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# Allergic Reactions to Measles-Mumps-Rubella Vaccination

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**ABSTRACT.** *Objective.* Immunization of egg-allergic children against measles, mumps, and rubella (MMR) is often deferred or even denied, although the safety of this vaccination has been clearly shown. Moreover, the majority of severe allergic reactions have occurred in egg-tolerant vaccinees. Other allergenic vaccine components have been sought, and gelatin has been suggested as one cause of allergic adverse events. The aim of this study was to further characterize the actual allergenic vaccine components.

*Methods.* Serum samples from 36 recipients of MMR vaccine with anaphylaxis, urticaria with or without angioedema, asthmatic symptoms, or Henoch-Schönlein purpura were analyzed by CAP System radioallergosorbent test (RAST) and immunospot methods to detect the allergenic vaccine component. To evaluate the correspondence between the findings in the CAP System RAST or the immunospot and clinical symptoms, histories of allergies and present hypersensitivity symptoms were assessed.

*Results.* Of the 36 participants, 10 were demonstrated to be allergic to gelatin. Seven of them had persistent allergic symptoms, possibly attributable to foods containing gelatin or cross-reactive allergens. The results of the immunospot suggested concomitant allergy to gelatin and egg, chicken, and feathers, as well as cow's milk, or they reflected allergen cross-reactivity.

*Conclusions.* Although severe allergic adverse events attributable to MMR vaccination are extremely rare, all serious allergic reactions should be further assessed to detect the likely causative vaccine component, including gelatin. The current recommendation for immunization of egg-allergic persons according to standard MMR vaccination schedules is reinforced. *Pediatrics* 2001;107(2). URL: <http://www.pediatrics.org/cgi/content/full/107/2/e27>; measles, mumps, and rubella vaccine, immunization, adverse effects, allergic reactions, gelatin allergy, CAP System, radioallergosorbent test, immunospot, immunoglobulin E.

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ABBREVIATIONS. MMR, measles-mumps-rubella; IgE, immunoglobulin E; RAST, radioallergosorbent test; FEIA, fluoroenzyme-immunoassay.

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Worldwide, the measles-mumps-rubella (MMR) vaccination has proven to be a very safe and effective health intervention.<sup>1-3</sup> Since the introduction of the MMR vaccine, immunization of egg-allergic individuals has, however, been a subject of controversy.<sup>4-6</sup> Although several studies have shown that most egg-sensitive persons can receive the MMR vaccine safely, their vaccination is still often delayed or denied.<sup>7-15</sup>

The vaccine strains of one of the most commonly used MMR vaccines, M-M-R<sub>II</sub> (Merck, West Point, PA) are grown in chick embryo cells (measles and mumps) and human diploid cell culture (rubella). Because the vaccine is not produced in eggs, it contains none or only a minute amount of egg protein, which usually is insufficient to cause allergic adverse events.<sup>4,6</sup>

Moreover, allergic reactions have been reported in vaccinees who tolerate eggs. Hypersensitivity to other vaccine constituents, such as gelatin or neomycin, which are present in the vaccine in larger quantities than is egg protein, has been proposed.<sup>16-22</sup>

In Finland, egg-allergic children are increasingly frequently immunized with a vaccine produced entirely in human diploid cells, and this vaccine, which contains the Rubini mumps virus strain, is widely used in other parts of Europe as well.<sup>23</sup> Recent studies from Switzerland<sup>23</sup> and Singapore<sup>24</sup> suggest, however, that the Rubini virus strain provides poor protection against mumps. Even in countries such as Finland, which have no indigenous mumps, groundless use of this vaccine poses a risk. These findings accentuate the importance of identification of the actual allergenic vaccine components.

## METHODS

### Participants

In November 1982 in Finland, a 2-dose MMR immunization schedule replaced the separate measles, mumps, and rubella vaccinations.<sup>3</sup> Children are vaccinated voluntarily and free of charge at 14 to 18 months and 6 years of age. Intermediate age groups were also immunized in catch-up programs during the first years. Recruits of the Defense Forces were included in 1986, and health care workers, nursing school students, and 11- to 13-year-old girls in 1988. Recently delivered mothers were vaccinated from 1988 to 1993.

