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Removal of gelatin from live vaccines and DTaP—an ultimate solution for vaccine-related gelatin allergy

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Abstract

From the early 1990s infants started to receive acellular pertussis vaccine combined with diphtheria and tetanus toxoids (DTaP) before live vaccines such as measles, rubella, and mumps vaccines, which contained gelatin as a stabilizer. Then, an increasing number of cases of anaphylactic/allergic reactions to those live vaccines were reported. Almost all these cases had a previous history of receiving three or four doses of DTaP containing gelatin.

Anaphylactic/allergic reactions to live measles vaccine were analyzed using information obtained from the Reporting System, a retrospective study, as well as from the Monitoring System, a prospective study. Dramatic decreases in anaphylactic/allergic reactions to live measles vaccines were observed immediately after each manufacturer marketed gelatin-free or gelatin (hypo-allergic)—containing live measles vaccine, and since the end of 1998 reports on anaphylactic/allergic reactions to live measles vaccine have almost ceased.

Keywords: Gelatin allergy; Anaphylactic/allergic reactions; Gelatin-in-DTaP; Gelatin-free vaccines

1. Introduction

In Japan, live measles vaccine was given to 1-year-old children and the primary series of whole cell pertussis vaccine combined with diphtheria and tetanus toxoids (DTP) were given to 2-year-old children, i.e., after live measles vaccine, since 1975. In 1981, acellular pertussis vaccine combined with diphtheria and tetanus toxoids (DTaP) took over DTP but the age of administration remained at 2 years [1,2]. There had been no serious problem. In December 1988, by governmental approval, the immunization schedule was changed so that the initial series of DTaP was given before live measles vaccine. Since then the shift in age of initial administration of DTaP from 2 years down to 3 months of age occurred gradually. Therefore, an increasing number of children started to receive the first three doses of DTaP before live measles vaccine, which was administered to 1 year or older children or other live vaccines such as rubella and mumps vaccines, which were usually given after live measles vaccine. From April 1994 infants were recommended by the Preventive Immunisation Law to complete the primary series of DTaP vaccinations during the first year of life, prior to live measles vaccine, which was given at one year of age. From January 1994 reports of cases of anaphylactic/allergic reactions to live vaccines, i.e., measles, rubella and mumps vaccines, started to accumulate. Virtually all children who manifested anaphylactic/allergic reactions to live vaccines and whose detailed vaccination histories were available had histories of three or four doses of gelatin-containing DTaP [3]. Laboratory testing showed increases in gelatin-specific IgG antibody and IgE antibody in sera of children who had received gelatin-containing DTaP [3], and gelatin-specific IgE antibodies were detected in almost all children who had anaphylactic reactions to

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Abbreviations: DTaP, acellular pertussis vaccine combined with diphtheria and tetanus toxoids; DTP, whole cell pertussis vaccine combined with diphtheria and tetanus toxoids.

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live vaccines [4]. These observations led to the hypotheses that anaphylactic/allergic reactions to live vaccines occurred as a consequence of gelatin allergy and that gelatin-in-DTaP was most probably the sensitizing allergen in most cases. Gelatin-in-vaccine related allergy drew public attention and all manufacturers in Japan started to develop gelatin-free vaccines. By the end of the 20th century, virtually all of the live and inactivated vaccines in Japan were gelatin-free.

The purpose of this paper is to report on the impact of removal of gelatin from live vaccines as well as from DTaP based on the incidence of anaphylactic/allergic reactions to live vaccines. We concentrated on live measles vaccine because it was one of the routine immunization vaccines with acceptance rates of over 90%, and all four manufacturers' live measles vaccines contained gelatin as a stabilizer and also because adverse reactions to measles vaccine have been studied by the Reporting System for Adverse Effects and by the Monitoring System, both organized by the Ministry of Health and Welfare (currently Ministry of Health, Labor, and Welfare).

2. Materials and methods

2.1. Live measles vaccine

Manufacturer A produced live measles vaccine containing gelatin, human serum albumin, and dextran 70 as stabilizers and has marketed gelatin-free live measles vaccine since December 1996. Manufacturer D produced live measles vaccine with gelatin but without human serum albumin. Since June 1998, D has produced live measles vaccine that was gelatin-free. Manufacturer B produced live measles vaccine containing gelatin but without human serum albumin. From July 1998, B used hypo-allergic gelatin. In September 2002, B withdrew live measles vaccine containing hypo-allergic gelatin and now produces gelatin-free live measles vaccine. Manufacturer C used to produce live measles vaccine containing gelatin and human serum albumin, but has marketed gelatin-free live measles vaccine since November 1998.

