medically important condition [18]. Adverse events were classified as anaphylaxis if they met level 1 or level 2 diagnostic certainty using the Brighton Collaboration case definition, and occurred within 2 hours of vaccination [19]. An adverse event report was classified as a hypersensitivity reaction if any of the major or minor dermatologic, mucosal, or respiratory criteria of the Brighton Collaboration case definition for anaphylaxis were present and occurred within 14 days of vaccination. Hypersensitivity reactions were classified as “immediate” if onset interval was <2 hours and “delayed” if onset interval was 2 hours to 14 days after vaccination. Reports were classified as central neurologic events if they met level 1 or level 2 diagnostic certainty of the Brighton Collaboration case definitions for aseptic meningitis, encephalitis, myelitis, acute disseminated encephalomyelitis (ADEM), Guillain-Barré syndrome (GBS), or generalized seizure [20–23]. Events characterized by neurologic features but without established Brighton Collaboration case definitions were reviewed by a medical panel and classified as central or peripheral neurologic events.

2.3. Data collection and analysis

VAERS reports and available medical records were reviewed. The incidence of adverse events per 100,000 vaccine doses distributed during the 4-year period was calculated for total, serious, hypersensitivity, and neurologic events. According to the manufacturer (Valneva Austria GmbH), a total of 802,229 JE-VC doses were distributed to the U.S. private market and military from May 1, 2012 through April 30, 2016. Data were not available regarding the number of doses administered, or the age or sex of vaccine recipients and could not reliably be estimated.

3. Results

3.1. AEFI following administration of JE-VC

During the 4-year period, 119 adverse events following receipt of JE-VC were reported to VAERS, for an overall rate of 14.8 adverse events per 100,000 doses distributed (Table 1). Seventy-three (61%) of the events occurred in males and the median age was 29 years (range: 5–79) (Table 2). Eleven events occurred in children aged <17 years and 54 in military personnel or their dependents. Event onset was a median of 1 day (range 0–38 days) after JE-VC administration. Sixty-three (53%) events occurred after a first dose, 26 (22%) after a second dose, and 10 (8%) after >2 doses of JE-VC.

In 39 (33%) of the 119 reports, JE-VC was the only vaccine administered (Table 2). Among the remaining 80 reports, a median of 2 additional vaccines (range 1–7) were administered concurrently. The most common concurrently administered vaccines included typhoid (n=43), rabies (n=23), anthrax (n=23), hepatitis A (n=11), smallpox (n=10), yellow fever (n=10), and tetanus containing vaccines (n=10). The median age was higher for persons receiving JE-VC alone (Table 3). The median onset interval and sex distribution did not differ significantly for adverse events following JE-VC administered alone or with other vaccines.

3.2. Classification of AEFI

Of the 119 AEFI reported to VAERS, 9 (8%) were classified as serious and 110 (92%) as non-serious (Table 1). Twenty-four (20%) AEFI were classified as hypersensitivity events and 10 (8%) as neurologic events. There were 85 non-hypersensitivity, non-neurologic events; 6 were classified as serious. Of the remaining 79 non-serious events, 23 were local reactions and the other 56 were primarily characterized by rash (n=16), headache (n=13), dizziness (n=11), nausea (n=10), pyrexia (n=8), syncope (n=8), vomiting (n=6), hyperhidrosis (n=6), fatigue (n=4), or tremor (n=4).

3.2.1. Serious adverse events—Nine (8%) AEFI were classified as serious for a reporting rate of 1.1 per 100,000 doses distributed (Table 1). Six (67%) of 9 occurred in males, and the median age was 23 years (range 15–75) (Table 2). For events with recorded dose number, 3 (60%) occurred after the first dose of JE-VC, 1 after the second dose, and 1 after the fifth dose. The single reported death occurred in a 42 year-old male who received only JE-VC and died following cardiovascular collapse, 8 days after vaccine administration (Table 4). Autopsy determined the cause of death as sudden cardiac death due to ischemic heart disease. The remaining 8 serious AEFI occurred following administration of JE-VC and other vaccines concurrently. Three events met criteria for anaphylaxis (n=1), immediate hypersensitivity (n=1), or central neurologic event (n=1) and are discussed below. The other 5 patients had neither hypersensitivity nor neurologic events (Table 4).

