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Adverse events associated with intranasal influenza vaccine in the United States

Neetu Vasu, Gisoo Ghaffari, Ethan T. Craig and Timothy J. Craig

Abstract

Methods: The goal of this review was to analyze the post-vaccination adverse effects associated with Live Attenuated Influenza Vaccine (LAIV) compared to those of the Injectable Trivalent Inactivated Vaccine (TIV) in patients with egg allergy and asthma. PubMed, Ovid, and Google searches were conducted. Searched articles relating to allergic reactions, asthma or food allergy, and LAIV were reviewed.

Results: Similar or superior efficacy of LAIV compared to TIV was reported by various studies. Respiratory symptoms were the most common adverse events following both vaccinations. Although no evidence was found of a direct causal relationship between intranasal influenza vaccine and anaphylaxis due to egg allergy, a number of cases of anaphylaxis were reported. To date, there are no studies directly comparing the frequency of anaphylactic reactions between the two vaccines.

Conclusions: The safety of LAIV in individuals with unstable asthma and egg allergy has not been established and it should be avoided in these populations. For patients with unstable asthma, TIV should remain the therapy of choice.

Keywords: asthma, egg allergy, vaccine, influenza vaccine, intranasal influenza vaccine, adverse effects, adverse events

Introduction

Influenza virus is a global cause of morbidity and mortality. In the United States, each year, 10–20% of adults and 15–40% of children develop symptomatic influenza resulting in 30,000–70,000 deaths, 100,000–150,000 hospitalizations, and up to \$3 billion in medical costs [Zangwill and Belshe, 2004]. Universal vaccination of children 6–59 months of age with conventional trivalent inactivated influenza vaccine (TIV) is currently recommended in the US [Belshe *et al.* 2007]. TIV has been in the market since at least 1960 [Zangwill and Belshe, 2004]. The search for an alternative vaccine that is easier to administer to a large scale population, and that possesses a milder side effect profile has been under investigation for many years.

Live, attenuated intranasal influenza vaccine (LAIV), also known as FluMist, was approved by the FDA in June 2003 as the first vaccine in the United States to be administered intranasally. Manufactured by MedImmune, Inc. (Gaithersburg, MD), LAIV is a live, attenuated,

cold adapted, trivalent vaccine, composed of three influenza viral strains (H1N1, H3N2, and B) [Flumist, 2006] and was approved for intranasal use among healthy individuals 5–49 years of age [Izurieta *et al.* 2005]. Cold adaptation has been shown to prevent replication in the lower respiratory tract [Jacobson and Poland, 2002].

According to the report by ACIP [Smith *et al.* 2006], when compared to injectable TIV, LAIV offers advantages of ease of use, longer duration of protection, better cross-protection for antigenic drift, higher efficacy, and two forms of immune protection (serum and mucosal) [Block, 2004]. Despite these benefits, LAIV is reported to have unique adverse events. The aim of this review is to analyze the adverse events associated with LAIV, with specific focus on safety for egg-allergic patients and patients with asthma.

Methods

A PubMed, Ovid, and Google search was conducted using the search terms: “intranasal

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influenza vaccine,” “intranasal influenza vaccine adverse event,” “intranasal influenza vaccine side effect,” “intranasal influenza vaccine egg allergy,” “FluMist,” and “FluMist egg allergy.”

Results

In July 1999, a randomized, controlled trial was conducted, testing the effectiveness of LAIV in healthy, working adults. Over a period of two months, 4561 persons were randomized to 3041 vaccine recipients and 1520 placebo recipients. Vaccine recipients had a 17.7% higher risk of experiencing a runny nose and a 10.3% higher risk of reporting sore throat the week after vaccine administration. Twenty-eight days post-vaccination, only five serious adverse reactions were reported in the vaccinated group, while four serious adverse reactions were reported in the placebo group. None of the adverse events were directly related to vaccine treatment and there was no mention of anaphylaxis or other allergic reactions, especially pertaining to egg allergy [Nichol *et al.* 1999].

In March, 2004, a review article addressed the safety and efficacy of TIV compared to LAIV. LAIV was found to be generally safe and well tolerated. Several symptoms occurred significantly more among children immunized with LAIV than among controls, including nasal congestion, fever, vomiting, abdominal pain, and muscle aches. Safety data from a large, prospective, randomized, double blind, placebo-controlled trial of LAIV in 9689 children from 1 to 17 years of age measured adverse events associated with clinic visits, ED visits, or hospitalizations. In children 18–35 months, the most common discharge diagnosis of LAIV recipients compared to placebo recipients was asthma (relative risk, 4, $P = 0.02$). No anaphylactic reactions or other serious adverse events were reported [Zangwill and Belshe, 2004].

In 2005, a review was conducted of all adverse events reported to the Vaccine Adverse Event Reporting System (VAERS), following the administration of live intranasal influenza vaccine during the 2003–2004 and 2004–2005 influenza seasons. Of the 54 allergic events reported, only 7 were possible anaphylaxis, 4 individuals having throat swelling, and 1 reporting periorbital swelling. Of these seven possible anaphylactic cases, none had prior history of allergy to egg or other vaccine components. The remaining 47 reports consisted of various allergic reactions

including rash, urticaria, or edema, mostly in the face and neck.

