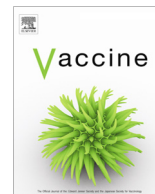




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Postmarketing safety surveillance of trivalent recombinant influenza vaccine: Reports to the Vaccine Adverse Event Reporting System

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ABSTRACT

On January 16, 2013, the Food and Drug Administration approved recombinant hemagglutinin influenza vaccine (RIV3) (*Spodoptera frugiperda* cell line; Flublok), which is the first completely egg-free flu vaccine licensed in the United States. To improve our understanding of the safety profile of this vaccine, we reviewed and summarized reports to the Vaccine Adverse Event Reporting System (VAERS) following RIV3. Through June 30, 2016, VAERS received 88 reports. Allergic reactions, including anaphylaxis, were the most common type of adverse event. Based on medical review, 10 cases met the Brighton Collaboration case definition of anaphylaxis, 21 reports described allergic reactions other than anaphylaxis, and 11 reports described signs and symptoms that suggested hypersensitivity. Other adverse events included injection site reactions, fatigue, myalgia, headache, and fever. The occurrence of anaphylaxis and other allergic reactions in some individuals may reflect an underlying predisposition to atopy that may manifest itself after an exposure to any drug or vaccine, and it does not necessarily suggest a causal relationship with the unique constituents that are specific to the vaccine product administered. Further research may elucidate the mechanism of allergic reactions following influenza vaccination: it is possible that egg proteins and influenza hemagglutinin play little or no role. Vaccination remains the single best defense against influenza and its complications. The information summarized here may enable policy makers, health officials, clinicians, and patients to make a more informed decision regarding vaccination strategies.

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1. Background

On January 16, 2013 the U.S. Food and Drug Administration (FDA) licensed trivalent recombinant hemagglutinin influenza vaccine (RIV3) (*Spodoptera frugiperda* cell line; Flublok) for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine [1]. RIV3 is prepared in a continuous insect cell line using a baculovirus vector; the process uses neither live influenza viruses nor eggs. Each 0.5 mL dose contains 135 µg hemagglutinin (HA) (45 µg of each of the three HA antigens recommended for trivalent influenza vaccines).

The Advisory Committee on Immunization Practices (ACIP) in the United States includes RIV3 in its recommendations regarding

the prevention and control of influenza with vaccines [2]. The safety of RIV3 was assessed in five randomized, placebo or active-controlled clinical trials [3–6]. Safety was assessed in 2497 adults aged 18–49 years, 972 adults aged 50–64 years, and 1078 adults aged ≥65 years [3]. The most common solicited adverse reaction in adults 18–49 years was local pain, with 37% and 8% among RIV3 and placebo recipients, respectively [3]. In clinical trials in adults aged ≥50 years, RIV3 was compared to trivalent inactivated influenza vaccines (TIV), and local and systemic reactions were similar in the two groups [3].

To improve our understanding of the safety profile of this vaccine, we reviewed and summarized reports to the Vaccine Adverse Event Reporting System (VAERS) following RIV3.

2. Methods

VAERS is a national system for passive surveillance of adverse events following vaccination [4–6]. Established in 1990, VAERS is jointly managed by the U.S. Food and Drug Administration (FDA)

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and Centers for Disease Control and Prevention and, in recent years, has received >30,000 reports per year. Reports are submitted by health care providers, vaccine recipients or their parents or guardians, vaccine manufacturers, and other interested parties. FDA medical officers review all serious reports, defined as events that are fatal, disabling, or life-threatening; require or prolong hospitalization; result in congenital anomalies; require medical intervention to prevent such outcomes; or are deemed to be other medically important conditions [7].

We searched VAERS for reports of adverse events after RIV3 from January 13, 2013 (date of U.S. licensure) through June 30, 2016. We reviewed serious [7] and non-serious adverse events, including both U.S. and international reports. We summarized the frequency, range, onset time, and severity of reported adverse events, with particular attention to deaths and other serious adverse events [7]. Duplicate reports were consolidated. Our clinical assessment of each case was based on the narrative description of the event, vaccine(s) administered, time course, treatment, medical history, any available medical records, and information about other exposures. Based on that medical review and assessment, we identified the principal clinical condition for each report. For reports of anaphylaxis, we applied the Brighton Collaboration case definition [8], in which Level 1 indicates the highest degree of diagnostic certainty, Level 2 moderate certainty, and Level 3 the lowest certainty (Appendix). We also evaluated demographics and medical history. Results were summarized with descriptive statistics.

As part of routine safety surveillance, FDA applied Empirical Bayesian data mining [9] to identify disproportionality [10] of vaccine-adverse event pairs, with adjustment for age, sex, and year in which the report was received.

