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

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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.

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.

INTRODUCTION

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

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: angiooedema, 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, angiooedema 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 fractioned 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 concurring 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)	Fractioned 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)	Fractioned 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, angiooedema 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 µg/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 µg/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.

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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.

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REFERENCES

1. World Health Organization. Human infection with pandemic A (H1N1) 2009 influenza virus: clinical observations in hospitalized patients, Americas. *Wkly Epidemiol Rec* 2009;84:301–8.
2. Norwegian Health Authorities. *Økt influensaaktivitet og ny vaksineanbefaling*. 2009. http://www.fhi.no/eway/default.aspx?pid=233&trg=MainLeft_6129&MainArea_5661=6129:0:15,5004:1:0:0:::0:0&MainLeft_6129=5544:80624::1:6130:13:::0:0
3. World Health Organisation. *Use of the Pandemic (H1N1) 2009 Vaccines*. http://www.who.int/csr/disease/swineflu/frequently_asked_questions/vaccine_preparedness/use/en/index.html
4. Centers for Disease Control and Prevention. *General Questions and Answers on 2009 H1N1 Influenza Vaccine Safety*. http://www.cdc.gov/h1n1flu/vaccination/vaccine_safety_qa.htm#c
5. American Academy of Pediatrics. Influenza. In: Pickering LK, Baker CJ, Kimberlin DW, *et al*, eds. *Red Book: 2009 Report of the Committee on Infectious Diseases*. 28th edn. Elk Grove Village, IL: American Academy of Pediatrics, 2009:400–12.
6. The Norwegian Health Authorities. 4 December 2009. http://www.fhi.no/eway/default.aspx?pid=233&trg=Area_5626&MainArea_5661=5619:0:15,4665:1:0:0:::0:0&MainLeft_5619=5626:81582::1:5625:1:::0:0&Area_5626=5544:81587::1:5628:3:::0:0
7. The Norwegian Health Authorities. 28 October 2009. http://www.fhi.no/eway/default.aspx?pid=233&trg=MainLeft_5565&MainArea_5661=5565:0:15,5034:1:0:0:::0:0&MainLeft_5565=5544:80779::1:5569:2:::0:0
8. Erlewyn-Lajeunesse M, Brathwaite N, Lucas JS, *et al*. Recommendations for the administration of influenza vaccine in children allergic to egg. *BMJ* 2009;339:912–15.
9. Norwegian Health Authorities. *Én dose Pandemrix tilstrekkelig for de fleste barn og voksne*. 15 December 2009. http://www.fhi.no/eway/default.aspx?pid=233&trg=MainLeft_5565&MainArea_5661=5565:0:15,5034:1:0:0:::0:0&MainLeft_5565=5544:81734::1:5569:2:::0:0
10. American Academy of Pediatrics. Active immunization. In: Pickering LK, Baker CJ, Long SS, *et al*, eds. *Red Book: 2006 Report of the Committee of Infectious Diseases*. 27th edn. Elk Grove Village, IL: American Academy of pediatrics, 2006:9–54.
11. Branum AM, Lukacs SL. *Food Allergy Among U.S. Children: Trends in Prevalence and Hospitalizations*. NCHS data brief, no 10. Hyattsville, MD: National Center for Health Statistics, 2008.
12. James JM, Zeiger RS, Lester MR, *et al*. Safe administration of influenza vaccine to patients with egg allergy. *J Pediatr* 1998;133:624–8.
13. Chung EY, Huang L, Schneider L. Safety of influenza vaccine administration in egg-allergic patients. *Pediatrics* 2010;125:e1024–30.
14. Gagnon R, Primeau MN, Des Roches A; PHAQ-CIHR Influenza Research Network. Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine. *J Allergy Clin Immunol* 2010;126:317–23.
15. Greenhawt MJ, Chernin AS, Howe L, *et al*. The safety of the H1N1 influenza A vaccine in egg allergic individuals. *ANN Allergy Asthma Immunol* 2010;105:387–93.
16. Sicherer SH, Morrow EH, Sampson HA. Dose-response in double-blind, placebo-controlled oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 2000;105:582–6.

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

~~**Vaccination of children with egg allergy with vaccine containing egg residue.**~~**Reactions of Norwegian Children With Severe Egg Allergy to an Egg-Containing Influenza A (H1N1) Vaccine – a Retrospective Audit.**

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Article summary

Article focus:

- We wanted to vaccinate the children severely affected by ~~their~~ egg allergy with the same vaccine that~~as~~ the rest of the N~~n~~orwegian population ~~got,~~ , was receiving at the time, and that vaccine contained egg residue.

