

Coordination of multidisciplinary resources for vaccination of egg-allergic individuals during an H1N1 (novel) influenza pandemic

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ABSTRACT

Egg allergy is a contraindication for influenza vaccination because of the presence of trace egg protein. Although recent reports suggest that egg-allergic individuals can be safely immunized with seasonal influenza vaccine, the safety of H1N1 influenza vaccine in this context has not previously been reported. This study was designed to investigate how to safely immunize high-risk populations during the H1N1 influenza pandemic for whom the vaccine would be contraindicated. Vaccination of egg-allergic children was conducted at a large, multispecialty practice. Pediatricians raised awareness of vaccination and referred egg-allergic individuals to allergists. Allergists performed skin testing to H1N1 vaccine and, if negative, performed graded vaccine desensitizations in the office. Mass immunization of egg-allergic individuals was achieved within a 3-week period after receipt of vaccine. Sixty-three children (average age, 3.7 years) were evaluated and skin tested to the H1N1 influenza vaccine. All had a clinical history of egg allergy and recent positive skin-prick to egg. All had negative skin-prick test to the H1N1 vaccine and received graded challenge with three divided doses. All 62 children were successfully immunized without allergic reactions. Vaccination of egg-allergic individuals during a pandemic can be safely and efficiently accomplished with the coordination of multidisciplinary resources. Although this was conducted at a multispecialty practice, we believe that this invaluable public health service can be done outside of this context. Allergists, with the help of local pediatricians and urgent care centers or hospitals, can effectively mobilize to help protect the most vulnerable populations during pandemics.

(Allergy Asthma Proc 31:507–510, 2010; doi: 10.2500/aap.2010.31.3396)

Each year, 10–40% of children are infected with the seasonal influenza virus, with perhaps 1% developing severe disease requiring hospitalization.¹ Those with chronic diseases (such as asthma, cystic fibrosis, diabetes, cancer, etc.) are at greater risk for severe infection or related complications. Although antiviral chemoprophylaxis is available, the influenza vaccine remains the most effective method for preventing infection. However, the influenza vaccine is manufactured using hen eggs and contains trace amounts of egg protein. Thus, vaccination is generally contraindicated in individuals with an egg allergy. This is of significant public health concern because hen egg is one of the top eight food allergens and affects an estimated 1.6–2.6% of children (up to 2 million children in the United States),^{2,3} thus resulting in the potential exclusion of a large cohort of children from

influenza vaccination. Furthermore, egg-allergic children are more likely to develop asthma as well as more severe asthma, placing them at even greater risk of influenza infection and its complications.^{4–6}

In 2009, the dilemma of whether (and how) to vaccinate this vulnerable pediatric population against influenza was thrust to the forefront by the global pandemic of novel influenza A (H1N1). In April 2009, the United States government declared a public health emergency due to the outbreak of H1N1 infections. By June 2009, H1N1 infection was reported across all 50 states, the District of Columbia, the U.S. Virgin Islands, and Puerto Rico. Contemporaneously, the World Health Organization declared a global pandemic and raised the alert level to phase 6. Although a vaccine against H1N1 was being developed, the concentration of egg protein contained in the vaccine was unknown. Similarly, it was not known whether egg-allergic individuals could safely receive this vaccine and what the risks of allergic reactions, including anaphylaxis, would be.

A recent review highlighted many of the issues to be considered in vaccinating egg-allergic individuals.⁷ Previous studies with seasonal influenza vaccine have shown that when the concentration of egg protein is

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<1.2 µg/mL, the vaccine can be administered safely to the vast majority of egg-allergic patients.⁸ Unfortunately, the amount of egg protein contained within influenza vaccines varies by product, manufacturer, and production lots and can range from undetectable to >40 µg/mL.⁹ A more recent editorial, which was not published at the time of this endeavor, reveals that many manufacturers now publish egg content in their product inserts. Furthermore, most, but not all, vaccine products now contain <1 µg of egg protein per 0.5-mL dose.¹⁰ Because of such variability, skin testing has been used as a way of assessing the likelihood of an allergic response to the vaccine. Several reports have indicated a predictive value for skin testing, because those with a negative skin test generally could be immunized,^{11–13} whereas vaccination could either be deferred or given in graded, divided doses in those with a positive skin test.^{14–16} Given these uncertainties, a pragmatic algorithm was proposed for skin testing before administration of the influenza vaccine in patients with a documented egg allergy.⁹ A similar judicious approach was advocated for administration of the novel H1N1 vaccine and involved skin testing followed by graded desensitization of egg-allergic patients even if testing to the vaccine was negative.¹⁷ This recommendation is logical because the 2009–2010 H1N1 vaccine was manufactured using the same processes and facilities as seasonal influenza vaccines. The egg protein content, and thus risk of reaction in egg-allergic individuals, would therefore appear similar between H1N1 and seasonal influenza products.

