

Minimum estimated incidence in Japan of anaphylaxis to live virus vaccines including gelatin

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Abstract

We have previously found that most occurrences of anaphylaxis to live virus vaccines are caused by gelatin present in the vaccines as a stabilizer. After we published the evidence for the role of gelatin in anaphylaxis, vaccine manufacturers in Japan began to eliminate gelatin from live virus vaccines. In the present study, we tried to estimate its incidence before the gelatin elimination was started. Physicians and vaccine manufacturers submitted serum samples from children with anaphylaxis to measles, mumps, rubella or varicella vaccine to National Institute of Infectious Diseases (NIID) for 3 years from April 1994 to March 1997. Specific IgE to gelatin was assayed at NIID or two manufacturers by the CAP and ELISA methods. There were 44 children with life-threatening severe anaphylaxis (airway obstruction or anaphylactic shock) during the 3-year period, 41 of whom had anti-gelatin IgE. There were 64 children with mild anaphylaxis (without airway obstruction); 62 had anti-gelatin IgE. There were 100 children with only systemic cutaneous signs; 81 had anti-gelatin IgE. The estimates for the incidence of the severe anaphylaxis in 1994–1996 are: 6.84, 7.31, 4.36, and 10.3 cases per million doses of gelatin-containing measles, rubella, mumps, and varicella vaccines, respectively. © 2000 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Anaphylaxis to measles–mumps–rubella (MMR) vaccines has been reported as extremely rare [1,2]. Although more than 70 million doses of MMR vaccines were used in the US in 1990–1995, only 33 cases of anaphylactic reactions were reported after the vaccinations [3]. This adverse reaction was thought to be also rare in Japan before 1993, when the first reported case of anaphylaxis to measles vaccine occurred [4]. Since then, many children have been reported to show the systemic immediate-type reactions, including ana-

phylactic shock, to measles, mumps, rubella, and varicella vaccines [5–8].

The anaphylactic reaction was suspected to be caused by gelatin allergy: Kelso et al. reported in 1993 that a child who suffered from anaphylaxis to gelatin-containing MMR vaccine had anti-gelatin IgE antibody [9]. However, in 1993 in Japan, there were no commercially available test kits for gelatin IgE determination. Thus, an ELISA for anti-gelatin IgE was developed at the National Institute of Infectious Diseases (NIID) for confirmation of the presence of the antibody [5]. Subsequently, the NIID researchers asked the Pharmacia Company to develop a kit for the measurement of anti-gelatin IgE in accordance with Pharmacia CAP system which is a de facto standard

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for measurement of specific IgE. After the establishment of the CAP system, anti-gelatin IgE concentrations were expressed as CAP units [5,10,11].

With increasing concerns about gelatin allergy among pediatricians who were involved in immunization for children, many serum specimens for gelatin IgE testing were sent from the physicians to NIID or to the manufacturers of the respective vaccines which the physicians were using. Thus, a training course for the ELISA technique was held at NIID for all the vaccine manufacturers in Japan; thereafter, two of the manufacturers (Kitasato and Biken) used the ELISA by themselves, and others transferred all the sera to NIID for testing.

In the meantime, it was revealed that diphtheria–tetanus–acellular pertussis (DTaP) vaccines produced by some manufacturers contained a small amount of gelatin as a spillover protein during the purification process of pertussis toxin. The possibility was raised that anti-gelatin IgE is produced by the gelatin-containing DTaP vaccines prior to immunization with gelatin-containing measles vaccines [8]. Sakaguchi and Inouye produced convincing evidence for the above hypothesis; they conducted a case-control study in which vaccination histories for gelatin-containing or gelatin-free DTaP vaccines were investigated among subjects with or without systemic immediate reactions to live virus vaccination [12]. The study showed that none of 54 children with such reactions had received gelatin-free DTaP vaccines. By contrast, among 101 control children without such reaction 29% had received gelatin-free DTaP vaccines [12].

Gelatin in all the live virus and DTaP vaccines produced in Japan had been eliminated, or replaced with gelatin of low allergenicity between 1997 and 2000 (personal communication from the manufacturers).

In the present paper, we estimated the minimum incidence of gelatin anaphylaxis to live virus vaccines in Japan before vaccine manufacturers began to eliminate gelatin from both DTaP and live virus vaccines. Vaccine-related researchers, physicians and all the vaccine manufacturers in Japan have cooperated for this study.

2. Materials and methods

2.1. Children

Physicians and vaccine manufacturers submitted to NIID clinical data and serum samples from children with systemic immediate-type reactions, including anaphylaxis, to live virus vaccines containing gelatin as a stabilizer. Furthermore, the two vaccine manufacturers which carried out the IgE test by themselves provided us the data on children with the systemic immediate-

type reactions to live virus vaccines. We used the data from 208 children who showed the allergic reactions. These data were collected during a 3-year time span (from April 1994 to March 1997; Japanese statistics data for 1 year are collected from April to next March).