Key message:

- It is safe to vaccinated ~~egg allergic~~ children ~~that is~~ with severe egg allergy ~~who are severely affected by their allergy with a vaccine with a low level of egg residue.~~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 tested positive for egg allergy with serum specific IgE and that has never been exposed to egg, should be treated as if they had had a serious reaction towards were egg allergic~~. 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 of this study:

~~-The strength of this study is that it is the same doctor thoroughly evaluated that has reviewed all of the patients before vaccination, and also when there~~

~~were~~~~evaluated~~ ~~the patients with possible reactions.~~ 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~~suspected reactions to the vaccine.

~~It is a thorough evaluation of all the patients before they are designated to get the vaccine split or as one dose.~~

-~~The~~ A weakness is that the number of ~~patients~~~~s are rather small.~~participants in the study is quite small.

Abstract

Location of study The outpatient clinic of the Department of Pediatrics at the University Hospital of North Norway in Tromsø, Norway.

Background In July 2009, the World Health Organisation recommended vaccination against the emerging pandemic influenza A(H1N1) virus. In October of the same year, the Norwegian Health Authorities (NHA) followed suit by recommending vaccination of the whole Norwegian population. For subjects with egg allergy this posed a problem as the only vaccine available in Norway until 4 December 4 2009 contained egg protein. ~~It was~~It was decided at our clinic that children allergic to egg should be given the vaccine, but in a strictly controlled environment.

Study participants ~~Eighty children~~Eighty children and adolescents with egg allergy were vaccinated with Pandemrix, a monovalent vaccine against influenza A(H1N1). Sixty-three of these patients (79%) had one or more other atopic diseases apart from egg allergy. Forty-two patients (52%) were given the vaccine as a single dose. The remainder received one-tenth of the dose followed 30 minutes later by nine-tenths. The vaccine used had an ovalbumin content <0.333 µg/ml. There were no serious adverse reactions. Only one child displayed a definite but mild reaction, while two exhibited symptoms that may or may not have been caused by the vaccine.

Conclusion This study indicates that it is safe to vaccinate children even if the suffer from severe egg allergy.

Ethical aspects

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~~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'.

~~The World Health Organisation recommended in July 2009 vaccination against pandemic influenza A H1N1 virus. Norwegian health authorities recommended October 2009 vaccination of the whole Norwegian population. For subjects with egg allergy this imposed a problem because the only vaccine available in Norway until December 4, 2009 (Pandemrix) contained egg protein. The pediatric outpatient clinic, University Hospital North Norway, vaccinated 801 children and adolescents with Pandemrix, monovalent vaccine against influenza A H1N1, 42 (52%) got the vaccine as one dose. The remainder received one-tenth of the dose followed 30 minutes later by 9-tenths. The Pandemrix vaccine used had an Ovalbumin~~

ovalbumincontent less than 0.33366 microgram/ml. A total of 634 patients (79%) had other atopic disease besides egg allergy. There were no serious adverse reactions, only one mild allergic reaction and further two possible reactions to the vaccine. This study indicates that it is safe to vaccinate children even with severe egg allergy selecting a split vaccine approach, according to the reaction against egg.

Introduction

The fall of 2009 showed an emerging pandemic of the influenza virus A H1N1. In July 2009, tThe World Health Organisation (WHO) recommended in July 2009 vaccination against the emerging pandemic Influenza A H1N1 this virus (1)(H1N1) virus.[1]. In October 2009 The Norwegian Hhealth Aauthorities (NHA) followed suit and recommended vaccination of the whole Norwegian population . (2) against the virus.[2] .

However, The information from the available monovalent influenza A(H1N1) vaccine at the time contained egg-protein (ovalbumin) residue and the WHO, American Center for Disease Control (ACDC) and American Academy of Pediatrics (AAPP) all (3,4,5) warned against vaccinating patients with severe egg allergy withthat it should not be used in patients with severe egg allergy.[3,4,5] the availableinfluenza vaccine, . The available monovalent Influenza A H1N1 vaccine Pandemrix from Glaxo Smith Kline (GSK). This vaccine contained egg protein (Ovalbuminovalbumin) residue. It was said that there

~~would be a~~An egg-free vaccine was expected, but would not be available ~~,.~~ ~~h~~~~H~~~~owever, the first doses of this vaccine were not available~~ in Norway before the first week of ~~December 2009~~December 2009 ~~(6)~~ and then only in a very limited number of doses.[6]

~~It was~~An NHA appointed advisory group ~~-~~recommended ~~(7)~~ that patients with egg allergy should be examined by a physician with a special competence in allergies and that~~.~~ ~~-p~~~~P~~atients with anaphylactic shock reactions to egg should not ~~get the vaccine~~be vaccinated at all.[7] In addition, it was recommended that patients who exhibit ~~, those with~~ a severe reaction to egg should be subjected to ~~have~~ a skin prick test to determine ~~, and then decide~~ whether or not the individual ~~should~~ could be safely vaccinated. The advisory group regarded one or more of the following reactions ~~as a A severe reaction~~ to egg as severe: ~~was regarded as one of the following reactions, urticaria~~, angioedema, airway oedema, asthma, ~~urticaria ,~~urticaria, rhinitis or vomiting.

