

Reactions of Norwegian children with severe egg allergy to an egg-containing influenza A (H1N1) vaccine: a retrospective audit

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To cite: Forsdahl BA.

Reactions of Norwegian children with severe egg allergy to an egg-containing influenza A (H1N1) vaccine: a retrospective audit. *BMJ Open* 2012;2:e000186. doi:10.1136/bmjopen-2011-000186

► Prepublication history and additional materials for this paper are available online. To view these files please visit the journal online (<http://bmjopen.bmj.com>).

Received 9 June 2011
Accepted 10 October 2011

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ABSTRACT

Design: Retrospective audit.

Setting: Secondary paediatric outpatient clinic, Tromsø, Norway.

Participants: The participants were 80 (62.5% boys and 37.5% girls) children and adolescents with a diagnosed egg allergy who had to be on an egg-free diet and be unable to eat any food containing any amount of egg, including egg-containing baked goods, without an allergic reaction to egg protein. We also included patients who were sensitised to egg but had never been exposed to egg or egg-containing baked goods and were on an egg-free diet. Other atopic diseases among the study participants were also registered.

Intervention: The vaccination took place from November to December 2009. The patients were vaccinated with a monovalent influenza A (H1N1) vaccine that had an ovalbumin content <0.33 µg/ml. They were divided into two groups, receiving the vaccine either as a single dose or as a fractionated dose. Patients were selected for the fractionated dose because of their prior reaction to egg or because they never had been exposed to egg.

Primary outcome: There were no serious adverse reactions to the vaccine; only one mild adverse reaction and two possible adverse reactions.

Results: Patients ranged in age from 10 months to 16.5 years. Thirty-eight (48%) patients received a fractionated dose. Sixty-three (79%) had one or more atopic disease apart from egg allergy. With regard to atopy, serum specific IgE levels or skin prick test, there were no significant differences between the groups receiving the vaccine as a fractionated or as a single dose.

Conclusions: The study confirmed that patients allergic to egg can be safely vaccinated with a regular influenza vaccine containing <0.333 µg/ml ovalbumin, even if these patients had displayed previous anaphylactic reactions to egg and had been diagnosed with concurrent atopic diseases.

INTRODUCTION

In July 2009, the WHO recommended vaccination against the emerging pandemic influenza A (H1N1) virus.¹ In October 2009,

ARTICLE SUMMARY

Article focus

- We wanted to vaccinate the children severely affected by egg allergy with the same vaccine that the rest of the Norwegian population was receiving at the time and that vaccine contained egg residue.

Key messages

- It is safe to vaccinate children with severe egg allergy with a vaccine containing a low level of egg residue, even if these children suffer from concurrent atopic diseases.
- The level of serum-specific IgE to egg does not predict a reaction to the vaccine.
- Children with a positive serum-specific IgE test to egg allergy, who had never been exposed to egg, should be treated as if they are allergic to egg.

Strengths and limitations

- The strength of this study is that it is the same doctor who thoroughly evaluated all the patients before vaccination also evaluated the patients with suspected reactions to the vaccine.
- A weakness is that the number of participants in the study is quite small.

the Norwegian Health Authorities (NHA) followed suit and recommended vaccination of the whole Norwegian population against the virus.²

However, the available monovalent influenza A (H1N1) vaccine at the time contained egg protein (ovalbumin) residue and the WHO, American Center for Disease Control and American Academy of Pediatrics all warned that it should not be used in patients with severe egg allergy.^{3–5} An egg-free vaccine was expected but would not be available in Norway before the first week of December 2009 and then only in a very limited number of doses.⁶

An NHA-appointed advisory group recommended that patients with egg allergy should

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be examined by a physician with a special competence in allergies and that patients with anaphylactic shock reactions to egg should not be vaccinated at all.⁷ In addition, it was recommended that patients who exhibit a severe reaction to egg should be subjected to a skin prick test (SPT) to determine whether or not the individual could be safely vaccinated. The advisory group regarded one or more of the following reactions to egg as severe: angioedema, airway oedema, asthma, urticaria, rhinitis or vomiting.

The paediatric outpatient clinic at the University Hospital North Norway meets about 6000 consultations per year, and approximately half of these consultations concern atopic diseases. In October 2009, Erlewyn-Lajeunesse *et al*⁸ recommended that patients allergic to egg should receive only vaccines containing <1.2 µg/ml ovalbumin and that a two-dose split protocol should be used in individuals with severe egg allergy. According to the producer, the available monovalent influenza A (H1N1) vaccine contained <0.333 µg/ml ovalbumin (personal correspondence with Hilde Bakke, Regulatory Advisor at GlaxoSmithKline, Norway. 6 July 2011).

