

SAFE ADMINISTRATION OF THE MEASLES VACCINE TO CHILDREN ALLERGIC TO EGGS

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Abstract *Background.* The safety of administering the combined measles–mumps–rubella (MMR) vaccine to patients who are allergic to eggs has been debated for decades because of concern about potential anaphylaxis, since the live attenuated virus used in the vaccine is grown in cultured chick-embryo fibroblasts.

Methods. We recruited 54 children (mean age, 18.5 months) who had not previously been vaccinated and were allergic to eggs. The children's histories of allergy were confirmed with skin tests and double-blind, placebo-controlled food-challenge tests; some children also underwent skin testing with the MMR vaccine. We then routinely administered the vaccine to the children in one subcutaneous (0.5-ml) dose.

PHYSICIANS face a clinical dilemma in deciding whether to administer measles vaccines to patients who are allergic to eggs, because of concern about anaphylaxis in response to the vaccines, which contain live attenuated virus prepared in chick-embryo fibroblast-cell cultures.¹ An estimated 0.5 percent of children have allergy to eggs.^{2,3} Given an estimated 4 million live births per year in the United States and a 95 percent vaccination rate, decisions about the use of these vaccines must be made each year for approximately 19,000 children with allergy to eggs (Vitek C, Centers for Disease Control and Prevention: personal communication). The American Academy of Pediatrics recommends the routine use of measles vaccines — including the combined measles–mumps–rubella (MMR) vaccine (Merck Sharp & Dohme, West Point, Pa.) — in patients with nonanaphylactic allergy to eggs and in patients with allergies to chicken or feathers.⁴ In contrast, they recommend that patients who have severe anaphylactic reactions after the ingestion of eggs should not receive these vaccines until skin tests have been performed. If skin-prick and intradermal tests are negative, the vaccine can be administered in the usual fashion. If not, six subcutaneous injections of the vaccine are administered in progressively increasing doses, a procedure that is both upsetting to the child and time-consuming.

Although several recent studies found that the administration of the MMR vaccine in a single dose was safe in patients who were allergic to eggs,⁵⁻¹⁰ the recommendations of the American Academy of Pediatrics remain unchanged.⁴ We prospectively studied the administration of the MMR vaccine in a single dose to

Results. All 54 children had positive results on skin testing with egg. Allergy to eggs was confirmed in 26 of the children by convincing histories of anaphylaxis after the ingestion of eggs, in 22 children by food-challenge tests, and in 6 patients by convincing histories of recent allergic reactions occurring after the ingestion of eggs. Of the 17 children who underwent skin testing with the MMR vaccine, 3 had positive results. All 54 children received the MMR vaccine as a single subcutaneous injection; none had an immediate or delayed adverse reaction.

Conclusions. The MMR vaccine can be safely administered in a single dose to children with allergy to eggs, even those with severe hypersensitivity. (N Engl J Med 1995;332:1262-6.)

patients who had allergy to eggs. In this report we describe our clinical experience, discuss previous reports of anaphylactic reactions after the administration of the vaccine to children without allergy to eggs, and propose specific changes in the current recommendations.⁴

METHODS

Children with clinical histories of allergy to eggs who were referred to our institutions from 1990 through 1994 were recruited for the study. The children had not previously received the MMR vaccine and ranged from 12 to 63 months in age (mean, 18.5). Evidence in the children's histories that suggested hypersensitivity to eggs included life-threatening anaphylactic reactions, urticaria, gastrointestinal symptoms, wheezing, and laryngeal edema after the ingestion of egg protein.

All the children underwent skin-prick testing with egg extract (1:10 wt/vol; Greer Laboratories, Lenoir, N.C.) mixed with an equal volume of glycerine, according to methods described elsewhere.^{11,12} A positive skin-test reaction was recorded when the mean diameter of the wheal was at least 3 mm greater than that of the wheal produced by the negative control (50 percent glycerinated saline). In addition, some of these patients underwent skin-prick testing with the full-strength MMR vaccine before being immunized.