3.2.2. Hypersensitivity events—Overall, 24 (20%) AEFI were classified as hypersensitivity events for a rate of 3.0 per 100,000 doses distributed (Table 1). Fifteen (63%) events were reported in males and median age was 27 years (range 5–65). Of the 22 reports with JE-VC dose number listed, 16 (67%) occurred after a first dose of

JE-VC, 4 (17%) after a second dose, and 2 (9%) after >2 doses. Fifteen (63%) events occurred after administration of JE-VC with other vaccines. There was 1 (4%) anaphylaxis, 7 (29%) immediate hypersensitivity, and 15 (63%) delayed hypersensitivity events; 1 event occurred within 1 day after administration but lacked more specific timing data to classify as immediate or delayed hypersensitivity. Two hypersensitivity events, 1 anaphylaxis and 1 immediate, were classified as serious (Table 4).

The serious anaphylaxis event occurred in a 19 year-old female after concurrent administration of anthrax, typhoid, and yellow fever vaccines. The patient was treated in the emergency department with intravenous fluids, epinephrine, corticosteroid, and antihistamine, and discharged home. The serious immediate hypersensitivity event occurred in a 23 year-old male with generalized erythema, wheezing, and seizure-like activity after receiving a fifth dose of JE-VC, together with anthrax and typhoid vaccines (Table 4). He was treated with epinephrine and antihistamine and recovered.

Of the 6 non-serious immediate hypersensitivity events, 3 occurred in males and the median age was 32 years (range 15–65) (Table 5). The median time to onset was 80 minutes (range 5–90). Five (83%) events occurred after a first dose of JE-VC, and 1 of those was after receiving JE-VC alone. The predominant clinical features of the 6 events were sensation of throat closure (n=1), hoarseness (n=1), generalized pruritus without skin rash (n=1), difficulty breathing without wheeze or stridor (n=2), and generalized erythema with difficulty breathing without wheeze or stridor (n=1).

Of the 15 non-serious delayed hypersensitivity events, 10 (67%) occurred in males and the median age was 22 years (range 5–52). The median time to onset was 1 day (range 0–8). Ten events (67%) occurred after a first dose of JE-VC. JE-VC was the only vaccine administered in 3 (30%) of these events. The predominant clinical features of these 15 events were generalized pruritus with skin rash (n=7), generalized urticaria (n=4), generalized pruritus without skin rash (n=1), generalized angioedema (n=1), swollen and itchy eyes (n=1), and facial swelling with sensation of throat closure (n=1).

3.2.3. Neurologic events—There were 2 central neurologic events, both seizures, for a reporting rate of 0.2 per 100,000 doses distributed (Table 1). One was classified as serious and occurred in a 15 year-old male 1 week after receiving a second dose of JE-VC and third dose of rabies vaccine (Table 4). According to the parent's report, the boy had partial and grand mal seizures. Retrospectively, the parents also described an undiagnosed and unreported possible complex partial seizure after administration of his first dose of JE-VC, administered concurrently with yellow fever, rabies, and typhoid vaccines approximately 1 month earlier. He had no prior history of seizures. Blood tests, imaging, and an electroencephalogram did not reveal any abnormality. One year later, the child was reported to be on medication for ongoing seizure activity and anxiety. The second, non-serious, seizure event occurred in a 19 year-old male after concurrent administration of JE-VC, influenza, polio, typhoid, and yellow fever vaccines. This was a tonic-clonic seizure lasting 1–1.5 minutes, associated with loss of consciousness and apnea. The patient was taken to the emergency department but not hospitalized. No events met case definitions for aseptic meningitis, encephalitis, myelitis, ADEM, or GBS.

There were 8 peripheral neurologic events for a reporting rate of 1.0 per 100,000 doses distributed (Table 1). All 8 were non-serious. Four (50%) occurred in males and the median age was 34 years (range 15–79) (Table 5). Events occurred a median of 2 days (range 0–16) after JE-VC administration. Three peripheral neurologic events occurred after a first dose of JE-VC and 4 occurred after a second dose of JE-VC. Four events (50%) occurred after administration of JE-VC concurrently with other vaccines. Peripheral neurologic events included paresthesias (n=6), somatosensory symptoms (n=1), and sensorineural hearing loss (n=1). The 6 paresthesia events occurred in persons with a median age of 37 years (range 24–79) and median onset interval of 2 days (range 0–16). The somatosensory symptoms were reported in a 15 year-old female with fever, body aches, and increased skin sensitivity following JE-VC and rabies vaccines. The report of sensorineural hearing loss occurred in a 32 year-old male with acute onset of unilateral hearing loss 3 days after receiving JE-VC; the audiogram in the affected ear was abnormal but MRI was normal.

