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Adverse events following purified chick embryo cell rabies vaccine in the Vaccine Adverse Event Reporting System (VAERS) in the United States, 2006–2016

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To the editor

Rabies is a life-threatening disease, and the benefits of vaccination far outweigh the risks in persons exposed to the virus [1]. Two cell culture rabies vaccines are available for use in the United States: human diploid cell vaccine (HDCV, Imovax Rabies, Sanofi Pasteur), and purified chick embryo cell vaccine (PCECV, RabAvert, Novartis Vaccines and Diagnostics) [2]. These vaccines are indicated for post- and pre-exposure prophylaxis to prevent human rabies [2]. HDCV and PCECV were licensed by the Food and Drug Administration in 1980 and 1997, respectively [2]. A study of HDCV in the Vaccine Adverse Event Reporting System (VAERS) did not find any safety issue of concern [3]. A previous post-licensure study of PCECV in VAERS during 1997–2005 did not find any safety concern but no safety study has been done since 2005 [4]. We re-assessed the safety of this vaccine in VAERS during 1/1/2006–12/31/2015.

VAERS is a national vaccine safety passive surveillance system, co-administered by the Centers for Disease Control and Prevention (CDC) and Food and Drug Administration that receives reports of AEs following immunization [5]. Anyone, including healthcare providers, vaccine recipients, vaccine manufacturers, and other reporters, can report and adverse event (AE). Reports are submitted voluntarily either directly from individual reporters, who may be reporting for themselves or others, or secondarily from vaccine manufacturers, that also receive reports and in turn submit them to VAERS. Details about the VAERS system have been descried elsewhere [5]. Reports are classified as serious based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, or a congenital anomaly [5]. Signs and symptoms of AEs are coded by trained personnel and entered into a database using the Medical Dictionary for Regulatory Activities (MedDRA), a clinically validated, internationally standardized medical terminology [3,5]. A MedDRA code may also be designated as a MedDRA preferred term (PT).

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We analyzed U.S. VAERS reports received by September 30, 2017 for persons vaccinated with PCECV during January 1, 2006 through June 30, 2017. We excluded non-U.S. reports and duplicate reports. Physicians reviewed all reports and all available medical records for serious reports and for anaphylaxis, Guillain-Barré Syndrome (GBS), and pregnancy. We assessed for disproportionately higher reporting of AEs after PCECV compared with HDCV and with other inactivated vaccines in the VAERS database. For each MedDRA PT, we compared the proportion of PCECV reports with the PT with the proportion of HDCV or other inactivated vaccine reports with the PT using the proportional reporting ratio (PRR) and its 95% confidence interval (CI) using Evan's criteria [6]. We clinically reviewed those HDCV reports containing PTs which exceeded the data mining threshold noted above.

VAERS received 604 reports after PCECV; 42 (7.0%) were coded as serious. No deaths were reported. PCECV was the only vaccine listed in 495 (82.0%) reports. The three most frequent MedDRA PTs among all reports were headache (119; 19.7%), pyrexia (115; 19.0%), and nausea (111; 18.4%). These PTs were also predominantly noted among serious reports (Tables 1a and 1b).

The most frequent AE diagnostic category noted among non-death serious reports was general disorders and administration site conditions, which accounted for 19 (45.2%) reports. Nervous system disorders accounted for 10 reports which included two reports of encephalitis/encephalopathy, and one report each of Guillain-Barré Syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (Tables 1a and 1b). Two reports of anaphylaxis were identified.

One report of GBS in an 18-year-old female following the second dose of PCECV was reported. No history of a recent infection was provided. She presented difficulty walking and foggy thinking and was hospitalized for 3 days and upon improvement was discharged. A 58-year-old male received PCECV and Hep A Hep B (Twinrix) vaccines and 90 days later presented progressive weakness, predominately in upper extremities, later followed by swallowing difficulty and paroxysmal dyspnea. Electromyographic studies done during hospitalization showed demyelination with decreased conduction velocities. He was treated with intravenous immunoglobulin with improvement of symptoms. There was no history of a recent upper respiratory or gastro-intestinal infection. The patient was diagnosed with CIDP.

A 28-year-old pregnant woman received two doses of RabAvert following a bat bite. Patient was not aware she was pregnant at the time of vaccination. She experienced a miscarriage 20 days after the second dose.

Data mining analysis did not reveal disproportional reporting with any PT.

