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EFFECT AND FOLLOW-UP STUDY ON VARICELLA VACCINE

NORIKO KATSUSHIMA, NATSUME YAZAKI and MICHIYO SAKAMOTO

Department of Pediatrics, Yamagata City Hospital Saiseikan, 1-3-26 Nanokamachi, Yamagata, 990 Japan

Attenuated live varicella vaccine (Oka strain) was used to vaccinate 242 children and 5 adults between August 1976 and December 1982; namely emergency vaccinations were given to 163 cases, including 35 high risk children, on 17 occasions, and non-emergency vaccinations were given to 84 cases including 7 high risk ones in remission. The viral doses varied from 250 to 3,000 PFU. Vaccinations prevented subsequent infection in all cases. Emergency vaccinations were given within 100 h after contact of the subjects with cases of varicella. Humoral and/or cellular immunity was acquired in 97.6% (40/41) of the high risk group and 91.8% (179/195) of the non-high risk group. As clinical reactions, rashes and fever developed in 43.9% (18/41) and in 17.0% (7/41) of high risk patients, and 7.8% (16/204) and 1.0% (2/204) of the non-high risk patients respectively. Reactions were generally slight, but were severe or atypical in 3 immunocompromized patients. Follow-up studies were carried out every year since 1980. Among the 41 high risk patients, herpes-zoster developed in 4, and varicella in 5 patients. Among the 179 non-high risk patients, there were no cases of herpes-zoster but 21 cases (12.3%) of varicella, which were mostly extremely mild. Six patients were revaccinated because of their humoral and/or cellular immunity decreased, and as a result acquired an immune response again. Criteria for varicella vaccination and details of the results of vaccination and follow-up studies are described.

INTRODUCTION

For many years we had been worried about the problems of occurrence of varicella in the ward: after one case subsequent cases inevitably follow, because varicella has a long incubation period, and is infective even before the onset of symptoms. Moreover, varicella may be severe or fatal in patients who are being treated with immunosuppressants in the ward. Zoster immune globulin or plasma is not available in Japan.

In 1974, Takahashi and his colleagues developed a live attenuated varicella vaccine. In August 1976, one of our staff, a 26-year-old lady doctor, examined all the patients in the pediatric ward. Soon after, varicella eruptions were noticed on her face. At 100 h after the onset of varicella in this doctor, we inoculated 15 patients, including seven high risk ones with Takahashi's vaccine. No secondary varicella occurred. Since then we have used varicella vaccine. This paper reports our criteria for vaccination, the clinical and immune responses

of the recipients, the efficacy of vaccine for prevention of secondary infections, some specific cases with severe reactions and follow-up studies on the vaccinees.

CRITERIA FOR VACCINATION

We postulated indicative criteria for vaccination and have vaccinated subjects according to these criteria. The following subjects should be vaccinated:

1. Susceptible high risk children who are in remission.
2. High risk children who come in contact with varicella.
3. Susceptible patients in the hospital who come in contact with varicella.
4. Susceptible doctors, nurses and students working in the pediatric ward and clinic.
5. Susceptible siblings of hospitalized patients, healthy children in the nursery, susceptible female adults, and others who wish to be vaccinated.

VACCINE AND VACCINATION

The vaccine used was attenuated live varicella vaccine (Oka strain). The viral dose given was 250 to 3,000 plaque forming units.

With their parents' consent, children were injected with this vaccine subcutaneously. Blood was obtained before and 4 to 6 weeks after vaccination for serological study. Antibody against varicella-zoster virus was measured by neutralization test or immunoadherence hemmagglutination test at the laboratory of the Department of Virology, Research Institute for Microbial Diseases, Osaka University. When the antibody titer was not elevated, the varicella skin reaction was performed. Vaccinees were observed carefully for at least 4 weeks after vaccination.