### Vaccine

M-M-R<sub>II</sub> has been the only vaccine in general use in Finland, but a vaccine produced entirely in human diploid cells has been administered to some allergic individuals since 1992. M-M-R<sub>II</sub> contains the more attenuated Enders-Edmonston strain of measles virus, the Jeryl Lynn B strain of mumps virus, and the Wistar RA 27/3 strain of rubella virus. Each dose also contains hydrolyzed

**TABLE 1.** Characteristics of Patients With Allergic Adverse Events Occurring Within One Hour

Patient	Elapsed Time to the Event ≤10 Minutes	Event	Age at Vaccination	Gender	Dose	Additional Symptoms	Serological Findings*	Simultaneous Vaccinations	Treatment
1	<1 min	Anaphylaxis	5 y 11 mo	M	II		Pneumococcus	IPV	
2	<1 min	Anaphylaxis	5 y 11 mo	M	II			IPV	
3	1 min	Anaphylaxis	3 y 4 mo	M	I	Otitis media	Pneumococcus		Epinephrine + corticosteroid
4	1 min	Anaphylaxis	6 y	F	I		Enterovirus		
5	1 min	Anaphylaxis	17 y 8 mo	M	I				Epinephrine + corticosteroid
6	1 min	Anaphylaxis	23 y	F	I				Epinephrine
7	2 min	Anaphylaxis	5 y 3 mo	M	I	Fever, sore throat	Pneumococcus		Epinephrine
8	2 min	Anaphylaxis	6 y 4 mo	F	II				
9	4 min	Anaphylaxis	6 y	F	I				
10	5 min	Anaphylaxis	5 y	M	I				Epinephrine
11	5 min	Anaphylaxis	5 y 11 mo	M	II				Epinephrine + corticosteroid
12	5 min	Anaphylaxis	5 y 11 mo	F	II			IPV	
13	5 min	Anaphylaxis	6 y	M	II			IPV	Epinephrine
14	5 min	Anaphylaxis	6 y 3 mo	M	II				Epinephrine + corticosteroid
15	5 min	Anaphylaxis	6 y 10 mo	M	I				
16	5 min	Urticaria	6 y	M	II				
17	10 min	Anaphylaxis	6 y 1 mo	M	II			IPV	
	≤1 hour								
18	15 min	Anaphylaxis	17 y 2 mo	F	II				Epinephrine
19	15 min	Urticaria + asthma	1 y 6 mo	M	I	Cough, rhinitis	<i>Moraxella catarrhalis</i> , enterovirus		Corticosteroid
20	30 min	Urticaria	6 y 2 mo	M	I				Antihistamine

IPV indicates inactivated poliovirus vaccine.

\* Based on previously described analysis.<sup>25</sup>

gelatin (14.5 mg), sorbitol (14.5 mg), sucrose (1.9 mg), human albumin (0.3 mg), and neomycin (0.025 mg). The vaccine is administered subcutaneously.

### Case Collection

A prospective follow-up of serious adverse events after MMR vaccination was conducted from November 1982 to December 1996 in the entire country.<sup>3,25</sup> A reportable reaction was a potentially life-threatening disorder (eg, anaphylaxis), an event leading to hospitalization, or a chronic disease possibly triggered by MMR vaccination. Along with a notification form, paired serum samples were sent to the central office of the project.

The reported cases of anaphylaxis, urticaria with or without angioedema, asthmatic symptoms, Henoch-Schönlein purpura, and Stevens-Johnson syndrome were presumed to be hypersensitivity-induced, and these patients comprised the study group.

Clinical details were collected from the notification forms and the medical records of the vaccinees. If the information was incomplete, the local nurses or doctors were interviewed. With the permission of the local authorities, certain vaccinees (described below) or their parents were contacted to obtain their medical histories in more detail.