In light of the available published safety data and recommendations, we sought to mass vaccinate egg-allergic patients against H1N1 during the global pandemic in a safe and effective manner in the setting of a large, multispecialty group practice. Administrative staff navigated with the state health department to obtain H1N1 vaccine and maintain compliance with regulatory requirements. Pediatricians raised family awareness of the importance for vaccination and referred egg-allergic individuals to allergists. Allergists performed skin testing and in-office vaccine desensitizations with the assistance of nursing staff. Finally, emergency medicine physicians in the attached Urgent Care Center provided additional support in the event of severe anaphylaxis.

PATIENTS AND METHODS

Patient Population

Between October and November 2009, pediatricians at our group identified egg-allergic children and discussed the important benefits of immunization against novel H1N1 influenza. They referred these individuals to our allergists for further evaluation of their egg allergy, risk factors for anaphylaxis, and discussion

with the families regarding benefits, risks, and procedure for influenza vaccine testing and desensitization. Existing allergy patients with a known history of egg allergy were also contacted for participation. All participants had a history of clinical reactions to egg including eczema, hives, vomiting, anaphylaxis, or other IgE-mediated symptoms. All patients were skin-prick tested to whole hen egg, the H1N1 vaccine, saline (negative), and histamine (positive) controls. Only those individuals with a positive skin test and clinical history of egg allergy were included.

Vaccine and Immunization Protocol

Our group obtained novel H1N1 influenza vaccine from the New Jersey Department of Health and Senior Services. We received a large supply of Fluzone (Sanofi-Pasteur, Swiftwater, PA) from a single production lot and supplied as multidose vials. The vaccine was handled, stored, and logged in accordance with government mandates. The egg protein content of this vaccine was not reported by the manufacturer.

Identified patients with egg allergy were skin-prick tested to the H1N1 vaccine. Patients who were skin test negative were immunized in three divided doses, whereas any patients who were skin test positive were to be advised not to undergo vaccination unless the benefits were judged to outweigh the risks because of significant underlying medical comorbidities for severe influenza infection. Graded dosing was recommended for those with negative skin tests to vaccine because there is ongoing controversy regarding the predictive value of skin tests in reliably identifying those at higher risk of reactions.^{11–13,18} For children between 6 and 35 months of age, immunizations were given in divided doses of 0.05 mL s.c., 0.1 mL i.m., and 0.1 mL i.m. For children ≥3 years old, doses were 0.05 mL s.c., 0.15 mL i.m., and 0.3 mL i.m. All doses were administered at 15-minute intervals. After the final dose, patients were observed for 30 minutes and reassessed for any adverse reactions before discharge (Fig. 1).

RESULTS

In a span of 3 weeks immediately after distribution of the H1N1 vaccine to our facility, we identified and evaluated 62 children with documented egg allergy (Table 1). The children ranged in age from 6 months to 14 years (mean, 3.7 years). All 62 children had positive skin-prick testing to egg, a corroborating positive ImmunoCAP titer to egg, and a convincing clinical history of egg allergy. The vast majority exhibited other forms of atopy, with 86% having been diagnosed with atopic dermatitis, 52% with bronchial hyperreactivity, and 44% with allergic rhinitis. Of the 62 children evaluated, none had a positive skin-prick reaction to

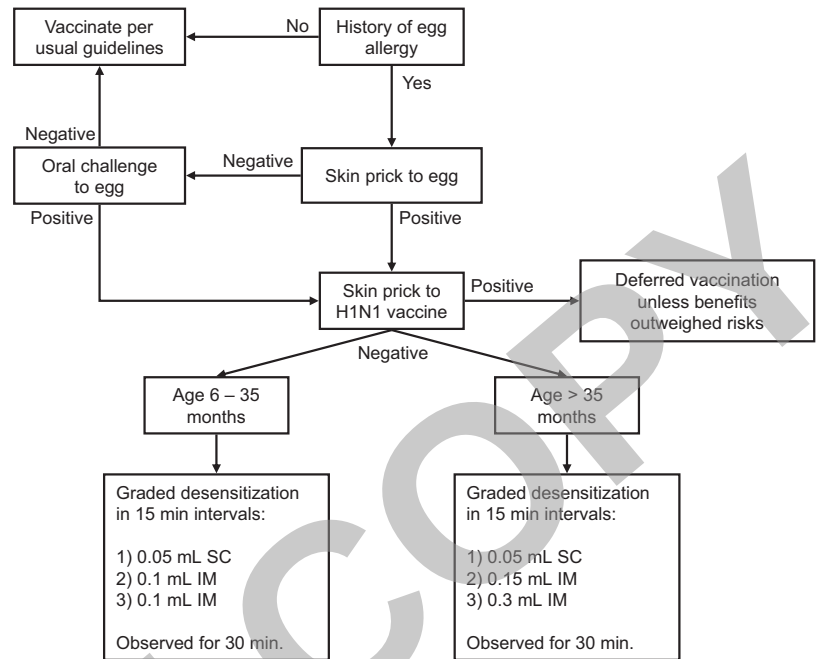


Figure 1. Evaluation protocol for H1N1 vaccine testing and desensitization in patients with egg allergy.