The pediatric outpatient clinic at the University Hospital North Norway ~~has~~sees about 6000 consultations per year, and approximately half of these consultations concern~~ing~~ atopic diseases. ~~In an article from October 2009 (8), it was recommended to use a two-arm approach when vaccinating patients allergic to egg with influenza vaccine containing less than 1.2 microgram/ml Ovalbumin~~~~ovalbumin~~~~.~~In October 2009 Erlewyn-Lajeunesse et al. 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.[8] According to the producer, ~~of~~ the ~~vaccine (GSK), Pandemrix~~ available monovalent Influenza A H1N1 vaccine ~~contained less than 0.33366 microgram/ml Ovalbuminovalbumin (9).~~ <0.333 µg/ml ovalbumin.[9]

We ~~wanted~~decided to vaccinate ~~the~~ children and adolescents allergic to egg with the recommendations ~~from the article (8).~~by Erlewynn-Lajeunesse et al.[8] ~~All the patients able to eat food containing even only the slightest amount of egg should receive the vaccine at the community centre and not at the hospital. Only patients unable to digest the slightest amount of egg, including egg-containing baked goods , without a reaction were vaccinated at the outpatient clinic. We vaccinated 81 children and adolescents.~~ 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 ~~to get two doses of the vaccine~~was that the patients should receive two doses of the vaccine. H~~, h~~owever before we could ~~vaccinate~~ administer the second ~~time~~dose, new information from the NHA became available in December 2009~~ (10), ~~indicating~~,~~ indicating that one dose of the vaccine produced a sufficient ~~the~~ immune response ~~was sufficient with one vaccine dose~~.[10]

The objective of this study was to determine the safety of ~~administring~~administering a monovalent Influenza A H1N1 vaccine to egg allergic patients following the guidelines in the article.[8]

~~The Regional Committee for research ethics had no objections to this study.~~

~~Material and~~ Method and material

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 six years and three 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~~two criteria and both had to be met. The first criterion was a diagnosed sensitisation to egg demonstrated by a positive skin prick test (SPT) or positive serum analysis for specific IgE- (SSIgE-) mediated egg allergy. The SPT was considered positive if a wheal of more than 3 mm formed; the SSIgE was analysed with either the Siemens Immulite~~® or~~® or the Phadia ImmunoCAP®.[11] 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~~been exposed to egg or ~~egg-containing~~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 (BF) 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~~written instructions on which type of vaccination the patient should receive, was completed. Included on the form was the dosage of intramuscular adrenaline, intravenous hydrocortisone and oral antihistamine to be administered in case of a severe allergic reaction.

The vaccinations took place from November 4 to December 1 2009. There were 50 (62,5%) boys and 30 1 (37,5 8%) girls. Mean age 6 years 3 6 months. The patients were partly under our care, and partly referred to us for vaccination from their general practitioner. There were two inclusion criteria, and both had to be met. The first criterion was a diagnosed allergy sensitation to egg, with a positive skin prick test (SPT), or positive serum analysis for specific IgE (SSIgE) mediated egg allergy. The SPT was considered positive with a wheal more than 3 mm, the SSIgE was analyzed with either Immulite from Siemens, or Immunocap from Phadia (11), values over 0.35 kU/L were considered positive. The second criterion was staying on an egg free diet, 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 sensitized to egg but never being exposed to egg or egg-containing baked goods that were on an egg free diet. We registered patients with other atopic diseases in the included patients only if they they were on current medication for asthma, allergy, eczema, or on a food avoiding diet other than egg. The other atopic diseases had been diagnosed by a physician prior to vaccination. No other diseases than atopic diseases was registered.

All patients received an appointment at the outpatient clinic. One nurse was assigned every day to do the vaccination. The same physician (BF) did all the interviews, examinations and evaluations for all patients, and decided whether they should get the vaccine fractioned or not. All patients had an interview and a physical examination. A form was filled out with a written ordination of

~~which vaccination the patient should receive. Included on the form was the dosage of i.m. adrenaline, i.v. hydrocortisone and p.o. anti-histamine in case of a severe allergic reaction.~~

~~All the patients could be vaccinated, all~~All the asthmatics on the programme were in a stable phase ~~of their asthma.~~and all patients could be vaccinated. Two of the children had a very severe atopic eczema at the time of vaccination~~:~~. o~~O~~ne of them was an inpatient ~~because of the~~as a result of severe eczema. ~~Any reaction occurring while the patients were at the outpatient clinic was registered by the nurse and examined by the same doctor that had done the initial assessment.~~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 ~~soreness~~pain at the injection site was ~~registered~~recorded.