### Specific Immunoglobulin E (IgE) Determinations

The collected sera were stored at -20°C until analyzed in 2000. Serum IgE antibodies to gelatin were measured by a commercial CAP System radioallergosorbent test (RAST) fluoroenzymeimmunoassay (FEIA; Pharmacia and Upjohn, Uppsala, Sweden). Specific IgE levels in serum ≥0.35 kU/L were considered positive (0.35–0.69 kU/L CAP class 1, 0.7–3.49 kU/L CAP class 2, and 3.5–17.49 kU/L CAP class 3).

To evaluate further IgE binding to the whole vaccine (M-M-R<sub>II</sub>, 1:1 and 1:10 v/v) and the main components of the vaccine, an immunospot method<sup>26</sup> was used. To minimize the effects of possible changes in the constituents of the vaccine during the study, we used 2 vaccine lots (expiration dates August 31, 1984 and November 10, 2000) and 2 gelatins (bovine/porcine [leaf form] and porcine [powdered]), both of food quality, 10 g/L for measuring the whole vaccine- and gelatin-specific IgE. Because gelatin

is derived from collagen by hydrolytic action, hydrolyzed collagen (1%, Crotein Q) was also tested. The porcine gelatin used currently by the manufacturer of the vaccine was unavailable.

The other vaccine components analyzed by the immunospot were egg (Soluprick 1:100 w/v, 1:1 and 1:10 v/v; ALK, Horsholm, Denmark), neomycin sulfate (10 g/L, Ph Eur), and human albumin (fraction V, 10%, Sigma A-1653, St Louis, MO). To assess concomitant allergy and possible allergen cross-reactivity, IgE binding to chicken meat (boiled, 1:2 w/v, 1:1 and 1:10 v/v), feathers (Soluprick 1:100 w/v, 1:1 and 1:10 v/v; ALK), and cow's milk powder (10 g/L, 1:1 and 1:10 v/v; Valio, Helsinki, Finland) was also measured.

The results were evaluated after comparison with nonatopic and atopic control sera. Serum from a nonatopic individual served as a negative control, and pools of sera from 46 egg-allergic and 18 cow's milk-allergic individuals as atopic controls (egg CAP: 40.8 kU/L and milk CAP: 28.3 kU/L).

The results were classified as strong positive, weak positive (indicating an intermediate result), or negative.

### RESULTS

In 1982 to 1996, 2 990 000 doses of M-M-R<sub>II</sub> vaccine were distributed to 1.8 million individuals, the vaccination coverage being ~95%.<sup>27</sup> In addition, in 1992 to 1996, 2570 doses of the egg protein-free vaccine were administered to allergic vaccinees.

During this surveillance for over 14 years, 73 presumably allergic reactions were reported<sup>25</sup>: 30 anaphylaxis, 30 urticaria (in 12 patients accompanied by angioedema and in 1 by asthmatic symptoms), 10 asthmatic symptoms, 2 Henoch-Schönlein purpura, and 1 Stevens-Johnson syndrome. The reporting rates were 1.0, 1.0, 0.3, 0.07, and 0.03 per 100 000 vaccine doses, respectively. No such reactions were reported after administration of the egg protein-free vaccine.

The immediate or nonimmediate allergic reactions of 36 vaccinees with serum samples available were further evaluated, with 18 cases of suspected anaphylaxis, 13 of urticaria (5 cases accompanied by angioedema and 1 by asthmatic symptoms), 4 of asthmatic symptoms, and 1 of Henoch-Schönlein purpura. The characteristics of these 36 participants are presented in Tables 1 and 2, and their histories of allergy are summarized in Tables 3 and 4.

Of these 36 reactions, 25 (69.4%) occurred after the first dose of MMR vaccine and 10 (27.8%) after the second dose; in 1 case this information was lacking. Ages at vaccination ranged from 14 months to 23 years (median: 5 years 11 months).

