Administration of the Adjuvanted pH1N1 Vaccine in Egg-allergic Children at High Risk for Influenza A/H1N1 Disease

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ABSTRACT

Background: In Canada, the pH1N1 influenza vaccine is recommended for children, particularly those less than 5 years of age or with chronic underlying disease. The pH1N1 vaccine, which contains residual allergenic egg white proteins, may pose a risk for vaccination of egg-allergic children.

Objective: To describe the outcome of pH1N1 influenza vaccine administration to egg-allergic children at risk for severe H1N1 disease.

Design/Method: Prospective observational cohort study. Children identified as at high risk for egg allergy and H1N1 influenza were vaccinated using a two-dose split protocol in a controlled medical setting. Children were given an initial test dose; if no reaction was noted, the remainder of the dose was administered and the children were followed for allergic reactions. Those who tolerated the split dose and required a second dose of vaccine were offered vaccination four weeks later as one injection.

Results: Sixty-two egg-allergic children considered at high risk for H1N1 disease received the adjuvanted pH1N1 vaccine. Egg allergy was diagnosed both clinically by an allergist and using skin and/or serum IgE testing. Within one hour of immunization, 2 children developed hives, 1 had a vasovagal response and 1 had a hypo-responsive episode. Fourteen children received the second H1N1 dose and 1 developed erythema and itching. There were no anaphylactic reactions.

Conclusion: Administration of the adjuvanted pH1N1 vaccine in egg-allergic children at risk for severe H1N1 influenza was safe when performed in a two-dose split protocol in a controlled medical setting.

Key words: Influenza A/H1N1; vaccine; child; allergy

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Can J Public Health 2011;102(3):196-99.

Influenza A/H1N1 usually causes mild disease in otherwise healthy children; however, more serious cases, and even death, have been reported in children and in those with pre-existing medical conditions.[1,2] Given the potential serious nature of this illness, administration of the newly developed adjuvanted pH1N1 vaccine (Arepanrix™ H1N1) could be beneficial and the vaccine has been recommended for children; particularly those less than 5 years of age or with chronic underlying disease.[3]

Similar to the seasonal influenza vaccine, the adjuvanted pH1N1 vaccine contains residual allergenic egg white proteins. Egg allergy is one of the most common food allergies in children[4] and allergic reactions have been reported in egg-allergic patients treated with the seasonal influenza vaccine.[5,6] However, reports have also been published on the safe vaccination of such patients.[7-9] In the setting of high-risk egg allergy, as defined by the Canadian Society of Allergy and Clinical Immunology (CSACI), it is suggested that egg-allergic patients be vaccinated with a physician present and in a location where access to emergency treatment is available.[10,11] Given the potential risk of allergic reaction in such patients, many parents and practitioners are reluctant to vaccinate. Therefore, egg-allergic patients, including those with chronic underlying disease at risk for serious Influenza A/H1N1 illness, fail to benefit from immunization.

In response to the recent Influenza A/H1N1 outbreak, the Children's Hospital of Eastern Ontario established a physician-supervised clinic to immunize egg-allergic patients at high risk for Influenza A/H1N1 disease. We proposed to document the risk of serious reactions in egg-allergic patients receiving the adjuvanted pH1N1 vaccine in a controlled medical setting. We hypothesized that the adjuvanted pH1N1 vaccine, with a small amount of egg protein and when given in a two-dose split protocol, would be well tolerated.

METHODS

We completed a prospective observational cohort study of children who were referred for H1N1 vaccination by Ottawa region allergists between November and December 2009 after being identified as at high risk for egg allergy and H1N1 disease. Informed written consent was obtained and the study protocol was approved by the Research Ethics Board.

Patients were considered at high risk for egg allergy on the basis of their clinical history along with a positive skin prick test and/or a positive serum egg IgE antibody level as documented by an allergist. Children at high risk for Influenza A/H1N1 disease were identified based on the Public Health Agency of Canada (PHAC)

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Conflict of Interest: None to declare.

