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STUDIES ON LIVE ATTENUATED MUMPS VACCINE. III. LONG-TERM FOLLOW-UP STUDY ON THE EFFICACY OF BIKEN VACCINE

SHIN ISOMURA, MITSUNOBU MIYAZU, HIDESHI NAGAI, HIROSHI NARUSE, MOTONOBU SHIBATA, TAKAYUKI ICHIKAWA and SAKAE SUZUKI

Department of Pediatrics, Nagoya University School of Medicine, Showa-ku, Tsurumaicho Nagoya 466, Japan

KOICHI YAMANISHI and MICHIAKI TAKAHASHI

Department of Virology, Research Institute for Microbial Diseases, Osaka University, Yamadaoka, Suita, Osaka 565, Japan

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SUMMARY Clinical and serological follow-ups were made on 24 children for 8 years after immunization against mumps with attenuated mumps vaccine, Biken vaccine. To evaluate the protective efficacy of the vaccine, matched controls were studied during the same period. Serological examination revealed that 91% of the controls were infected with mumps and 83% of them contracted the disease during the studied period. However, none of the vaccinees developed clinical infection after close contact with mumps patients. There was no substantial decrease in the antibody titers in unexposed vaccinees after vaccination.

INTRODUCTION

In the preceding paper of this series (Isomura et al., 1976), we reported clinical and serological follow-up studies on children who had been immunized against mumps with live attenuated mumps vaccine, Biken vaccine, 3 and 4 years previously. Serological examination showed that persistence of circulating antibody was satisfactory during the 3 and 4 year periods and clinical observation showed excellent effectiveness of vaccine administration: none of the vaccinees contracted mumps after close contact with mumps patients.

This paper reports further clinical and serological follow-up studies on the children for 8 years after a single injection of Biken vaccine. To evaluate the efficacy of the vaccine, we compared the incidence of mumps among vaccinees with that among nonvaccinated control children.

MATERIALS AND METHODS

1. *Vaccine schedules*

Twenty-four seronegative children of 3 to 5 years old were immunized against mumps by a single injection of Biken vaccine (Urabe strain of mumps

virus; Yamanishi et al., 1970) in 1971 and 1972. Their homes were in various parts of Kasugai City, Aichi Prefecture, and their socio-economical backgrounds differed widely. All the vaccinees showed successful seroconversion by the neutralization test (NT) after vaccination.

2. *Clinical follow-up on vaccinees*

Questionnaries were sent once a year to parents of vaccinees, to ask the frequency of contact of vaccinees with mumps patients and the incidence of mumps among the vaccinees. The extent of exposure and contraction of mumps were ascertained by interviewing the mothers at the time of blood sampling.

3. *Non-vaccinated control group*

A total of 22 seronegative, healthy children of matched ages were randomly selected from the same residential areas in Kasugai City. They were asked whether they had come in contact with cases of mumps and whether they had contracted the disease during the period of study.

4. *Collection and examination of serum samples*

Serum samples were collected from vaccinees at frequent intervals at least once every two years during an eight-year period. Serum samples from children in the control group were obtained from samples of venous blood in the summer of 1971 and in the summer of 1979. The NT titers of sera were measured as described previously (Isomura et al., 1973).

5. *Grading of the extent of exposure to mumps*

The extent of exposure to mumps was ascertained from mothers and classified as follows: Grade 1, heavy, household contact group; grade 2, indoor contact group; grade 3, mild outdoor contact group (Isomura et al., 1976). In this paper, children with close contact to mumps mean those of grade one or grade two.

Children whose mothers reported two or more contacts with cases of mumps during the period were classified in the heavy contact group.

RESULTS

1. *Persistence of NT antibody following Biken vaccine*

The results of the tests for mumps neutralizing antibody are shown in Table 1 and Fig. 1.

TABLE 1. *Duration of mumps antibody after vaccination*

Time after vaccination	No.	Mumps NT titer[a]	
		Range in titer	GMT[b]
6 weeks	24	1.5-5.0	3.1
2 years	24	1.0-8.0	4.73
4 years	24	1.0-8.0	4.67
6 years	18	1.0-5.5	3.39
8 years	21	1.0-5.0	2.93

[a] 2^n

[b] GMT=Geometric mean antibody titer.