In 17 cases, the reaction developed within 10 minutes of vaccination (16 anaphylaxis and 1 urticaria). Three individuals experienced the reaction within 1 hour, and 7 within 24 hours. The remaining 9 events appeared 3 to 15 days postvaccination. Twenty-four patients (66.7%) received medication, and all patients recovered uneventfully.

Concurrent infections were detected by serology in 10 vaccinees (27.8%).<sup>25</sup> Simultaneous immunizations were administered to 7 (19.4%).

Previous history of hypersensitivity was noted in 15 of the 36 vaccinees (41.7%) at the time of vaccination. Egg allergy was present in 1 child, who had asthmatic symptoms 24 hours postvaccination, but his serology was positive for concurrent *Moraxella catarrhalis* infection.<sup>25</sup> Two children with urticaria and 1 with anaphylaxis had outgrown their egg sen-

sitivity. Asthma had been previously diagnosed in 2 individuals with anaphylaxis, 1 with asthmatic symptoms, and 1 with urticaria.

In addition, a 6-year-old boy had a history of anaphylaxis after ingestion of egg and had active asthma (patient 20 in Tables 1–4). An MMR skin-prick test was conducted twice before his vaccination. The first test induced a wheal of 3 mm, which was equivalent to that of the positive control (histamine dihydrochloride 10 mg/mL), but the second test was negative. He was vaccinated with M-M-R<sub>II</sub> in hospital. Mild generalized urticaria developed within 30 minutes, but there were no signs of angioedema or asthma. He received antihistamine and became symptomless in 30 minutes.

Seven patients were skin-prick tested with MMR vaccine after the reported event, all with negative results.

#### Gelatin CAP System RAST

Of the 36 sera tested, 5 (13.9%) were gelatin CAP System RAST-positive (Tables 3 and 4). The positive results were detected in 2 vaccinees with anaphylaxis, 2 with urticaria (in the other child accompanied by symptoms of asthma), and 1 with symptoms of asthma. Three of these had gelatin-specific IgE of CAP class 2, and 2 of class 3 (range: 1.0–7.1 kU/L).

#### Immunospot

Distinct binding of IgE antibodies to gelatin was demonstrated in 10 of the 36 serum samples (27.8%;

**TABLE 2.** Characteristics of Patients With Allergic Adverse Events Occurring After One Hour

Patient	Elapsed Time to the Event ≤24 Hours	Event	Age at Vaccination	Gender	Dose	Additional Symptoms	Serological Findings*	Simultaneous Vaccinations	Treatment
21	2.5 h	Asthma	7 y 1 mo	M	I				Corticosteroid + terbutalin + teophyllin
22	6 h	Asthma	1 y 7 mo	F	I			Hib	Corticosteroid + salbutamol + antihistamine
23	9 h	Anaphylaxis	20 y 11 mo	F	I				Corticosteroid
24	12 h	Urticaria†	1 y 2 mo	M	I				Antihistamine
25	24 h	Urticaria	1 y 7 mo	M	I	Tonsillitis			Epinephrine
26	24 h	Urticaria†	6 y	M	I	Fever	Pneumococcus, <i>Chlamydia pneumoniae</i>		Antihistamine
27	24 h	Asthma	1 y 8 mo	M	I	Rash	<i>Moraxella catarrhalis</i>		Antihistamine
28	>24 hours 3 d	Urticaria†	13 y	F	?	Fever, vomiting, conjunctivitis	Pneumococcus		Corticosteroid + antihistamine
29	3 d	Purpura	2 y 2 mo	F	I				Corticosteroid + antihistamine
30	4 d	Urticaria	4 y 2 mo	F	I		<i>Haemophilus influenzae</i>		Antihistamine
31	9 d	Urticaria	1 y 5 mo	M	I	Fever, diarrhea	Pneumococcus		Corticosteroid + antihistamine
32	10 d	Urticaria	1 y 6 mo	F	I	Lymphadenopathy			Antihistamine
33	10 d	Urticaria	1 y 6 mo	F	I			Hib	
34	10 d	Urticaria†	6 y 3 mo	M	I	Fever			Corticosteroid
35	13 d	Asthma	1 y 7 mo	M	I	Fever, cough, otitis media			Epinephrine + corticosteroid + salbutamol
36	15 d	Urticaria†	1 y 6 mo	M	I				Antihistamine

Hib indicates *H influenzae* type b vaccine; purpura, Henoch-Schönlein purpura.