We decided to vaccinate children and adolescents allergic to egg with the recommendations by Erlewyn-Lajeunesse *et al*.⁸ The only patients to be vaccinated at the outpatient clinic were those unable to digest the slightest amount of egg, including egg-containing baked goods. Originally, the recommendation from the NHA was that the patients should receive two doses of the vaccine. However, before we could administer the second dose, new information from the NHA became available in December 2009, indicating that one dose of the vaccine produced a sufficient immune response.⁹

The objective of this study was to determine the safety of administering a monovalent influenza A (H1N1) vaccine to egg allergic patients following the guidelines in the article.⁸

MATERIALS AND METHODS

Setting

The vaccination drive took place at the outpatient clinic of the Department of Pediatrics at the University Hospital of North Norway in Tromsø, Norway. Vaccinations were administered from 4 November to 1 December 2009.

Study participants

A total of 80 children were vaccinated: 50 (62.5%) boys and 30 (37.5%) girls. Mean age was 6 years and 3 months. Some of the patients were under our care, while others had been referred to us for vaccination by their general practitioner.

Criteria for inclusion in the study

There were two criteria and both had to be met. The first criterion was a diagnosed sensitisation to egg demonstrated by a positive SPT or positive serum specific IgE (SSIgE)-mediated egg allergy. The SPT was considered

positive if a weal of >3 mm formed; the SSiGE was analysed with either the Siemens Immulite or the Phadia ImmunoCAP (personal correspondence with Ann Karin Lien, Immunology Lab, University Hospital North Norway. 10 March 2011). Values >0.35 kU/l were considered positive.

The second criterion was that the patient had to be on an egg-free diet and be unable to eat any food containing any amount of egg, including egg-containing baked goods, without an allergic reaction to egg protein. We also included patients who were sensitised to egg but had never been exposed to egg or egg-containing baked goods and were on an egg-free diet.

Concurrent atopic diseases

We recorded other atopic diseases in the included patients only if they were on current medication for asthma, allergy or eczema or if they were on a diet that avoided food other than egg. The other atopic diseases had been diagnosed by a physician prior to vaccination. No other diseases than atopic diseases were recorded.

Course of action

An appointment was made for all patients at the outpatient clinic. Every day, one nurse was assigned to administer the vaccine. The same physician (BAF) conducted all interviews, examinations and evaluations for all patients and decided whether they should receive a fractionated- or a single-dose vaccine. All patients were interviewed and physically examined. A form that contained written instructions on which type of vaccination the patient should receive was completed. Included on the form was the dosage of intramuscular epinephrine, intravenous hydrocortisone and oral antihistamine to be administered in case of a severe allergic reaction.

All the asthmatics on the programme were in a stable phase, and all patients could be vaccinated. Two of the children had a very severe atopic eczema at the time of vaccination; one of them was an inpatient as a result of severe eczema. If any reaction to the vaccine occurred while a patient was at the outpatient clinic, it would be recorded by the nurse and the patient would be examined by the same doctor who had conducted the initial assessment. Every reaction except pain at the injection site was recorded.

We adopted the approach advised in the case of mass vaccination and took no new blood samples for the purpose of diagnosing allergy, relying on the available information.

Dose and administration

The vaccine dose was age dependent, 0.25 ml for those younger than 10 years and 0.5 ml for those older than 10 years.

The enrolled patients were divided into two groups as described by Erlewyn-Lajeunesse *et al*.⁸ One group was given fractionated doses of the vaccine: first a tenth and after 30 min the remaining nine-tenths of the dose. The other group got the vaccine as a single dose.

The criterion which determined whether a patient should receive the fractionated dose was that he or she must have suffered from prior anaphylaxis, cardiovascular complications or collapse when exposed to egg protein. This included respiratory symptoms, hypotension, circulatory shock and severe abdominal pain.

The criterion which determined whether a patient should receive the single dose was that he or she should have suffered from mild gastrointestinal and dermatological reactions when exposed to egg protein, including urticaria, angioedema and vomiting.

