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Post-licensure surveillance of quadrivalent inactivated influenza (IIV4) vaccine in the United States, Vaccine Adverse Event Reporting System (VAERS), July 1, 2013–May 31, 2015

Penina Haber[a,*], Pedro L. Moro[a], Paige Lewis[a], Emily Jane Woo[b], Christopher Jankosky[b], Maria Cano[a]

[a] Immunization Safety Office, Division of Healthcare Quality Promotion, National Center Emerging and Zoonotic Infectious Diseases (NCEZID), Centers for Disease Control and Prevention (CDC) , 1600 Clifton Rd NE, Atlanta GA 30329, United States
[b] Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Biostatistics and Epidemiology, Silver Spring, MD, United States

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ABSTRACT

Background: Quadrivalent inactivated influenza vaccines (IIV4) were first available for use during 2013–14 influenza season for individuals aged ≥6 months. IIV4 is designed to protect against four different flu viruses; two influenza A viruses and two influenza B viruses.
Methods: We searched the Vaccine Adverse Event Reporting System (VAERS) for US reports after IIV4 and trivalent inactivated influenza vaccine (IIV3) from 7/1/2013–5/31/2015. Medical records were requested for non-manufacturer reports classified as serious (i.e. death, hospitalization, prolonged hospitalization, life-threatening illness, permanent disability). The review included automated data analysis, clinical review of all serious reports, reports of special interest, and empirical Bayesian data mining.
Results: VAERS received 1,838 IIV4 reports; 512 (28%) in persons aged 6 months–17 years of which 42 (8.2%) were serious reports; 1,265 (69%) in persons aged >18 years of which 84 (6.6%) were serious reports; two in children <6 months and 59 in persons of unknown age. Injection site erythema (24%), fever (14%) and injection site swelling (17%) were the most frequent adverse events among persons aged 6 months–17 years, while injection site pain (16%), pain (15%) and pain in extremity (13%) were the most frequent among persons aged 18–64 years given the vaccine alone. Among non-death serious reports, injection site reactions, constitutional symptoms, Guillain-Barré syndrome, seizures, and anaphylaxis were the most frequently reported adverse events. Data mining detected disproportional reporting for incorrect vaccine administration with no associated adverse events. Adverse events following IIV4 reported to VAERS were similar to those following IIV3.
Conclusions: In our review of VAERS reports, IIV4 had a similar safety profile to IIV3. Most of the reported AEs were non-serious. Our findings are consistent with data from pre-licensure studies of IIV4.
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1. Introduction

In 2013, the World Health Organization (WHO) recommended inclusion of a second type B influenza virus in quadrivalent inactivated influenza vaccines (IIV4) for the 2013–2014 influenza season (WHO) [1]. However, one of the quadrivalent vaccine was approved during 2012 and distributed in the subsequent influenza season of 2013–14 [2]. On February 27, 2013, three IIV4 products were approved for use in the general population and were available for the 2013–14 influenza season[3]: Fluarix® Quadrivalent, (GlaxoSmithKline, Research Triangle Park, North Carolina) which on December 14, 2012 was approved for use in persons ≥3 years of age [2]; Fluzone® Quadrivalent (Sanofi Pasteur, Swiftwater, Pennsylvania) which on June 7, 2013 was approved for use in persons ≥6 months of age [4]; and FluLaval® Quadrivalent GlaxoSmithKline, which on August 16, 2013 was approved for use in persons ≥3 years of age [5]. In September 2013, The Advisory Committee on Immunization Practices stated that although IIV4 includes a second B virus, there is no preferential recommendation over IIV3 [6], and vaccination should not be delayed if only IIV3 is available.

In pre-licensure clinical trials, the most common adverse events (AEs) were as follows: FluLaval Quadrivalent: local reactions, muscle aches, irritability, headache, fatigue, and arthralgia [5]; Fluzone Quadrivalent: local reactions, irritability, drowsiness, malaise,

* Corresponding author. Tel.: +1 404 498 0676; fax: +1 404 498 0666.
E-mail address: PHaber@cdc.gov (P. Haber).