Double-blind, placebo-controlled food challenges were carried out as described previously.^{13,14} Reactions were considered positive when there were objective cutaneous, respiratory, or gastrointestinal symptoms within two hours after the food challenge. Challenges were not performed if there was a convincing history of anaphylaxis (indicated by a history of generalized urticaria, laryngeal edema, bronchospasm, or hypotension) after the ingestion of food containing egg. All negative responses to the challenge were confirmed by open challenge with a normal portion of a food containing egg.

After skin testing and food challenges were performed, all children in the study were given the MMR vaccine in the usual fashion, in one 0.5-ml subcutaneous injection, and their reactions were assessed. Exact 95 percent confidence intervals for reaction rates were computed from the binomial distribution with use of the statistical software package StatXact-Turbo (Cytel Software, Cambridge, Mass.).

RESULTS

We prospectively evaluated the subcutaneous administration of the MMR vaccine in a single 0.5-ml dose to 54 children who were allergic to eggs. The children were vaccinated in 1990 through 1994 at either Johns Hopkins Hospital in Baltimore or the Arkansas Children's Hospital in Little Rock. All the children had histories and skin-test results compatible with hypersensi-

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Table 1. Clinical Characteristics of 54 Children with Allergy to Eggs.

CHARACTERISTIC	No.
Sex (M/F)	37/17
Median age at diagnosis of allergy*	30 mo
Range	6 months–11.5 yr
Positive skin-test response to egg (no.)	54
Positive skin-test response to undiluted MMR (no./no. tested)	3/17
Evidence of egg allergy (no.)	
Convincing history	26
Positive food-challenge test	22
Recent severe reaction to ingestion of egg	6
Reaction to MMR administered as a single dose (no.)	0

*In a few children (n = 4) the diagnosis of egg allergy was not documented by a challenge test until several years after the administration of the MMR vaccine.

tivity to eggs (Table 1). In 26 children there was a convincing history of severe, generalized anaphylactic symptoms after the ingestion of egg; therefore, these children were not subjected to the food challenge. In 22 children the history of egg hypersensitivity was confirmed by a positive food-challenge test. Symptoms that appeared during the challenge test involved the skin (urticaria, angioedema, or erythema) in 17 of the 22 children tested (77 percent), the gastrointestinal tract (vomiting, diarrhea, or abdominal pain) in 11 (50 percent), and the respiratory tract (wheezing, nasal congestion, or laryngeal edema) in 13 (59 percent). The remaining six children were not challenged because they had recently had an allergic reaction to the ingestion of egg protein. All 54 allergic children were safely immunized with the MMR vaccine, including the 3 children with positive responses to skin testing with the vaccine. No child in the study had an immediate or delayed adverse reaction to vaccination with the MMR vaccine.

DISCUSSION

Our study confirms that the administration of a single 0.5-ml dose of the MMR vaccine to children who have allergy to eggs is safe. No immediate anaphylactic reactions were observed, even in children with severe hypersensitivity to eggs. A cumulative total of 222 patients with egg allergy have now safely received the single-dose MMR vaccine at our institutions.^{5,15}

Approximately 30 years ago, Kamin et al.^{16,17} reported the safe administration of a measles vaccine (Edmonston strain) to 22 children with allergy to eggs whose histories were confirmed by food challenges. Another group reported the safe administration of a measles vaccine (Lirugen, Dow Chemical, Indianapolis) to a child with severe hypersensitivity to eggs.¹⁸ During the 1980s, Miller et al.¹⁹ and Greenberg and Birx²⁰ administered the MMR vaccine to a combined total of 19 children who were allergic to eggs without any reported symptoms of anaphylaxis. More recently, Kemp et al.⁶ successfully immunized 32 children who were allergic to eggs, without any adverse reactions (the vaccines

used were the attenuated Schwartz strain of virus, prepared by Rimevax, Smith Kline and French, Rixensart, Belgium; and M-M-Vax, Merck Sharp & Dohme). Lavi et al.²¹ safely immunized 90 such children using one dose of the M-M-R II vaccine (Merck Sharp & Dohme). Finally, investigators from Italy administered the measles vaccine safely to 23 children with severe egg allergy confirmed by positive open food challenges.⁷ Subsequently, the same group has safely immunized an additional 60 children with allergy to eggs.⁸