One of the recommendations in the article was not followed.⁸ The article recommended that patients with a known allergy to egg, but who had never been exposed to egg in any form should get the vaccine as a single dose at the hospital. Because the reaction of these patients to egg was unknown, it was decided to vaccinate them with a fractionated dose.

The patients waited 30 min between the fractionated doses and 60 min after the final fractionated dose. The patients who received a single dose waited 30 min before they leave the clinic. The patients and parents were encouraged to provide us with feedback should a patient experience a delayed allergic reaction after returning home.

All patients and parents were informed that the NHA had discouraged using this particular vaccine in individuals with egg allergy, but that there was reason to believe that they could still be vaccinated and that some published articles agreed.⁸ They were also informed that the vaccine was administered at the outpatient clinic in case of an adverse reaction. Both patients and parents expressed their confidence in the treatment and information they were given.

Statistical analysis

We used Wilcoxon rank sum test, χ^2 test and Student t test to test for statistical significance. A p value of <0.05 was considered significant.

RESULTS

Study population

A total of 80 (100%) patients (50 boys and 30 girls) were enrolled and were all vaccinated. Mean age was 6.25 years, ranging from 10 months to 16.5 years. Mean age of those getting the vaccine fractionated was 6 years 9 months and those getting single dose vaccine were 6 years 3 months (table 1).

A total of 73 patients (91%) had a positive SSiGE test, although we did not know the exact value of the SSiGE test in two of them. The remaining seven (9%) had shown a reaction to egg in only the SPT. Median SSiGE level to egg protein, for the whole group, was 17.0 kU/l. Eleven (15%) patients had an SSiGE >99 kU/l, while 25 (35%) patients had an SSiGE between 0.8–8.3 kU/l.

Of the 80 patients, 38 (48%) were given the fractionated dose and 42 (52%) received the vaccine as a single dose. There is a statistical difference in age between the

Table 1 Number (N) of vaccinated patients, mode of vaccination, age range and mean (%) with concurrent atopic diseases in addition to allergy to egg, serum-specific IgE range and median, according to allergic reaction to egg

Allergic reaction to egg	Patients, N (%)	Mode of vaccination	Age in months range (mean)	Atopy (%)	Asthma (%)	Food allergy (%)	Inhalation allergy (%)	Eczema (%)	SSiGE kU/l range	SSiGE kU/l median
Serious reaction to egg	19 (24)	Fractionated vaccine dose	29–198 (95)	16 (84)	11 (58)	5 (26)	7 (37)	9 (47)	1.0–>99	12.8
Never exposed to egg	19 (24)	Fractionated vaccine dose	10–120 (55)	16 (84)	11 (58)	10 (53)	5 (26)	11 (58)	1.7–99	20.4
Mild reaction to egg	42 (52)	Single vaccine dose	11–193 (75)	31 (74)	17 (40)	17 (40)	12 (29)	18 (43)	0.8–>99	22.9
Total	80 (100)		10–198 (75)	63 (79)	39 (49)	32 (40)	24 (30)	38 (48)	0.8–>99	17.0

The criterion for serious allergic reaction to egg was that the patient must have suffered from prior anaphylaxis, cardiovascular complications or collapse. This includes respiratory symptoms, hypotension and circulatory shock, and severe abdominal pain when exposed to egg or egg-containing baked goods. Never exposed to egg means the parents stated that the kids had never been exposed to egg or egg-containing baked goods. The criteria for mild allergic reaction to egg were prior mild gastrointestinal and dermatological reactions, including urticaria, angioedema and vomiting when exposed to egg or egg-containing baked goods.

Food allergy refers to a diagnosed food allergy apart from egg allergy.

SSiGE refers to serum-specific IgE to egg protein.

patients never being exposed to egg and those having a severe allergic reaction to egg. The groups were indistinguishable with regard to SSiGE level and time since the SSiGE level had been done. There was also no difference in the median and the range of SSiGE between the two groups. SSiGE had been measured between 1 month and 10 years before, with a mean time of 28.6 months. Half of the patients who had their SSiGE measured were older than 1 year, and the SSiGE had a median value of 25.4 kU/l.

A surprisingly high number of patients (19 (24%)) had, according to their parents, never been exposed to egg. These patients had for some reason been tested for egg allergy, the tests had shown elevated SSiGE to egg protein, and consequently, they had avoided egg thereafter. The testing took place before they had an opportunity to be exposed to egg. At our clinic, patients with suspicious allergies to other foods or a severe atopic eczema will routinely be tested for food allergies, including egg allergy.