As a first control, serum samples from 26 children (14 boys, 12 girls; mean age $\pm$ SD, 2 years 4 months $\pm$ 1 year) who had no reaction to measles vaccine containing gelatin (1 mg/dose) were collected. As a second control, serum samples from 200 children (113 boys, 87 girls; mean age $\pm$ SD, 1 year 6 months $\pm$ 11 months) who had no reaction to combined measles–rubella vaccines containing gelatin (1 mg/dose) were collected. As a third control, serum samples from 50 children (mean age $\pm$ SD, 2 years 4 months $\pm$ 1 year 1 month), who had no allergic reaction to the varicella vaccine, were kindly supplied by Dr. Takao Ozaki, Showa Hospital, Konan, Japan.

2.2. Systemic immediate-type reactions to live virus vaccines

Systemic immediate-type reactions are classified into three groups: (1) life-threatening severe anaphylaxis consisting of cutaneous signs (e.g., systemic urticaria, angioedema) plus airway obstruction (with laryngeal edema or wheezing) or anaphylactic shock (with hypotension and vascular collapse); (2) mild anaphylaxis consisting of the cutaneous signs plus respiratory symptoms (wheezing and/or cough or laryngeal edema) without airway obstruction; (3) systemic cutaneous signs alone consisting of only systemic urti-

Table 1
Gelatin contents in live virus vaccines from 1994 to 1996 in Japan

Manufacturer	Gelatin in vaccines (mg/dose)			
	Measles	Rubella	Mumps	Varicella
A	1 ^a	1 ^b	1 ^a	– ^c
A	10 ^d	–	10 ^d	–
B	2.5 ^e	2.5 ^e	–	13.5 ^f
C	–	0	0	–
D	1.5 ^g	0	0	–
E	1 ^h	1 ^h	1 ⁱ	–

^a In 1998, gelatin was replaced with low allergenic gelatin.

^b In 1999, gelatin was removed from this vaccine.

^c –: no production.

^d Manufacturer (A) produced these vaccines that included 10 mg of gelatin as polygelin; these vaccines were available only from September 1993 to April 1994.

^e In 1997, gelatin was removed from these vaccines.

^f In 2000, gelatin was removed from the vaccine.

^g In December 1996, gelatin was removed from this vaccine.

^h In 1998, gelatin was removed from these vaccines.

ⁱ The vaccine was available until 1995.

Table 2
Estimated doses of live virus vaccines inoculated in Japan

Year ^a	Measles vaccine (gelatin)		Rubella vaccine (gelatin)		Mumps vaccine (gelatin)		Varicella vaccine (gelatin)	
	(+)	(–)	(+)	(–)	(+)	(–)	(+)	(–)
1994	1,112,417	0	— ^b	—	208,400	181,599	190,203	0
1995	1,287,824	0	862,675	822,237	130,354	214,790	223,716	0
1996	1,106,849	274,985	641,163	689,879	120,074	225,950	265,594	0

^a Japanese statistical year (from April to next March).

^b Before 1994, rubella vaccine was used only for immunization of 15-year-old girls in Japan.

caria or angioedema. These systemic reactions appeared within 1 h after vaccination.

2.3. Vaccines in Japan

In Japan, measles, mumps, rubella and varicella vaccines are available (Table 1). Measles vaccines are produced by four manufacturers: all the vaccines contained bovine gelatin in amounts ranging from 1 to 10 mg/dose (Table 1). Rubella vaccines are produced by five manufacturers: the vaccines from three manufacturers contained bovine gelatin in amounts ranging from 1 to 2.5 mg/dose. Mumps vaccines are produced by four manufacturers: the vaccines from two manufacturers contained bovine gelatin in amounts ranging from 1 to 10 mg/dose. Varicella vaccines are produced by one manufacturer: the vaccine contained both bovine gelatin (1 mg/dose) and hydrolyzed bovine gelatin (12.5 mg/dose) as a stabilizer.

2.4. Doses of vaccines

Table 2 shows estimated doses of gelatin-containing live virus vaccines used in Japan from 1994 to 1996. Total doses of measles and rubella vaccines inoculated were estimated from the report of the Committee on Immunization [13–15].

In 1994, Japanese Immunization Law was revised and most infants began to receive rubella vaccines in 1995; before 1994, the vaccines were used only for immunization of 15-year-old girls in junior-high schools.

Total doses of mumps and varicella vaccines were not available in the report of the Committee on Immunization. They were estimated by personal communication from vaccine manufacturers.

2.5. Measurement of gelatin-specific IgE antibody

The CAP system (Pharmacia, Uppsala, Sweden) was used to determine the concentration (Ua/ml) of IgE to bovine gelatin at NIID [6]. This system is a method to measure specific IgE based on allergens conjugated to an encapsulated cellulose polymer and on fluorescence detection system.