\* Based on previously described analysis.<sup>25</sup>

† Accompanied by angioedema.

**TABLE 3.** Positive Results of Gelatin CAP System RAST\* and Immunospot† Tests of Patients With Allergic Adverse Events Occurring Within One Hour

Patient	Time From Vaccination to Serum Sample (Days)‡	RAST	Immunospot	History of Allergic Disorders§	Allergy Tests After Vaccination§
1	0/14		Egg+, milk+		
2	3				Neomycin patch test-negative
3	98/0				
4	29/1				
5	0	1.0	Gelatin A+, feather+	Egg allergy previously   Asthma, atopic eczema, hay fever	
6	35				
7	1				MMR, pollen, and animal SPT-negative
8	0		Milk+		
9	0		Milk+		
10	16/0				MMR, pollen, and animal SPT-negative
11	0				
12	56		Milk+		
13	42		Milk+		
14	1			Atopy (undefined) Asthma	MMR SPT-negative
15	14/0		Milk+	Atopic eczema, hay fever, cow's milk allergy	
16	0		Milk++		
17	72/49		Milk+		MMR SPT-negative
18	7	4.0	Gelatin A and B++, meat++, feather++	Chicken and fish allergy (diagnosed postvaccination)	Chicken and fish RAST-positive
19	0	7.1	Gelatin A and B++, collagen++, egg++, meat++, milk++	Egg allergy previously,   asthma and fish allergy (diagnosed postvaccination)	MMR SPT-negative, cow's milk and cat SPT-positive
20	0	1.1	Gelatin A and B++, egg++, meat++, feather++, milk++	Asthma, egg and cow's milk allergy, MMR SPT-negative before vaccination	

SPT indicates skin-prick test.

\* kU/L, positive result  $\geq 0.35$  kU/L.

† Tested: whole vaccine, gelatin A (bovine/porcine), gelatin B (porcine), hydrolyzed collagen (collagen), hen's egg (egg), chicken meat (meat), hen's feather (feather), neomycin, human albumin, cow's milk (milk). Positive results: ++ strong positive, + weak positive.

‡ Zero indicates that the sample was taken on the vaccination day. If separate samples were used for the tests, the sample used for CAP System RAST is stated first.

§ Information based on medical records and notification forms or personal interviews.

|| Tolerant at the time of vaccination.

Tables 3 and 4). The reported reactions among these 10 vaccinees were 5 urticaria (in 1 case accompanied by asthmatic symptoms), 3 asthmatic symptoms, and 2 anaphylaxis. Four had strong positive results and 6 weak positive (11.1% and 16.7%, respectively). The IgE binding was more evident to the bovine/porcine gelatin. Of the 10 patients, 2 showed reactivity also against hydrolyzed collagen.

All 5 patients with increased IgE to gelatin in the CAP System RAST showed specific IgE binding to gelatin also in the immunospot. In addition, 5 patients had weak positive results in the immunospot, suggesting the better sensitivity of this method. However, 2 of the 5 patients with positive immunospot results but the by-definition negative CAP System RAST had weak reactivity against gelatin also in the CAP System RAST (0.1 kU/L). Sera from non-atopic and atopic controls showed no binding to gelatin.

Nine patients (25.0%) showed egg-specific IgE in the immunospot (6 strong and 3 weak positive). The reported reactions were 5 urticaria (1 with asthmatic symptoms), 2 asthmatic symptoms, 1 anaphylaxis, and 1 Henoch-Schönlein purpura.

IgE binding to chicken was demonstrated in 8 patients (22.2%); 5 with urticaria (1 with asthmatic

symptoms), 2 with asthmatic symptoms, and 1 with anaphylaxis.

