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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.

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.

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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 to 2012, a total of 42 adverse events were reported to the U.S. Vaccine Adverse Events Reporting System (VAERS) following

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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 h 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 h and "delayed" if onset interval was 2 h 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),

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.

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