

Allergic Reactions After Egg-Free Recombinant Influenza Vaccine: Reports to the US Vaccine Adverse Event Reporting System

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The Vaccine Adverse Event Reporting System has received reports of allergic reactions following immunization with egg-free recombinant influenza vaccine, among patients with a self-reported egg allergy or previous allergic reaction to inactivated influenza vaccine. These results suggest that allergic reactions following influenza vaccination are not necessarily related to egg proteins.

Keywords. influenza; vaccine; allergy; hypersensitivity; egg.

On 16 January 2013, the US Food and Drug Administration (FDA) licensed trivalent recombinant hemagglutinin influenza vaccine (RIV3) (*Spodoptera frugiperda* cell line; Flublok) for active immunization of adults 18–49 years of age against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine [1]. This product is the first completely egg-free influenza vaccine for use in the general public. In June 2013, the Advisory Committee on Immunization Practices (ACIP) [2] voted 13–0 to include RIV3 in the egg algorithm for influenza vaccine recommendations. For the 2013–2014 influenza season, recommendations for individuals with a history of egg allergy included the following:

Persons who report having had reactions to egg involving such symptoms as angioedema, respiratory distress, light headedness, or recurrent emesis; or who required epinephrine or another emergency medical intervention may

receive RIV3, if aged 18 through 49 years and there are no other contraindications. [2]

As part of routine postmarketing safety surveillance, physicians at FDA monitor spontaneous reports of possible adverse events. During the first influenza season in which RIV3 was available for public use, FDA identified allergic and anaphylactic reactions in people with self-reported allergies to eggs and/or egg-based influenza vaccines. FDA reviewed individual adverse event reports to characterize the range, severity, and time course of symptoms, and evaluate the possibility that the vaccine caused or contributed to the adverse event.

METHODS

The Vaccine Adverse Event Reporting System (VAERS) is a national system for passive surveillance of adverse events following vaccination [3–5]. Established in 1990, VAERS is jointly managed by the FDA and Centers for Disease Control and Prevention and, in recent years, has received >30 000 reports per year. These reports of suspected vaccine side effects are submitted by healthcare providers, vaccine recipients, vaccine manufacturers, and other interested parties. FDA medical officers manually review all serious reports (events that are fatal, disabling, or life-threatening; require or prolong hospitalization; result in congenital anomalies; or require medical intervention to prevent such outcomes [6]). The review includes a clinical assessment based on the narrative text, vaccine(s), time course, treatment, medical history, medical records, and information about other exposures.

The search parameters of the VAERS database included all reports that listed RIV3 as a primary vaccine, from 16 January 2013 (date of US licensure) through 31 July 2014. Reports of allergic and anaphylactic reactions were identified based on descriptions of signs and symptoms that are typically observed in type I hypersensitivity reactions [7], such as wheezing, dyspnea, stridor, urticaria, angioedema, pruritus, hypotension, and vomiting. The results were summarized with descriptive statistics.

As part of routine safety surveillance, the FDA applied empirical Bayesian data mining [8] to identify disproportionality ($EB05 \geq 2$ [9]) in reports coded with allergy-related MedDRA preferred terms, such as *hypersensitivity*, *anaphylactic reaction*, *anaphylactoid reaction*, *anaphylactic shock*, and *allergy to vaccine*.

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RESULTS

Through 31 July 2014, VAERS received a total of 18 reports of adverse events following vaccination with RIV3. Twelve reports (Table 1) described signs and symptoms that were consistent with acute hypersensitivity reactions after administration of RIV3. The quantity and quality of clinical detail varied, but the cases were all considered to be possible anaphylaxis. The cases were notable for the rapidity and severity of symptoms, even after antihistamines and epinephrine were administered. Based on the available information, 3 cases appeared to meet criteria for level 2 anaphylaxis, according to the Brighton Collaboration case definition [7].