A high number of patients (63 (79%)) had atopic diseases other than those caused by egg allergy and 39 (49%) patients were on treatment for asthma. A total of 38 (48%) patients suffered from ongoing eczema.

There were 43 (54%) patients with other allergies apart from egg allergy, including food and inhalation allergies. Overall, these 43 patients suffered from a total of 134 recorded allergies. Food allergies were the most common (32 (40%) patients), while 24 (30%) of the patients presented with an inhalation allergy.

There are no statistical significant differences between the groups never being exposed to egg, a severe allergy to egg or a mild allergy to egg, regarding atopy, asthma, food allergies other than egg allergy, inhalation allergies or eczema.

Responses to the vaccine

All patients and their parents were encouraged to contact the outpatient clinic after the vaccination if a delayed allergic reaction occurred, but nobody reported any such reaction.

Of the 80 patients enrolled in the programme, only four displayed symptoms shortly after vaccination. Their histories and reactions are discussed below.

Patient A (2 years 8 months old)

This patient had a mild allergic reaction to the vaccine. The vaccine was given as a fractionated dose. The SSiGE (measured in the month before vaccination) was 1.7 kU/l, and the patient had never before been exposed to egg. The patient had a diagnosis of asthma and food allergies to milk, fish, peas and peanuts. A few minutes after the second dose, the patient displayed a weal of 1 cm on the left side of the lower lip, a self-limiting rash on the thighs and also had loose stools. No cardiovascular or respiratory reaction was experienced. The patient was given an oral antihistamine—mainly because the travelling time to home would be long—and left the clinic 1 h after the second dose.

Patient B (11 months old)

This patient also received a fractionated dose and showed symptoms that could perhaps be attributed to the vaccine. The patient had never before been exposed to egg and had an SSiGE >99 kU/l, tested in the month before vaccination. The patient had severe ongoing eczema and multiple food allergies (milk, wheat, barley, oats, rye, fish and peanuts). After the first dose, the right ear was more erythematous, and after the second dose, a slight swelling developed around the eye on the same side. It was difficult to distinguish this response from the other eczema symptoms as they vary significantly. The patient displayed no cardiovascular or respiratory reaction.

Patient C (8 years and 7 months old)

This patient showed symptoms that could perhaps be as a result of the vaccine. The last SSiGE value (measured 3 years before vaccination) had been 14.6 kU/l, and the patient had never been exposed to egg. The last SPT was done 10 months prior to vaccination and was positive with a weal of 10 mm. The patient had a diagnosis of asthma, inhalation allergy (grass pollen) and food allergies (milk, fish), was given a fractionated dose and started to sneeze after the second dose. There were no cardiovascular symptoms, and pulmonary auscultation also showed no bronchoconstriction. The sneezing was self-limiting and happens regularly at home, according to the parents.

Patient D (16 years old)

This reaction took the longest to resolve, but the symptoms were eventually attributed to fear of being exposed to an egg-containing vaccine as the patient had previously had an anaphylactic reaction to egg-containing food. The patient had a diagnosis of asthma and had an SSiGE >99 kU/l, measured in the month before vaccination. The patient had been anxious before coming to the clinic and had skipped breakfast. The patient experienced abdominal pain after the first fractionated dose and had to lie down and was repeatedly examined, and the conclusion was that there was no allergic reaction. The vaccine was further fractionated four times, and the last administration was six-tenths of the dose. Total time spent at the outpatient clinic was 3 h, but the patient felt fit when leaving. The method used to vaccinate this patient (extended fractionating) is similar to the extended-fractionating method described in the American Academy of Pediatrics Committee on Infectious Disease's Red Book.¹⁰ We decided on multiple fractionating for this patient because the psychological symptoms could have masqueraded as allergic reactions. By administering the vaccine in very small steps, the patient felt reassured that there would be no severe allergic reaction. Without such reassurance, the vaccination might have become so uncomfortable for the patient that it could have become impossible to complete.

After this incident, all the teenagers were asked if they had had breakfast and those who did not had to eat before being vaccinated.

DISCUSSION AND CONCLUSIONS

Of the patients who participated in this study, one showed a clear adverse reaction to the egg-containing vaccine and two had a possible adverse reaction. All reactions were mild and needed no immediate intervention. Because they had an egg allergy, all the patients in the group were considered at high risk, even more so because 79% of them suffered from other atopic diseases as well.

