

CORRESPONDENCE

Evaluation of flu vaccines with regard to their egg protein content

DOI:10.1111/j.1399-3038.2011.01158.x

Approximately 20% of the US population contracts influenza every year. Flu vaccines have been used as a preventive measure since 1945. However, as a result of the production methods utilized for generating influenza vaccines, significant egg allergy is a contraindication to vaccination. Sensitivity to egg is among the leading causes for food allergy in children, affecting approximately 1.6% of pediatric population in the United States (1). Vaccines that are produced by injecting influenza virus into fertilized chicken eggs may contain small amounts of egg protein allergens, and immunization with these vaccines has been reported to provoke anaphylactic reactions in susceptible children (2). The American Academy of Pediatrics (AAP) recommends that influenza vaccines produced in eggs not be used in patients with severe systemic allergic reactions to egg. The AAP also states that prior to immunization, children with egg allergy and asthma should undergo prick skin testing with any influenza vaccine containing ovalbumin (3).

Previous studies indicate that even patients with significant egg allergy can be safely vaccinated in a 2-dose protocol when the preparation contains <1.2 µg/ml ovalbumin (4).

The aim of our study was to evaluate influenza vaccine samples and select the lowest ovalbumin-containing lots for administration to egg-allergic patients. A highly sensitive competitive ELISA was developed to measure ovalbumin levels as low as 1 ng/ml. We measured and compared egg-white protein concentrations of several flu vaccine lots from 1997 to 2010 to identify lots that were safe for administration in

egg-allergic patients. Based on the results of our studies, over the last several years, we have administered influenza vaccine to patients, known to be sensitive to hen's egg, without adverse events.

Since the 1997–1998 flu season, 67 lots of vaccine have been tested, demonstrating manufacturer-to-manufacturer, as well as lot-to-lot variability (Fig. 1). In brief, Immulon 4HBX medium binding (Thermo Fisher Scientific Inc. Waltham, MA) plates were coated with Sigma Ovalbumin Grade VII (St. Louis, MO, USA) overnight at a concentration of 3000 ng/cm². Standard curve dilutions from 1 to 30,000 ng/ml and sample serial dilutions from 1:2 to 1:32 were prepared. Aliquots containing standard curve and vaccine sample dilutions were incubated with rabbit anti-ovalbumin (Millipore, Billerica, MA, USA) antibody solution at concentration of 3.3 nM for 2 h at 37°C. These reaction mixtures were then transferred to the plates previously coated with ovalbumin and blocked with 2% Bovine Serum Albumin (BSA) in Phosphate-buffered saline with Tween 20 at room temperature and incubated for 1 h at 31°C. Following thorough washing, the plates were incubated with detecting goat anti-rabbit IgG – Peroxidase antibody (Sigma, St Louis, MO, USA) for 1 h at room temperature, washed and developed with SureBlue TMB 1-Component Microwell Peroxidase Substrate (KPL, Gaithersburg, MD, USA). The results were read on a Spectra Max ELISA reader and analyzed with SoftMaxPro v5 software, Molecular Devices Inc., Sunnyvale, CA. The brands and lots with the lowest level of

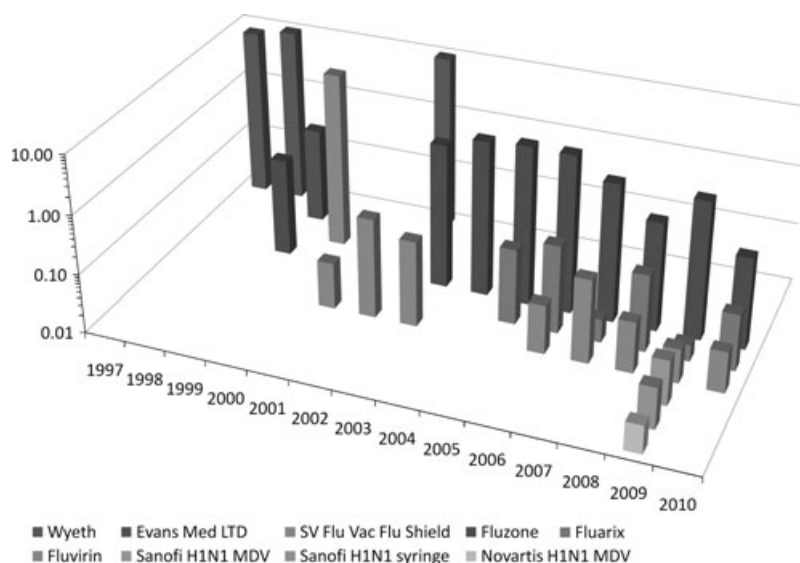


Figure 1 Ovalbumin content (µg/ml) of influenza vaccines from 9 commonly used manufacturers from 1997 to 2010.