Protection of human subjects: this work was performed as part of routine public health surveillance based on existing documents. No interventional treatments, exposures, or procedures were performed.

3. Results

Our search yielded 88 reports, including 4 reports (5%) that met the regulatory definition of serious [7] (Table 1). The vast majority

Table 1
Overview of reports for recombinant influenza hemagglutinin vaccine (VAERS 2013–2016).

	n = 88
Age ^a (years)	
Mean (standard deviation)	44.7 (12.95)
Median	43
Range	4–88
Sex	
Female	85 (97%)
Male	3 (3%)
Seriousness	
Non-serious	84 (95%)
Serious ^b	4 (5%)
Allergy history ^c	
Egg	39 (44%)
Egg only	12
Egg and other allergies	27
Non-egg only	13 (15%)
No allergies reported	36 (41%)
Previous reaction to influenza vaccine ^c	11 (13%)

^a In 7 reports, the age was not reported.

^b Events reported as disabling, life-threatening, fatal, requiring hospital admission, prolonging a hospital stay, resulting in a congenital anomaly, or requiring medical intervention to prevent such an outcome [7]; other medically important conditions [7] are also included.

^c As reported by the patient or healthcare provider.

of RIV3 recipients were adult females (Table 1). More than half of the reports (52; 59%) stated that the patient had a history of allergies, including 39 (44% of all reports) individuals with a self-reported history of egg allergy (Table 1). No deaths were reported.

Allergic reactions, including anaphylaxis, were the most common type of adverse event (31 reports; 35%) (Table 2). Based on medical review, 10 cases met the Brighton Collaboration case definition of anaphylaxis [8]: two that were Brighton Level 1, seven Brighton Level 2, and one Brighton Level 3. The onset of anaphylaxis was <24 h for all cases, and in some cases symptoms began 5–10 min after RIV3 receipt. Treatment of individual patients included combinations of the following: antihistamines, corticosteroids, epinephrine, albuterol, or supplemental oxygen. Nine of the 10 reports stated that the patient had a history of allergies: five individuals were reportedly allergic to eggs and other substances (e.g., shellfish, erythromycin, penicillin, and latex), and the other four did not list egg allergies but reported other allergies (e.g., feathers, peanuts, penicillin, sulfa drugs, and “flu shot with egg”). Four of the 10 reports of anaphylaxis stated that the patient had experienced anaphylaxis or allergic reaction (e.g., hives) after other influenza vaccines.

Twenty-one reports described allergic reactions that did not meet the Brighton Collaboration case definition of anaphylaxis [8]. However, 19 of these reports stated that the patient was evaluated in the emergency department or physician's office, with 14 reports describing interventions (e.g., epinephrine, antihistamines, and corticosteroids) that may have prevented or curtailed anaphylaxis. Sixteen of the 21 reports stated that the patient had a history of atopy: two reports listed only an egg allergy, three listed only non-egg allergies (penicillin, latex, and unspecified allergies), and 11 reports stated that the patient was allergic to eggs and other substances. Among the five reports that did not list any allergies, one mentioned a medical history of “reaction to flu vaccine – hives, itch.”

Eleven additional reports described signs and symptoms that suggested hypersensitivity: generalized rash/pruritus, facial erythema and swelling, or urticaria (9 reports), and oral, perioral, or pharyngeal paresthesia or inflammation (2 reports). The reports did not contain sufficient information for us to determine whether these events constituted allergic reactions.

Table 2
Adverse events reported after vaccination with recombinant influenza hemagglutinin vaccine (VAERS 2013–2016).

Principal clinical condition ^a	Non-serious n = 84	Serious ^b n = 4	Total n = 88
Anaphylaxis	7	3	10
Allergic reaction	21	0	21
Injection site reaction/arm pain	21	0	21
Constitutional signs/symptoms	9	0	9
Rash, pruritus, urticaria	9	0	9
Dizziness/vertigo	4	0	4
No adverse event ^c	3	0	3
Arthritis/arthralgia	2	0	2
Lymphadenopathy	2	0	2
Oral paresthesia/pain/dysgeusia	2	0	2
Sinusitis/upper respiratory infection	1	1	2
Influenza (strain not specified)	1	0	1
Parsonage-Turner	1	0	1
Spontaneous abortion	1	0	1

^a Primary adverse event based on clinical review of the initial VAERS report, follow-up reports, and medical records (if available).

^b Events reported as disabling, life-threatening, fatal, requiring hospital admission, prolonging a hospital stay, resulting in a congenital anomaly, or requiring medical intervention to prevent such an outcome [7]; other medically important conditions [7] are also included.

^c Two women received RIV3 during pregnancy and no adverse event was reported; a 4-year-old boy inadvertently received RIV3.