Safety of vaccination in patients allergic to egg

The study confirmed that patients allergic to egg can be safely vaccinated with a regular influenza vaccine containing $<0.333 \mu\text{g/ml}$ ovalbumin, even if these patients had displayed previous anaphylactic reactions to egg and had been diagnosed with concurrent atopic diseases. By following the guidelines in the article, we were able to vaccinate the patients allergic to egg.⁸ If future influenza vaccines were to contain considerably larger amount of ovalbumin, we would consider using the same guidelines as in this study.

Significance of concurrent atopic diseases

According to the 2008 data brief by the National Center for Health Statistics, individuals who are younger than 18 years and had food allergy have an increased risk of other atopic diseases.¹¹ The increased risk is 29.4% for asthma, 27.2% for eczema and 31.5% for inhalation allergies. Our study population had a higher prevalence of all these atopic diseases (asthma 49%, eczema 48%, inhalation allergy 30%, other food allergy 40%)—in other words, they were more affected by atopic disease than is to be expected, even in individuals allergic to egg.

Other studies investigating the safety of vaccinating with products that contain egg residue have not considered the aspect of other concurrent atopic diseases.^{12–15} Concurrent atopic diseases are of concern in vaccination, but we showed that even though our study population was affected more heavily than one would expect, these patients could still be safely vaccinated.

Significance of no previous exposure to egg

The patient with an allergic reaction to the vaccine and the two patients with possible reactions had never before been exposed to egg. This could indicate that a cautious approach is needed in the vaccination of individuals who had tested positive for egg allergy but had never been exposed to egg. When immunised with egg-containing vaccine, these patients should be treated as if they had in fact exhibited a reaction to egg exposure.

Significance of SSiGE/SPT

Practitioners treating patients with food allergies should be aware that the level of SSiGE or size of SPT does not predict the severity of a food reaction.¹⁶ The patients in our study who were given the fractionated-dose vaccine had displayed the most severe allergic reactions to egg. Yet we found no difference in SSiGE levels of those who

received the fractionated dose and those who received the vaccine as a single dose. This finding emphasises that SSiGE levels should not determine whether the vaccine should be fractionated or not.

Significance of age

There was a significant age difference between the patients who had never been exposed to egg and those with a severe reaction to egg. We believe the reason for this is that it is difficult to keep children on an egg-free diet. The moment they are exposed to egg, they are relegated to put in one of the two other groups, with a known allergic reaction to egg.

Dose fractionation

In this study, we chose to vaccinate either with a fractionated or a single dose. All patients tolerated the 10% dose, and ultimately received the 90% dose, and only one patient showed a mild reaction. This indicates that in the case of a vaccine with an ovalbumin level of $<0.333 \mu\text{g/ml}$, all patients could in fact have received the vaccine as a single dose without serious complications.

Risk of overestimating allergic reactions

Every centre administering vaccines knows the protocols that should be followed in the event of an allergic reaction to a vaccine. When patients with prior anaphylactic reactions to egg are vaccinated, it is important that the centre administering the vaccine also has experience of allergies. If not, allergic reactions could be overestimated as a result of misinterpretation of symptoms, as could have been the case with patient D in our study.

Acknowledgements I thank my colleagues Roald Bolle MD and Martin Sørensen MD at the outpatient clinic at the University Hospital of North Norway for their help in conducting this study, as well as Marit Leonardsen RN for coordinating the study. My thanks also to Signe Forsdahl for helping me with the manuscript.

Funding There is no study sponsor, and BAF has received no funding for this manuscript.

Competing interests BAF has completed the Unified Competing Interest form and declared that he has no relationship with any company for the submitted work. BAF has no relationship with any company that might have an interest in the submitted work in the previous 3 years. The wife of BAF, partners or children has no financial relationships that may be relevant to the submitted work. BAF has no non-financial interest that may be relevant to the submitted work.

Ethics approval We obtained the written consent of the parents of the case histories presented in this article. We did not obtain approval for the study from the Regional Committee for Research Ethics in Northern Norway before commencing the vaccination drive, but we applied for approval in November 2010. The Committee responded that it considered the vaccination drive as 'part of ordinary treatment', even though it could have been experimental and that the project therefore fell outside its mandate. However, it added that we as the applicants had the right to 'publish the treatment'.

Contributors There are no other contributors to this article.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data available.

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