Specific IgE to bovine gelatin were determined by a fluorometric ELISA, as described earlier, by the two vaccine manufacturers (Biken and Kitasato) [5].

2.6. Statistical analysis

Data analysis was performed using the SAS system (Ver 6.11, Cary, NC).

3. Results

3.1. Systemic immediate-type reactions to measles vaccine

Table 3 shows data of 111 children (53 boys, 58 girls; mean age $\pm$ SD, 1 year 10 months $\pm$ 11 months) who had the systemic immediate-type reactions to measles vaccine for 3 years. Of the 111 children, 24 showed severe anaphylaxis, 35 had mild anaphylaxis without severe symptoms, and 52 had systemic cutaneous signs only. Of the 111, 94 children (86%) had anti-gelatin IgE ranging from 1.2 to 251 Ua/ml (mean value $\pm$ SD, 25.4 $\pm$ 40.7) (Table 3). As a negative control, all 226 children who showed no reaction to measles or combined measles–rubella vaccines containing gelatin (1 mg/dose) had no anti-gelatin IgE.

Table 3
Systemic immediate-type reactions to measles vaccine in children

Year ^a	Anaphylaxis		Cutaneous sign	Total
	Severe	Mild		
1994	5 (5) ^b	4 (3)	9 (7)	18 (15)
1995	10 (9)	14 (13)	17 (16)	41 (38)
1996	9 (7)	17 (17)	26 (17)	52 (41)
Total	24 (21)	35 (33)	52 (40)	111 (94)

^a Japanese statistical year (from April to next March).

^b Number in parentheses is the number of children with antigelatin IgE.

Table 4
Systemic immediate-type reactions to rubella vaccine in children

Year ^a	Anaphylaxis		Cutaneous signs	Total
	Severe	Mild		
1994	0	0	0	0
1995	6 (6) ^b	3 (3)	10 (9)	19 (18)
1996	5 (5)	10 (10)	16 (13)	31 (28)
Total	11 (11)	13 (13)	26 (22)	50 (46)

^{a,b} The same as in Table 3.

3.2. Systemic immediate-type reactions to rubella vaccine

Table 4 shows the data of 50 children (29 boys, 21 girls; mean age $\pm$ SD, 2 years 8 months $\pm$ 1 year 2 months) who had systemic immediate-type reactions to rubella vaccine. In 1994, we found no cases of systemic immediate-type reactions to this vaccine, because few infants received the vaccine before 1994. Of the 50 children, 11 showed severe anaphylaxis, 13 had mild anaphylaxis without severe symptoms, and 26 had only systemic immediate-type urticaria. Of the 50, 46 children (92%) had anti-gelatin IgE ranging from 1.1 to 351 Ua/ml (mean value $\pm$ SD, 23.5 ± 56.6) (Table 4).

3.3. Systemic immediate-type reactions to mumps vaccine

Table 5 shows data of 17 children (10 boys, seven girls; mean age $\pm$ SD, 2 years 8 months $\pm$ 11 months) who had systemic immediate-type reactions to mumps vaccine (Table 5). Of the 17 children, two showed severe anaphylaxis, seven had mild anaphylaxis without severe symptoms, and eight had only systemic immediate-type urticaria. All 17 children had anti-gelatin IgE ranging from 0.82 to 62.9 Ua/ml (mean value $\pm$ SD, 19.1 ± 17.4) (Table 5).

Table 5
Systemic immediate-type reactions to mumps vaccine in children

Year ^a	Anaphylaxis		Cutaneous signs	Total
	Severe	Mild		
1994	0	3(3) ^b	0	3(3)
1995	1(1)	2(2)	4(4)	7(7)
1996	1(1)	2(2)	4(4)	7(7)
Total	2(2)	7(7)	8(8)	17(17)

^{a,b} The same as in Table 3.

Table 6
Systemic immediate-type reactions to varicella vaccine in children

Year ^a	Anaphylaxis		Cutaneous signs	Total
	Severe	Mild		
1994	1 (1) ^b	0	0	1 (1)
1995	1 (1)	2 (2)	2 (2)	5 (5)
1996	5 (5)	7 (7)	12 (9)	24 (21)
Total	7 (7)	9 (9)	14 (11)	30 (27)

^{a,b} The same as in Table 3.

3.4. Systemic immediate-type reactions to varicella vaccine

Table 6 shows data of 30 children (21 boys, nine girls; mean age $\pm$ SD, 2 years 7 months $\pm$ 1 year) who had systemic immediate-type reactions to varicella vaccine. Of the 30 children, seven showed severe anaphylaxis, nine had mild anaphylaxis without severe symptoms, and 14 had only systemic immediate-type urticaria. Of these 30, 27 children (90%) had anti-gelatin IgE ranging from 1.4 to 324 Ua/ml (mean value $\pm$ SD, 27.4 ± 69.3). As a negative control, all 50 children had no anti-gelatin IgE.