3.3 AEFI in the pediatric age group

Among the 11 events reported in children aged <17 years, 6 (55%) occurred in males, and the median age was 13 years (range 5–16). Nine (81%) events occurred after receiving JE-VC with other vaccines. Seven (64%) events occurred after a first dose of JE-VC. The only serious event occurred in the 15 year-old with generalized seizures, described above. One immediate hypersensitivity event occurred in a 15 year-old male and was characterized by urticaria and difficulty breathing after concurrent administration of JE-VC and rabies vaccine. There were 3 delayed hypersensitivity event reports. The first was generalized angioedema in a 5 year-old female with onset 8 days after administration of JE-VC alone. The second and third were reports of generalized pruritus with skin rash reported in a 9 year-old female and her 6 year-old male sibling, both with history of allergies, and both following receipt of rabies and typhoid vaccines in addition to JE-VC. The single peripheral neurologic event in a 15 year-old girl is described above. The 5 non-hypersensitivity, non-neurologic events included reports of thyroiditis (n=1), disorientation (n=1), vomiting and upper abdominal pain (n=1), fever and pain in legs (n=1), and syncope with abdominal pain, rash, and pruritus (n=1).

3.4 AEFI in military personnel

Among the 54 AEFI reported in military personnel or their dependents, 34 (63%) events occurred following JE-VC administered with other vaccines. The most commonly co-administered vaccines included anthrax (n=22), typhoid (n=22), and smallpox (n=8). The majority of military reports were among males (43/54, 80%) while the majority of civilian reports were among females (35/65, 54%). The median age of vaccinees in military reports (32 years) was higher than that of civilians (25 years).

4. Discussion

From 2012–2016, >800,000 doses of JE-VC were distributed and 119 adverse events following JE-VC administration were reported to VAERS, including 11 events in children aged <17 years. The overall rate of 14.8 adverse events per 100,000 doses distributed remained stable compared to the initial 3 years following licensure (15.2 per 100,000) [13].

The rate was also similar to or lower than the 15.0 and 23.7 adverse events per 100,000 doses distributed reported to VAERS for the previously available mouse brain-derived JE vaccine (JE-MB) [14,24]. The majority of reports were non-serious and no unexpectedly high reporting rates for specific events were identified.

This is the first analysis of AEFI reported to VAERS since licensure of JE-VC for use in children aged <17 years. Eleven events in children were reported with 1 classified as serious. The types of adverse events reported in children were comparable to those in adult vaccinees. The low number of reported adverse events are reassuring but the lack of age-specific vaccine administration data precludes calculation of reporting rates among children. Although other vaccine safety and medical databases possibly could be used to estimate incidence rates, given the total number of doses distributed, a small number of doses administered would be expected, particularly for children. Therefore, although these VAERS data generally concur with vaccine safety monitoring data from>1,400 children who received JE-VC during pre-licensure clinical trials [5,11,25], additional post-marketing evaluation is warranted as more children receive the vaccine.

Overall, the rate of serious AEFI (1.1 per 100,000 doses distributed) was similar to those previously reported for JE-VC and JE-MB (both 1.8 per 100,000 doses distributed) [13,18]. Of the 9 serious events, 8 (89%) occurred following receipt of 1 or more vaccines in addition to JE-VC. The only serious event reported after JE-VC alone was a fatal cardiovascular event that was attributed to underlying ischaemic heart disease. A large number of JE-VC doses are administered to U.S. military personnel and 45% of the adverse events were reported from this population. This explains our finding that the majority of reports were among male vaccinees, most of whom also received other vaccines, including less commonly administered and more reactogenic vaccines such as anthrax and smallpox [26,27].