No fatalities or hospitalizations were reported, although 1 patient was held in the emergency department for overnight observation. All of the patients were women, ranging in age from 36 to 57 years (Table 1). Ten of the 12 patients reported a history of allergies (particularly to eggs) or previous reactions to other influenza vaccines. In all cases, RIV3 was listed as the only vaccine; that is, there were no concomitant immunizations. The 2013–2014 influenza season was the first year in which this vaccine was available; therefore, there were no reports of positive rechallenge (ie, same reaction after subsequent doses of the vaccine).

The data mining analysis did not reveal elevated values for any of the allergy-related preferred terms after RIV3.

DISCUSSION

VAERS has received reports of allergic reactions following vaccination with egg-free recombinant influenza vaccine, among patients with a self-reported egg allergy or previous allergic reaction to inactivated influenza vaccine. The results of this limited analysis suggest that allergic reactions following influenza vaccination are not necessarily related to egg proteins. Vaccine providers and other healthcare professionals, as well as consumers, should be aware that allergic reactions—sometimes requiring emergency medical intervention—have occurred following routine immunization with RIV3. Some patients experienced persistent wheezing and swelling—even after receiving epinephrine, nebulizers, and antihistamines. Without prompt recognition and treatment, the reactions might have become life-threatening. On 29 October 2014, the manufacturer's package insert [10] was revised to include the following under postmarketing experience: "Immune system disorders: anaphylaxis, anaphylactoid reactions, allergic reactions, and other forms of hypersensitivity."

The reactions reported to VAERS may be skewed by self-selection of patients who have chosen RIV3 because of current or past medical conditions, differential prescribing practices among healthcare providers, heightened monitoring and reporting of adverse events among atopic patients, stimulated

reporting for a novel vaccine, and other potential sources of bias and confounding. The small number of cases in this series and the heterogeneity of the reported reactions limit the ability to draw any definitive conclusions about a possible causal relationship with RIV3. It is not appropriate to estimate relative risks or rates based on VAERS reports, using product distribution data as a denominator. More specifically, these sparse data should not be used to compare the risk of allergic reactions after RIV3 to the published risk estimates [11–13] of anaphylaxis after egg-based influenza vaccines, and the proportion of hypersensitivity reactions after RIV3 should not be compared to the proportion in the rest of VAERS. It is entirely possible that many people with a history of egg allergies or allergic reactions to egg-based influenza vaccines received RIV3 and experienced no difficulties whatsoever. The observation of allergic reactions may reflect a pre-existing susceptibility to hypersensitivity among some individuals, rather than a causal relationship with the vaccine. There might also be a reporting bias because of the product's novel formulation. The preponderance of female patients is consistent with the higher proportion seen throughout VAERS [3]; it may also reflect differential utilization of primary care and preventive services among women, particularly healthcare workers.

Because of inconsistent report quality, there was great variability in the information provided about each patient's allergy history. In particular, there was little or no information about the severity, presentation, duration, and diagnosis of the allergy to eggs or influenza vaccines. Such details would be valuable for assessing the reactions and the risk for a future allergic reaction. For example, transient self-limited perioral paresthesia is quite different from a reaction that includes laryngospasm, bronchoconstriction, and hypotension necessitating intubation, mechanical ventilation, and vasopressor support.

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 [3]. However, passive surveillance systems such as VAERS are subject to many limitations, including underreporting, incomplete information in many reports, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups [3–5]. Because of these and other limitations, it is usually not possible to verify causal associations between vaccines and adverse events based on spontaneous reports to VAERS. Nevertheless, VAERS data have been used to describe a range of potential vaccine side effects and to look for unexpected patterns in demographics and clinical characteristics that might lead to hypotheses about relationships between vaccines and adverse events that can be tested with epidemiologic studies [14]. Independent data from the FDA's Mini-Sentinel System [15] may help to estimate the risk of anaphylaxis and other allergic reactions after RIV3, compared with other

Table 1. Allergic Reactions Reported Following Recombinant Influenza Vaccine: Vaccine Adverse Event Reporting System 2013–2014