~~No new blood samples were taken for diagnosing allergy, as we relied on the available information. This is the same approach that has to be taken if a mass vaccination has to take place.~~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 ~~of vaccine~~ was age dependent, 0.25 ml for those under 10 years of age, and 0.5 ml for those over 10 years.

The enrolled patients were divided into two groups as described ~~by M Erlewyn-Lajenuesse et al~~in the article ~~(8). The groups got either a fractioned dose of vaccine with first 1/10 dose and after 30 minutes the remaining 9/10 of the dose.~~ by Erlewyn-Lajeunesse et al. [8] One group was given fractionated doses of the vaccine: first a tenth and after 30 minutes the remaining nine-tenths of the dose. The other group got the vaccine as a single dose.

~~The other group got the vaccine as a single dose.~~ The criteriona ~~for getting the fractioned dose were, prior anaphylaxis, cardiovascular complications or collapse. This includes respiratory symptoms, hypotension and circulatory shock and severe abdominal pain, when exposed to egg protein~~which ~~determined whether a patient should receive the fractionated dose~~, 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~~a for the single dose was mild gastrointestinal and dermatological reactions, including urticaria, angioedema and vomiting, when exposed to egg protein~~

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] ~~d (8). M Erlewyn-Lajunnesse et.al.~~ The article recommended that patients with a known allergy to egg, but ~~without ever being~~ 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 ~~these patients~~them with a fractionated~~ed~~ dose.

The patients waited 30 minutes between the fractionated doses, and 60 minutes after the final fractionated dose. The patients who received ~~receiving~~ a single dose waited 30 minutes before they left the clinic. The patients and parents were encouraged to ~~give us feedback if there was a delayed allergic reaction after they got home.~~provide us with feedback should a patient experience a delayed allergic reaction after returning home.

~~All patients and parents were informed that vaccinating patients with egg allergy with this vaccine was discouraged by the NHA, but there were reason~~

~~to believe that they still could be vaccinated, and some articles published indicated the same (8, 12). They were also informed that the vaccination was done at the outpatient clinic in case of a reaction. Both patients and parents expressed their confidence in the treatment and information they were given.~~ 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 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, ~~en …….,Chi~~, Chi square and Student t-test to ~~-~~test for statistical significance. A~~, a~~ p-value <0,05 was considered significant.

Results

Study population A total of 8~~0~~1 (100%)patients (50 boys and 3~~0~~1 girls) were enrolled, ~~and all of them got~~and were all vaccinated. Mean age was 6,25~~.5~~ years, ranging from 10 months to ~~22.2~~ 16,5years. ~~The oldest patient in this~~

~~study was a mother who came to get her daughter vaccinated, and ended up being vaccinated herself.~~ Mean age of those getting the vaccine fractioned was 6 years 9 months, and those getting single dose vaccine were 6 years 3 months.

~~Table 1 shows the number of vaccinated patients according to age, fractioning of vaccine dose , previous exposure to egg and concurring atopic diseases.~~

~~Table 1. Number (N) of vaccinated patients, % with fractioning of vaccine dose, % with previous exposure to egg, % with concurring atopic disease in addition to allergy to egg according to age~~

~~Age group (years)~~	~~Number of patients (%)~~	~~Fractioned dose (%)~~	~~Never exposed to egg (%)~~	~~Atopy (%)~~	~~Asthma (%)~~	~~Food allergy (%)~~	~~Inhalation allergy (%)~~	~~Eczema (%)~~
~~0-4~~	~~38 47%)~~	~~18 (47%)~~	~~10 (26%)~~	~~29 (76%)~~	~~15 (39%)~~	~~17 (45%)~~	~~6 (16%)~~	~~24 (63%)~~
~~5-9~~	~~23 28%)~~	~~12 (52%)~~	~~8 (35%)~~	~~16 (70%)~~	~~9 (39%)~~	~~7 (30%)~~	~~6 (26%)~~	~~8 (35%)~~
~~10-14~~	~~16 20%)~~	~~6 (38%)~~	~~1 (6%)~~	~~15 (94%)~~	~~12 (75%)~~	~~7 (44%)~~	~~11 (69%)~~	~~6 (38%)~~
~~15-19~~	~~3 (4%)~~	~~2 (67%)~~	~~0~~	~~3 (100%)~~	~~3 (100%)'~~	~~1 (33%)~~	~~1 (33%)~~	~~0~~
~~20->~~	~~1(1%)~~	~~1 (100%)~~	~~0~~	~~1 (100%)~~	~~1 (100%)~~	~~0~~	~~1 (100%)~~	~~0~~
~~Sum~~	~~81 (100%)~~	~~39 (48%)~~	~~19 (23%)~~	~~64 (79%)~~	~~40 (49%)~~	~~32 (40%)~~	~~25 (31%)~~	~~38 (47%)~~

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

Allergic reaction to egg.	Number of patients (%)	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%)	Fractioned 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%)	Fractioned 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 were prior anaphylaxis, cardiovascular complications or collaps. 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 that 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 means diagnosed food allergy besides egg allergy.~~
~~SSIgE means serum spesific IgE to egg protein.~~

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-spesific IgE to egg protein.