ovalbumin were chosen for immunization of egg-allergic patients to avoid adverse events. The concentration of ovalbumin in the same brand varied from year to year (Flumist® (MedImmune LLC, Gaithersburg, MD, USA), 0.05–0.8 µg/ml; Flushield® (Wyeth Laboratories, Marietta, PA, USA), 6.90–38.30 µg/ml; Fluarix® (GlaxoSmithkline Biologicals, Dresden, Germany), 0.025–0.31 µg/ml; Fluzone® (Sanofi Pasteur, Inc. Swiftwater, PA, USA), 0.30–8.05 µg/ml; Fluvirin® (Novartis Vaccines and Diagnostics Limited, Speke, Liverpool, UK), < 0.01–0.55 µg/ml). For some of the recent lots of specific vaccines, the levels of ovalbumin were undetectable. Fluarix® appeared to be the most consistent (standard deviation = 0.12 µg/ml) among all tested brands from year to year and contained significantly lower ovalbumin concentrations.

Batch-to-batch variability of egg content appears to have improved in most currently available influenza vaccines, but still necessitates an informed and cautious approach to vaccination of egg-allergic individuals (5). Recent reports indicate that skin-testing may produce false-positive results (5). Previous studies show that graded-dose protocols can be safely used when administering influenza vaccine to egg-allergic patients (5). Low ovalbumin-containing flu vaccines in conjunction with graded-dose protocols increase the safety of administration.

Unless the egg content of the specific vaccine is known, caution must be exercised when administering the flu vaccine to egg-allergic patients (4). New vaccines, such as the Novartis H1N1 and seasonal flu vaccines Fluarix® and Fluvirin®, contain ≤ 1 µg of ovalbumin per dose as per manufacturer product insert, which was confirmed by our assay.

According to our data, influenza vaccines manufactured over the past few years contain very low quantities of ovalbumin. Fluarix® and Fluvirin® are two vaccines that based on the results of our sensitive competition ELISA have the lowest content of ovalbumin. Based on a recent retrospective study performed by our pediatric allergists, administration of Fluarix® and Fluvirin® produced no serious allergic reactions among egg-allergic pediatric patients who underwent a two-dose protocol for administration of these vaccines, with only a small percentage of patients developing mild allergic symptoms (6).

Marina E. Goldis, Ludmilla Bardina, Gustavo Gimenez, Jing Lin & Hugh A. Sampson
Mount Sinai School of Medicine, New York, NY, USA
E-mail: Marinaelli2001@yahoo.com

References

1. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol* 2006; **117**: S470–5.
2. Lack G. Clinical Update. Food Allergy. *New Engl J Med*. 2008; Sep 18; **359**(12): 1252–60.
3. Pickering LK, Baker CJ, Long SS, McMillan JA, eds. Red Book: 2006 Report of the Committee on Infectious Diseases, 27th edn. Elk Grove Village, IL: American Academy of Pediatrics, 2006: 35.
4. James JM, Zeiger RS, Lester MR, et al. Safe administration of influenza vaccine to patients with egg allergy. *J Pediatr*. 1998;**133**:624–8, Fort Collins, USA: Colorado Allergy and Asthma Centers.
5. Settipane RA, Siri D, Bellanti JA. Allergy and Asthma Proceedings, Volume 30, Number 6, November/December. 2009: 660–5(6).
6. Thanik ES, Cox AL, Sampson HA. Administration of a low egg-containing influenza vaccine [Fluarix®] in an egg-allergic pediatric population. *J Allergy Clin Immunol* 2010; **125**: S1. AB25