Table 1. Characteristics of the Study Population

Characteristic	First pH1N1 Vaccine Dose	Second pH1N1 Vaccine Dose
Total number of patients	62	14
Mean age, years (range)	4.5 (10mos-16yrs)	2.4 (10mos-5yrs)
Gender		
Male, No. (%)	42 (67.7)	11 (78.6)
Female, No. (%)	20 (32.3)	3 (21.4)
Egg allergy		
Skin test positive, No. (%)	36 (58.1)	10 (71.4)
Serum IgE positive, No. (%)	1 (1.6)	1 (7.1)
Skin testing + serum IgE positive, No. (%)	25 (40.3)	3 (21.4)
High-risk H1N1 diagnosis		
Age, No. (%)	37 (59.7)	13 (92.9)
Asthma, No. (%)	36 (58.1)	8 (57.1)
Age + asthma combined, No. (%)	14 (22.6)	7 (50.0)
Heart disease, No. (%)	2 (3.2)	0 (0.0)
Immunocompromised household contact, No. (%)	1 (1.6)	0 (0.0)

recommendations for the use of the Influenza A/H1N1 vaccine: children less than 5 years of age or with chronic underlying disease, including heart disease, diabetes, asthma and chronic lung disease, kidney disease, blood disorders, severe obesity, liver disease, people with weakened immune systems and those with neurological disorders.[3]

On vaccination day, subjects underwent a medical history and physical examination. Exclusion criteria included a fever, respiratory illness or other acute illness. The protocol used for vaccination was based on the CSACI Guidelines, which allow for the administration of the Influenza A/H1N1 vaccine to egg-allergic children at high risk for Influenza A/H1N1 disease, under the following conditions: using a two-dose split protocol in a controlled medical setting with monitoring for allergic reactions.[11]

The product monograph (October 2009) states that the adjuvanted pH1N1 vaccine (Arepanrix™ H1N1) contains trace residual amounts of egg proteins (ovalbumin). Verbal communication with the manufacturer estimated the amount of egg proteins to be less than 165 ng/mL (0.165 mcg/mL). Patients 6 months to 9 years of age received the total 0.5 mL of the vaccination in an evenly split dose 4 weeks apart, while those patients 10 years of age and older received the total 0.5 mL vaccination during one visit. All patients received an initial test dose of 0.05 mL (10% of total vaccine dose) of vaccine administered intramuscularly followed by 30 minutes of observation. If there were no signs of allergic reaction, patients 6 months to 9 years of age received the remainder of their half dose of vaccine (0.2 mL), while patients 10 years of age and older received the remainder of their full dose (0.45 mL). All patients were then observed for 1 hour for any signs of allergic reaction. This was completed in a physician-supervised setting equipped with appropriate emergency treatment materials, including a resuscitation cart and a medication stock (Salbutamol inhalers and Epinephrine, Hydrocortisone and Diphenhydramine injections).

Patients 6 months to 9 years of age who tolerated the split dose and required a second dose of vaccine were contacted and offered the second dose 4 weeks later. Those who returned underwent the same medical history and physical examination as mentioned above. They then received the remaining 0.25 mL of the vaccine intramuscularly in one injection and were observed for 1 hour for allergic reactions.

RESULTS

Table 1 shows the patient characteristics of those who received the first and second pH1N1 vaccine dose. A total of 62 patients (67.7% of whom were male) received the first pH1N1 vaccine dose, while 14 patients (78.6% of whom were male) returned and received the second pH1N1 vaccine dose. The mean age was 4.5 years and 2.4 years for those who received the first and second pH1N1 vaccine dose, respectively. All patients received a diagnosis of egg allergy by the referring allergist. Table 1 presents the skin testing and serum IgE results.

All 62 immunized children were considered at high risk for Influenza A/H1N1 disease. There were 37 (59.7%) children at risk because of being age less than 5 years, 36 (58.1%) because of asthma and 2 (3.2%) because of congenital heart disease, and 1 (1.6%) child had an immunocompromised household contact.

Table 2 summarizes the adverse events following administration of the pH1N1 influenza vaccine. Of the 62 children receiving the first pH1N1 vaccine dose, there were no reactions following the test dose. When given the remaining dose, two children developed hives and were treated with Benadryl and one patient developed a vasovagal response requiring symptomatic management. One patient developed a hypo-responsive episode at the end of the 1-hour follow-up and after a short period of observation in the emergency department had an uneventful recovery. Of the 14 children who returned for the second pH1N1 vaccine dose, one developed erythema and itching of the face and required Benadryl. This child had not had a reaction to the first pH1N1 vaccine dose. Out of the 30 patients who did not return for their second pH1N1 dose, 11 had received it at their family physician's office, 2 had received it elsewhere and 17 did not return our follow-up call. None of the children experienced an anaphylactic reaction.