Specific binding to cow's milk was observed in 17 patients (47.2%), 7 with strong and 10 with weak positive results. Feathers induced positive results in 5 patients (13.9%).

No binding of IgE to the whole vaccine, neomycin, or human albumin was observed by the immunospot. The absence of IgE binding in the nonatopic control serum and lack of human albumin-specific IgE excluded unspecific IgE binding.

For 10 of the 18 patients (55.6%) with reported anaphylaxis, the physician treating the vaccinee suspected the reaction to be fainting instead of actual anaphylaxis, so only 3 of these received epinephrine. One of these patients showed IgE binding to gelatin and feathers (patient 5). Four vaccinees had IgE binding only to milk and 1 to egg and milk; 4 had negative results.

A 20-year-old woman had anaphylaxis 9 hours after vaccination, shortly after eating chicken (patient 23). Allergy to chicken or spices was suspected, but only total serum IgE was measured after the event; it was slightly elevated (200 kU/L; reference range: <110 kU/L). Her CAP System RAST and immunospot results remained negative.

**TABLE 4.** Positive Results of Gelatin CAP System RAST\* and Immunospot† Tests of Patients With Allergic Adverse Events Occurring After One Hour

Patient	Time From Vaccination to Serum Sample (Days)‡	RAST	Immunospot	History of Allergic Disorders§	Allergy Tests After Vaccination§
21	1		Gelatin A and B+, meat+	Asthma, atopic eczema, pollen allergy	
22	14		Gelatin A+, collagen+, egg++, milk++	Asthma (diagnosed postvaccination), atopic eczema	MMR, egg, and neomycin SPT-negative
23	7			Hay fever	Elevated total serum IgE
24	21/1		Egg++, meat++	Egg allergy previously	Cat and dog RAST-positive
25	2		Meat+, milk+		MMR SPT-negative
26	3			Penicillin and orange allergy	
27	1	1.1	Gelatin A and B+, egg++, meat++, feather++	Atopic eczema, egg and fish allergy	
28	7		Milk++		
29	16		Egg+, feather+, milk+		
30	4		Gelatin A+, egg+, meat+, milk+	Asthma, atopic eczema	
31	40		Milk++	Atopy (undefined)	
32	19/61				
33	63		Gelatin A+, egg++		
34	11		Gelatin A+		
35	36/16			Asthma (diagnosed postvaccination)	Pollen and animal SPT negative
36	20		Milk++		

SPT indicates skin-prick test.

\* kU/L, positive result  $\geq 0.35$  kU/L.

† Tested: whole vaccine, gelatin A (bovine/porcine), gelatin B (porcine), hydrolyzed collagen (collagen), hen's egg (egg), chicken meat (meat), hen's feather (feather), neomycin, human albumin, cow's milk (milk). Positive results: ++ strong positive, + weak positive.

‡ Zero indicates that the sample was taken on the vaccination day. If separate samples were used for the tests, the sample used for CAP System RAST is stated first.

§ Information based on medical records and notification forms or personal interviews.

|| Tolerant at the time of vaccination.

The immunospot results of patient 18 are presented in Fig 1.

#### Later Clinical Symptoms

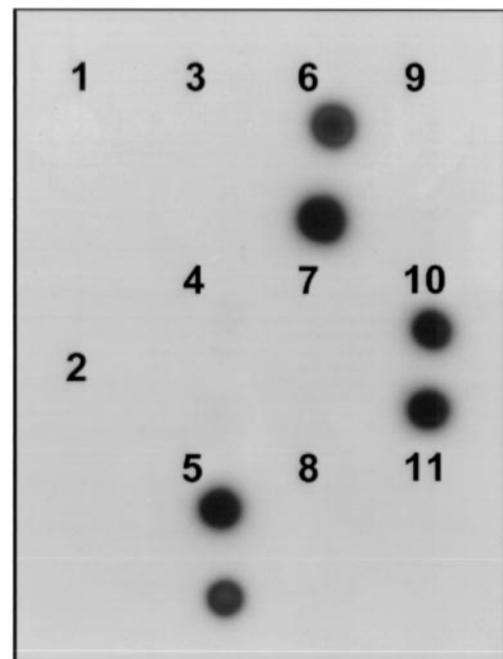
To relate the positive results in the CAP System RAST or the immunospot to later allergic symptoms, the vaccinees with gelatin-specific IgE or their parents were interviewed in May 2000.