TABLE 1. *Details of emergency vaccinations 1976. 8–1982. 12*

	Date	Reasons for vaccination	Time until vaccination (days)	Dose in PFU	No. of vaccinees	No. of high risk patients	Subsequent clinical varicella
1	1976. 8	varicella in doctor	5	1,000	15	7	none
2	1976. 12	varicella in ward	1	1,000	12	3	none
3	1977. 6	varicella in ward	1	3,000	4	2	none
4	1977. 7	varicella in ward	1	3,000	3	1	none
5	1977. 7	varicella in ward	1–3	3,000	2	0	none
6	1978. 9	varicella in ward	3	3,000	1	1	none
7	1979. 1	varicella in ward	1	300–3,000	17	7	none
8	1979. 4	varicella in ward	1	300–3,000	9	4	none
9	1979. 5	varicella in ward	2	300–3,000	12	0	none
10	1979. 7	varicella in nursery	1	500–1,000	13	0	none
11	1979. 12	varicella in ward	3	250	17	3	none
12	1980. 12	varicella in ward	2	750	5	1	none
13	1981. 3	varicella in ward	1–2	750	5	2	none
14	1981. 9	varicella in ward	1	500	8	0	none
15	1981. 11	varicella in ward	3	500	10	1	none
16	1982. 2	varicella in ward	1	500–1,000	21	3	none
17	1982. 12	varicella in mother	2	850	2	0	none
				250–3,000	163	35	

RECIPIENTS OF VACCINE

In all, 247 subjects received the vaccine between August 1976 and December 1982. Emergency vaccinations were done in 164 patients, including 35 high risk children, and non-emergency vaccinations were done in 83 cases, including 7 high risk cases in remission, 5 nurses and students and others who wished to be vaccinated.

The 42 high risk patients consisted of 18 with nephrotic syndrome, 12 with malignant diseases, including 7 cases of acute lymphatic leukemia, 2 cases of neuroblastoma and 1 case each of acute myelomonocytic leukemia, Burkitt's lymphoma and hepatoblastoma, 3 cases of idiopathic thrombocytopenic purpura, 3 cases of anaphylactoid purpura, 2 cases of congenital hypoplastic anemia and 1 case each of urticaria, Kawasaki's disease, infantile spasm and allergic gastroenteropathy.

Between 1976 and 1982, there were 15 occasions of unexpected occurrence of varicella in the pediatric ward. In addition, there was one in nursery, and another in a home where mother caught varicella. All susceptible children who would remain in hospital for more than the incubation period of varicella were vaccinated. Subjects were judged susceptible when they had no history of the disease. Without exception, there were no successive varicella infections after vaccination. The details of the emergency vaccinations are listed in Table 1.

The time from contact with a case of varicella until vaccination was one day in 96 subjects, two days in 20 subjects, three days in 32 subjects and five days, but in 100 h in 15 subjects. Vaccination of one after six days was ineffective.

CLINICAL AND IMMUNE RESPONSES

The clinical and immune responses of the recipients are summarized in Table 2. Of 41 high risk patients, 18 (43.9%) developed rashes and 7 (17.0%) exhibited fever. Of 204 non-high risk subjects, only 16 (7.8%) developed rashes and 2 (1.0%) exhibited fever. In 35 of 41 high risk patients, the antibody reactions was good by the neutralization and immunoadherence hemmagglutination tests 4 to 6 weeks after vaccination. Four of the others gave positive reactions in the skin tests. In all, 40 of 41 (97.6%) acquired immunity. Antibody responses were seen in 91.4% of the non-high risk group, and positive skin tests were observed in the other 8 cases. Immunity to varicella was acquired in 91.8%. Four cases (marked by *a* in Table 2) were omitted from effective numbers, because they were found to have varicella immediately after vaccinations.