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anorexia, and myalgia, and headache [4]; and Fluarix Quadrivalent: local reactions, irritability, muscle aches, headache, and fatigue [3]. We analyzed reports to VAERS following IIV4 from July 1, 2013 through May 31, 2015 to assess safety of IIV4 during the two initial seasons, using IIV3 reports as a comparator vaccine.

2. Methods

2.1. Data source

VAERS is a national spontaneous reporting system, established in 1990 and co-administered by the Centers for Disease Control and Prevention (CDC) and FDA that accepts reports of AEs following immunization [7,8]. VAERS accepts reports from vaccine manufacturers, healthcare providers, vaccine recipients (or their parents/guardians). The VAERS form collects information on demographic characteristics of the vaccine recipient, type of vaccine(s) received and AEs experienced. A Report may be classified as serious based on the Code of Federal Regulations if one or more of the following are reported: death, life-threatening illness, hospitalization, prolongation of hospitalization, or permanent disability [10]. For serious reports from sources other than manufacturers, medical records are routinely requested. Signs and symptoms of AEs are coded using an internationally standardized terminology from the Medical Dictionary for Regulatory Activities (MedDRA) [9]. Each report may be assigned one or more MedDRA Preferred Terms (PTs); PTs are not confirmed medical diagnoses.

We analyzed VAERS reports for individuals who received IIV4 from July 1, 2013 through May 31, 2015. We included reports of persons who received Fluarix Quadrivalent, FluLaval Quadrivalent, or Fluzone Quadrivalent. We excluded reports with unknown influenza vaccine name and/or vaccine manufacturer and non-US reports. Duplicate reports were consolidated.

We compared the AEs reported after IIV4 with the corresponding IIV3 vaccines that were available during the same time period: Fluarix, FluLaval, and Fluzone (excluding Fluzone High-Dose and Fluzone Intradermal). Reports were sub-divided into two age groups: 6 months–17 years, and >18 years.

2.2. Descriptive statistics

We calculated descriptive statistics including the mean and median age of vaccinated individuals, AE onset interval (from vaccination date [day 0] to the reported onset of first symptoms), and the most common MedDRA PTs. We also reviewed reports pertaining to children <6 months of age (who would have received the vaccine in error) and included persons of unknown or unspecified age. We used SAS (version 9.3, SAS Institute, Inc., Cary, NC, USA) for data analysis.

2.3. Clinical review

We conducted clinical review of reports which involved review of all documentation (VAERS reports, medical records, autopsy report) on the AE and an assessment of the clinical characteristics of the medical event, condition/s following vaccination which motivated its reporting to VAERS. We also conducted clinical review for non-serious reports in the following categories, which were not mutually exclusive: (1) pre-specified conditions based on previous studies or clinical judgment including Guillain-Barre syndrome [GBS], anaphylaxis, febrile seizures, and vaccinations during pregnancy [11–19]; and (2) reports suggesting that IIV4 was administered "off label" or accidentally to individuals outside the age indication for each vaccine. For the review of serious cases, we ascertained the primary event (the event that appeared to be the main reason for the report to VAERS) and categorized the case based on the MedDRA System Organ Class (SOC) [9].

Cause of death was determined from information in the autopsy report, death certificate or medical records. We did not assess causality between the AE and the vaccine or whether a vaccination error contributed to an AE. Reports of GBS and anaphylaxis were classified using the Brighton Collaboration criteria and in addition we used physician's diagnosis documented on the medical records [12,13]. For GBS, we reviewed any available information about nerve conduction studies, nadir of neurological symptoms, physical exam findings (e.g. weakness, hyporeflexia), cerebrospinal fluid analysis, magnetic resonance imaging. For reports of anaphylaxis, we noted tryptase and radio-allergosorbent test results, if they were available.