A total of 73 patients (910%) had a positive SSIgE test, ~~however for 2 of these patients the exact value of SSIgE test was not known to us.~~although we did not know the exact value of the SSIgE test of two of them. The remaining seven ~~7~~8 (910%) ~~patients had only the skin prick test showing reaction to egg~~had shown a reaction to egg in only the skin prick. ~~.~~

M~~The m~~edian SSIgE level ~~against~~to egg-protein, for the whole group, was ~~14~~17.0 kU/L. Eleven~~11~~ (15%) patients had an SSIgE >99 kU/L, while 25 (35%)patients had an SSIgE between 0.8<~~-~~8.3 kU/L.

~~Table 2. Range and median value of age and SSIgE according to age group and whether the dose was fractioned or not.~~

~~Age group (years)~~	~~Single or fractioned dose~~	~~Age range in years~~	~~Age (median)~~	~~SSIgE range (kU/L)~~	~~SSIgE median (kU/L)~~
~~0-4~~	~~fractioned dose~~	~~0.8 – 4.3~~	~~2 years 6 months~~	~~1.6- >99~~	~~21.1~~

0-4	single dose	0.9 – 4.6	2 years 11 months	0.8- >99	46.0
5-9	fractioned dose	6.0 – 9.5	7 years 2 months	1.3 >99	19.7
5-9	single dose	5.0 – 9.9	6 years 11 months	1.6- >99	12.5
10-14	fractioned dose	10.0 – 13.8	12 years 7 months	1.0 - >99	12.3
10-14	single dose	10.0 – 14.3	12 years 3 months	0.8 - >99	16.2

Of the 801 patients, 389 (48%) got the vaccine fractioned were given the fractionated dose and 42 (52%) received the vaccine as a single dose. There is a statistical difference in age between the patients never being exposed to egg, and those having a severe allergic reaction to egg. The groups weregroups were indistinguishable with regard to SSIgEto 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 one month and 10 years before, with a mean time 28.6time 28.6 months. Half of the patients who had their SSIgE measured were older than one year, and the SSIgE had a median value of 25.4 kU/L.

The groups of patients receiving the vaccine fractioned or as one dose were indistinguishable regarding age, SSIgE level, and time since the SSIgE level was done. BToth the median and the range of SSIgE shows no differences between the groups receiving the vaccine fractioned or not. The range for when the SSIgE was done was one month to ten years, the mean time for

~~when the SSIgE was taken was 28,6 months. Half of the SSIgE was older than 1 year, and the median value of those were 25,4 kU/l.~~

A surprisingly high number of patients - 19 (2~~4~~3%) - had according to their parents, never been exposed to egg. These patients had for some reason been tested for egg allergy, ~~.~~ t~~T~~he tests had shown elevated SSIgE to ~~levels against~~ egg protein, and ~~they had~~ consequently they had avoided egg thereafter. The testing ~~had happened~~ took place before they had ~~had a chance~~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 - 6~~3~~4 (79%) - had ~~other~~ 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.

~~than food allergy to egg and 39~~40 ~~(49%) patients were treated for asthma.~~

~~There was a slight difference between the two groups regarding other atopic disease in addition to egg allergy as 32 (82%) of the patients getting fractioned dose and 30 (71%) of those getting single dose had other atopic diseases, asthma being the main difference.~~

~~A total of 38 (48%) patients had an ongoing eczema.~~ There were 43 (54%) patients with other allergies ~~besides~~apart from egg allergy, ~~that~~ includinges ~~both~~ food and inhalation allergies. All in all, 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 were registered 134 allergies among the 43 patients. Food allergies were the most common with 32 (40%) patients, 24 (301%) of the patients presented with an inhalation allergy.~~ There ~~were~~ are ~~-~~no statistical significant differences between the ~~three~~ groups never being exposed to egg, a severe allergy to egg or a mild allergy to egg, ~~getting fractioned or single dose vaccine~~ regarding ~~atopy, asthma, food allergies besides egg allergy, inhalation allergies or eczema,~~atopy, asthma, food allergies other than egg allergy, inhalation allergies or eczema. ~~food or inhalation allergy.~~