Two recent reports summarize the safe administration of the MMR vaccine (Merck Sharp & Dohme) in a single dose to children with allergy to eggs who had positive reactions in skin tests of egg.^{9,10} In the first report, by Aickin et al.,⁹ 242 of 410 children had documented allergic reactions after the ingestion of egg: 33 had generalized urticaria, angioedema, and stridor or wheezing, 101 had generalized urticaria and angioedema or vomiting, and 108 had histories of localized facial urticaria or erythema. The results of skin testing with the vaccine were not useful in predicting subsequent allergic reactions to immunization. In the other report, by Freigang et al.,¹⁰ no adverse reactions were observed after the administration of the MMR vaccine to 500 children allergic to eggs, including 33 who had had anaphylaxis with respiratory distress after the ingestion of egg.

Rare anaphylactic reactions have been reported after the routine administration of the MMR vaccine to patients allergic to eggs.²² One retrospective study reported generalized urticaria, angioedema, and wheezing in two children (one of whom had a decrease in blood pressure) after the administration of measles vaccine (Merck Sharp & Dohme). A convincing history of hypersensitivity to eggs was lacking, however, for one of the patients. Moreover, neither child had undergone skin testing or a blinded food challenge. Specific IgE antibodies to ovalbumin, the measles vaccine, and the MMR vaccine were detected in serum from both patients. In addition, six patients with allergy to eggs who had positive skin tests were immunized with incremental doses of the vaccine every 15 to 20 minutes, up to the full dose of 0.5 ml. The authors therefore recommended that patients with a history of anaphylaxis after the ingestion of eggs undergo skin-prick and intradermal testing with the vaccine. If the test was positive, the vaccine was to be administered in a series of graded injections.²² Although these results have not been confirmed by other investigators,^{5-10,14,20} previously published recommendations for the administration of measles vaccines to patients who are allergic to eggs²³ were revised.⁴

Adverse reactions have been reported to both intradermal testing and the administration of the MMR vaccine in multiple, low-dose injections. One patient with an allergy to eggs had generalized urticaria and pruritus during intradermal skin testing with the vaccine, and another had local swelling and wheezing.²⁴ Previous studies have not found systemic reactions in patients with allergy to eggs who underwent intra-

dermal skin testing with measles vaccines.^{5,9,16,18-21,25} We estimate that the dose of ovalbumin-like material injected intradermally would have been less than 1 pg, an amount that seems unlikely to produce such reactions.⁵ In addition, of 24 children who were allergic to eggs, had positive skin-test reactions to the diluted MMR vaccine, and were given the vaccine in several graded doses,¹⁸ 3 had generalized urticaria that resolved spontaneously without medical treatment between the second and fourth injections. In a related study, systemic hypersensitivity reactions were observed in two patients with allergy to eggs who received graded doses of the MMR vaccine.²⁵ One patient had repeated vomiting and irritability without hypotension; in another there was urticaria, circumoral cyanosis, and evidence of desaturation on oximetry (without any change in heart rate or blood pressure). Both patients completed the graded-dose protocol safely and did not require treatment with epinephrine. In the patient in whom transcutaneous oxygen saturation dropped without changes in either heart rate or blood pressure, the diagnosis of anaphylaxis appears suspect. The dose of egg protein injected subcutaneously (estimated to be less than 20 pg of an ovalbumin-like material) seems extremely small to have precipitated these reactions. The multiple-sequential-injection schemes

Table 3. Anaphylactic Reactions to Measles or MMR Vaccine in Patients without Allergy to Eggs.