Other common adverse events included injection site reactions (local pain, swelling, and redness), as well as constitutional signs and symptoms, such as fatigue, myalgia, headache, and fever (Table 2). Among the remaining adverse events, there was no conspicuous clustering of clinical syndromes or organ systems. An 86-year-old woman developed an upper respiratory infection that her family reported as life-threatening. A chest radiograph did not suggest pneumonia, and the woman was evaluated and treated as an outpatient. At the time of the report, she was recovering. A 40-year-old woman developed pain, paresthesia, and weakness in the vaccinated arm, with symptoms beginning within 5 h of vaccination. She was diagnosed with Parsonage-Turner syndrome (brachial neuritis) and was treated with physical therapy, non-steroidal anti-inflammatory drugs, corticosteroids, and electrical stimulation therapy. At the time of the report, her symptoms were partially resolved. Three reports stated that RIV3 was administered to pregnant women. One report described a spontaneous abortion, and the other two did not mention any adverse events. There were no reports describing a positive rechallenge, i.e., same or similar reaction after subsequent dose of RIV3. There was one report of a vaccination error: a 4-year-old boy inadvertently received RIV3, and no adverse event was reported.

Data mining revealed disproportional reporting [9,10] for RIV3 during the 2014–15 influenza season, with elevated values for the Preferred Terms *throat tightness* and *hypersensitivity*, but not during the 2013–14 and 2015–16 influenza seasons. The reports containing these Preferred Terms referred to allergic reactions, as described above.

4. Discussion

Routine postmarketing safety surveillance of RIV3 reveals that the vast majority of adverse events reported to VAERS were non-serious, a finding which is consistent with the experience with inactivated influenza vaccine [11]. Injection site reactions and transient constitutional symptoms were observed during clinical trials of RIV3; in this review those two clinical categories constituted one-third of adverse events reported to VAERS.

As previously described [12], anaphylaxis and other allergic reactions were reported, particularly among individuals with a self-reported egg allergy or other atopic history. The reactions reported to VAERS may be skewed by self-selection of patients who choose RIV3 because of their medical history. In this summary, nearly half of reports (42; 48%) described anaphylaxis, allergic reactions, or signs and symptoms that suggested hypersensitivity. The occurrence of such reactions in some individuals may reflect an underlying predisposition to atopy that may manifest itself after an exposure to any drug or vaccine, and it does not necessarily suggest a causal relationship with the unique constituents that are specific to the vaccine product administered. Further research may elucidate the mechanism of allergic reactions following influenza vaccination. It is possible that egg proteins in inactivated influenza vaccines play little or no role, and that hypersensitivity reflects a complex interaction of current and past environmental exposures in an immunologically vulnerable milieu.

Severe allergic reactions to egg-based influenza vaccines in persons with egg allergy are uncommon [13–17]. In a randomized, prospective, double-blind, placebo controlled trial, Greenhawt et al. [18] evaluated the safety of TIV in children with a history of severe egg allergy, including anaphylaxis. Both the step-wise and single-dose administration of TIV were well-tolerated [18]. Chung et al. [19] evaluated a two-dose graded influenza vaccine and/or a vaccine skin test in children aged 6 months to 18 years, and results suggest that egg-allergic patients without anaphylaxis to egg may safely receive the influenza vaccine in a two-dose graded fashion without a vaccine skin test. Howe et al. [20] evalu-

ated egg-allergic patients aged 6–36 months who received TIV, including 17 with medically documented anaphylaxis to egg, and demonstrated that TIV can be safely given to that population. Webb et al. [21] evaluated seasonal and/or H1N1 influenza vaccine in individuals with egg allergy, including 22% with a history of anaphylaxis to egg; the results suggest that most individuals with egg allergy—even those with severe egg allergy—can safely receive a single dose of influenza vaccine.

Nevertheless, life-threatening hypersensitivity following influenza vaccination occurs in some individuals. RIV3 is considered egg-free, but it does not eliminate the risk of anaphylaxis in egg-allergic individuals. ACIP states “Persons who report having had reactions to egg involving such symptoms as angioedema, respiratory distress, lightheadedness, or recurrent emesis; or who required epinephrine or another emergency medical intervention, may receive RIV3 if they are aged ≥ 18 years and there are no other contraindications” [2]. However, the committee also states, “A previous severe allergic reaction to influenza vaccine regardless of the component suspected of being responsible for the reaction is a contraindication to further receipt of the vaccine [2].” Most importantly, ACIP states, “Regardless of allergy history, all vaccines should be administered in settings in which personnel and equipment for rapid recognition and treatment of anaphylaxis are available” [2].