~~Description of reactions~~Responses to the vaccine

~~Despite that the patients and their parents were encouraged to contact the outpatient clinic after the vaccination if a delayed allergic reaction occurred; nobody reported any problems after being vaccinated.~~

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~~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 also been diagnosed with asthma and food allergies to milk, fish, peas and peanuts. A few minutes after the second dose the patient displayed a wheal of one centimetre on the left side of the lower lip, a self-limiting rash on the thighs and also one loose stool. No cardiovascular or respiratory reaction was experienced. The patient was given an oral antihistamine – mainly because the travelling time home would be long – and left the clinic one hour 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 and SSIgE >99kU/L, tested in the month before vaccination. The patient suffered from severe ongoing eczema and multiple food allergies (milk, wheat, barley, oats, rye, fish, 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 three years before vaccination) had been 14.6 kU/L and the patient had never ~~before~~ been exposed to egg. The last SPT was done 10 months prior to vaccination, and was positive with a wheal of 10 ~~millimetre~~millimetres. The patient had also been diagnosed with 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 also been diagnosed with 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 three hours, 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 AAP Committee on Infectious Disease's Red Book.[13] 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.

~~Four patients had symptoms shortly after the vaccination. The first patient had a confirmed mild allergic reaction to the vaccine. The two other patients had symptoms that perhaps could be related to a reaction against the vaccine. The fourth patient had symptoms due to fear of being exposed to a vaccine containing egg. The three first patients had never been exposed to egg, and the fourth patient had experienced anaphylactic reaction eating food containing egg. All of four patients got a fractioned vaccine, and all had an~~

~~SSIgE taken within the last month before vaccination, except for the 8 year old who had a 3 year old SSIgE.~~

~~The patient with the mild reaction was a 2 years and 8 months, asthma, food allergies (milk, fish, peas, peanuts), SSIgE 1.7 kU/L and never been exposed to egg. Few minutes after the second dose there was a wheal of one centimetre on the left lower side of the lip, a self-limiting rash down the thighs, and also one loose stool. No cardiovascular or respiratory involvement. The patient got an oral antihistamine, but that was mostly because of a long travel home by car, and left the clinic one hour after the second dose.~~

~~Two patients had possible reactions to the vaccine.~~

~~One 11 months old with severe ongoing eczema, and multiple food allergy (milk, wheat, barley, oats, rye, fish, peanuts) SSIgE > 99kU/L, had never been exposed to egg. The right ear was more erythematous, and a slight swelling around the eye on the same side after the second dose. This reaction was difficult to distinguish from the rest of his eczema symptoms that varies a lot. No cardiovascular or respiratory involvement. The other patient was 8 years and 7 month old and had asthma, inhalation allergy (grass-pollen) and food allergies (milk, fish). SSIgE 14.6 kU/L, and had never exposed to egg. The patient started to sneeze after the second dose. There were no cardiovascular involvement and no bronco-constriction when pulmonary auscultation was~~

done. The sneezing was self-limiting, and something that happens on a regular basis at home, according to the parents.

The reaction that took the longest time to resolve was a 16 year old, patient with asthma, SSIgE >99 kU/L. There had been an earlier anaphylactic shock to egg, the patient had been anxious before coming to the clinic, and had skipped breakfast. The patient experienced abdominal pain after the first fractioned dose. The patient had to lie down, was repeatedly examined, with the conclusion of no allergic reaction. The vaccine is further fractioned 4 times, last dose was 6/10 of the dose. Total time spent at the outpatient clinic is 3 hours, but the patient felt well when leaving the outpatient clinic. The method used to get this patient vaccinated is more similar to the method described in RED Book (13) with an extended fractioning of the dose. The reason to vaccinate this patient with a multiple fractioning of the dose was psychological symptoms disguising as allergic reactions. By taking it stepwise in very small steps, the patient felt assured that there would be no severe allergic reaction. If the patient had not been assured in this way, it would have been uncomfortable for the patient, to the degree that it would have been impossible to complete the vaccination.

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

Discussion and conclusions

~~Injecting a person with the intent of vaccination also brings the potential of an adverse reaction. In this study there was one adverse reaction, and two possible adverse reactions.~~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 ~~of the~~ reactions were mild and needed ~~, with~~ no ~~need for~~ immediate intervention. Because they had an egg allergy, all the patients in the group were considered at high ~~risk ,~~risk, even more so because 79% of them suffered from other atopic diseases as well.