Table 1 Patient population

Parameter	Value
Age, yr, average ($\pm$ SD)	3.7 ($\pm$ 3.0)
Gender, n (%)	
Male	34 (55%)
Female	28 (45%)
Atopy, n (%)	
Atopic dermatitis	53 (86%)
Bronchial hyperreactivity	32 (52%)
Allergic rhinitis	27 (44%)
Egg allergy, mean ($\pm$ SD)	
Skin prick, wheal, mm	7.2 ($\pm$ 2.6)
ImmunoCAP, kU/L	8.81 ($\pm$ 13.16)
Reaction to eggs, n (%)	
Dermatologic	36 (58%)
Gastrointestinal	15 (24%)
Respiratory	0 (0%)
Other	13 (21%)

the H1N1 vaccine. All children received the vaccine in three divided doses. There were no adverse or allergic reactions observed in any of the patients. There were 59 children who were <10 years of age. These individuals were recalled 1 month later to receive a second dose of H1N1 vaccine. Because the same product from the same lot number was used, no additional skin testing was performed at the second visit. Instead, the second dose was given in a single, age-appropriate dose followed by 30 minutes of observation before discharge. Again, there were no adverse or allergic reactions observed.

DISCUSSION

Our results show that effective public health policy implementation and prevention of disease during a major influenza pandemic is possible for children in which vaccination is generally contraindicated due to an allergy to a vaccine component. In this study, we were able to vaccinate 62 egg-allergic children within a span of 3 weeks in an efficient and safe manner. This required the close collaboration of administrative staff, pediatricians, allergists, and emergency medicine physicians. Although we accomplished this in a large, multispecialty group practice setting, we believe this is feasible in the community at large if pediatricians, allergists, and urgent care centers or emergency rooms ally themselves to maximize vaccination rates for all vulnerable populations.

The usefulness of skin testing before influenza immunization of egg-allergic individuals is still controversial. In one study, four patients with an egg allergy and positive skin test to the vaccine were able to receive the immunization in two divided doses without significant allergic reactions.⁸ A more recent study compared the allergic reaction rates between 146 participants who were first skin tested to the vaccine and 115 participants who were not. The rate of local and systemic reactions were similar for both groups (~21%).¹⁸ Thus, skin testing did not appear to be predictive for those who would have an adverse reaction. However, it is surprising that such a high proportion of individuals with a negative skin-prick test to the vaccine developed a reaction. In a similar study presented at a national meeting, researchers found that of 349 egg-allergic children, 291 were skin test negative to the

influenza vaccine and tolerated a single, full dose without any adverse reactions. In contrast, 58 were skin test positive and of these subjects, 26% developed local allergic reactions to graded immunization.¹⁶ These results support the notion that skin testing is helpful in identifying children at higher risk of adverse reactions.

In light of this controversy, we chose a cautious approach consistent with the recommendations offered by the American Academy of Allergy, Asthma, and Immunology.¹⁷ We skin tested all children to the influenza vaccine and planned to defer vaccination in those with a positive skin test. Those with a negative skin test still underwent vaccine desensitization *via* graded challenge as an additional layer of safety. It is likely that the majority of those with a positive skin test would have tolerated vaccine desensitization without anaphylaxis; however, all of our patients had a negative skin test to the H1N1 vaccine. In contrast, 20% of the same participants had a concomitant skin-prick test that was positive to the 2009–2010 seasonal influenza vaccine from the same manufacturer (data not shown). This is consistent with the variability in egg protein content from lot-to-lot and product-to-product, and may account for the different rates of reaction reported in other studies.

CONCLUSIONS

Vaccination against influenza remains the most effective preventive measure available. In spite of that, up to 2 million children a year are excluded from immunization because of a prior history of egg allergy. We show that with a close partnership between pediatricians or pediatric primary care providers, allergists, and local emergency medicine physicians these children can be safely vaccinated with proper evaluation and precautions. Areas for further investigation include larger studies to evaluate the usefulness of skin testing in identifying persons at higher risk of allergic reaction to vaccination and whether graded desensitization is necessary for those with negative skin tests. Given that 59 children with negative skin tests to the H1N1 influenza vaccine had no adverse events from a second dose of the vaccine administered as a single dose, we conclude that the initial graded challenge was most likely unnecessary.

ACKNOWLEDGMENTS

The authors thank all of the dedicated and talented individuals who work at Summit Medical Group and who help us to fulfill our

daily mission of delivering high-quality, efficient, and patient-focused care.

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