2.2. DTaP

In Japan, three consecutive doses of DTaP were given at 3–8 week intervals and the fourth dose was given 12–18 months after the third dose of the initial series. Six manufacturers produced DTaP, which differed with regard to gelatin content. DTaP of Manufacturer B and Manufacturer D never contained gelatin. DTaP of Manufacturer A, C and F contained carry-over gelatin at less than 0.0067 w/v %, and DTaP of Manufacturer E contained 0.2% gelatin added as a stabilizer. The total marketing share of gelatin-containing DTaP was approximately 75%.

Manufacturer F has marketed DTaP free of gelatin since November 1997. Manufacturer E removed gelatin from DTaP in December 1997. Manufacturer C has marketed DTaP free of gelatin since August 1998. Manufacturer A removed gelatin from DTaP in February 1999, and all DTaP in Japan became gelatin-free.

2.3. National projects on research for adverse reactions to live measles vaccine

In accordance with the amendment of the Preventive Immunization Law in October 1994, two national projects on research concerning adverse reactions to routine immunization started: the Reporting System for Adverse Effects and the Monitoring System. Immediate allergic reactions to live measles vaccine such as anaphylaxis, urticaria, local reactions, and generalized rash were analyzed using information obtained from those two systems between April 1996 and March 2002.

2.3.1. Reporting System for Adverse Effects

Reporting System for Adverse Effects, a retrospective study, started in October 1994. Specified adverse effects i.e., immediate allergic reactions such as anaphylaxis or generalized urticaria, encephalitis or encephalopathy, convulsion, motor disturbances, neurological disturbances, and abnormal reactions such as rash, local reactions, etc., should be reported to the Ministry of Health and Welfare. Usually home doctors submitted the reports. The cases were arranged according to the date of vaccination. Anaphylaxis was defined as an allergic reaction with cardiovascular shock and/or respiratory symptoms. Some cases manifested multiple adverse events. For example, one patient had fever, generalized urticaria, and local reaction. All such manifestations were counted individually. Therefore, the total number of symptoms was greater than the total number of cases. The information was collected by the national government, analyzed and reported twice each year.

2.3.2. Monitoring System

This is a prospective study. Sentinel doctors all around Japan report results of observations for 28 days after routine immunization. Ten thousand recipients for each routine immunization are monitored annually. Information is collected by the Ministry of Health and Welfare, analyzed, and reported every 6 months.

3. Results

Table 1 shows the annual number of doses of live measles vaccine and number of cases reported to the

Table 1
Number of doses of live measles vaccine and number of reported cases by the Reporting System for Adverse Events (October 1994–March 2002)

Period	Oct. 1994–Sept. 1995	Oct. 1995–Mar. 1996	Apr. 1996–Mar. 1997	Apr. 1997–Mar. 1998	Apr. 1998–Mar. 1999	Apr. 1999–Mar. 2000	Apr. 2000–Mar. 2001	Apr. 2001–Mar. 2002
Number of doses	1,048,522	552,130	1,112,511	1,116,218	1,096,243	1,157,908	1,137,868	1,221,130
Number of cases with adverse events	73	99	145	107	34	31	35	27
Rate per 10,000 doses	0.74	1.79	1.30	0.96	0.31	0.27	0.31	0.22

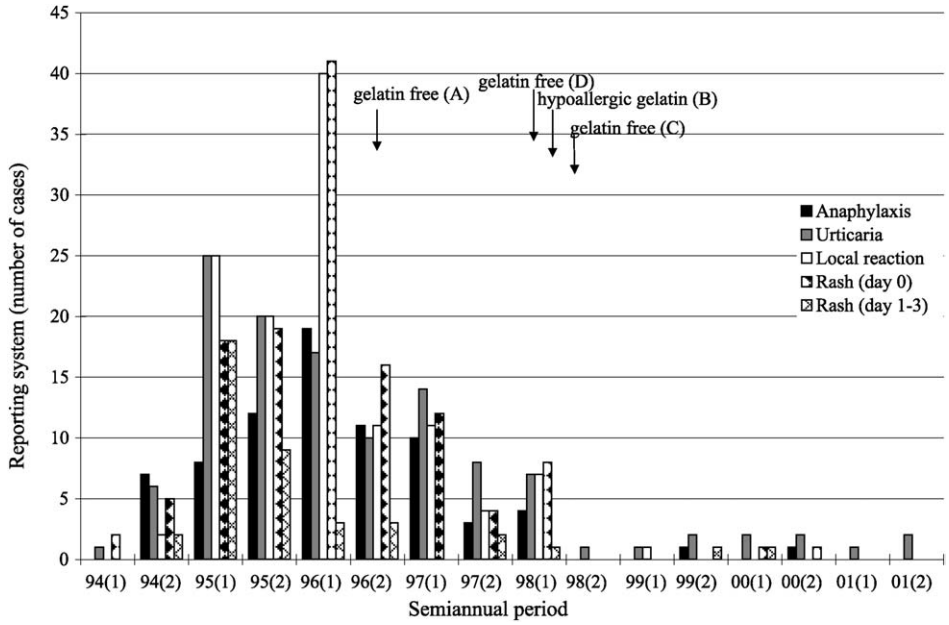

Fig. 1. Adverse effects of live measles vaccines reported to the Reporting System for Adverse Effects. The first semi-annual period starts in April and ends in September of the same year. A second semi-annual period starts in October and ends in March of the following year.

