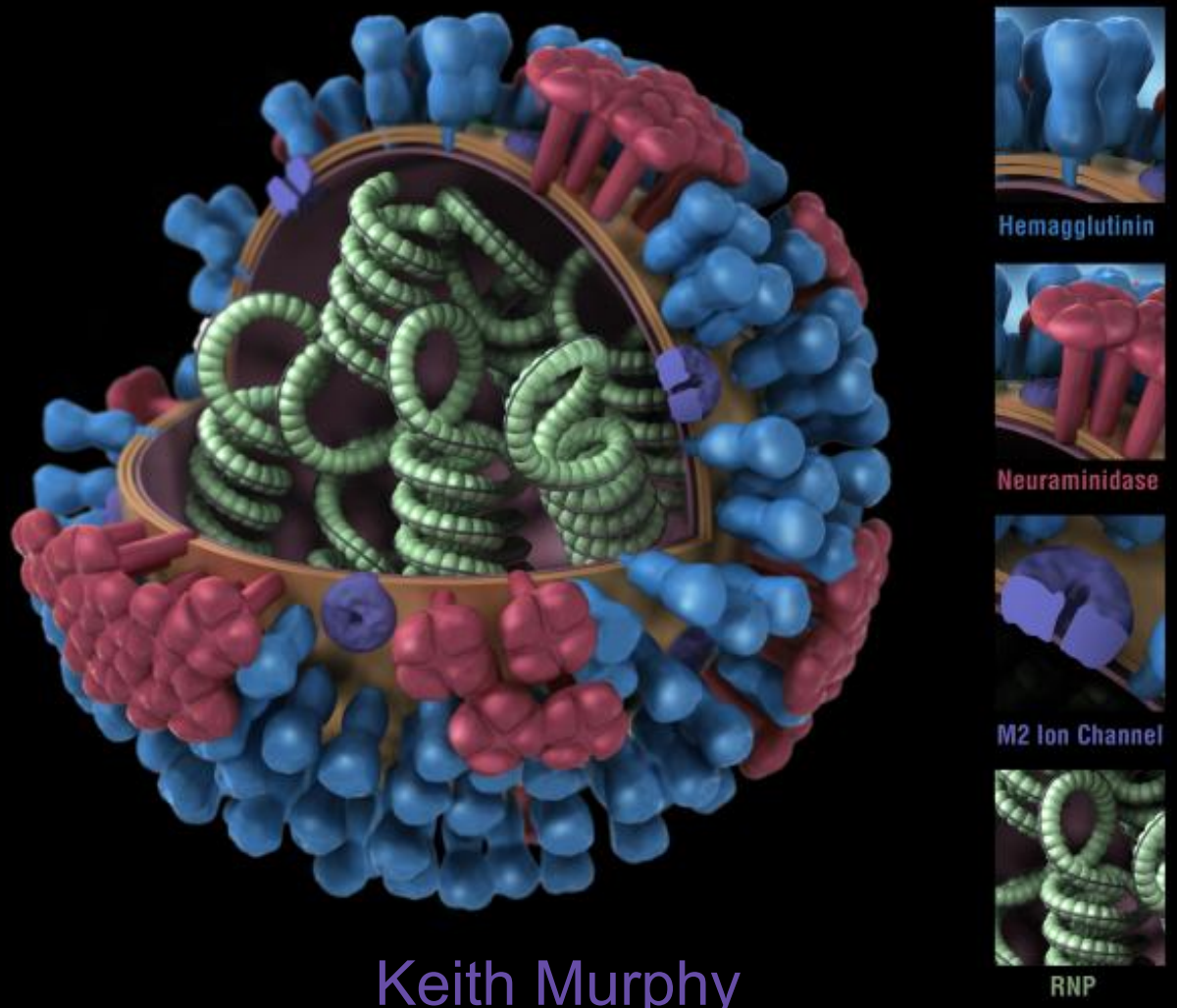
Egg Allergy and Influenza Vaccination



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Med/Peds

(Originally created: January 5, 2010)

Image via http://phil.cdc.gov/

What is the issue?