2.4. Disproportionality analysis (data mining)

We applied Empirical Bayesian (EB) data mining methods to identify disproportionality [20,21] of vaccine-AE reporting, that is, PTs that were reported more frequently than expected following IIV4 vaccines compared with other vaccines (including IIV3), with adjustment for age, sex, and other variables. We used published criteria by Szarfman et al. [21] to identify, for each licensed IIV4 product, adverse events that were reported more frequently after IIV4 than other vaccines (i.e. EB05 $\geq$ 2, where EB02 represents the lower bound of the 90% confidence interval surrounding the EB geometric mean). We reviewed reports and available medical records for AEs that met or exceeded that threshold.

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.

3. Results

3.1. Descriptive analysis

During the study period, VAERS received a total of 1,838 US IIV4 reports, 521 during 2013–14 season and 1276 during 2014–15 season. Of these reports, 512 (28%) were in persons aged 6 months–17 years which included 36 non-death serious reports and six death reports; 1,265 (69%)) in persons aged >18 years, which included 78 non-death serious reports and six death reports; two were children <6 months and 59 were in persons of unknown age (Table 1a and 1b). Among adult reports, 199 (11%) were in persons aged $\geq$ 65 years. Characteristics of these reports were similar to that of adults 18–64 years and the most common PTs were pain in the extremity (19%), injection site erythema (17%), fever and injection site pain, both (15%).

Report characteristics and the most frequent MedDRA PTs for IIV4 reports during the 2013–15 influenza seasons compared with IIV3 reports during the same two seasons are summarized in Table 1a and 1b.

3.2. Clinical review

3.2.1. Death reports

We identified 12 death reports after IIV4, six in children and six in adults. Most of these reports (10; 83%) listed IIV4 as the only vaccine administered on that date. Nine individuals had an underlying chronic condition or other complex medical history. There was no evident clustering in the causes of death, pre-existing comorbidities, age, or interval from vaccination to death.

3.2.2. Non-death serious reports

The two most frequently reported categories of non-death serious SOCs were nervous system disorders (33, 25.9%) and general

Table 1a
Characteristics of VAERS reports following IIV4 compared with IIV3 in children aged 6 months–17 years, 2013–15.

	IIV4 reports 6 mos–17 years *n* (%) = 512	IIV3 reports 6 mos–17 years *n* (%) = 1,418
Male	255 (50)	692 (49)
Serious*	42 (8)	109 (8)
Median age (range) in years	5 (0–17)	4 (0–17)
Median onset interval (range) in days†	1 (0–145)	1 (0–139)
IIV given alone	287 (56)	618 (44)
Most common MedDRA preferred terms, IIV vaccines given alone¶	Injection site erythema 72 (25) Injection site swelling 49 (17) Fever 41 (14) Urticarial 34 (12) Injection site warmth 31 (11) Erythema 30 (11) Injection site pain 25 (9) Rash 21 (7) Vomiting 20 (7) Local swelling 17 (6)	Injection site erythema 105 (17) Injection site swelling 99 (16) Fever 72 (12) Erythema 63 (10) Urticaria 52 (8) Injection site warmth 51 (8) Rash 49 (8) Vomiting 38 (6) Pruritus 37 (6) Injection site pain 32 (5)

Table 1b
Characteristics of VAERS reports following IIV4 compared to IIV3 in adults aged ≥18 years, 2013–15.

	IIV4 reports† ≥18 years *n* (%) = 1,265	IIV3 reports† ≥18 years *n* (%) = 3,546
Male	303 (24)	820 (23)
Serious*	84 (7)	266 (8)
Median age (range) in years	50 (18–95)	50 (18–95)
Median AE onset interval (range) in days†	0 (0–152)	0 (0–366)
IIV given alone	1036 (82)	2812 (79)
Most common MedDRA preferred terms, IIV vaccines given alone¶	Injection site pain 170 (16) Pain 158 (15) Pain in extremity 138 (13) Injection site erythema 122 (12) Fever 115 (11) Headache 105 (10) Injection site swelling 91 (9) Erythema 88 (8) Pruritus 84 (8) Dizziness 77 (7)	Pain 401 (14) Injection site pain 390 (14) Pain in extremity 361 (13) Headache 318 (11) Injection site erythema 293 (10) Fever 283 (10) Dizziness 270 (10) Nausea 244 (9) Dyspnoea 234 (8) Chills 222(8)

