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Brief report

Febrile seizures after 2010–2011 influenza vaccine in young children, United States: A vaccine safety signal from the vaccine adverse event reporting system

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ABSTRACT

During the 2010–2011 influenza season, the Centers for Disease Control and Prevention and the Food and Drug Administration conducted enhanced vaccine safety monitoring for possible febrile seizures in all trivalent influenza vaccine (TIV) products in the United States using the Vaccine Adverse Event Reporting System (VAERS). We used Empirical Bayesian data mining techniques to assess disproportionate reporting after TIV and reviewed febrile seizure reports in children aged <5 years. On November 23, 2010, the combination of the coding term "febrile convulsion" and the Fluzone® TIV product exceeded a predetermined threshold in the VAERS database. By December 10, we confirmed 43 reports of febrile seizure following TIV in children aged 6–23 months. Clinical features of most reports were consistent with typical uncomplicated febrile seizures, and all children recovered. Further epidemiologic assessment of a possible association between TIV and febrile seizures was undertaken in a separate, population-based vaccine safety monitoring system.

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1. Introduction

The Vaccine Adverse Event Reporting System (VAERS), co-managed by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA), is the US spontaneous reporting system for adverse events (AEs) after vaccination, and VAERS surveillance for influenza vaccines is implemented annually [1–3]. In 2010, Australia reported a new finding of increased risk of febrile seizures in young children following receipt of 2010 Southern Hemisphere trivalent inactivated influenza vaccine (TIV) from one manufacturer, CSL Biotherapies [4–6]. Because of this finding, CDC and FDA instituted enhanced surveillance in VAERS for febrile seizures after US TIV in children aged <5 years.

2. Methods

VAERS accepts reports from healthcare providers, manufacturers, vaccine recipients, and others. Healthcare providers are required to report AEs listed in the VAERS Table of Reportable Events following Vaccination, which does not include febrile seizures after TIV, and are encouraged to report other clinically significant AEs after vaccination [7]. Reported AEs are entered into a database and coded using Medical Dictionary for Regulatory Activities (MedDRA) terms [8]. From July 1, 2010 through December 10, 2010, we used complementary strategies to monitor febrile seizures after US 2010–2011 TIV products: disproportionate reporting analysis and clinical review of individual reports. Foreign reports were excluded. Because VAERS is a routine surveillance program that does not meet the definition of research, it is not subject to institutional review board review and informed consent requirements.

On a bimonthly basis, beginning in October 2010, Empirical Bayesian data mining [9] was conducted to identify AEs reported more frequently than expected following TIV, using published criteria [10]. We evaluated all 2010–2011 influenza vaccine product-specific AE pairs with reporting proportions at least twice that of other vaccines in the VAERS database (i.e., lower bound of the 90% confidence interval of the Empirical Bayesian Geometric Mean [EB05] > 2). The primary analysis required a minimum count of one vaccine-AE combination, and was adjusted for sex, year of initial report receipt, and age group. A secondary age stratified analysis was also conducted using standard pre-specified age groups used at FDA; this analysis was adjusted for sex and year received only. To limit comparisons to other vaccines that might be more similar, we also conducted these analyses using a restricted VAERS database which only included reports following inactivated vaccines (i.e., if a live vaccine was administered with or without inactivated vaccine, these reports were excluded).

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Table 1
Data mining results for reports of febrile convulsion after 2010–2011 Fluzone® in VAERS.

Date	Number of Reports	EBGM[a]	EB05[b]
November 23, 2010			
All ages	35	3.66	2.52
Age 0–<18 months[c]	22	4.10	2.68
Age 0–<18 months (database restricted to inactivated vaccines)	15	4.08	2.50
December 10, 2010			
All ages	41	3.36	2.44
Age 0–<18 months	28	4.15	2.92
Age 0–<18 months (database restricted to inactivated vaccines)	18	3.95	2.62

[a] Empirical Bayesian Geometric Mean, the point estimate of disproportionality for MedDRA coding term-adverse event combinations.
[b] Lower bound of the 90% confidence interval of the EBGM.
[c] The 11 pre-defined data mining age groups identified by Empirica include (0–<18 months, 18–<54 months, 54 months to <12.5 years, 12.5 years to <16.5 years, 16.5 years to <29.5 years, 29.5 years to <45.5 years, 45.5 years to <64.5 years, 64.5 years to <75.5 years, 75.5 years to <85.5 years, 85.5 years and above, and age unknown). FDA Center for Drug Evaluation and Research epidemiology staff selected these age groups during development of the Empirical Bayesian application which is used for all pharmaceuticals regulated by FDA. The age groups were intended to facilitate examination of product-event combinations in populations such as children, females of childbearing age, and the elderly.