Patient	Age and Sex	Symptoms	Onset Time	Allergy History ^a	Comment
1	48, F	Hives, facial/upper body flushing, and slight edema as well as increasingly persistent cough, raspy voice, and vomiting	10 min	Erythromycin, egg products, asparagus, mushrooms, peanuts: rash	Diagnosis: allergic reaction; also has fibromyalgia
2	49, F	Itching burning all over hives arms, legs, back seen in emergency department; treatment not specified	2 d	Multiple: egg and others	
3	42, F	Itchy, raised rash on face and arms, no difficulty swallowing/breathing; given loratadine and diphenhydramine	15 min	Reaction to flu vaccine—hives, itch	
4	43, F	Flushing; itching; throat tightening; erythematous excoriations on arms/legs clinic: oral diphenhydramine and epinephrine ×2; emergency department: intravenous diphenhydramine and steroids, follow-up primary care provider and allergist	<5 min	Flu vaccine, penicillin, feathers, environmental allergies	Diagnosis: allergic reaction to influenza vaccine; dermatitis
5	44, F	Diffuse erythematous red rash, malaise, and headache	<1 d	No egg allergy but patient requested egg-free vaccine	Immunocompromised (methotrexate for systemic lupus erythematosus); chronic cough
6	36, F	Red blotches to her neck, she said she felt itchy; denied respiratory distress or difficulty transported by emergency health services to emergency department; diphenhydramine and prednisone	15 min	Thimerosal-free flu vaccine: hives, itching	
7	43, F	Swelling of the eyes, lips, tongue, throat, headache, rash above right eye, difficulty breathing, “racing” of heart, blood pressure increased, took 2 diphenhydramine before vaccine; 1 d after vaccine went to emergency department; methylprednisolone, cetirizine, albuterol nebulizer, saline; given prescriptions for prednisone taper and EpiPen	Few minutes	Eggs, ciprofloxacin, and tramadol	
8	57, F	Swollen, red, itchy, inflamed face		1.5 d	Eggs; animal dander; environmental
9	49, F	Anaphylactic reaction	<1 d	Allergies (not specified)	
10	36, F	Hives; spread to entire body over 3–4 d; gave self famotidine and Benadryl; called physician 10 days after vaccination; prescription for Medrol pack ×2	1 d	Egg; also local urticaria after tetanus toxoid	
11	47, F	Nauseous, lips numb, head dizzy, felt miserable, blood pressure increased, red blotches on skin; called physician; diphenhydramine; refused to go to emergency department	<1 d	Latex, shellfish, eggs	
12	47, F	Arm burning, itching, swollen; distal tingling, headache, head congestion; gave self albuterol; called physician; prescription for steroid taper	Immediate	Egg; peanuts; gluten; clams; scallops; peppers	

^a As reported by patient.

influenza vaccines. The Clinical Immunization Safety Assessment Project [16] might be able to identify patients who have a high risk of immediate, life-threatening anaphylaxis following vaccination, and possibly determine which vaccine component (s) are associated with allergic reactions.

The benefits of influenza vaccination are well-established, and universal vaccination of individuals aged 6 months and

older is recommended [2]. Nevertheless, ACIP recommendations state that “[a] previous severe allergic reaction to influenza vaccine, regardless of the component suspected to be responsible for the reaction, is a contraindication to future receipt of the vaccine” [2]. The severity of the previous reaction should be assessed by a physician with expertise in the management of allergic reactions [2], and the risks and benefits of

influenza vaccination should be discussed, taking into account each person's current and past medical conditions and risk of complications associated with wild-type influenza.

Notes

Acknowledgments. Adverse events can be reported to the Vaccine Adverse Event Reporting System, PO Box 1100, Rockville, MD 20849-1100. Toll-free: 1-800-822-7967; fax: 1-877-721-0366. Email: info@vaers.org (<https://vaers.hhs.gov/esub/index>).

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The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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