In this 10-year review of the safety of PCECV in VAERS, we found that the adverse events reported were consistent with a previous post-licensure study [4] and we did not observe any new or unexpected AEs. The vast majority of AEs were non-serious and already known to be associated with PCECV. The most common AEs reported were consistent with systemic reactions (e.g., headache, fever) described in pre-licensure studies and in the initial post-marketing surveillance review of PCECV in VAERS [2,4]. Additionally, data mining

analysis did not reveal disproportionate reporting of any AE. Some of the neurological conditions observed during the period of this review were similar (e.g. encephalitis) to those reported during the first review for this vaccine in 1997–2005 [4]. One report of PCECV administered to a pregnant woman was reported to VAERS. Pregnancy is not considered a contra-indication or precaution for post-exposure prophylaxis. Few studies have assessed the safety of rabies vaccines in pregnant women; these have not shown any increased rate of spontaneous abortion, preterm births or fetal abnormalities associated with exposure to rabies vaccines [2,3]. Pre-exposure prophylaxis may also be indicated during pregnancy if there is a high risk of exposure to rabies [2].

VAERS is useful for identifying rare AEs. Any safety concern or 'signal' should be studied in other systems or through the design of epidemiological studies [5]. VAERS is a spontaneous systems that has important limitations which include over- or under-reporting, biased reporting, and inconsistency in quality and completeness of reports [5]. VAERS generally cannot assess causality between an AE and receipt of a vaccine.

Our findings are reassuring. Most AEs were non-serious and have previously been described. There were no new or unexpected adverse events identified.

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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.

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Table 1a

Most frequent MedDRA PT codes after rabies vaccine (PCECV, RabAvert®) in serious[a] and non-serious reports in VAERS among person vaccinated January 1, 2006 through June 30, 2017.

MedDRA Preferred Term[b]	Serious (n = 42)	Non-serious (n = 562)	Total (n = 604)
	n (%)		
Headache	16 (38.1)	103 (18.3)	119 (19.7)
Pyrexia	9 (21.4)	106 (18.9)	115 (19.0)
Nausea	12 (28.6)	99 (17.6)	111 (18.4)
Dizziness	9 (21.4)	73 (13.0)	82 (13.6)
Pain	8 (19.0)	64 (11.4)	72 (11.9)
Arthralgia	11 (26.2)	56 (10.0)	67 (11.1)
Myalgia	8 (19.0)	56 (10.0)	64 (10.6)
Urticaria	2 (4.8)	53 (9.4)	55 (9.1)
Paraesthesia	7 (16.7)	47 (8.4)	54 (8.9)
Fatigue	8 (19.0)	45 (8.0)	53 (8.8)
Vomiting	7 (16.7)	46 (8.2)	53 (8.8)
Rash	3 (7.1)	47 (8.4)	50 (8.3)
Chills	5 (11.9)	44 (7.8)	49 (8.1)

[a]Reports are classified as serious based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, or a congenital anomaly.

[b]One report may contain more than one PT name; therefore percentages may sum to greater than 100%.

Table 1b

Diagnostic categories for non-death serious reports of adverse events after human diploid cell rabies vaccine (PCECV, RabAvert®).

Diagnostic category	**PCEC (N = 42)**
	N (%)
General disorders and administration site conditions	19 (45.2)
Nervous system disorders	10 (23.8)
Encephalitis/encephalopathy [a]	2
Guillain-Barré Syndrome	1
Other [b]	7
Immune system disorders	3 (7.1)
Non-anaphylaxis allergic reactions	2
Serum sickness	1
Infections and Infestations	2 (4.8)
Musculoskeletal and connective tissue disorders	2 (4.8)
Cardiac disorders	2 (4.8)
Gastrointestinal disorders (pancreatitis)	2 (4.8)
Neoplasms benign, malignant and unspecified (ovarian tumor)	1 (2.4)

[a]One of the patients, a 26 year-old male, received Twinrix, Japanese encephalitis, and Tdap concomitantly with PCECV. The possible association with vaccination was ruled out by the attending physician. The second patient was a 3year-old male who was diagnosed with static encephalopathy and autism spectrum disorder. He received the rabies vaccine due to a bite by a rabies infected bat.

[b]Other nervous system conditions include two reports of paresthesias, and one report each of coma after possible prolonged seizure, sleep apnea, cognitive difficulties/papular rash, altered mental status/seizures and new onset seizures.