~~The group being vaccinated in this study was considered a high risk group because of their egg allergy, and even more so when 79% of the patients had other atopic diseases besides egg allergy. The approach taken in this study shows it is possible to vaccinate egg allergic patients, even those with anaphylaxis to egg and concurring atopic disease, with a regular influenza vaccine, that has less than 0.333 mikrogram/ml66 mg/ml Ovalbuminovalbumin content.~~

~~The findings of C. Kelly and V. Gangur that there is a sex disparity in food allergic children under 18 years of age (14), which males predominates, correlates well with our study group where 63% of the patients under 18 are males.~~**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 µg/ml ovalbumin, even if these patients had displayed previous anaphylactic reactions to egg and had been diagnosed with concurrent atopic diseases. ~~Patients getting the vaccine fractioned had a higher prevalence of asthma, than the ones getting the vaccine as a single dose. Asthma in patients with food allergy increases the risk of anaphylaxis. (15) Respiratory involvement was also one of the inclusion criterions for getting the vaccine fractioned, this can explain the difference in asthma prevalence between the patients getting the vaccine fractioned or as a single dose.~~ 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 ~~to use~~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 (NCHS), individuals who are under 18 years of age and suffer from food allergy, have an increased risk of other atopic diseases.[14] 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.

~~The NCHS data brief from 2008 (14.) showed that patients with food allergy under the age of 18 years had an increased risk of other atopic diseases, asthma 29,4 %, eczema 27,2% and inhalation allergies 31,5%. Our study population had higher prevalence for all of these atopic diseases (asthma 49%, eczema 48%, inhalation allergy 30%, other food allergy 40%). demonstrating that our study population is a selected group more affected by atopic disease than is to be expected, even among those allergic to egg.~~

~~The other studies that have looked at the safety of vaccinating with vaccine containing egg residue, has not looked into the aspect of concurring other atopic diseases. (15, 16, 17, 12)~~

~~Concurring atopic diseases is of concern when vaccinating, but we have showed that even though our study population were more affected than expected with concurring atopic disease, they could still be vaccinated.~~

Other studies investigating the safety of vaccinating with products that contain egg residue have not considered the aspect of other concurrent atopic diseases.[15, 16, 17, 12] 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.

~~The one patient with a definite reaction to the vaccine, and the two with possible reactions to vaccine had never been exposed to egg. This may~~

~~warrant for a cautious approach when vaccinating anyone tested positive for egg allergy, but never have been exposed to egg. These patients should be treated as if they had had severe reactions to egg exposure when vaccinating with a vaccine containing egg residue.~~

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 and 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~~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.[18] 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~~emphasizes 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.

~~When handling patients with food allergies, one must be aware that the level of SSIgE or size of SPT does not predict the severity of a food reaction. (18~~20~~)~~

~~The patients in our study getting the vaccine fractioned have the most severe allergic reactions to egg. Yet we find no difference in SSIgE levels between the ones getting the vaccine fractioned or as a single dose. This finding emphasize that the level of SSIgE should not determine whether the vaccine should be fractioned or not.~~

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 µg/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.

~~In this study we chose to vaccinate either with a fractioned dose or a single dose. All the patients tolerated the 10% dose, and ultimately received the 90% dose with only one mild reaction. This shows that we could have given all the patients the vaccine as a single dose when the ovalbumin level is <0,333 mikrogram/ml.~~

~~This study shows that also patients with prior serious allergic reactions to egg can be vaccinated using a fractioned vaccine approach. Every centre giving vaccines are educated for the task in an event of an allergic reaction to the vaccine. When vaccinating patients with prior anaphylactic reactions to egg, it is important that the centre given the vaccine also have experience with allergies. If not there will be an overestimation of allergic reactions, as demonstrated by the fourth patient in our study.~~

~~The approach that were taken in this study can be used when there is a need for mass vaccination, A simple questionnaire can replace the interview, making the evaluation process simpler, and more effective in a mass vaccination setting.~~

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~~I would like to thank my colleagues Roald Bolle MD and Martin Sørensen MD at the outpatient clinic for their help in doing this study, and Marit Leonardsen RN for coordinating everything. I would like to thank Signe Forsdahl for helping me with the manuscript.~~

I would like to 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.

Competing interests

Bård Anders Forsdahl has completed the Unified Competing Interest form and declare that BAF 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.

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Contributorship

There are no other contributors to this article.

References

1. World Health Organization ~~weekly epidemiologocal record. 2009, Vol. 84(30):301□308.~~Human infection with pandemic A(H1N1) 2009 influenza virus: clinical observations in hospitalized patients, Americas. Weekly *Epidemiological Record.* 2009, 84(30):301□308.