In parallel with VAERS data mining activities, each possible febrile seizure event was identified and reviewed on a daily basis. We conducted automated searches of VAERS reports in children aged <5 years who received 2010–2011 TIV using the MedDRA terms convulsion, grand mal convulsion, status epilepticus, convulsions local and febrile convulsion. In addition, VAERS staff manually reviewed all incoming reports in children aged <5 years after 2010–2011 TIV for potential signs and symptoms of seizures. While VAERS routinely requests medical records for non-manufacturer reports coded as serious[1], during the 2010–2011 influenza season VAERS staff requested medical records for all possible seizures reported to VAERS after TIV in children <5 years. CDC and FDA physicians reviewed each of these VAERS reports and associated records. A febrile seizure was considered verified if a medical provider diagnosed either "febrile seizure" or "seizure" with documented fever ≥100.4°. Level of diagnostic certainty for seizures was classified according to the Brighton Collaboration case definition [11,12].

3. Results

In the data mining analysis, disproportionately higher reporting for "febrile convulsion" combined with 2010–2011 Fluzone® was observed for reports received by November 23, 2011, compared with other vaccines in the VAERS database (Table 1). Thirty-five reports with the "febrile convulsion" term were verified after review by a VAERS team physician. In the subsequent data mining analysis for reports received by December 10, 2010, the signal persisted. Forty-one reports with the febrile convulsion code were identified (including the 35 earlier reports); one report did not describe an incident case and was ruled out (Table 1). Of the 40 remaining reports, 33 (83%) were in children aged <2 years. In the age-stratified data mining analysis, the EB05 did not exceed 2.0 in any of the age strata other than 0–<18 months. Similar findings were observed after 2010–2011 Fluzone® when data mining analysis was restricted to only include inactivated vaccines. Taken together, we assessed the clinically relevant age for the signal to be in children 6–23 months. Additionally, disproportionate reporting for febrile seizures was not detected following 2010–2011 TIV products other than Fluzone®.

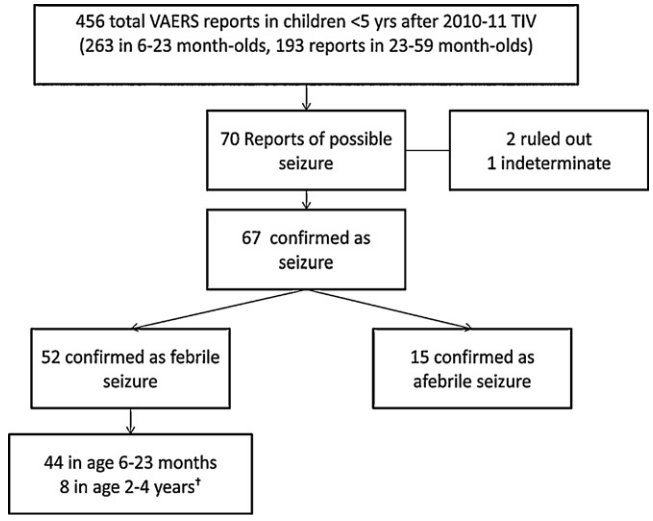

Fig. 1. Assessment of febrile seizure reports to VAERS after US 2010–2011 trivalent inactivated influenza vaccine (TIV) 7/01/2010–12/13/2010. † 43 of 44 reports in 6–23 months and all reports in 2–4 years were Fluzone®.

For the clinical review component, we identified 456 total reports after 2010–2011 TIV in children aged <5 years. Of these, 70 were assessed as possible seizures and reviewed; medical records were available for all reports. In addition to the 40 reports coded with "febrile convulsion" identified in the data mining analysis, clinical review verified 11 additional reports of febrile seizure after 2010–2011 Fluzone® using the broader search strategy (Fig. 1). Of the 51 confirmed reports, 43 (84%) were in the 6–23 months age group. Most (86%) of the 43 children had onset of febrile seizures on the same day or one day after receipt of Fluzone®. Of 25 subjects with adequate information who had febrile seizure onset within 24 h of Fluzone®, 15 (60%) had onset less than 12 h and 10 (40%) had onset 12–23 h after vaccination.

Among the children aged 6–23 months, 16 (37%) received no other vaccine at the time Fluzone® was administered, while those who received at least one other vaccine concomitantly with Fluzone® received the 13-valent pneumococcal conjugate vaccine most often ($n = 14$) (Table 2). Of 42 children aged 6–23 months with sufficient information, 36 received dose 1 of 2010–2011 Fluzone® before the febrile seizure. Thirty children received medical attention in the emergency department and were discharged home and eight children were hospitalized overnight. Two other children required intensive care unit management for status epilepticus; each had received MMR and other vaccines with Fluzone® and had seizure onset 7–10 days after vaccination. All children recovered. Twenty-one (49%) of 43 reports confirmed as febrile seizure in children 6–23 months by CDC–FDA physician review also met the Brighton case definition for generalized convulsive seizure after Fluzone®, which includes Brighton levels 1–3 (Table 2). Twenty-two (51%) of the reports were classified as Brighton level 4.

4. Comment

Rapidly detecting and assessing vaccine safety signals is an important component of US immunization safety monitoring activities [13]. The ability of VAERS staff to perform Empirical Bayesian disproportionate reporting analysis (data mining), while conducting clinical reviews of reports proved useful for a preliminary assessment of the signal for febrile seizures after TIV in young

[1] Resulted in death, life threatening illness, hospitalization, prolongation of hospitalization, or permanent disability.