STUDY	YEAR	NO. OF PATIENTS	POSITIVE SKIN TEST			REACTION TO VACCINATION
			SKIN TEST WITH EGG	SKIN PRICK WITH VACCINE	INTRADERMAL TEST WITH VACCINE	
<i>no. positive/no. tested</i>						<i>no. with reaction/ no. vaccinated</i>
Fasano et al. ⁵	1992	2	0/2	1/2	1/2	2/2
Aukrust et al. ²⁶	1980	6	0/6	1/6	—	6/6
Van Asperen et al. ²⁷	1981	3	—	—	—	3/3
McEwen ²⁸	1983	15	—	—	—	15/15
Pollock and Morris ²⁹	1983	9	—	—	—	9/9
Thurston ³⁰	1987	2	—	—	—	2/2
Kelso et al. ³¹	1993	1	0/1	1/1	—	1/1
Total		38	0/9	3/9	1/2	38/38

themselves may have contributed to the adverse reactions in these studies.^{20,25}

The administration of the measles or MMR vaccine to patients with allergy to eggs has been evaluated in numerous studies with a combined total of 1265 patients (Table 2).^{5-10,15-22,24,25} None of the 284 patients whose histories were confirmed with blinded oral challenges with egg had any adverse reactions, indicating that at least 99 percent of children with challenge-proved egg allergy can receive this vaccine in one subcutaneous dose without severe anaphylactic reactions (exact 95 percent confidence interval, 99.0 to 100 percent). Furthermore, the MMR vaccine was safely administered in single-dose fashion to all 1209 patients

Table 2. Administration of Measles or MMR Vaccine to Patients with Allergy to Eggs.*

STUDY	YEAR	NO. OF PATIENTS	POSITIVE FOR EGG ALLERGY		REACTION TO VACCINATION	
			SKIN TEST	FOOD CHALLENGE	ONE DOSE	GRADED DOSES
<i>no. positive/no. tested</i>						<i>no. with reaction/no. vaccinated</i>
Current study	1995	54	54/54	22/22	0/54	—
Fasano et al. ⁵	1992	140	140/140	132/140	0/140	—
Kemp et al. ⁶	1990	32	31/32	ND	0/32	—
Bruno et al. ⁷	1990	23	18/23	23/23	0/23	—
Businco et al. ⁸	1991	60	60/60	60/60	0/60	—
Aickin et al. ⁹	1994	242	242/242	ND	0/242	—
Freigang et al. ¹⁰	1994	500	500/500	ND	0/500	—
Beck et al. ¹⁵	1991	28	25/28	20/20	0/28	—
Kamin et al. ¹⁶	1963	11	11/11	11/11	0/11	—
Kamin et al. ¹⁷	1965	11	10/11	11/11	0/11	—
Brown and Wolfe ¹⁸	1967	1	1/1	1/1	—	0/1
Miller et al. ¹⁹	1983	4	4/4	4/4	0/4	—
Greenberg and Birs ²⁰	1988	15	15/15	ND	0/15	—
Lavi et al. ²¹	1990	114	114/114	ND	0/90	3/24†
Herman et al. ²²	1983	8	NR	NR	2/2‡	0/6
Puvvada et al. ²⁴	1993	10§	NR	NR	0/6	0/2
Trotter et al. ²⁵	1994	12	12/12	ND	0/9	1/3¶
Total		1265	1237/1247	284/292	2/1227	4/36

*ND denotes not done, and NR not recorded.

†Three of 24 patients vaccinated with graded doses had urticaria during vaccination, but no medical therapy was required.

‡One patient did not have a convincing history of egg allergy.

§Two patients were not immunized because they had reactions described as anaphylactic during intradermal skin tests with the vaccine.