Because of the risk of influenza-related complications among pregnant women, flu vaccination is recommended during pregnancy [22]. However, most studies of the safety of flu vaccine in pregnancy have focused on inactivated, egg-based vaccines [22]. The safety and efficacy of Flublok in pregnancy have not yet been established [3]. In our review of VAERS, we identified one report of spontaneous abortion and two pregnancies for which no adverse event was reported. Thus information on this topic is quite limited, and further research is needed.

Strengths of VAERS include its national scope, size, timeliness, ability to detect events that were not observed during prelicensure trials, and surveillance among special populations [4]. However, passive surveillance systems such as VAERS are subject to many limitations, including underreporting, incomplete information, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups [4–6]. Because of these and other limitations, it is usually not possible to verify causal associations between vaccines and adverse events from spontaneous reports to VAERS. Nevertheless, VAERS data have been used to describe a range of potential vaccine adverse events and to look for unexpected patterns in demographics and clinical characteristics that might lead to hypotheses that can be tested with epidemiologic studies [23].

5. Conclusion

Vaccination remains the single best defense against influenza and its complications. ACIP states, “For persons for whom more than one type of vaccine is appropriate and available, ACIP does not express a preference for use of any particular product over another” [2]. The information summarized here may enable policy makers, health officials, clinicians, and patients to make a more informed decision regarding vaccination strategies. Flublok Quadrivalent [24] was approved on October 7, 2016, and continuous postmarketing safety surveillance will be vital for understanding the benefits and risks of recombinant influenza vaccine.

Disclosures

The authors have no conflicts of interest or funding to disclose. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of CDC.

Authorship

EJW read and summarized adverse events reports. MC and PLM reviewed adverse event reports. MC, CJ, PLM, and EJW wrote and revised the manuscript.

Protection of human subjects

This work was performed as part of routine public health surveillance based on existing documents. No interventional treatments, exposures, or procedures were performed.

Conflict of interest

None.

Funding

None; the work was completed as part of the federal government's routine safety surveillance.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.vaccine.2017.08.047>.

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Appendix. Brighton Collaboration case definition of anaphylaxis (reprinted from Vaccine 25 (2007) 5675-5684 [8])

For all levels of diagnostic certainty

Anaphylaxis is a clinical syndrome characterized by

- sudden onset AND
- rapid progression of signs and symptoms AND
- involving multiple (≥ 2) organ systems, as follows

Level 1 of diagnostic certainty

- ≥ 1 major dermatological AND
- ≥ 1 major cardiovascular AND/OR ≥ 1 major respiratory criterion

Level 2 of diagnostic certainty

- ≥ 1 major cardiovascular AND ≥ 1 major respiratory criterion

OR

- ≥ 1 major cardiovascular OR respiratory criterion AND
- ≥ 1 minor criterion involving ≥ 1 different system (*other than* cardiovascular or respiratory systems) OR
- (≥ 1 major dermatologic) AND (≥ 1 minor cardiovascular AND/OR minor respiratory criterion)

Level 3 of diagnostic certainty

- ≥ 1 minor cardiovascular OR respiratory criterion AND
- ≥ 1 minor criterion from each of ≥ 2 different systems/categories

The case definition should be applied when there is no clear alternative diagnosis for the reported event to account for the combination of symptoms.

Major and minor criteria used in the case definition of anaphylaxis

Major criteria

Dermatologic or mucosal

- generalized urticaria (hives) or generalized erythema
- angioedema, localized or generalized
- generalized pruritus with skin rash

Cardiovascular

- measured hypotension
- clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following:
 - tachycardia
 - capillary refill time >3 s
 - reduced central pulse volume
 - decreased level of consciousness or loss of consciousness

Respiratory

- bilateral wheeze (bronchospasm)
- stridor
- upper airway swelling (lip, tongue, throat, uvula, or larynx)
- respiratory distress—2 or more of the following:
 - tachypnoea
 - increased use of accessory respiratory muscles (sternocleidomastoid, intercostals, etc.)
 - recession
 - cyanosis
 - grunting

Minor criteria

Dermatologic or mucosal

- generalized pruritus without skin rash
- generalized prickle sensation
- localized injection site urticaria
- red and itchy eyes

Cardiovascular

reduced peripheral circulation as indicated by the combination of at least 2 of the following:

- tachycardia
- a capillary refill time of >3 s without hypotension
- a decreased level of consciousness

Respiratory

- persistent dry cough
- hoarse voice
- difficulty breathing without wheeze or stridor
- sensation of throat closure
- sneezing, rhinorrhea

Gastrointestinal

- diarrhoea
- abdominal pain
- nausea
- vomiting

Laboratory

- Mast cell tryptase elevation > upper normal limit