Eruptions due to vaccination were generally few and slight. Owing to careful observation, no eruptions were missed. The rashes consisted of red papules or vesicles, and they healed mostly without scars. Nine cases in the high risk group and ten cases in the non-high risk group had less than ten eruptions, and less than 50 eruptions were observed in 7 and 6 cases in these respective groups. Two cases

TABLE 2. *Clinical and immune responses to vaccination*

	No. of subjects vaccinated	Eruption	Fever 37.5 C	Antibody response	Positive skin reaction	Immunity acquired
High risk group	41+1[a]	18/41	7/41	36/41	4/4	40/41
		43.9%	17.1%	87.8%	100%	97.6%
Non-high risk group	204+3[a]	16/204	2/204	171/187	8/8	179/195
		7.8%	1.0%	91.4%	100%	91.8%
Total	245+4[a]	34/245	9/245	207/228	12/12	219/236

[a] Cases in which varicella developed immediately after vaccination.

TABLE 3. *Reactions due to vaccination*

No. of eruptions	High risk	Non-high risk
1-10	9	10
11-50	7	6
Numerous	2	0
Temperature		
37.5 C	2	2
38 C	4	0
39 C	1	0

had numerous eruptions. The incidence of fever was lower than that of rash, and all febrile cases developed eruptions (Table 3).

The time from vaccination until the appearance of eruptions was 12 to 19 days in the non-high risk group, but 12 to 34 days in the high risk group (Fig. 1).

In the high risk group, the incidence of side reactions differed according to the state of the underlying disease. Among the 7 patients in the state of complete remission, eruptions were observed in 2 and fever in none. Among the 21 patients with the disease of active state who were receiving high doses of immunosuppressants, eruptions were seen in 12 and fever in 7. Among 13 patients who were not receiving hardly any treatment, eruptions were seen in 3 and fever in none.

There was no evidence of aggravation of the underlying diseases after vaccination in any case.

CASES WITH SEVERE CLINICAL REACTIONS

Three cases with severe, atypical reactions were observed. The first was a 4-year-old girl suffering from infantile spasm, who was receiving ACTH treatment. She received emergency vaccination with 3,000 PFU of vaccine. After 14 days, fever and vesicles disseminating over her whole body were observed. The second case was a 9-year-old boy suffering from Burkitt's lymphoma, and receiving high doses of immunosuppressants. He was in remission at the time of injection of 750 PFU of vaccine. After 16 days, a varicelliform rash appeared over the whole body, with a high fever that lasted for 20 days. After recovery from this first episode, disseminated atypical verruca-like eruptions developed, which persisted for 30 days. He also had slight fever for 15 days. The vaccine strain of varicella-zoster virus was detected in fluid from the vesicles. In this case, cellular immunity was markedly

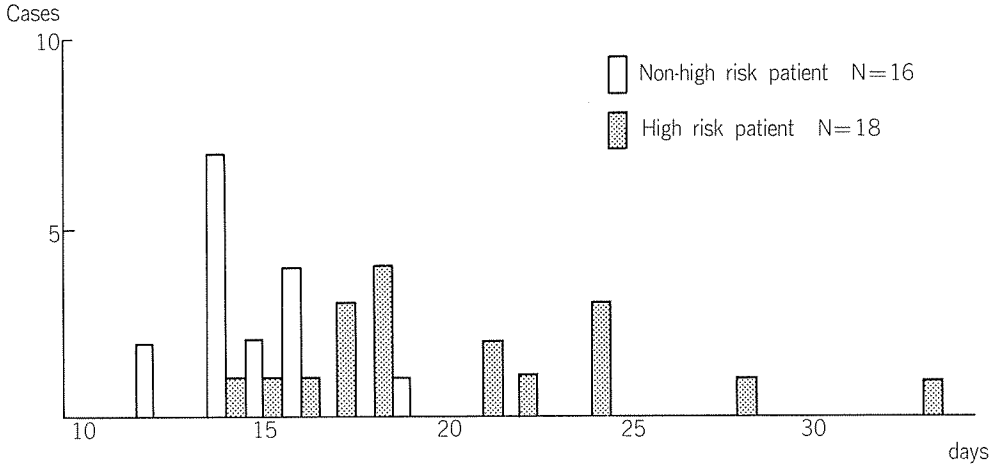

FIGURE 1 Time from vaccination till appearance of eruptions as side reactions.

