

Influenza Vaccine and Egg Allergy: Nearing the End of an Evidence-Based Journey

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Up until just a few years ago, the administration of influenza vaccine to patients with egg allergy was contraindicated based on the not-illogical concern that the injection of a vaccine that contained egg protein into a person with IgE antibodies directed against such protein could cause anaphylaxis.¹ Numerous studies had been published that indicated that influenza vaccine could be safely administered to recipients with egg allergy²; however, as recently as 2010, the notion that patients with egg allergy could be given the influenza vaccine as a single dose without prior vaccine skin testing was so controversial that a *Clinical Pearls* article in the *Journal of Allergy and Clinical Immunology* that proposed this had to be relabeled an *Editorial*.³

There have now been a total of 28 studies published on this subject, in which, collectively, 4315 subjects with egg allergy, including 656 with histories of anaphylactic reactions to the ingestion of eggs, have received influenza vaccine with no serious reactions.² Such reassuring data led to a dramatic shift in recommendations from the Advisory Committee on Immunization Practices beginning in 2011, which indicated that patients with egg allergy who developed only hives with egg ingestion (the only reaction in the majority of such patients) should receive influenza vaccine in the usual manner and be observed for 30 minutes afterward, and that patients with more severe reactions to the ingestion of egg should be referred to an allergist for vaccination.⁴ The vaccine practice parameter for allergists also recommends that even patients with severe egg allergy receive the vaccine as a single dose while under observation.⁵ An additional statement, endorsed by the Joint Task Force on Practice Parameters, states that, given the overwhelmingly reassuring safety data, special observation periods or allergy referrals are unnecessary for any patient.⁶

Several smaller steps were taken along the way. These included skin testing patients with influenza vaccine in an attempt to identify those who would react and administering the vaccine in graded doses. However, even patients with egg allergy and with positive skin test results to the vaccine and those administered the vaccine as a single dose also tolerated the vaccine,² and such measures are no longer recommended.⁷ The reassuring safety

profile of influenza vaccine in recipients with egg allergy is due to the amount of egg protein in all available vaccines being below the threshold required to elicit a reaction even in sensitized persons.² Thus, the previously recommended practice of seeking out a particular brand of influenza vaccine with a particularly low amount of egg protein is no longer necessary.

Two vaccines that are not grown in eggs have recently been introduced. One grows influenza virus in cell culture and is approved for those 18 years of age and older. The other produces recombinant protein in an insect cell line and is approved for those ages 18 to 49 years. These vaccines could be considered for the rare adult with egg allergy; however, these are not preferred over egg-based vaccines, which can be used with the patient under observation, and a vaccination opportunity should not be missed because an egg-free vaccine is not immediately available.⁸ These vaccines should not be used “off label” in children, where their safety and efficacy have not been demonstrated.^{2,8}

One of the final missing pieces of information on this topic is addressed in an important article by Des Roches et al⁹ in this issue of the *Journal of Allergy and Clinical Immunology: In Practice*. Intranasally administered live attenuated influenza vaccine (LAIV) is also grown in eggs and contains a small amount of residual egg protein (<0.24 µg/dose), just as with the injectable inactivated influenza vaccines (IIV). Thus, given the overwhelming safety data on the administration of IIV to recipients with egg allergy, one would imagine that LAIV would be similarly well tolerated. However, all prior studies on this topic used IIV, and there were, until now, no data on the safety of LAIV in this regard. Des Roches et al⁹ studied 68 children (median age, 6.5 years) with egg allergy, defined as an allergic reaction within 1 hour of egg ingestion and positive skin test or specific IgE antibody to egg protein. They also included 55 control children without a history of egg allergy.⁹ All of the patients were administered LAIV in the usual manner and kept under observation for 1 hour, during which no allergic reactions were observed. A telephone follow-up 24 hours later revealed a somewhat higher rate of nonspecific adverse reactions in the subjects with egg allergy than in the controls, but none were suggestive of allergic reactions.⁹ Although this is the only published study on the use of LAIV in recipients with egg allergy and included only 68 subjects, the results are consistent with the multitude of published studies that describe literally thousands of patients with egg allergy who have uneventfully received IIV that contained as much or more egg protein.²

Thus, it appears that the use of LAIV in children with egg allergy is safe. This is particularly important because this year, for the first time, for the 2014 to 2015 influenza season, LAIV is preferred over IIV for children ages 2 to 8 years due to its superior efficacy.⁸ It should be noted, that, if LAIV is not immediately available, then IIV should be used, so as not to miss an immunization opportunity.