The rate of hypersensitivity events (3.0 per 100,000 doses distributed) also was similar to previous reports for JE-VC (4.4 per 100,000 doses) and lower than reports for JE-MB (6.3–8.4 per 100,000 doses) [13,14,24,28]. Almost two-thirds of the hypersensitivity events occurred in patients administered multiple vaccinations concurrently raising the possibility of an association with a non-JE-VC vaccine. The rate of neurologic events (1.2 per 100,000 doses distributed) was comparable to the rate reported for the first 3 years post licensure (2.2 per 100,000 doses) [13]. However, the rate of central neurologic events (0.2 per 100,000 doses distributed) was lower than the previous VAERS analysis for JE-VC (1.1 per 100,000) and similar to the rate for JE-MB (0.3 per 100,000 doses distributed) [13,14]. This is reassuring as the comparatively higher rate found in the first VAERS analysis had raised some concerns. Both central neurologic events in this analysis were seizures and occurred after administration of JE-VC together with other vaccines. Although not statistically significant, the seemingly lower rate might also be due to a greater number of doses of JE-VC distributed (>800,000) compared to the previous analysis (>275,000) and waning of vigilance in reporting adverse events beyond the early post marketing period.

This analysis is subject to several limitations. VAERS is passive surveillance system, which is prone to underreporting, particularly for mild adverse events [16,17,29,30]. True rates of

adverse events could not be calculated because denominator data for overall and age- and sex-specific doses administered were not available. Finally, VAERS data cannot generally be used to determine causality, especially among persons who received multiple vaccines.

5. Conclusions

Our analysis continues to support the good safety profile of JE-VC in adults. However, since JE-VC has been licensed for only 3 years in children and the numbers of doses administered by age group is not known, post marketing surveillance should continue to identify serious adverse events, particularly in this age group. Healthcare providers and their patients should report suspected adverse events following vaccination with JE-VC to VAERS.

Acknowledgements

The authors thank the VAERS staff for their data collection efforts and Paige Lewis for assisting with supplemental data requests. The authors also thank medical panel reviewers Dan Pastula and Erin Staples.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention. Mention of a product or company name does not constitute endorsement by the CDC.

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Table 1

Number and reporting rate per 100,000 doses distributed of adverse events reported to VAERS following receipt of inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC), United States, May 2012–April 2016.[a]

	Serious		Non-serious		Total	
	No.	**(Rate)**	**No.**	**(Rate)**	**No.**	**(Rate)**
Hypersensitivity	2	(0.2)	22	(2.7)	24	(3.0)
Anaphylaxis	1	(0.1)	0	(0.0)	1	(0.1)
Immediate, non-anaphylaxis	1	(0.1)	6	(0.7)	7	(0.9)
Delayed	0	(0.0)	15	(1.9)	15	(1.9)
Neurologic	1	(0.1)	9	(1.1)	10	(1.2)
Central neurologic events	1	(0.1)	1	(0.1)	2	(0.2)
Peripheral neurologic events	0	(0.0)	8	(1.0)	8	(1.0)
All adverse events	9	(1.1)	110	(13.7)	119	(14.8)

[a]VAERS, Vaccine Adverse Event Reporting System

Table 2

Characteristics of serious and non-serious adverse events reported to VAERS following receipt of inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC), United States, May 2012–April 2016.[a]

	Serious (*N*=9)		Non-serious (*N*=110)		Total (*N*=119)	
	No.	(%)	No.	(%)	No.	(%)
Male sex	6	(67)	67	(61)	73	(61)
Age group						
<17 years	1	(11)	10	(9)	11	(9)
17–39 years	5	(56)	74	(67)	79	(66)
40–59 years	2	(22)	19	(17)	21	(18)
≥60 years	1	(11)	7	(6)	8	(7)
JE-VC vaccine dose						
First	3	(33)	60	(55)	63	(53)
Second	1	(11)	25	(23)	26	(22)
>2 doses	1	(11)	9	(8)	10	(8)
Unknown	4	(44)	16	(15)	20	(17)
JC-VC administration						
Alone	1	(11)	38	(35)	39	(33)
With other vaccines	8	(89)	72	(65)	80	(67)
Event classification						
Hypersensitivity	2	(22)	22	(20)	24	(20)
Neurologic	1	(11)	9	(8)	10	(8)
Other event	6	(67)	79	(72)	85	(71)