†IIV4: Fluarix Quadrivalent, FluLaval Quadrivalent, Fluzone Quadrivalent Fluarix, FluLaval, Fluzone; not including two reports in children <6 months and 59 reports in persons of unknown age including one serious non-death report.
*A report may be classified as serious based on the Code of Federal Regulations if one or more of the following are reported: death, life-threatening illness, hospitalization, prolongation of hospitalization or permanent disability.
*Including 17 death reports after IIV3 and 12 death reports after IIV4.
†Onset interval in days from time of vaccination to first symptoms of adverse event.
¶MedDRA preferred terms are not mutually exclusive; the most frequent MedDRA terms listed are limited to reports where LAIV3 or LAIV4 were administered alone.

disorders and administration site conditions (32, 25.2%). The most frequent specific AEs were injection site reactions, GBS, seizures, and anaphylaxis (Table 2).

3.2.2.1. Guillain-Barré Syndrome (GBS). We identified 14 reports of possible GBS after IIV4 during 2013–2015, of which 13 were classified as serious. The median onset interval of symptoms was 13 days (range 0–24 days). Median age was 45 years (range 21 months–67 years); eight cases were female and six were male. Twelve cases met the Brighton Collaboration case definition [12] for GBS (six level 1, five level 2, one level 3), one did not meet Brighton criteria but was diagnosed as GBS by a physician according to medical records, and one non-serious case involved treatment in an emergency department but did not include medical records so the diagnosis could not be verified. We attempted to review nerve conduction studies, cerebrospinal fluid analysis, and magnetic resonance imaging, but some reports did not provide any documentation. Twelve reports listed IIV4 as the only vaccine administered, two received also Pneumovax and one Varivax. Two patients reportedly presented with upper respiratory infection or influenza-like-illness within 7–14 days prior to vaccination. Based on the most recent information at the time the VAERS form was submitted, 11 of the 14 reported cases had fully recovered.

3.2.2.2. Anaphylaxis. We identified 19 reports of possible anaphylaxis. Brighton criteria [13] were applied to six reports: two cases met the Brighton Collaboration criteria for level 1 and four met level 2 criteria. Six reports - diagnosed anaphylaxis did not meet Brighton criteria but were physician-diagnosed anaphylaxis. Two reports of possible anaphylaxis did not have medical records and could not be verified. The remaining five reports described allergic-type reactions but did not meet Brighton criteria. We attempted to review results of tryptase and radio-allergosorbent testing, but the reports did not include this information. Of the 19 reports, six were classified as serious. Of the 19 reports, 12 required epinephrine (10 anaphylaxis and two non-anaphylaxis allergic reactions). In three reports, IIV4 was given with other vaccines, thus impeding the ability to assess a possible relationship with IIV4. None of the reports stated that the patient had a history of egg

Table 2
Medical conditions* in serious reports following IIV4, VAERS, 2013–2015.

Medical Condition*	Total n=127 n (%)
Deaths[†]	**12 (9.4)**
Neurological system disorders	**33 (25.9)**
Guillain-Barré Syndrome	13
Seizures	11
Numbness/tingling	2
Other neurological[a]	7
General disorders and administration conditions	**32 (25.2)**
Injection site reactions	18
Multiple symptoms (injection site reaction, chills, diarrhea)	2
Atypical chest pain (non-cardiac)	3
Fever of unknown origin	2
Other[b]	7
Immune system disorders	**9 (7.1)**
Anaphylaxis	6
Non-anaphylaxis allergic reactions	2
Kawasaki disease	1
Infections and infestations	**7 (5.5)**
Respiratory, thoracic and mediastinal disorders	**6 (4.7)**
Musculoskeletal and connective tissue disorders	**5 (3.9)**
Vascular disorders	**3 (2.4)**
Renal and urinary disorders	**3 (2.4)**
Gastrointestinal disorders	**3 (2.4)**
Cardiac disorders	**4 (3.1)**
Blood and lymphatic system disorders	**3 (2.4)**
Ear and labyrinth disorders	**2 (1.6)**
Skin and subcutaneous tissue disorders	**3 (2.4)**
Eye disorders	**2 (1.6)**

