Measles immunisation in children with allergy to egg

Richard Aickin, David Hill, Andrew Kemp

Abstract

***Objective*—To examine the occurrence of adverse reactions to measles vaccine given as a single dose to children with egg allergy, and to determine if the administration of single dose to children with a positive result in an intradermal skin prick test with the vaccine is associated with adverse reactions.**

***Design*—Review of results of immunisation and prospective study of 96 consecutively presenting children given intradermal skin testing with the vaccine.**

***Setting*—Children's allergy centre.**

***Subjects*—410 children sensitive to egg referred to the allergy unit for advice about measles immunisation.**

***Main outcome measures*—Nature and severity of reactions associated with the administration of measles vaccine.**

***Results*—All children had a positive result in a skin prick test with egg white, and five had a positive result in a skin prick test with vaccine. Of 96 consecutive children, 46 had a positive result in an intradermal test with vaccine. After immunisation with a full dose (0·5 ml) of vaccine adverse reactions were associated with a mild reaction in four children, none of whom required treatment. Only one of the 46 children with a positive result in an intradermal vaccine skin test had a reaction associated with vaccine administration. None of the children with a positive result in a skin prick test with measles vaccine reacted to the vaccine. The rate of minor reactions to the vaccine not requiring treatment was 0·98% (95% confidence interval 0·27% to 2·48%) and serious reactions requiring treatment was 0% (0% to 0·9%).**

***Conclusion*—Children with IgE mediated allergic reactions to egg protein should be investigated and managed by practitioners with special knowledge in this subject. Measles immunisation should be performed in a setting where any adverse reactions can be dealt with appropriately. Skin tests and measles vaccine and desensitisation are not necessary.**

Department of Allergy, Royal Children's Hospital, Melbourne, Australia
Richard Aickin, *fellow in ambulatory paediatrics*
David Hill, *director, department of allergy*
Andrew Kemp, *director, department of clinical immunology*

Correspondence to:
Dr A S Kemp, Department of Clinical Immunology, Royal Children's Hospital, Flemington Road, Parkville, Victoria 3052, Australia

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Introduction

Measles immunisation in children with allergy to egg remains controversial. The measles and mumps components of measles and mumps (MM-Vax) and measles, mumps, rubella (MMR-II) vaccines are produced by passage of virus in a culture of fibroblast cells from chick embryos.[1] The vaccines contain nanogram quantities of protein that cross reacts with ovalbumin.[2] Hypersensitivity reactions to measles vaccine in children allergic to egg have been reported.[3-5] As most anaphylactic reactions to measles vaccine have occurred in children not allergic to eggs other components (such as gelatin) may be responsible.[6] The American Academy of Pediatrics recommends skin testing with vaccine before its administration to children with egg allergy[7] and that children who test positive to the vaccine should undergo a desensitisation process of six injections with the vaccine. These recommendations seem to be influenced by medico-legal considerations[8] as much as by the scientific evidence and have been challenged.[2,9] We present data on a series of 410 children with egg allergy who have had measles immunisation without any notable adverse reactions.

Subjects and methods

Data were collected by review of the records of children referred to the children's allergy centre, Royal Children's Hospital, in 1986-92. We examined the records of 529 children who received measles immunisation. Children were included in the study if they had a history of an immediate hypersensitivity reaction after eating egg or a history of immediate reaction to other foods with a positive result of a skin test with egg white and had never eaten egg. Children for whom there was insufficient documentation were excluded. We identified 410 children for whom there were enough data for inclusion. Department policy during this time was for all children to be immunised.

CLASSIFICATION OF EGG ALLERGY

Most children developed an immediate reaction after ingestion of egg protein. Clinical reactions to egg were classified into four grades: grade 1—localised facial erythema/urticaria; grade 2—generalised urticaria/angioedema or vomiting, or both; grade 3—generalised urticaria/angioemeda and stridor or wheeze; and grade 0—never eaten egg, but immediate hypersensitivity to other foods and positive result in skin test with egg.[9] Some children had a definite history of hypersensitivity to egg but insufficient information was recorded to classify the severity of the reaction with certainty. These children were recorded as "unspecified."

Data were encoded in digital form on computer file and analysed by using the SPSS/PC+ statistical software package. We used χ^2 analysis and one way analysis of variance to investigate relations between variables.

MEASLES IMMUNISATION

Measles immunisation was performed on the same day as or within four weeks of skin testing. Children were observed for four hours for rash, blood pressure, and respiratory symptoms. Before 1989 a divalent measles-mumps vaccine was used (Enders' attenuated Edmonsten strain, MM Vax, Merck Sharp and Dohme), and after this time trivalent mumps, measles, and rubella vaccine was used (Enders' attenuated Edmonsten strain MMR II).

SKIN TESTING

A drop of egg white extract (Hollister Steir, Spokane,

Washington), undiluted measles vaccine, histamine 1 mg/ml, histamine 10 mg/ml (positive controls), and diluent solution (negative control) were applied to the flexor aspect of the forearm. The skin was pricked with a single use lancet (Hollister Steir, Spokane, Washington) for each solution. Positive controls were read at 10 minutes, other sites were read at 15 minutes.