- Both IM and intranasal forms of the vaccine are cultivated in chorioallantoic fluid from chicken embryos.

- Ovalbumin is the dominant protein (50 - 80%), and thought to represent the major allergen.

So, who cares?

- Egg allergy affects 2.6% of children by age 3, with a point prevalance of 1.6%[1]
- Estimated US population of 308,415,956.[2]

- That's 5,000,000 kids!

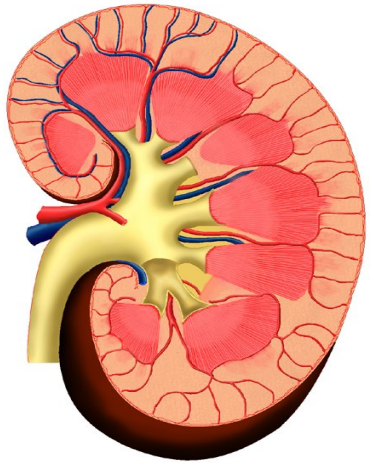
- Anaphylaxis is rare, however this may be artificially lowered because egg-allergic patients avoid influenza vaccines.
- One reported case of fatal anaphylaxis.[3]

1.Eggesbø M, *et al*. The prevalence of allergy to egg: a population-based study in young children. *Allergy* 2001;56:403-11.
2.http://www.census.gov/main/www/popclock.html. Accessed 01/03/2010.
3.Bierman CW, *et al*. Safety of influenza vaccination in allergic children. *J Infect Dis* 1977;136(suppl):S652-5.

Stupid eggs.

So why not make the vaccine some other way?

- There are novel culture media under investigation, but none currently available in the USA.
- Celvapan (Baxter)
  - Influenza H1N1
  - Grown in mammalian culture
- Optaflu (Novartis)
  - Seasonal influenza
  - Grown in MDCK (Madin Darby Canine Kidney)



1. Erlewyn-Lajeunesse, *et al*. Recommendations for the administration of influenza vaccine in children allergic to egg. *BMJ* 2009;339:b3680.

Bierman CW, *et al*.
Safety of influenza vaccination in allergic children.
J Infect Dis 1977;136(suppl):S652-5.

- Looked at 142 children (allergic to chicken, eggs or feathers)
- Skin tested with vaccine, and excluded if positive (12 kids).

- Out of 130 children
  - No immediate allergic reaction
  - 3 had negative delayed reactions:
    1. Flare of eczema 24-hours post (placebo, with thimerosal)
    2. Urticaria 8-hours post, controlled by antihistamines
    3. Local reaction 70mm 2-hours post, scattered hives 4-6 hours, and progressed to erythema multiforme 8 days later.

*** **In the discussion**: "The importance of this study is underscored by the anaphylactic death after influenza immunization of a child known to be allergic to egg in a Seattle physician's office eight years ago."

Davies R, *et al*.
Egg allergy, influenza vaccine and immunoglobulin E antibody.
J Allergy Clin Immunol 1976;57:373-83.

(Abstract reviewed)

- Skin prick testing to influenza vaccine, did not vaccinate anyone.
- Chose 22 patients with a definite history of egg allergy.
- 7 out of 22 had positive skin test
  - 2 of the 7 had "previously been given influenza vaccine and both had developed adverse reactions."

Miller JR, *et al*.
The safety of egg-containing vaccines for egg-allergic patients.
J Allergy Clin Immunol 1983;71:568-73.

(Abstract reviewed)

- 42 patients with history of egg sensitivity
- Skin tested with:
    1. egg antigens,
    2. 6 egg-propagated vaccines, and
    3. oral egg challenge.
- Vaccination withheld from 3 patients who had a history of severe reaction after egg ingestion and strongly positive skin reactivity to egg and vaccine.