[†] Causes of death included: Asphyxia due to food aspiration, Undetermined cause, Sudden unexpected death in childhood, Acute exacerbation of reactive airway disease due to Enterovirus respiratory infection, Ventricular tachycardia leading to cardiac arrest/cardiogenic shock, Dilated cardiomyopathy, Multiorgan failure secondary to acute upper gastrointestinal hemorrhage, Pulmonary embolism due to deep vein thrombosis, Septicemia due to pneumococcal bacteremia, Cardiogenic shock, inferior wall myocardial infarction, Parkinson's disease, Heart failure.

[*] MedDRA System Organ Class (SOC).

[a] One report each of Bell's palsy, encephalopathy, numbness/tingling, generalized muscle weakness, tremors, transverse myelitis, and myasthenia gravis.

[b] One report each of syncope, dizziness/near syncope, fever, influenza-like illness, chronic pain (with subjective weakness in extremities), cellulitis at site of pneumococcal vaccination, and adverse vaccine reaction/Systemic Inflammatory Response Syndrome.

allergy or allergic reaction to previous influenza vaccine. For each IIV4 product compared with other vaccines, no disproportionate reporting was found for either GBS or anaphylaxis.

3.2.2.3. Febrile seizures. We identified 18 reports of febrile seizures; 12 were verified. Age ranged from 4 to 35 months; 11 reports were in males and seven in females. Median onset interval from vaccination to febrile seizure onset was 12 h (range 0–12 days). Four febrile seizures were classified as serious. In 14 (78%) reports, IIV4 was given concurrently with other vaccines. All 18 children reportedly recovered.

3.2.2.4. Vaccination in pregnancy. We identified 36 reports of pregnant women who received IIV4 with a median age of 32 years (range 15–42 years); 34 received IIV4 alone. Twenty-three reports specified the trimester of pregnancy: nine in first trimester, nine in second trimester, and five in the third trimester. Three reports described an AE related to pregnancy: spontaneous abortion, uterine bleeding, and trisomy (one report each). Twelve reports described AEs that were not directly related to the pregnancy, e.g. injection site reactions, allergic reactions, and musculoskeletal symptoms. Twenty-one reports did not describe an AE.

3.2.2.5. Vaccine administration outside the recommended age. VAERS received two non-serious reports in children aged <6 months who received Fluzone Quadrivalent; A 4-month-old female experienced fever and watery diarrhea. A 2-month-old female was vaccinated with IIV4, but no AEs were reported.

There were also 18 reports of children aged <3 years who received Flu Laval Quadrivalent or Fluarix Quadrivalent, which are both approved for use in patients 3 years and older. Two children, aged 8 months and 13 months, each experienced vomiting, fever, jerky movements, and dyspnea. A 6-month-old female experienced rotator cuff syndrome/injection site pain. All three reportedly recovered. The other 15 reports did not mention an AE.

3.3. Data mining

During the 2013–2014 influenza season, empirical Bayesian analysis did not detect any EB05 >2 for Fluarix Quadrivalent, FluLaval Quadrivalent, or Fluzone Quadrivalent. For the 2014–2015 influenza season, data mining analysis revealed disproportional reporting compared with other vaccines for the PTs "incorrect dose administered" ($n = 21$) and "underdose" ($n = 17$) following IIV4 compared with other vaccines. These reports were non-serious, and they did not describe any adverse effects *per se*.