Intradermal tests were performed by injection of 0·02 ml of 1:100 dilution of measles vaccine in normal saline (as recommended by the American Academy of Pediatrics[7]) and a negative control of 0·02 ml of normal saline. Skin tests were expressed in mm diameter of weal greater than control or as a ratio of the diameter of the test reaction to the diameter of the reaction to histamine 1 mg/ml on a standard 1-5 scale.[10] For intradermal tests any weal over 2 mm more than the control was recorded.

The age of the child at the time of the first and the most recent reaction to egg, dose of egg, severity of reaction to egg, age at immunisation, reactions to vaccine, and results of skin tests were recorded.

Results

We studied 410 children. The mean (median) age at immunisation was 26·2 (17·0) months. One hundred and fifty seven children were given measles and mumps vaccine; 253 children received trivalent measles, mumps, and rubella vaccine.

SKIN PRICK TEST RESULTS

The mean (median) skin prick test result with egg white was 7·7 (8·0) mm (SD 5·0 mm). Table I shows the skin test result of clinical reactions to vaccine with children divided into groups according to the grade of clinical reaction to egg. Five children (1·2%) had a positive result in a skin prick test with the vaccine. None of these five children had a reaction after immunisation with the standard dose of vaccine given as a single injection. None of the 33 children who had a history of severe reaction to egg with respiratory symptoms (grade 3) had a reaction after measles immunisation. Children with more severe reactions to egg were not more likely to have a positive result in a prick test with vaccine than were those with milder reactions.

TABLE I—*Results of skin prick tests with egg white and measles vaccine in children allergic to egg*

Grade of clinical reaction to egg	Total number	Skin prick test with egg* (according to scale of 1-5†)					Positive result of skin test with vaccine	Reaction after immunisation
		1	2	3	4	5		
3	33	0	1	9	20	3	0	0
2	101	3	4	18	65	11	2	3
1	108	3	5	23	64	11	1	0
0	124	3	4	20	87	8	1	1
Unspecified	44	0	2	8	34	0	1	0
Total	410	9	16	78	270	33	5	4

*Totals do not add up to 410 because data were missing for four children. †Scale described in methods.

TABLE II—*Results of intradermal tests with measles vaccine in children allergic to egg*

Grade of clinical reaction to egg	Total number	Total No negative	Total No positive (≥2 mm)	No positive (2 mm)	No positive (3-4 mm)	No positive (≥5 mm)	Reactions after immunisation
3	8	6	2	0	2	0	0
2	25	11	14	3	9	2	1
1	28	13	15	3	4	8	0
0	24	13	11	2	4	5	0
Unspecified	11	7	4	0	2	2	0
Total	96	50	46	8	21	17	1

TABLE III—*Reactions after immunisation to measles in children allergic to egg*

Case No	Grade of clinical reaction to egg (dose of egg)	Age at time of most recent reaction to egg	Age at immunisation	Results of skin prick test with egg*	Results of skin prick with vaccine	Result of intradermal test with vaccine	Nature of reaction after immunisation
1	2 (Contact)	12 Months	13 Months	4	Negative	Weal of 3 mm	Perioral urticaria at 1 hour (no treatment needed)
2	2 (5 ml)	6 Months	15 Months	4	Negative	Not done	Vomited once, no rash
3	0 (Nil)	Never exposed	17 Months	4	Negative	Not done	Wheeze noted at one hour, resolved by two hours
4	2 (5 ml)	12 Months	18 Months	5	Negative	Not done	Flushed, distressed, and vomited at 1½ hours

*In mm larger than control weal.

INTRADERMAL TEST RESULTS

Intradermal testing with vaccine was performed in 96 consecutive children of the total of 410. The clinical features of these children did not differ on χ^2 analysis from the children who had only skin prick tests. Previous authors have used differing definitions for a definite positive reaction for intradermal tests.[2,4] The results are shown according to the weal size to allow comparison with earlier studies (table II). If a reaction of 2 mm or more greater than the control is accepted as definite then 46 children had a positive result. With 3 mm as the threshold 38 had a positive result; with 5 mm as the threshold 17 had a positive result.

REACTIONS AFTER IMMUNISATION

Only four of the 410 children had a reaction after immunisation (table III). The reactions were mild and did not require treatment. They were not necessarily due to immediate hypersensitivity to an injected antigen. None of the children who reacted had a positive result in a prick test with vaccine. These four children did not differ significantly from the rest of the study group in any of the variables. Only one of the children who reacted to vaccine had an intradermal test. This was a 13 month old girl with a history of generalised urticaria and vomiting after exposure to a trace of egg at 12 months. She had a 3 mm weal on intradermal testing. She developed isolated perioral urticaria one hour after immunisation.

The rate of minor adverse reactions (not requiring treatment) was 0·98% (95% confidence interval with the exact binomial method 0·27% to 2·48%). The rate of serious adverse reactions (requiring treatment) was 0% (0·0% to 0·9%).