TABLE 4. *Data on three cases with severe side reactions due to varicella vaccine*

Disease	Infantile spasm	Malignant lymphoma (Burkitt)	Acute lymphatic leukemia (T cell type)
Age	4 mo	9 yr	2 yr 9 mo
Sex	F	M	M
Treatment	ACTH 0.25 mg×10	P 1,445 mg, VCR 7.5 mg 6MP 585 mg, CPH 2,200 mg radiation 2,400 r.	P 1,365 mg, VCR 5 mg MTX 56 mg
Wbcc	12,200	2,400	14,400
Lymphocyte %	33	13	15
Immunoglobulins			
IGA mg/dl	≒60	133	66
IGM	≒40	72	134
IGG	550	11,236	660
Vaccination PFU	3,000	750	750
Eruptions	numerous all stages of eruptions-scar	first, numerous varicelliform, hemorrhagic → scar for 20 days second, numerous verruca-like, pigmented atypical rash for 30 days	solitary herpes-like eruption → disseminated vesicles → crust → scar for 33 days
Temperature	39 C 4 days	38 C 20 days+15 days	38 C 35 days
Cellular immunity	ND[a]	markedly depressed	sustained
Virus from vesicles	ND	vaccine virus	vaccine virus
Serum antibody titer IAHA	4–8	<2–128–32	<2–4
Varicella skin test	ND	−	+

Abbreviations: P, Prednisolone; VCR, Vincristine; 6MP, 6 mercaptopurine; MTX, Methotrexate; CPH, Cyclophosphamide.

[a] Not done.

depressed by the blastogenesis method, and a negative result was obtained in the varicella skin test. On the other hand, his serum antibody titer was elevated. The third case was a 2-year-old boy suffering from T-cell type leukemia who was receiving induction therapy. He received emergency vaccination with 750 PFU of vaccine. After 34 days, one vesicle developed on his loin, and this gradually increased in size. Then vesicles resembling those of herpes-zoster became disseminated. His fever lasted for 35 days. Cellular immunity was sustained by blastogenesis. The vaccine strain of varicella zoster virus was detected in fluid from the vesicles. A varicella skin test gave a positive reaction. The total doses of immunosuppressants used, clinical signs, labolatory data and immunological data in these three cases are shown in Table 4.

FOLLOW-UP STUDY ON VACCINEES

We first used this vaccine seven years ago, and we are following up vaccinees, and checking for herpes-zoster and varicella every year. Data on patients vaccinated by 1980 were investigated. High risk patients were examined completely and non-high risk patients were requested to complete questionnaires. In the high risk group, herpes-zoster developed in four and varicella in five cases by August 1983. After revaccination, there were no case of varicella. The protection rate of varicella, protected/contacts was from 69.2% to 100%. About half the non-high risk group came in contact with varicella each year and gradually

TABLE 5. *Follow-up of protection against varicella and incidence of herpes-zoster*

Year of follow-up	1980		1981		1982		1983	
Time after vaccination	6 mo-3 yr 10 mo		7 mo-5 yr		10 mo-6 yr		7 mo-7 yr	
	High risk group	Non-high risk group	H	N-H	H	N-H	H	N-H
No. of vaccinees	32	79	35	115	37	113	42	179
No. of deaths[a]	2	0	3	0	6	0	6	0
Herpes-zoster[a]	2	0	3	0	4	0	4	0
Natural varicella[a]	4	2	5	8	5	13	5	21
Contacts with varicella/ No. of follow-ups	13/25	33/79	21/25	58/115	12/26	50/113	9/29	68/179
No. protected/ No. of contacts	9/13	31/33	20/21	56/58	12/12	45/50	9/9	60/68
Protection rate	69.2%	95.2%	95.2%	90.5%	100%	90%	100%	88.2%

[a] Accumulated number of patient.

cases of varicella increased. For example, from 1982 to 1983, there were eight cases of varicella and 68 cases of contact, so the protection rate was 88%. The incidence of varicella until 1983 was 12.3%. There were no cases of herpes-zoster in this group (Table 5).