4. Discussion

During the 2013–2014 and 2014–2015 influenza seasons, approximately 70 million doses of IIV4 were distributed for use in the United States (data shown with permission of GSK and Sanofi). Our review of AEs reported to VAERS following IIV4 did not identify any unexpected AEs or new safety concerns. This represents the first post-licensure safety assessment of IIV4 and adds to the existing body of evidence on the safety of seasonal influenza vaccines. The AEs reported to VAERS following IIV4, whether administered alone or with other vaccines, in the two age-groups were similar to those reported after IIV3.

Approximately, 93% of IIV4 reports were non-serious and the most common AEs were mild, self-limited conditions (e.g. injection site reactions and fever) that were also observed during the prelicensure clinical trials [3–5].

GBS is an acute, immune-mediated demyelinating disorder of the peripheral nervous system. Although the 1976 swine flu vaccine was found to be causally associated with GBS [11], evidence of a possible association of GBS with inactivated seasonal influenza vaccines has been inconsistent [14,22–25]. Given this potential association, GBS is closely monitored by CDC and FDA using VAERS and other systems [26]. Our study verified 13 GBS reports with symptom onset within 42 days of vaccination for a reporting rate of 0.19 cases per million doses of vaccine distributed, which is below the estimated background incidence of GBS [25,27]. Our data mining analysis did not identify any disproportionate reporting for GBS for any of the IIV4 products, compared with other vaccines.

Anaphylaxis may be causally associated with vaccination in rare instances including with influenza vaccines [14,15]. For all three of the IIV4 products, the contraindications include "severe allergic reactions (e.g. anaphylaxis) to any component of the vaccine, including egg protein, or following a previous dose of any influenza vaccine" [3–5]. We verified 12 cases of anaphylaxis reported to VAERS after IIV4 with reporting rate of 0.17 per million influenza doses distributed, which is below the expected rate of 1.35 per million IIV3 vaccine doses [28]. Most recently, there is increasing evidence the IIV is safe when administered to persons with egg allergy, [29]. None of the anaphylaxis reports in this series mentioned an egg allergy or allergic reaction to previous vaccine. Thus, this potentially life-threatening event can occur even in the absence of any known or suspected hypersensitivity.

We verified 12 reports of febrile seizures in children; 80% of children in these reports received other vaccines on the same visit.

During the 2010–2011 influenza season, a vaccine safety signal for febrile seizures after trivalent inactivated influenza vaccine among children aged 6–23 months was identified in VAERS [16] and subsequent studies supported the potential for an association during this season [17,18]. In other years, an increased risk of febrile seizure has not been found following sole administration of IIV3 [30].

Inactivated influenza vaccines are recommended at any time during pregnancy, due to the risk of influenza-related complications among pregnant women [6,31]. Vaccination during pregnancy with IIV3 has been found to be safe [32,33]. Our review of VAERS data did not identify any safety concerns with regard to IIV4 vaccination in pregnancy.

VAERS has many important limitations, including underreporting, incomplete information, varying quality of reports, and lack of an unvaccinated comparison group [7,8]. Medical records of serious reports obtained through follow-up may not contain important key clinical and/or laboratory information. Because of these limitations, it is usually not possible to determine causal associations between vaccines and AEs from VAERS reports. However, as a national surveillance system, VAERS can be used to rapidly detect rare AEs and potential vaccine safety problems, which can be further explored in carefully designed epidemiological studies [34]. Our review of VAERS reports following IIV4 did not identify any new safety signals, which are similar to the results of prior VAERS study [35].

5. Conclusion

Influenza vaccination is the best way to protect against influenza disease and its complications [6,36]. IIV4 vaccines provide protection against two influenza A and two influenza B viruses [3–6]. In our review of VAERS, we did not identify any safety concerns for IIV4 vaccination. Most of the AEs reported to VAERS following IIV4 were non-serious and were similar to those reported after IIV3.

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 or the Food and Drug Administration.

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