[a]VAERS, Vaccine Adverse Event Reporting System

Table 3

Characteristics of adverse events reported to VAERS following receipt of inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC) when administered alone or with other vaccines, United States, May 2012–April2016.[a]

	JE-VC administered alone (*N*=39)		JE-VC administered with other vaccines (*N*=80)	
	No.	**(%)**	**No.**	**(%)**
Male sex	23	(59)	50	(63)
Median age in years (range)[b]	32	(5–79)	26	(6–75)
Median time to onset in days (range)	1	(0–16)	1	(0–38)
Serious adverse events	1	(3)	8	(10)
JE-VC vaccine dose				
First	16	(41)	47	(59)
Second	11	(28)	15	(19)
>2 doses	6	(15)	4	(5)
Unknown	6	(15)	14	(18)
Event classification				
Hypersensitivity	9	(23)	15	(19)
Neurologic	4	(10)	6	(8)
Other event	26	(67)	59	(74)

[a] VAERS, Vaccine Adverse Event Reporting System

[b] P<0.05

Table 4

Serious adverse events reported to VAERS following receipt of inactivated Vero cell culture-derived Japanese encephalitis vaccine, United States, May 2012–April 2016.[a]

Event type	Days postadministration	Age (yrs)	Sex	Primary symptoms or condition	Concurrent vaccines[b]
Hypersensitivity					
Anaphylaxis	0	19	F	Localized angioedema, sensation of throat closure	Anthrax, typhoid, yellow fever
Immediate, non-anaphylaxis	0	23	M	Generalized erythema, seizure-like activity (loss of consciousness, loss of bladder control, muscle contractures, foaming at the mouth)	Anthrax, typhoid
Neurologic					
Central	7	15	M	Ongoing seizures	Rabies
Other					
Death	8	42	M	Sudden collapse, ischemic heart disease	None
Other	22	42	M	Cardiomyopathy	Anthrax, meningococcal, smallpox, typhoid
Other	12	21	M	Acute myocarditis, myocardial infarction, congestive heart failure	Smallpox
Other	24	19	F	Angina pectoris	Anthrax, smallpox, typhoid, varicella
Other	2	35	M	Systemic febrile reaction and acute vaccinia syndrome	Anthrax, smallpox
Other	7	75	F	Acute kidney injury, myopathy	Pneumococcal, typhoid

[a]VAERS, Vaccine Adverse Event Reporting System

Table 5

Characteristics of non-serious adverse events reported to VAERS following receipt of inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC), United States, May 2012–April 2016.[a]

	Hypersensitivity (N=21)[b]				Neurologic (N=9)					
	Immediate (N=6)		Delayed (N=15)		Central (N=1)		Peripheral (N=8)		Other (N=79)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Male sex (%)	3	(50)	10	(67)	1	(100)	4	(50)	48	(61)
Age group (%)										
<17 years	1	(17)	3	(20)	0	(0)	1	(13)	5	(6)
17–39 years	4	(67)	11	(73)	1	(100)	5	(63)	52	(66)
40–59 years	0	(0)	1	(7)	0	(0)	1	(13)	17	(22)
≥60 years	1	(17)	0	(0)	0	(0)	1	(13)	5	(6)
Median age in years (range)	32	(15–65)	22	(5–52)	19	(19–19)	34	(15–79)	28	(7–69)
Median time to onset (range)	80 mins	(5–90)	1 day	(0–8)	0 days	(0–0)	2 days	(0–16)	1 day	(0–38)
JE-VC vaccine dose (%)										
First	5	(83)	10	(67)	1	(100)	3	(38)	41	(52)
Second	0	(0)	3	(20)	0	(0)	4	(50)	17	(22)
>2 doses	0	(0)	1	(7)	0	(0)	1	(13)	7	(9)
Unknown	1	(17)	1	(7)	0	(0)	0	(0)	14	(18)
JC-VC administration (%)										
Alone	2	(33)	7	(47)	0	(0)	4	(50)	25	(32)
With other vaccines	4	(67)	8	(53)	1	(100)	4	(50)	54	(68)

[a] VAERS, Vaccine Adverse Event Reporting System

[b] Timing of 1 hypersensitivity event was ≤1 day but not otherwise specified and is not included