2. ~~The~~ Norwegian H~~h~~ealth A~~a~~uthorities. ~~updated webpage October 23 2009. http://www.pandemi.no/pandemi/aktuelt/statusrapporter/_kt_influensaaktivitet_og_ny_vaksineanbefaling_609974~~ Økt influensaaktivitet og ny vaksineanbefaling, 23 October 2009. http://www.pandemi.no/pandemi/aktuelt/statusrapporter/kt_influensaaktivitet_og_ny_vaksineanbefaling_609974

3.~~TheWHO webpage~~World Health Organisation. Use of the pandemic (H1N1) 2009 vaccines. http://www.who.int/csr/disease/swineflu/frequently_asked_questions/vaccine_preparedness/use/en/index.html

4. ~~ACDC webpage. http://www.cdc.gov/h1n1flu/vaccination/vaccine_safety_qa.htm#c~~Centers for Disease Control and Prevention. General questions and answers on 2009 H1N1 influenza vaccine safety. http://www.cdc.gov/h1n1flu/vaccination/vaccine_safety_qa.htm#c

5. ~~American Academy of Pediatrics. Influenza. In: Pickering LK, ed. Red Book 2009 Report of the committee on infectious disease. 28 ed. Elk Grove Village, IL: American Academy of pediatrics 2009:400-12~~American Academy of Pediatrics. Influenza. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2009 Report of the Committee on Infectious Diseases.* 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009:400-12

6. The Norwegian health authorities updated webpage December 4 2009. http://www.pandemi.no/pandemi/aktuelt/vaksine_til_personer_med_alvorlig_eggallergi_er_kommet_647414

7. The Norwegian H~~h~~ealth A~~a~~uthorities 28 ~~updated webpage~~ October ~~28~~ 2009. http://www.fhi.no/eway/default.aspx?pid=233&trg=MainLeft_5565&MainArea_5661=5565:0:15,5034:1:0:0:::0:0&MainLeft_5565=5544:80779::1:5569:6:::0:0

8. ~~Erlewyn-Lajeunesse M, Braathwaite N, Lucas JSA, Warner JO. Recommendations for the administration of influenza vaccine in children allergic to egg. BMJ 2009;**339**:b3680 page 912-5~~Erlewyn-Lajeunesse M, Brathwaite N, Lucas JSA, Warner JO. Recommendations for the administration of influenza vaccine in children allergic to egg. BMJ 2009;**339**: 912-5

9 9. Personal correspondance Hilde Bakken Glaxo Smith Kline Norway julyOctober 201109.Personal correspondence with Hilde Bakke, regulatory advisor at GlaxoSmithKline Norway, July 2011.

10. NORWEGIAN HEALTH AUTHORITIES. ÉN DOSE PANDEMRIX TILSTREKKELIG FOR DE FLESTE BARN OG VOKSNE, DECEMBER 15 2009.

11. Personal correspondance with Ann Karin Lien, Immunology lab University Hospital North Norway March 10 2011.

12. 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**:624-8

13. 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 2006:9-54James 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**:624-813. American Academy of Pediatrics. Active immunization. In: Pickering LK, Baker CJ, Long SS, McMillan JA, eds. *Red Book: 2006 Report of the Committee of Infectious Diseases.* 27th ed. Elk Grove Village, IL: American Academy of pediatrics; 2006:9-54

~~14. Kelly C, Gangur V. Sex disparity in food allergy: Evidence from the Pubmed database. J Allergy (Cairo). 2009;2009:159845. Epub 2009 Jul 2~~

~~15. Wüthrich B, Ballmer-Weber BK. Food-induced anaphylaxis. Allergy. 2001; 56 Suppl 67:121-4~~

14. Branum AM, Lukacs SL. Food allergy among U.S. children: Trends in prevalence and hospitalizations. NCHS data brief, no 10. Hyattsville, MD: National Center for Health Statistics. 2008

15. Chung EY, Huang L, Schneider L. Safety of influenza vaccine administration in egg-allergic patients. Pediatrics. 2010 May; **125(5):**e1024-30. Epub 2010 Apr 5.

16. Gagnon R, Primeau MN, Des Roches A, Lemire C, Kagan R, Carr S, Ouakki M, Benoit M, De Serres G; PHAQ-CIHR Influenza Research Network. Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine. J Allergy Clin Immunol. 2010 Aug; **126(2):**317-23. Epub Jun 25.

17. Greenhawt MJ, Chernin AS, Howe L, Li JT, Sanders G. The safety of the H1N1 influenza a vaccine in egg allergic individuals. ANN Allergy Asthma Immunol. 2010 Nov;**105(5):**387-93.

18. Sicherer SH, Morrow EH, Sampson HA. Dose-response in double-blind, placebo-controlled oral food challenges in children with atopic dermatitis. J Allergy Clin Immunol. 2000 Mar;**105(3):**582-6.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-5
Objectives	3	State specific objectives, including any pre-specified hypotheses	3-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	-
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	-
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	-

		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9-10-11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	-
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.