3.5. Minimum estimate of the incidence of severe anaphylaxis to the vaccines

Table 7 shows the minimum estimate of the incidence, between statistical years 1994 and 1996, of severe anaphylaxis to the live virus vaccines. The mean incidence of severe anaphylaxis to each gelatin-containing vaccine in 1994–1996 are: 6.84, 7.31, 4.36, and 10.3 cases/million doses measles, rubella, mumps, and varicella vaccines, respectively. The difference of the incidence among vaccines is not statistically significant.

Table 7
Minimum estimate of the incidence of severe anaphylaxis to each vaccine including gelatin

Severe anaphylaxis	Vaccine			
	Measles	Rubella	Mumps	Varicella
1994	4.49 ^a	— ^b	0	5.26
1995	7.77	6.96	7.67	4.47
1996	8.13	7.80	8.33	18.8
Total	6.84	7.31	4.36	10.3

^a The number of case per million doses of each vaccine.

^b Before 1994, rubella vaccine was used only for immunization of 15-year-old girls in Japan.

4. Discussion

After the first reported case of anaphylaxis to measles vaccine occurred in 1993 [4], there was an increase in the numbers of anaphylactic cases to live virus vaccines in Japan. Recently, it was suggested that there is a strong causal relationship between gelatin-containing DTaP vaccination, anti-gelatin IgE production, and the risk of anaphylaxis following subsequent immunization with live virus vaccines which contain a large amount of gelatin [8,12]. Since December 1996, Japanese vaccine manufacturers had made strong efforts to eliminate gelatin from live virus vaccines (Table 1), and had removed it completely by 1999 from the DTaP vaccines, which contained a small amount of gelatin and which might have sensitized some children with anti-gelatin IgE. Most of vaccine-associated gelatin anaphylaxis are expected to disappear shortly.

We think that all the cases of life-threatening severe anaphylaxis were referred to NIID or vaccine manufacturers by the physicians for measurement of anti-gelatin IgE, though only a portion of cases with mild systemic urticaria was referred. If this is correct, then the mean incidence of severe anaphylaxis in 1994–1996 is calculated as 6.84, 7.31, 4.36, and 10.3 cases/million doses of gelatin-containing measles, rubella, mumps, and varicella vaccines, respectively. The difference of the incidence among vaccines is not statistically significant. The mean incidence for mumps vaccines was lower than those for other vaccines, because the incidence of severe anaphylaxis to the vaccine in 1994 was 0%. In 1995 and 1996, the incidence for mumps vaccines was similar to those for other vaccines, which might be a reasonable result, since these vaccines contained a similar amount of gelatin.

The incidence of anaphylaxis to MMR vaccines in the US was reported as 0.5 cases/million doses [3], one order of magnitude less than that in Japan, suggesting that Japanese children were sensitized with anti-gelatin IgE at a higher rate than the US children. Nakayama et al. also reported the incidence of anaphylaxis to gelatin-containing vaccines from Kitasato Institute (a vaccine manufacturer): 11.9 cases/million doses for measles vaccine, 6.52 cases/million doses for rubella vaccine, and 18.5 cases/million doses for mumps vaccine [8].

We postulated that the change in immunization schedule in Japan may have caused the occurrences of gelatin anaphylaxis [8,12]. Before 1993, there had been no published anaphylactic events caused by live virus vaccines in Japan. The first case of anaphylaxis to measles vaccine occurred in 1993 [4]. Since then, we have had cases of many anaphylaxis to measles, mumps, rubella and varicella vaccines [5–8]. We suspect that such a sudden incidence is related to the

change in immunization schedule of gelatin-containing DTaP vaccines. In 1981, acellular pertussis vaccines replaced the whole-cell (DTwP) vaccines and was used for immunization of 2-year-old. In December 1988, the Ministry of Health and Welfare, following 7 years of safe and effective use of DTaP, recommended its use for routine vaccination of 3-month-old infants. Since 1989, children 3–24-month-old began to receive DTaP vaccines. In 1994, the Immunization Law was revised and almost all infants began to receive DTaP vaccines before measles vaccination. In contrast, US children have long received several doses of DTwP vaccine prior to MMR vaccination. However, prior to 1996, the gelatin-free DTwP vaccines were used [16]. Such vaccines would not be capable of causing gelatin sensitization. Further, MMR vaccines used in the US (MMR-II, Merck) contain relatively high dose of gelatin, but the used gelatin is low allergic porcine gelatin digested by papain. These might account for the lower rate of reported anaphylaxis to subsequent doses of gelatin-containing vaccines in the US.

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