¶Of three patients who received the vaccine in graded doses, one patient had vomiting and irritability without specific symptoms of anaphylaxis, and another had urticaria, circumoral cyanosis, and desaturation on pulse oximetry without any change in heart rate or blood pressure.

with positive skin-test responses to egg, indicating that at least 99.75 percent of children who are allergic to eggs who have positive skin tests can receive this vaccine in the usual fashion without severe anaphylactic reactions (exact 95 percent confidence interval, 99.75 to 100 percent). Only 2 (0.16 percent) of the 1227 patients who were allergic to eggs who received the vaccine in the usual way, as a single dose, had any symptoms suggesting anaphylaxis. These combined data indicate that over 99 percent of children who are allergic to eggs can safely receive this vaccine in the routine fashion (exact 95 percent confidence interval, 99.41 percent to 99.98 percent). We estimate that a total of 8000 patients with allergy to eggs would have to be safely vaccinated with the MMR vaccine to demonstrate statistically that 99.9 percent of such patients can safely receive this vaccine.

A total of 38 immediate, anaphylactic-type reactions to the measles or MMR vaccine have been reported in patients without allergy to eggs

(Table 3).^{5,26-31} Four of the nine patients tested with the vaccine had positive skin tests. One of these reports implicated gelatin, a stabilizing component of the vaccine, as the cause of an anaphylactic reaction in an adolescent without allergy to eggs.³¹ In addition, data concerning adverse reactions to measles vaccines from 1990 to the present were obtained from the Vaccine Adverse Event Reporting System, a program of the Centers for Disease Control and Prevention and the Food and Drug Administration (Nazario J, Vaccine Adverse Event Reporting System: personal communication). Twenty-five cases of generalized anaphylaxis after the administration of the MMR vaccine were identified, but there was no evidence of egg allergy in the available medical reports. In summary, anaphylaxis after immunization against measles can occur in patients without allergy to eggs, a fact that suggests that these reactions may be related to some component of the vaccine other than egg protein.

Although there are detectable amounts of egg-related antigens in measles vaccines, which are grown in cultures of chick-embryo fibroblasts, the amounts are far less than in the vaccines produced in embryonated eggs against influenza and yellow fever. Reports range from no detectable egg protein³² to 1 ng of ovalbumin²² per dose in the MMR vaccines. Fasano and colleagues⁵ determined that 37 pg of a material that cross-reacts with ovalbumin was present in the standard 0.5-ml MMR-vaccine injection. It is not known whether the immune system of a patient with egg allergy recognizes this detectable egg protein in the vaccine as antigenically similar to proteins that provoke reactions after the ingestion of eggs. Investigations of components of the vaccine other than egg protein, such as gelatin,³¹ are needed to help explain the cases of anaphylaxis after the administration of the MMR vaccine to patients without egg allergy (Table 3).

The reliability of the procedures for conducting skin tests with the measles vaccine that are currently outlined by the American Academy of Pediatrics⁴ is not supported by our study or by previously published data (Table 2). Patients with and without egg allergy can have positive skin-test reactions to the vaccine and still be safely immunized.^{5,9,19,25,33} Specifically, patients with allergy to eggs who have positive skin tests with the MMR vaccine have been immunized safely, without anaphylaxis. Moreover, of the patients without allergy to eggs who had anaphylactic reactions after receiving the measles vaccine, approximately half had positive reactions on skin testing with the vaccine.^{5,26-28,31} This suggests that these reactions may consist of nonspecific irritation or a reaction to some other component of the vaccine besides egg protein.

Convincing evidence supports the safety of the routine administration of measles vaccines to all children who have allergy to eggs. We therefore propose a revision of the current policy regarding the administration of these vaccines to patients with allergy to eggs.⁴ Skin-prick or intradermal testing with the MMR vaccine does not need to be performed, regardless of whether there is a history of allergy to eggs. One injection of the

vaccine, rather than a series of graded doses, should be given, followed by 90 minutes of observation in a clinic setting with equipment for emergency medical treatment, if necessary, immediately available. There is a very small chance of an adverse reaction in any child, even those without allergy to eggs. Anaphylactic reactions after the administration of vaccines should be reported and investigated fully, with attention to all the components of the vaccine. Package-insert information should be revised to reflect the safety of the vaccine, even for patients with egg allergy. The current guidelines lead to delay in administration of this important vaccine to patients who have allergies to eggs and unnecessarily place them at risk for measles, which is a potentially serious viral illness.

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