- 37 out of 42 patients received vaccine with no reactions or minimal ones (pruritus, headache and apprehension).

Murphy KR, *et al*.
Safe administration of influenza vaccine in asthmatic children hypersensitive to egg proteins.
J Pediatr 1985;106:931-3.

- 6 children, ages 4 to 7 with
  - chronic severe asthma and
  - documented reactions to egg (physician observed).
- Puncture skin testing to egg white, egg yolk, vaccine
- Intradermal testing with 1:100 dilution of vaccine
- All of the patients had:
  - positive puncture to egg white and yolk,
  - negative puncture test with vaccine, and
  - positive to intradermal tests with vaccine

Continued... →

Murphy KR, *et al*.
Safe administration of influenza vaccine in asthmatic children hypersensitive to egg proteins.
J Pediatr 1985;106:931-3.

- Vaccine given based on multistep protocol previously shown to work for measles vaccine[1]:
  1. 0.05 mL diluted to 1:100
  2. 0.05 mL diluted to 1:10
  3. 0.05 mL full strength
  4. 0.10 mL full strength
  5. 0.15 mL full strength
  6. 0.20 mL full strength

Given every 15 minutes.

- No reactions after 11 of 12 injections. (One child with mild wheezing)

1. Herman JJ, et al. Allergic reactions to measles (rubeola) vaccine in patients hypersensitive to egg protein. J Pediatr 102:196,1983.

James JM, *et al*.
Safe administration of influenza vaccine to patients with egg allergy.
J Pediatr 1998:133:624-8.

- Multicenter trial, 1994 through 1997
- 83 subjects:
  - 27 with a convincing history of anaphylaxis after eating egg or egg products
  - 31 with a positive history and positive skin test to egg
  - 25 with positive response to a blinded oral challenge to egg
- Excluded if:
  - Asthma under poor control (FEV1 < 70%),
  - acute febrile illnesses (T > 101° F)
  - unstable medical condition, immune deficiency or neoplastic disease

Continued... →

James JM, *et al*.
Safe administration of influenza vaccine to patients with egg allergy.
J Pediatr 1998:133:624-8.

- Administration via two-step protocol:
  1. First dose 1/10th
  2. Second dose 9/10th

  Given 30 minutes apart

- They note that the detectable egg protein in their vaccines ranged from 0.02 to 1.2 mcg/mL over the 3 years.

Continued... →

James JM, *et al*.
Safe administration of influenza vaccine to patients with egg allergy.
J Pediatr 1998:133:624-8.

- All patients were safely immunized.
- 4 patients with egg allergy had positive skin test to vaccine without reaction to vaccine.
- No severe adverse reactions
- 8 mild adverse reactions, including throat itching, small hive, local itching, mild URI, delayed fussiness.

- Therefore, administration in two doses may be no different than administration of a single dose (when egg protein content can be reliably determined).

Esposito S *et al*.

Safe administration of an inactivated virosomal adjuvanted influenza vaccine in asthmatic children with egg allergy.

Vaccine 2008;26:4664-8.

- Used Inflexal V, a novel virosome-based influenza vaccine.
- Not available in USA
- Purification process results in lowest amount of ovalbumin (0.001 mcg per dose)
- 88 children with egg allergy given the whole dose as a single injection
- Monitored for 4 hours: O_2 sat, HR, RR, BP

- No difference between the two groups.
- Adverse events, described as mild:
    1. A child with mild egg allergy: bronchospasm
    2. Child with severe egg allergy: erythema
    3. Control subject: bronchospasm

Seasonal Influenza Vaccine

(Approved for use in USA by FDA)