Of the 10 gelatin-hypersensitive vaccinees, 9 were contacted 4 years 8 months to 17 years 5 months after MMR vaccination. Only 2 (patients 30 and 33) reported no allergic symptoms.

Patient 18 experienced another anaphylactic reaction after eating chicken 1 year after MMR vaccination, and chicken and fish allergy were diagnosed. Frequent gastrointestinal symptoms, such as stomachache, nausea, or diarrhea were reported by patients 19, 21, 22, and 34. Angioedema or blistering of the mouth or throat was reported by patients 19, 21, and 27. All of them associated their symptoms with food, especially with chicken, egg, fish, or pudding.

Persistent atopic eczema was reported by patients 5 and 22. None of the vaccinees were aware of the gelatin hypersensitivity.

Three of the 9 vaccinees (patients 19, 22, and 34) were revaccinated with MMR 4 years 5 months to 14 years after the first dose. Two developed no symptoms, whereas patient 19 experienced cough and sneezing postvaccination.



**Fig 1.** Positive immunospot results of patient 18 to gelatin A, gelatin B, and chicken. (IgE binding to feathers was detected after longer exposure.) IgE binding was analyzed to MMR vaccine: 1) old (expiration date August 31, 1984), 2) new (expiration date November 10, 2000), 3) human albumin, 4) neomycin, 5) gelatin A (bovine/porcine, leaf form), 6) gelatin B (porcine, powdered), 7) hydrolyzed collagen, 8) egg, 9) feathers, 10) chicken, and 11) cow's milk.

## DISCUSSION

High vaccination coverage is a prerequisite for the success of all immunization programs aiming at disease eradication.<sup>1</sup> Exclusion of relatively large populations, such as egg-allergic children, from standard vaccination schedules, has to be based on thorough evaluation of the risks and benefits of immunization.

Safety of MMR vaccination of egg-sensitive persons has been studied thoroughly. In 1987, 122 of 135 severely atopic individuals (90.4%) of whom 56% had confirmed egg allergy were immunized with MMR vaccine by Juntunen-Backman et al.<sup>7</sup> No severe allergic symptoms developed, and the only reactions found were mild generalized urticaria and fever, each in 1 child.<sup>7</sup>

In the United Kingdom, 200 egg-allergic children were skin-prick tested with measles or MMR vaccine, and only 5 had positive reactions.<sup>14</sup> One of these 5 developed anaphylaxis after a subsequent intradermal test. All the other 199 individuals received measles or MMR vaccine without problems.<sup>14</sup> In 7 studies in Canada, the United States, and Australia, a total of 1281 children with hypersensitivity to egg were safely immunized with measles-mumps or MMR vaccine.<sup>8–13,15</sup>

Current opinion favors vaccinating despite egg allergy, but a cautious approach is recommended if the vaccinee has a history of anaphylactic or other serious immediate reaction after ingestion of egg or after previous vaccinations.<sup>6,17</sup> These severely hypersensitive individuals should be referred for specialist evaluation, and immunization in a supervised setting is, in most cases, feasible. The recent recommendation in the United Kingdom also encourages vaccination in hospital of individuals with a milder egg allergy and with concurrent asthma.<sup>6</sup> Allergy to feathers or chicken meat is not a contraindication.<sup>9</sup>

The usefulness of skin-prick or intradermal testing of egg-allergic individuals before vaccination has been debated also, and several studies have found poor positive and negative predictive values.<sup>4,10–13</sup> Moreover, these tests, as such, can also trigger anaphylaxis.<sup>14</sup>

Because more allergic reactions after MMR vaccination have occurred in individuals without egg hypersensitivity,<sup>6</sup> other allergenic vaccine components have been sought. Previous systemic reactions to neomycin contraindicate vaccination but are extremely rare. Contact dermatitis from neomycin does not prevent immunization.<sup>17</sup> None of the reactions in our study were attributable to neomycin.