Herpes-zoster in the high risk group was mild in 3 cases, and atypical in one case. All cases healed without neurological sequelae, but one patient died soon after the disease due to relapse of leukemia.

Natural varicella in vaccinees was generally mild. Extremely mild varicella with only 1 to 10 eruptions and no fever was seen in 4 cases in the high risk group, and 8 in the non-high risk group. Mild varicella with 11 to 50 eruptions were seen in 10 cases in the non-high risk group, and moderate and normal varicella were seen in 1 and 3 cases, respectively. There was no severe case of varicella.

The times from vaccination until natural varicella infections, ranging from 6 months to 5 years, are shown in Fig. 2. Among the 26 cases infected, 5 cases showed no antibody response, but 2 of these gave a positive skin tests. Paired sera were not obtained in 2 cases, but 19 cases were comfirmed to have acquired humoral immunity after vaccination. Five high risk patients and 5 healthy children who wished to be vaccinated were included.

REVACCINATION

Since clinical varicella has been observed in vaccinees by exogenous infection, those who showed depressed immunity were revaccinated. The need for revaccination was determined from the skin reaction when the subjects came in contact with cases of varicella. Revaccination was necessary in 6 patients. All but one of them had acquired cellular and humoral immunity after the initial vaccination, but after 6 months to 4 years their skin reactions became negative, and their serum antibody levels were depressed. After revaccination, all cases again showed an antibody response (Table 6).

SUMMARY

The following results and conclusions were obtained in this study.

1. Emergency vaccination of susceptible persons protects them completely from infection with varicella if given within 5 days (100 h) after exposure to the virus.
2. Vaccination should be done as soon as possible after contact with varicella patients.
3. Immune responses are good in both high risk and non-high risk patients.
4. Underlying diseases are not aggravated