Other adverse events reported are listed in Table 1 in decreasing order of incidence including respiratory illness (47.2%), constitutional (14.6%), other (9.6%), abdominal symptoms (7.2%), ear–nose–throat symptoms (3.9%), neurological (2.2%), cardiovascular (2.2%), and ocular symptoms (1.5%) [Izurieta *et al.* 2005].

A recent review conducted by MedImmune analyzed serious adverse events from all clinical trials within 28 days after vaccination in adults and within 42 days in children. In those children receiving active vaccine compared to placebo, significant differences were noted in the incidence of headache and runny nose/nasal congestion following the first dose, and significant differences were noted in incidence of runny nose/nasal congestion and cough following the second dose. A summary of this study and incidence of adverse events is included in Table 2.

In a subset of adults 18–49 years of age from the Adult Efficacy Trial, statistically significant events were noted in all categories of cough, runny nose, sore throat, chills, and tiredness/weakness. A summary of this study and incidence of adverse events is included in Table 3.

Other adverse events noted, without numerical data, included nausea, rash, epistaxis, hypersensitivity reactions (including anaphylaxis, facial edema, urticaria), and Bell’s palsy [Flumist, 2006].

The most recent article in the New England Journal of Medicine concluded that among young children, LAIV had significantly better efficacy than TIV. An evaluation of the risks and benefits indicated that LAIV is effective and safe for children 12–59 months of age who do not have history of asthma or wheezing [Belshe *et al.* 2007]. Safety data were available for 8352 children. There were fewer cases of influenza in the group receiving LAIV than in the group that received TIV (153 vs. 338 cases, $P < 0.001$). Wheezing within 42 days after the first dose of LAIV was more common than after TIV administration, especially among children 6–11 months of age. Rate of hospitalization for any cause during the six months after vaccination were higher among recipients of LAIV than TIV.

Table 1. Reported adverse events (VAERS), 2003–2005, following administration of intranasal influenza vaccination [4].

Main condition	All reports: No.(%) N = 460	All serious reports: No.(%) N = 40
Respiratory (influenza-like illness, vaccine failure, rhinitis, pharyngitis, tracheitis, secondary transmission, sinusitis, asthma, pneumonia, other)	217 (47.2)	15 (37.5)
Constitutional (weakness/tiredness, fever, headache, dizziness, arthritis)	67 (14.6)	4 (10)
Allergic (possible anaphylaxis, other allergic)	54 (11.7)	6 (15)
Abdominal symptoms	33 (7.2)	1 (2.5)
Ear–nose–throat (epistaxis, nose ulcer, redness, ear infection, oral herpes simplex)	18 (3.9)	0 (0)
Ocular (edema, retinal hemorrhage, eye pain)	7 (1.5)	1 (2.5)
Neurological (Guillain–Barre syndrome, Bell's palsy, febrile seizures, encephalomyelitis, encephalitis, other)	10 (2.2)	7 (17.5)
Cardiovascular (pericarditis, myocardial infarction, chest pain/discomfort)	10 (2.2)	3 (7.5)
Other (vaccine administration error, other reports)	44 (9.6)	3 (7.5)

Table 2. Summary of solicited events from healthy children 60–71 months of age observed within ten days after each dose of vaccine and placebo [3].

	Post-dose one		Post-dose two	
	FluMist	Placebo	FluMist	Placebo
No. of subjects who returned with diary cards	214	95	161	75
Event	%	%	%	%
Any event	65.0	62.1	66.5	53.3
Cough	25.7	32.6	38.5	30.7
Runny nose/nasal congestion	48.1	44.2	46.0	32.0
Sore throat	12.6	18.9	9.3	16.0
Irritability	17.8	15.8	9.9	9.3
Headache	17.8	11.6	6.8	16.0
Chills	6.1	5.3	2.5	4.0
Vomiting	4.7	3.2	5.6	12.0
Muscle aches	6.1	4.2	5.0	4.0
Decreased activity	14.0	12.6	10.6	13.3
Fever				
Temp 1	10.3	9.5	4.3	4.0
Temp 2	2.3	2.1	0.6	1.3
Temp 3	0.0	0.0	0.0	0.0

Table 3. Summary of solicited events observed within seven days from healthy adults 18–49 years of age after each dose of vaccine and placebo [3].

	FluMist	Placebo
No. of subjects who returned with diary cards	2548	1290
Event	%	%
Any event	71.9	62.6
Cough	13.9	10.8
Runny nose	44.5	27.1
Sore throat	27.8	17.1
Headache	40.4	38.4
Chills	8.6	6.0
Muscle aches	16.7	14.6
Tiredness/Weakness	25.7	21.6
Fever		
Oral Temp > 100°F	1.5	1.3
Oral Temp > 101°F	0.5	0.7
Oral Temp > 102°F	0.1	0.0
Oral Temp > 103°F	0.0	0.0

The incidence of other serious adverse events did not differ significantly between the two groups.