DISCUSSION

Infection with Influenza A/H1N1 is associated with increased risk of morbidity and mortality, particularly in those less than 5 years of age or with chronic underlying disease. Over half (58.1%) of our egg-allergic subjects had asthma, which places them at high risk for serious influenza A/H1N1 illness and related complications. In this study, we found that administration of the adjuvanted pH1N1 vaccine in egg-allergic children at high risk for Influenza A/H1N1 disease was safe when performed in a two-dose split protocol in a controlled medical setting. Only 3 children in total, following 138 vaccine doses, experienced mild allergic symptoms (hives), which responded to Benadryl. One child had a vasovagal response and one child had a hypo-responsive episode with full recovery following a short period of observation. There were no anaphylactic reactions.

Although influenza A/H1N1 usually causes mild disease in otherwise healthy children, many studies have reported more serious

Table 2. Adverse Events Following Influenza A/H1N1 Vaccination

Parameter	First pH1N1 Vaccine Dose (N=62)		Second pH1N1 Vaccine Dose (N=14)
	Test Dose	Remaining Dose	
Adverse event (%; 95% CI)			
Hives, No.	0 (0.0; 0.0-4.6)	2 (3.2; 0.05-9.8)	1 (7.1; 0.04-28.1)
Vasovagal response, No.	0 (0.0; 0.0-4.6)	1 (1.6; 0.07-7.3)	0 (0.0; 0.0-18.1)
Hypo-responsive episode, No.	0 (0.0; 0.0-4.6)	1 (1.6; 0.07-7.3)	0 (0.0; 0.0-18.1)
Adverse event treatment (%; 95% CI)			
Benadryl, No.	0 (0.0; 0.0-4.6)	2 (3.2; 0.05-9.8)	1 (7.1; 0.04-28.1)
Transfer to emergency department, No.	0 (0.0; 0.0-4.6)	1 (1.6; 0.07-7.3)	0 (0.0; 0.0-18.1)

cases, and even death, among young children and those with chronic underlying disease. In a review of 251 hospitalized children with H1N1 influenza, children under the age of 4 years were at increased risk for severe disease (i.e., higher rates of hospitalization, ICU admission, oxygen requirements, mechanical ventilation); 75% of those admitted were <2 years of age and 32% had one or more pre-existing conditions, including asthma, immunosuppression, chronic lung disease, neurologic disorder, and heart disease.[1] Furthermore, a pre-existing diagnosis of asthma was significantly associated with the risk of admission to the intensive care unit, while a pre-existing neurologic disorder and chronic lung disease specifically increased the odds of death.[1] Other studies have also shown that children admitted to hospital with H1N1 influenza were significantly more likely to have asthma[2,12-15] and that H1N1-positive children with asthma or neurological disorders have an increased risk of influenza-related complications and/or death.[2,12,14,16,17] Given the potential serious nature of Influenza A/H1N1 infection, PHAC recommends the use of the newly developed adjuvant pH1N1 vaccine (Arepanrix™ H1N1) in children less than 5 years of age or with chronic underlying disease.[3]

The adjuvanted pH1N1 vaccine, manufactured in egg-containing media, is potentially hazardous if administered to an egg-allergic individual and presents a relatively common clinical dilemma. Egg allergy is one of the most common food allergies in infants and young children,[4] with an estimated prevalence of between 0.5% and 2.5%.[18] Furthermore, co-existing food allergy and asthma is a significant problem in the pediatric population and the prevalence of egg allergy has been shown to be higher in asthmatic children.[19] The literature has reported a number of adverse allergic events in patients with egg allergy treated with the influenza vaccine;[5,6] however, fortunately anaphylaxis is rare and estimated at an incidence of approximately one in a million doses.[20] In a large population-based study, 11 episodes of non-fatal anaphylaxis were reported after administration of 48 million doses of influenza vaccine.[5] The potential risk of allergic reaction in such patients has promoted fear and controversy over the administration of the influenza vaccine in patients with egg allergy, and therefore many egg-allergic children fail to benefit from immunization. Of greater concern are those patients with coexisting egg allergy and underlying chronic disease, such as asthma, at high risk for serious influenza A/H1N1 illness who are denied protection from immunization because of their egg allergy.

