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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 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 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.

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.

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