Vaccines	**Ovalbumin** (mcg)	Latex	Thimerosal (mcg mercury)	Antibiotics	Formaldehyde (mcg)	Gelatin
Afluria	**≤ 1**	no	24.5	neomycin, polymixin B		
Agriflu	**≤ 0.4**	no	none	neomycin, kanamycin	< 10	
FluLaval	**≤ 1**	no	25	none	≤ 25	
Fluarix	**≤ 1**	YES	none		< 50	
Fluvirin	**≤ 1**	no	< 1	neomycin, polymixin B		
Fluzone	**≤ 5**	no	25	none	< 100	0.05%
Fluzone High-Dose	**≤ 5**	no	25	none	< 100	
FluMist	**≤ 0.24**					

Influenza vaccine ovalbumin content in 1970s:

20 to 45 mcg

per dose![3]

1. From Prescribing Information Package Inserts accessed on 01/02/2010 via: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094045.htm
2. Kelso JM, et al. Influenza vaccination in individuals wtih egg allergy. UpToDate. http://www.uptodate.com. Oct 7, 2009. Accessed 12/30/2009.
3. Davies R, *et al*. Egg allergy, influenza vaccine and immunoglobulin E antibody. *J Allergy Clin Immunol* 1976;57:373-83.

How much does it take?

For vaccinations?

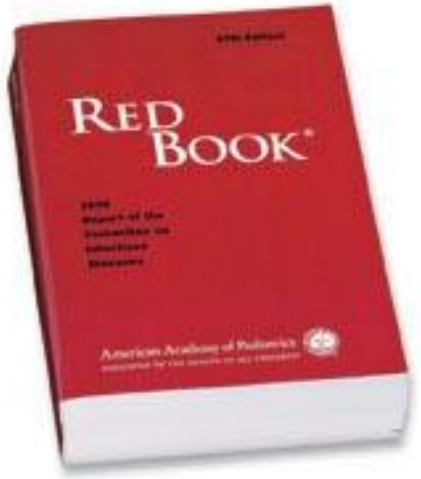
- The consensus based on James *et al* and Esposito *et al* is a level of ovalbumin ≤ 1.2 mcg per mL is safe

For consumption?

- LOAEL (Lowest observed adverse-effect level
- 130 mcg of egg white proteins[1]
- 2 mg of raw egg white (200 mcg protein)[2]

1. Taylor SL *et al*. Factors affecting the determination of threshold doses for allergenic foods: how much is too much? *J Allergy Clin Immunol* 2002;109:24-30.
2. Morisset M, *et al*. Thresholds of clinical reactivity to milk, egg, peanut and sesame in immunoglobulin E-dependent allergies: evaluation by double-blind or single-blind placebo-controlled oral challenges. *Clin Exp Allergy* 2003;33:1046-1051.

AAP Guidelines



Essentially per Murphy *et al.*

- If a negative scratch/prick/puncture test (1:10 dilution), and intradermal test (1:100), then the full vaccine may be given.

- However, if positive, they suggest this multistep protocol:

1.0.05 mL diluted to 1:10
2.0.05 mL full strength
3.0.10 mL full strength
4.0.15 mL full strength
5.0.20 mL full strength

Given at 15 to 20 minute intervals.

1.American Academy of Pediatrics. Active Immunization. In: Pickering LK, *et al*. *Red Book: 2009 Report of the Committee on Infectious Diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009:48-9.

AAAAI Guidelines

Essentially the same as the AAP.

- A consistent clinical history of anaphylaxis to egg
- Skin prick testing with the (full strength) vaccine (may choose to use in vitro IgE antibody testing)
- Intradermal skin testing with a 1:100 dilution of the vaccine
- These are negative, administer full dose of vaccine

- If positive, they recommend a graded dose protocol be used, and offer an example (same as AAP, with 15-minute intervals)

1.Li JT, *et al*. Administering the H1N1 influenza vaccine in patients with suspected egg allergy. *American Academy of Allergy Asthma and Immunology*. Treatment Guidelines. Sept 1, 2009. http://www.aaaai.org

Access this talk
http://keithmurph