The Canadian Immunization Guide notes that egg-allergic individuals should not be routinely vaccinated with the influenza vaccine; however, those considered at risk for influenza complications should be evaluated by an allergy specialist for possible immunization.[21] While the overall risk of a serious systemic allergic reaction appears to be low, a limited number of studies have been published on the safe vaccination of egg-allergic patients.[7,8,10,11,22,23] In a multicentre trial, a two-dose protocol was used to administer the influenza vaccine to 83 egg-allergic patients, all of whom tolerated vaccination without any significant allergic reactions.[8] In another trial, 44 asthmatic children with egg allergy were given the adjuvanted influenza vaccine with low egg protein content in a one-dose protocol. Two egg-allergic patients developed adverse reactions including erythema and bronchospasm, and one control subject with no egg allergy developed bronchospasm.[7] The CSACI statement advises that in the setting of high-risk egg allergy, defined as previous respiratory or cardiovascular reaction, generalized hives or those with poorly controlled asthma, egg-allergic patients can be vaccinated using a two-dose protocol with a physician present and where access to emergency treatment is available.[11]

There were several limitations to our study. The observational study design and lack of blinding are potential sources of bias, however, the simple study design, close observation and straightforward outcome measures yielded clear results in terms of vaccine reaction. We were limited in our sample size, based on allergist referral, with a small return rate for the second pH1N1 vaccine dose. A larger number of patients would be required to document the risk of rarer reactions, such as anaphylaxis.

In conclusion, following a two-dose split protocol with close medical supervision allowed us to safely administer the adjuvanted pH1N1 vaccine in egg-allergic children at high risk for H1N1 disease. The benefits of H1N1 vaccination are great and similar clinics may help promote better availability of vaccination to egg-allergic patients at increased risk for severe disease.

REFERENCES

1. Libster R, Bugna J, Coviello S, Hijano D, Dunaiewsky M, Reynoso N, et al. Pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Argentina. *N Engl J Med* 2010;362:45-55.
2. O'Riordan S, Barton M, Yau Y, Read SE, Allen U, Tran D. Risk factors and outcomes among children admitted to hospital with pandemic H1N1 influenza. *CMAJ* 2010;182(1):39-44.
3. Public Health Agency of Canada. Recommendations for the use of the H1N1 flu vaccine. Available at: http://www.phac-aspc.gc.ca/alert-alerte/h1n1/vacc/rec-h1n1-eng.php (Accessed December 1, 2009).
4. Heine RG, Laske N, Hill DJ. The diagnosis and management of egg allergy. *Curr Allergy Asthma Rep* 2006;6:145-52.
5. Retailliau HF, Curtis AC, Storr G, Caesar G, Eddins DL, Hattwick MA. Illness after influenza vaccination reported through a nationwide surveillance system, 1976-1977. *Am J Epidemiol* 1980;111:270-78.
6. Bierman CW, Shapiro GG, Pierson WE, Taylor JW, Foy HM, Fox JP. Safety of influenza vaccination in allergic children. *J Infect Dis* 1977;136(Suppl):S652-S655.
7. Esposito S, Gasparini C, Martelli A, Zenga A, Tremolati E, Varin E, et al. Safe administration of an inactivated virosomal adjuvanted influenza vaccine in asthmatic children with egg allergy. *Vaccine* 2008;26:4664-68.
8. James JM, Zeiger RS, Lester MR, Fasano MB, Gern JE, Mansfield LE, et al. Safe administration of influenza vaccine to patients with egg allergy. *J Pediatr* 1998;133:624-28.
9. Anolick R, Spiegel W, Posner M, Jakabovics E. Influenza vaccine testing in egg sensitive patients. *Ann Allergy* 1992;68:69.
10. Erlewyn-Lajeunesse M, Brathwaite N, Lucas JSA, Warner JO. Recommendations for the administration of influenza vaccine in children allergic to egg. *BMJ* 2009;339:912-15.