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It also is of interest in the study by Des Roches et al⁹ that 40 of the 68 children with egg allergy (59%) who uneventfully received LAIV also had mild asthma, but experienced no asthma exacerbations. Some studies, but not others, have shown an increased rate of wheezing episodes after receipt of LAIV in children younger than age 3 years.⁷ Based on these data, the Advisory Committee on Immunization Practices recommends that LAIV, which is otherwise approved for healthy persons 2 to 49 years of age, not be administered to children 2 to 4 years of age with a diagnosis of asthma or a history of wheezing.⁸ Results of studies have not demonstrated any increase in asthma episodes after receipt of LAIV in recipients ages 5 years and older, but most studies excluded patients with severe asthma, and thus, in this age group, asthma is considered a precaution rather than a contraindication for LAIV vaccination.⁸

One aspect of this topic that has garnered increasing attention is the consequence of not vaccinating. The majority of patients with egg allergy are children. Influenza results in more than 20,000 hospitalizations and more than 100 deaths each year in the United States in children.² Most of this influenza-related morbidity and mortality occurs in children who were not vaccinated, and thus not vaccinating children with egg allergy leaves them at risk for the adverse consequences of influenza infection.

Many of the studies on the safety of administration of influenza vaccine to children with egg allergy included control groups, which showed similar low rates of urticaria and other reactions that could suggest an allergic mechanism.² Most of the rare reports of anaphylactic reactions to influenza vaccine occurred in recipients without egg allergy or whose allergy status was unknown.² Thus, it is possible that influenza vaccine can cause anaphylactic reactions in susceptible recipients due to IgE-mediated reactions to other vaccine constituents or through non-IgE-mediated mechanisms. For this reason, it is recommended that personnel who administer vaccines (not just influenza vaccine but any vaccine) be prepared to recognize and treat anaphylactic reactions.¹⁰ Further, the rare patients who have urticarial or anaphylactic reactions after immunization itself should be evaluated by an allergist, to include vaccine skin testing, to determine whether or not the reaction was IgE mediated and, if so, which component of the vaccine was responsible.⁵

Our journey began at a time when the administration of influenza vaccine to patients with egg allergy was contraindicated;

this was based on sound theory but not on sound evidence. We now have ample evidence that influenza vaccine, both the injectable IIV and the intranasally administered LAIV, can be safely administered to recipients with egg allergy who should be vaccinated to protect them from a disease that leads to thousands of hospitalizations and deaths annually. Very rare recipients of influenza (or any other) vaccine will experience anaphylactic reactions, but this cannot be predicted based on their egg allergy status, and the risk of not vaccinating clearly exceeds the risk of vaccinating. Our journey will be complete when practitioners have had time to develop confidence in these evidence-based recommendations and when influenza vaccine manufacturers appreciate that withholding their product from recipients with egg allergy exceeds the risk of administering it and remove egg allergy as a contraindication in their product labeling.

REFERENCES

1. Fiore AE, Uyeki TM, Broder K, Finelli L, Euler GL, Singleton JA, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep* 2010;59:1-62.
2. Kelso JM. Administering influenza vaccine to egg-allergic persons. *Expert Rev Vaccines* 2014;13:1049-57.
3. Kelso JM. Administration of influenza vaccines to patients with egg allergy. *J Allergy Clin Immunol* 2010;125:800-2.
4. Centers for Disease Control and Prevention (CDC). Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morb Mortal Wkly Rep* 2011; 60:1128-32.
5. Kelso JM, Greenhawt MJ, Li JT, Nicklas RA, Bernstein DI, Blessing-Moore J, et al. Adverse reactions to vaccines practice parameter 2012 update. *J Allergy Clin Immunol* 2012;130:25-43.
6. Kelso JM, Greenhawt MJ, Li JT. Update on influenza vaccination of egg allergic patients. *Ann Allergy Asthma Immunol* 2013;111:301-2.
7. Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices—United States, 2013-2014. *Morbidity & Mortality Weekly Report* 2013;62:1-43.
8. Grohskopf LA, Olsen SJ, Sokolow LZ, Bresee JS, Cox NJ, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2014-15 influenza season. *MMWR Morb Mortal Wkly Rep* 2014;63:691-7.
9. Des Roches A, Samaan K, Graham F, Lacombe-Barrios J, Paradis J, Paradis L, et al. Safe vaccination of egg allergic patients with live attenuated influenza vaccine. *J Allergy Clin Immunol Pract* 2015;3:138-9.
10. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity & Mortality Weekly Report* 2011;60:1-64.

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