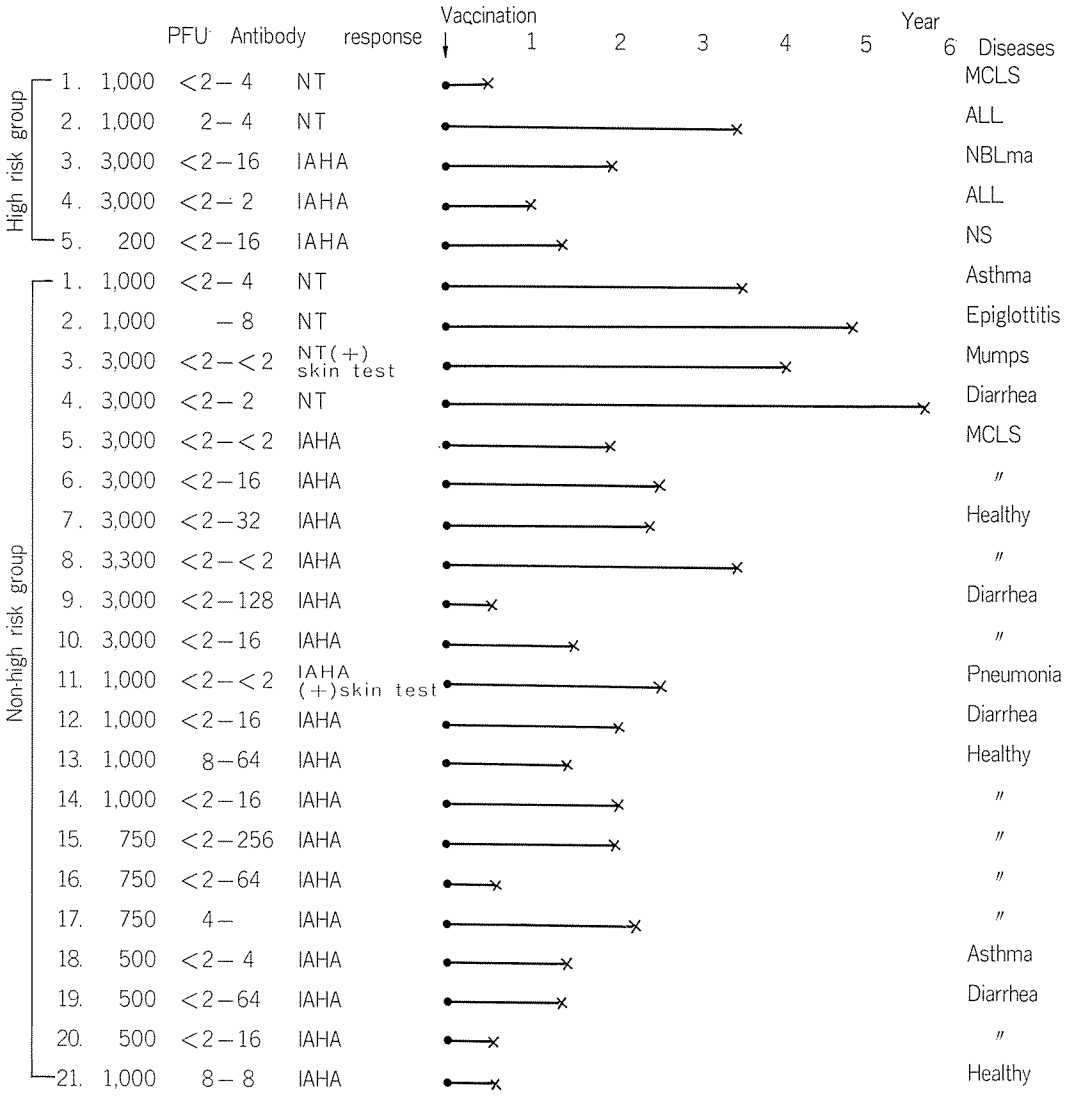

FIGURE 2 Time from vaccination till natural varicella infection. (1983. 7)
Abbreviations: MCLS, Mucocutaneus lymphnode syndrome (Kawasaki's disease); ALL, Acute lymphatic leukemia; Nblastoma, Neuroblastoma; NS, Nephrotic syndrome.

by vaccination.

5. Clinical reactions were common in the high risk group, and slight in the non-high risk group.
6. Marked eruptions, sometimes atypical, was seen in cases receiving intensive immunosuppressive therapy.
7. Eruptions due to the vaccine appeared later in high risk patients.
8. Herpes-zoster was seen in the high risk group.
9. Natural varicella infection may occur even in subjects who show a good immune response, but it is generally mild.

TABLE 6. *Revaccination with varicella vaccine*

	Underlying disease	Initial vaccine dose (PFU)	Additional vaccine dose (PFU)	Time after 1st vaccination	Antibody response		Skin reaction	
					1st	2nd	1st after vaccination	2nd before vaccination
					NT, IAHA	IAHA		
1	Nephrotic syndrome	3,000	500	4 yr 1 mo	<2-2	<2-16	##	−
2	Nephrotic syndrome	3,000	500	4 yr 1 mo	4-8	<2-8	##	−
3	Neuroblastoma	250	750	1 yr 4 mo	<2-8	<2-32	+	−
4	Nephrotic syndrome	750	500	6 mo	2	<2-8		−
5	Nephrotic syndrome	3,000	850	3 yr 4 mo	<2-4	<2-8		−
6	Chronic nephritis	300	850	3 yr	<2-<2	<2-16	##	−

10. The immunity of high risk patients should be checked regularly. If the immunity level is depressed, revaccination is recommended.
11. The vaccinee should be told at the time of vaccination, that he may catch varicella in the future.

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