Reporting System for Adverse Events. The incidence of adverse events per 10,000 doses of live measles vaccine was the highest during October 1995 and March 1996, i.e., 1.79 per 10,000 doses. Since then the rate has decreased steadily and in April 2001 and March 2002 the rate was the lowest, i.e., 0.22 per 10,000 doses. There was an 88% reduction.

Fig. 1 shows cases of anaphylactic/allergic reactions since the introduction of the Reporting System for Adverse Events. A dramatic decrease in anaphylactic/allergic reactions was noted when Manufacturer A removed gelatin from live measles vaccine. A further decrease was noted shortly after Manufacturers D and C marketed gelatin-free vaccine, and Manufacturer B marketed hypo-allergic gelatin containing vaccine. Since October 1998, only a few cases of immediate allergic reactions such as anaphylaxis and urticaria has been reported annually. Annual total doses of live measles vaccine in Japan have reached 1.1 to 1.2 million. Thus approximately 1 or 2 immediate allergic reactions are reported per 1 million doses. So far no deaths due to immediate allergic reactions have been reported.

There have been no reports of anaphylaxis by the Monitoring System at April 2003. Fig. 2 shows the number of reports of urticaria by the Reporting System for Adverse Events and by the Monitoring System for the live measles vaccine of Manufacturer A in semi-annual periods. The marketing share of Manufacturer A was approximately 50%, so that the number of doses of Manufacturer A's vaccine during the semi-annual period was estimated to be about 250,000 or one-fourth of 1 million. In the first semi-annual period of 1995 (April 1995 to September 1995) 17 cases of urticaria were reported by the Reporting System for Adverse Events within 24 h of vaccination and in the second semi-annual period of 1996 (October 1996 to March 1997) three were reported. Since then the number of reports has not exceeded two; i.e., an 82% reduction from 1995. In the Monitoring System incidences of urticaria appearing on day 0 or day 1 consistently not more than 0.65%.

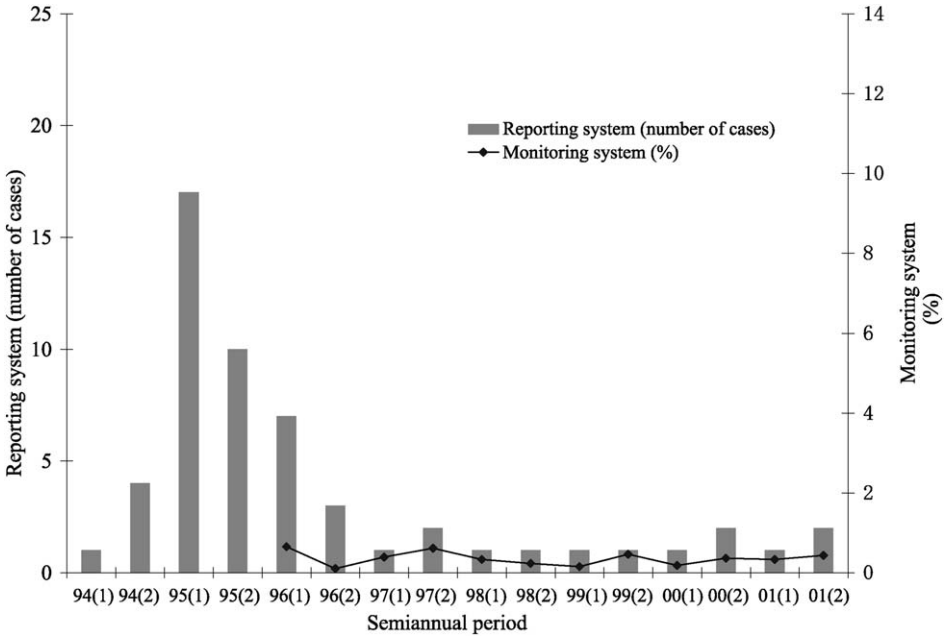

Fig. 2. Urticaria caused by Manufacturer A's live measles vaccine. The number of reports of urticaria by the Reporting System for Adverse Events are shown by bars. Incidences of urticaria reported by the Monitoring System are shown by dots and lines.