11. The Canadian Society of Allergy and Clinical Immunology. Statement: Administration of H1N1 and seasonal influenza vaccine to egg allergic individuals. Available at: www.csaci.ca/include/files/CSACI_H1N1_Statement.pdf Updated October 15, 2009 (Accessed December 1, 2009).
12. Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. *N Engl J Med* 2009;361:1935-44.
13. Miroballi Y, Baird JS, Zackai S, Cannon J-M, Messina M, Ravindranath T, et al. Novel influenza A(H1N1) in a pediatric health care facility in New York City during the first wave of the 2009 pandemic. *Arch Pediatr Adolesc Med* 2010;164(1):24-30.
14. Centers for Disease Control and Prevention. Surveillance for pediatric deaths associated with 2009 pandemic influenza A (H1N1) virus infection: United States, April-August 2009. *MMWR Morb Mortal Wkly Rep* 2009;58(34):941-47.
15. 2009 pandemic influenza A (H1N1) virus infections: Chicago, Illinois, April-July 2009. *MMWR Morb Mortal Wkly Rep* 2009;58:913-18.
16. Hackett S, Hill L, Patel J, Ratnaraja N, Ifeyinwa A, Farooqi M, et al. Clinical characteristics of paediatric H1N1 admissions in Birmingham, UK. *Lancet* 2009;374:605.
17. Lister P, Reynolds F, Parslow R, Chan A, Cooper M, Plunkett A, et al. Swine-origin influenza virus H1N1, seasonal influenza virus, and critical illness in children. *Lancet* 2009;374:605-7.
18. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: A meta-analysis. *J Allergy Clin Immunol* 2007;120:638-46.
19. Simpson AB, Glutting J, Yousef E. Food allergy and asthma morbidity in children. *Pediatr Pulmonol* 2007;42:489-95.
20. Bohlke K, Davis RL, Marcy SM, Braun MM, DeStefano F, Black SB, et al. Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* 2003;112:815-20.
21. Public Health Agency of Canada. Canadian Immunization Guide Seventh Edition - 2006. Available at: http://www.phac-aspc.gc.ca/publicat/cig-gci/p02-04-eng.php (Accessed April 19, 2010).
22. Murphy KR, Strunk RC. Safe administration of influenza vaccine in asthmatic children hypersensitive to egg proteins. *J Pediatr* 1995;106:931-33.
23. Committee on Infectious Diseases, American Academy of Pediatrics. Active Immunization. In: Pickering LK, Baker CJ, Long SS, McMillan JA (Eds.), *Red Book: Report of the Committee of Infectious Diseases,* 27th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2006;9-54.

Received: July 9, 2010
Accepted: November 20, 2010

RÉSUMÉ

Contexte : Au Canada, le vaccin contre la grippe pH1N1 est recommandé pour les enfants, en particulier ceux qui ont moins de 5 ans ou une maladie chronique sous-jacente. Ce vaccin, qui contient une quantité résiduelle de protéines de blanc d'œuf (un allergène), peut poser un risque pour les enfants allergiques aux œufs.

Objectif : Décrire le résultat de l'administration du vaccin contre la grippe pH1N1 à des enfants allergiques aux œufs et à risque de contracter une forme grave de grippe H1N1.

Conception/Méthode : Étude prospective observationnelle de cohorte. Des enfants désignés comme étant à risque élevé de faire une allergie aux œufs et d'attraper la grippe H1N1 ont été vaccinés selon un protocole en deux doses divisées dans un environnement médical contrôlé. Les enfants ont reçu une première dose d'essai; ceux qui n'ont fait aucune réaction ont reçu le reste de la dose, et les enfants ont été suivis au cas où ils fassent des réactions allergiques. Ceux qui ont toléré la dose divisée et qui avaient besoin d'une seconde dose se sont fait offrir la vaccination quatre semaines plus tard en une seule injection.

Résultats : Soixante-deux enfants allergiques aux œufs considérés comme étant à risque élevé de contracter la grippe H1N1 ont reçu le vaccin anti-pH1N1 adjuvé. L'allergie aux œufs a été diagnostiquée cliniquement par un allergologiste ainsi que par des tests cutanés et/ou sériques de dépistage par recherche d'IgE. Dans un délai d'une heure après la vaccination, deux enfants ont fait de l'urticaire, un enfant a eu une réaction vasovagale, et un autre a eu un épisode hyporéactif. Quatorze enfants ont reçu la seconde dose du vaccin anti-H1N1, et l'un d'eux a présenté un érythème et des démangeaisons. Il n'y a eu aucune réaction anaphylactique.

Conclusion : L'administration du vaccin adjuvé anti-pH1N1 aux enfants allergiques aux œufs à risque de contracter une forme grave de grippe H1N1 était sans danger lorsque effectuée selon un protocole en deux doses divisées dans un environnement médical contrôlé.

Mots clés : virus A de la grippe sous-type H1N1; vaccins; enfant; allergènes

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