In 1993, Kelso and collaborators<sup>16</sup> demonstrated by the immunoblotting method the presence of gelatin-specific IgE in an egg-tolerant 17-year-old female who developed anaphylaxis after MMR vaccination. Sakaguchi et al<sup>18–20</sup> showed a strong relationship between gelatin in monovalent measles, mumps, or rubella vaccines and immediate-type allergic reactions in 27 vaccinees tested by the CAP System. Nonimmediate-type hypersensitivity to gelatin in vaccines was described by Taniguchi et al<sup>21</sup> and Sakaguchi et al,<sup>28</sup> and anti-gelatin immunoglobulin G was suggested to play a role in the nonim-

mediate reactions.<sup>28</sup> Anaphylaxis has also been reported after administration of gelatin-containing varicella vaccine.<sup>29</sup>

Because most gelatin-induced events have been reported from Japan, a question as to the role of ethnicity in gelatin hypersensitivity has been raised.<sup>22</sup> Our series does not support this theory, because gelatin allergy was detected by the immunospot and CAP System RAST methods in 27.8% of Finnish vaccinees with immediate or nonimmediate allergic adverse events.

Egg hypersensitivity was detected in 9 patients (25.0%). Interestingly, the positive results in gelatin-specific IgE binding overlapped with egg, chicken, and feather reactivity. Of the 10 patients with positive results to gelatin in the immunospot, 4 had also egg- and chicken-specific IgE. In addition, 2 vaccinees showed IgE binding to gelatin and egg, and 2 to gelatin and chicken. Concurrent IgE binding to gelatin and feathers was detected in 4 patients.

Because the prevalence of cow's milk allergy is estimated to be 2.5% in infants and decreases with age,<sup>30</sup> the proportion of vaccinees with positive immunospot results to cow's milk (47.2%) in this study is surprisingly high. Businco<sup>5</sup> speculated on possible cross-reactivity between cow's milk and gelatin. We detected both gelatin- and milk-specific IgE in 4 vaccinees.

Timing the serum sample collection differently would have perhaps increased our positive results. Specific IgE antibodies do not always appear immediately after an allergic event, and collection of a blood sample very soon after the reaction may lead to a negative result.<sup>31</sup>

Gelatin, which is prepared by the hydrolysis of collagen from various animal sources, is used as a stabilizer pharmaceutically and in foods such as yogurt, pudding, pastry, instant whipped cream, and candies. Hypersensitivity to gelatin in candy has been reported,<sup>32</sup> but allergic reactions seem to be more common toward pharmaceutically used gelatin, with even fatal reactions occurring against gelatin-containing plasma substitutes.<sup>33</sup>

A separate question is how gelatin allergy has already developed in some children during the first year of life. Precooked infant foods<sup>21</sup> or previous administration of gelatin-containing vaccines, such as diphtheria-tetanus-pertussis vaccine, have been postulated as sensitizing allergens.<sup>20,22</sup>

More research is needed to characterize in more detail the role of gelatin in immediate and nonimmediate allergic reactions to vaccines, and its possible cross-reactivity with egg, chicken, and feathers, as well as cow's milk. The vaccine component responsible for every severe allergic reaction should be sought, and the commercially available gelatin CAP System RAST is a useful tool. If gelatin emerges as a common allergen, less reactogenic stabilizing materials should be developed, as has already been done in Japan.<sup>34</sup>

This study provides additional evidence of the extreme rarity of severe allergic reactions induced by MMR vaccination. Our findings support the view of vaccinating most egg-allergic individuals according

to normal vaccination schedules. As with all vaccinations, adequate treatment should, however, be immediately available when MMR vaccine is administered, should the need arise. If systemic reactions develop, hypersensitivity to gelatin should be considered.

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