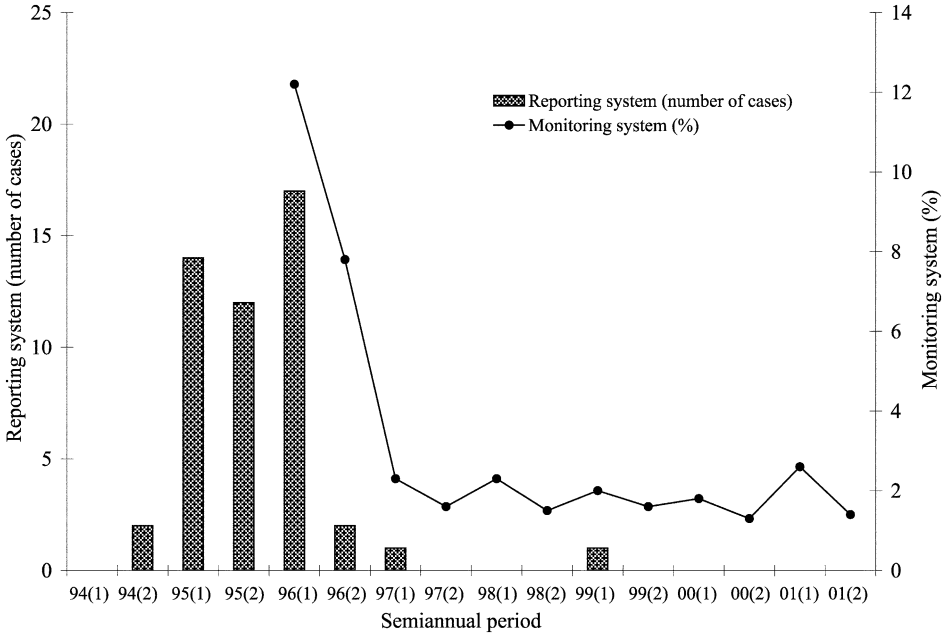

Fig. 3. Local reactions to Manufacturer A's live measles vaccine. The number of reports of local reactions by the Reporting System for Adverse Events are shown by bars. Most of the local reactions reported by the Reporting System for Adverse Events are those associated with generalized urticaria or rash. Incidences of local reactions reported by the Monitoring System are shown by dots and lines.

Fig. 3 shows local reactions to Manufacturer A's live measles vaccine. Local reactions dropped dramatically in the period from April 1996 to April 1997 both in the Reporting System for Adverse Events and the Monitoring System. The number of Adverse Events reports in the first semi-annual period of 1996 was 17, but this dropped suddenly to two in the second semi-annual period of 1996. Since April 1997 incidences of local reactions by the Monitoring System have not exceeded 2.6%, although the incidence in the first semi-annual period of 1996 was 12.2% and that in the second period was 7.8%.

4. Discussion and conclusion

Gelatin, a product obtained by the partial hydrolysis of collagen, is widely used in foods and pharmaceuticals. In the past, most commercially available vaccines, both live and inactivated, contained gelatin as a stabilizer and allergic reactions to gelatin contained in MMR vaccine were reported [5]. However, gelatin-allergy to vaccines was thought to be a rare phenomenon. It was not known what factors predisposed recipients to vaccine related gelatin allergy.

Sudden increases in reports on gelatin allergy occurring with administration of live vaccines such as measles, rubella, and mumps vaccines could only be explained by the change in immunization policy, i.e., until 1988 the primary series and booster dose of DTaP were given after live vaccines such as the measles vaccine, but since 1994 the primary series of DTaP has been given prior to live vaccines. Although we became aware that gelatin allergy occurred, we did not know how frequently it occurred or what kinds of adverse events were associated with gelatin.

Our study on adverse events of live measles vaccines at a time when stabilizers of both live measles vaccine and DTaP were changed revealed, (i) gelatin was one of the strongest allergens, (ii) DTaP was an adjuvant vaccine containing aluminum hydroxide and minute amounts of carry-over gelatin contained in DTaP were able to sensitize infants to gelatin so that they manifested allergic/anaphylactic reactions to subsequently administered live vaccines which contained gelatin, and (iii) clinical symptoms of gelatin allergy including anaphylaxis, urticaria, local reactions, and rash within 3 days of vaccination, as shown by the disappearance of those symptoms soon after gelatin was removed from three manufacturers' live measles vaccine (A, D, C) and hypo-allergic gelatin was used in one manufacturer's live measles vaccine (B).

In February 1999, all DTaP products became free of gelatin. Children who received the initial three doses of DTaP in 1999 received live measles vaccines in 2000 or 2001 when the live measles vaccines of three manufacturers were already gelatin-free and that of one manufacturer contained hypo-allergic gelatin. Therefore, the effect of removal of gelatin from DTaP could not be evaluated by the Reporting System for Adverse Events or by the Monitoring System.

As shown in Fig. 3, some weak allergens may still remain in live measles vaccine but they cause only local reactions and no generalized anaphylactic/allergic reactions. We consider that the problem of allergy to vaccines has been solved.

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