Discussion

One of the aims of this review was to determine whether any comparative advantage existed between LAIV and TIV use in egg-allergic patients or in those with asthma. After the available literature was reviewed, no evidence was found that suggested a direct or causal relationship between LAIV and anaphylaxis due to egg allergy; however, a few isolated cases of anaphylaxis without defined etiology were reported as stated in the 2006–2007 FluMist package insert and 2005 VAERS review [Izurieta *et al.* 2005].

LAIV is comprised of three viral strains that are replicated in incubated eggs. These viral harvests are then blended and diluted with allantoic fluid derived from eggs to produce the final influenza vaccine. Due to the involvement of eggs in the production of LAIV and the few isolated cases of anaphylaxis reported, LAIV has been contraindicated in individuals with a history of hypersensitivity, especially anaphylactic reactions, to any component of LAIV, including eggs or egg products. Because of the screening for egg allergy as exclusion for the vaccine the safety of this cohort cannot be established. Also, due to the lack of clinical research regarding safe use of

LAIV in egg-allergic patients it appears that this contraindication should remain.

According to the 2005 VAERS review, 47.2% of the adverse events reported to VAERS during 2003–2005 following the administration of intranasal influenza vaccination were respiratory related [Izurieta *et al.* 2005]. This database demonstrated runny nose, nasal congestion, and cough as significant adverse events post-vaccination in both pediatric and adult efficacy trials. In addition, according to Zangwill *et al.* and their data assessment of the California Kaiser Permanente Health Care Plan [Zangwill and Belshe, 2004], asthma was the leading discharge diagnosis in a group of children who received the intranasal influenza vaccine. Although these reports suggest respiratory symptoms as being the leading adverse event post-vaccination, the statistical significance of the latter study is questionable. However, it still appears that TIV, due to the proven safety record in asthma is the preferred therapy for influenza prophylaxis in patients with unstable asthma.

Conclusion

A summary of clinical trials and reviews assessing adverse events associated with intranasal influenza vaccine is given in Table 4. Currently, LAIV offers no advantages over the TIV for patients with egg allergy or asthma. Comparative data are lacking comparing TIV and LAIV especially in relation to these specific side effects. LAIV is contraindicated in individuals with a history of hypersensitivity, especially anaphylactic reactions, to any component of LAIV, including eggs or egg products. Since subjects with egg allergies are not included in clinical trials of LAIV, the risk of anaphylaxis in this cohort following vaccine could not be fully assessed. In addition, the literature fails to document any cases of accidental administration of LAIV to those with a history of egg allergy to determine the true risk. The unique side effect profile associated with LAIV causing significant wheezing up to 42 days following vaccine administration precludes this vaccine from administration to asthmatic patients who have unstable asthma. For this population, TIV appears to remain the vaccine of choice. However, it is the author's opinion that LAIV is safe to use in patients with asthma unless the asthma is unstable. Based on the current efficacy and safety studies, LAIV is a safe and effective alternative to TIV for healthy subjects 5–49 years of age who do not have egg allergy or unstable

Table 4. Summary of clinical trials and reviews assessing adverse events associated with intranasal influenza vaccine [8,1,4,3].

Reference	Type of study	Population	Results
Nichol, <i>et al.</i> [1999]	Randomized, controlled	4561 healthy, working adults	• 17.7% higher chance of experiencing runny nose • 10.3% higher chance of experiencing sore throat • No allergic reaction
Zangwill Belshe, [2004].	Double blind, placebo-controlled	9689 children, 1–17 years of age	No serious adverse event or anaphylactic reaction reported
Izurieta <i>et al.</i> [2005]	Reported Adverse Events (VAERS), 2003–2005, following administration of intranasal influenza vaccination		• Seven possible anaphylactic reactions (no person with prior history of egg allergy): – four individuals with throat swelling – one individual with periorbital edema • 47.2% respiratory-related reactions
Flumist [2006]	Serious adverse events from all clinical trials for 28 days after vaccination in adults and 42 days in children.	• Children 60–71 months • Adults 18–49 years of age	• Children – highest incidents of headache, runny nose/nasal congestion, and cough • Adults – highest incidents of cough, runny nose, sore throat, chills, and tiredness/weakness

asthma and in fact the efficacy of LAIV appears to be slightly better.

Conflict of interest statement

None declared.

Questions:

1. Intranasal *Influenza* live virus vaccine, like injectable inactivated *Influenza* vaccine, is contraindicated in which diagnosis?

- a. asthma
- b. egg allergic

- c. atopic
- d. latex allergic
- e. gelatin allergic

ans- b

2. Intranasal *Influenza* live virus vaccine should be used with caution in patients with asthma because of which adverse effect?

- a. Allergic reactions
- b. Upper respiratory infection
- c. generation of IgA

- d. generation of IgE
- e. induction of IgG

ans- b

3. An advantage of intranasal *Influenza* live virus vaccine over injectable inactivated *Influenza* vaccine is?

- a. induction of IgG
- b. induction of IgA
- c. lack of egg allergen in the preparation
- d. much greater safety
- e. protection against avian influenza

ans: b

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