Discussion

The value of skin testing as a predictor for hypersensitivity reactions to measles vaccine is unproved. Previous studies indicate that a positive result in a skin prick with measles vaccine is common (2-7% of atopic children) and not related to immediate reactions to immunisation.[2,11] Most studies have been limited by small numbers of children. Our study describes 410 children with egg allergy who have been successfully immunised with live attenuated measles vaccine. We included 124 children who had never eaten egg but who had a history of immediate hypersensitivity to other food and a positive result in a skin test with egg white because there is strong evidence to support the correlation between strongly positive skin test reactivity and the development of clinical symptoms on ingesting the allergen.[10,12] Although such children are not included in current recommendations for screening, they represent one third of cases referred.

All 410 children had skin prick testing with vaccine before immunisation. A standard single injection method of immunisation was used without any desensitisation procedure. A positive result on prick testing with vaccine occurred in five (1·2%) children and a reaction to immunisation in four (0·9%) children, none of whom had a positive result in a vaccine skin prick test. The practice of restricting skin testing and desensitisation in the children most severely allergic to egg[13] is not supported by our results as all of the

reactions occurred in children with grade 2 or grade 0 egg allergy. None of the children with grade 3 egg allergy had positive results in skin prick or intradermal tests (5 mm weal) with vaccine or a reaction after immunisation.

THRESHOLD FOR POSITIVE RESULT

Intradermal testing with vaccine has been recommended for children allergic to egg with a negative result in a vaccine skin prick test,[3 4 7] followed by desensitisation in children who have a positive result in either type. Others have suggested using skin prick tests alone as an indication for desensitisation.[13] In our study 96 children had intradermal tests with diluted vaccine. The number of children with a positive result in an intradermal test is determined by the size of weal which is regarded as meaningful. Our results of 18% positive with 5 mm as the threshold are consistent with those previously reported by Lavi *et al*, who found 17% positive.[4] Taking a 3 mm weal as positive increases the rate to 40% in our group and 50% in another study[2] (of only six subjects).[2] In the only other study of comparable size in which children with a positive result in a vaccine skin test had been given measles immunisation Lavi *et al* identified 24 of 114 children allergic to egg with positive results in an intradermal ($\geq$5 mm) or a skin prick test with vaccine.[4] All these subjects were desensitised with a graded vaccine challenge, and three of the 24 (12·5%) developed generalised urticaria between the second and fourth vaccine dose. In contrast, none of our 22 subjects with positive results in a vaccine skin test on identical criteria developed generalised urticaria. These findings do not provide support for a graded dose regimen. The apparently higher rate of reactions with desensitisation raises the possibility that this might increase the reaction rate. The one child who had a clinical reaction to the vaccine in our intradermal positive group had an intradermal result of 3 mm. If a 5 mm weal is used as the threshold, none of the intradermal positive children had a reaction to vaccine. If a 3 mm weal is used, 2·6% (one of 38) of the intradermal positive children had a reaction to vaccine.

LOW RISK OF REACTIONS

This study does not answer the question of how common adverse events are after measles immunisation in children who are not allergic to egg or what the relative risk is for children with egg allergy. We believe that the findings in our 410 cases and the 247 cases previously described who have not had desensitisation[2 9 13-15] and the epidemiological data suggest that the risk is low. The reactions to immunisation were mild and did not require active treatment. As the children were under close observation the reactions may not have been reported under normal circumstances. Thus the incidence of such reactions in the general population is unknown. Furthermore, the reactions were much less severe than those which have been described in children not allergic to egg.[16 17] Children allergic to egg may not have a higher rate of serious reactions to vaccines than the general population. Our data suggest that at least 99% of children with egg allergy can have measles immunisation without any notable adverse reaction (using 95% confidence intervals).

We agree with the opinion of Fasano *et al* that guidelines regarding skin testing and administration of mumps, measles, and rubella vaccine to children allergic to egg should be reviewed.[2] We conclude that neither skin prick nor intradermal testing with measles vaccine is useful, and the scientific validity of this process can be questioned. A positive result on either skin prick or intradermal testing with the vaccine is not sufficiently predictive of a reaction to the vaccine to warrant withholding immunisation or using desensitisation procedures. We believe that children with a history of allergic reactions to egg should have their allergy investigated and managed by practitioners with specific knowledge in this subject. Measles immunisation should be performed in a setting where any adverse reactions can be dealt with appropriately but vaccine skin tests and desensitisation are not necessary.

Clinical implications

- Measles immunisation is often deferred or delayed in children allergic to egg
- Skin testing followed by desensitisation with graded doses of vaccines has been recommended to minimise adverse reactions to vaccine
- Allergy to egg protein is not a contraindication to measles immunisation
- A positive reaction to skin testing with a vaccine does not predict a notable adverse reaction to vaccination
- The scientific basis of skin testing and desensitisation with measles vaccine in children allergic to egg is not established

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