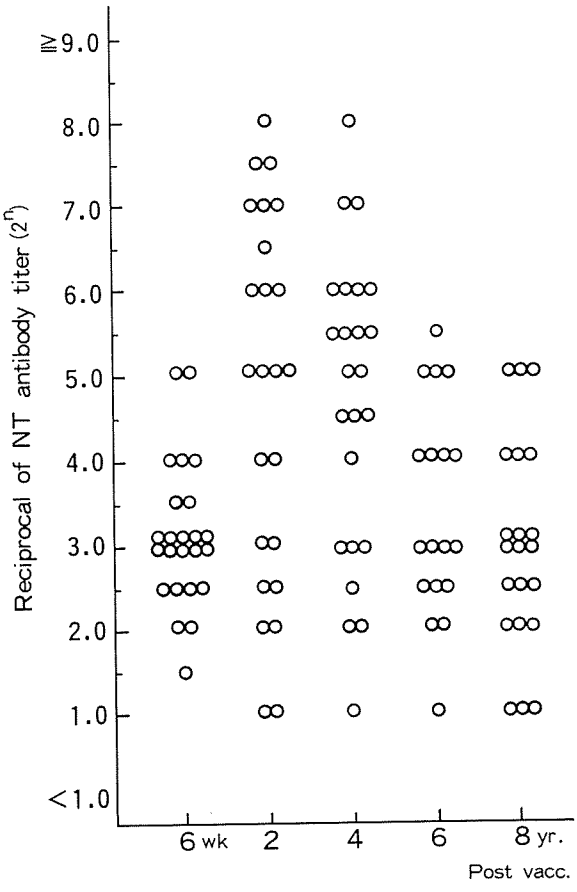

FIGURE 1. Duration of NT antibody after Biken vaccine.

Not all persons were present during the total eight year period. There was no substantial decrease in the geometric mean NT antibody titer during the studied period. Of 24 vaccinees, 16 showed 4-fold or more increases in antibody titer in the time interval studied, suggesting that natural reinfection had occurred during this period. Significantly, none of the vaccinated children became seronegative during the eight year period.

2. *Serological response of vaccinees after close contact with mumps patients*

Seventeen vaccinees came in household and/or indoor contact with mumps patients during the study period, but none of the vaccinees developed mumps after exposure. The NT antibody titers of these 17 children during the period are shown in Fig. 2. After close contact with mumps patient, a serological booster effect was observed in children whose antibody level had been as low as $2^{3.0}$ before exposure (Fig. 3).

3. *Persistence of NT antibody in children with mild or no contact with mumps*

The NT antibody levels in children with mild or no contact with mumps during the study period are shown in Fig. 4. Individual titers rose, fell or remained the same. However, none became negative with in eight years after vaccination.

4. *Distribution of NT antibody levels in the control group*

Twenty nonvaccinated control children be-

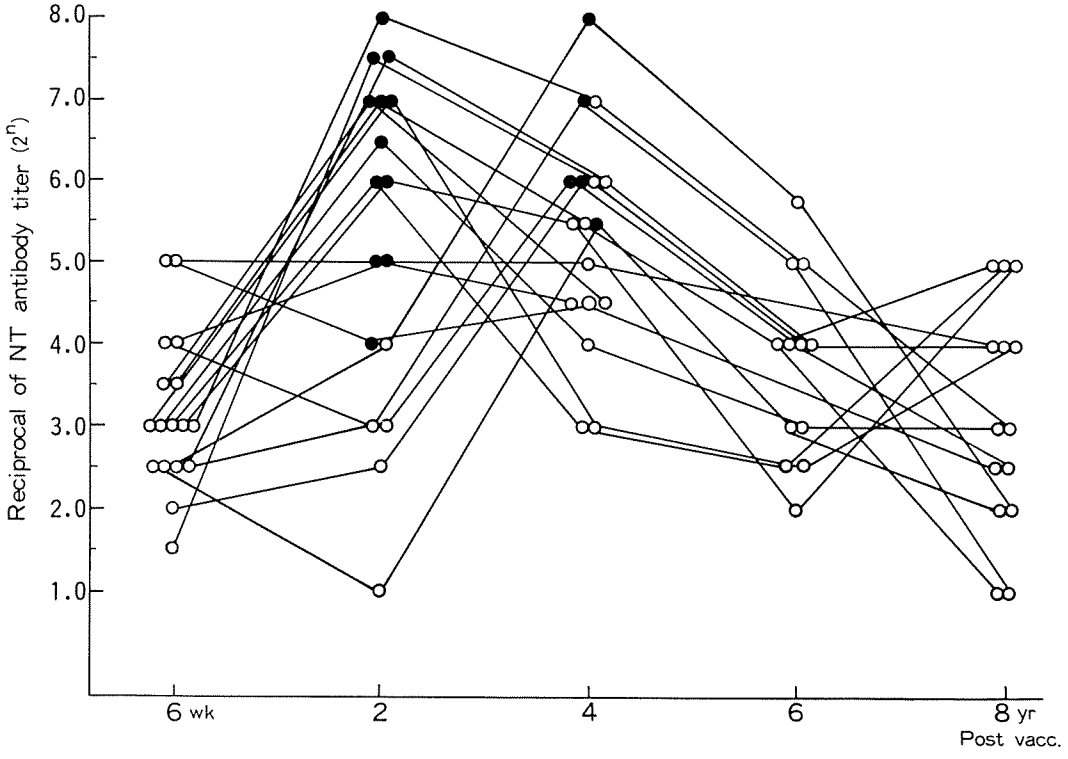

FIGURE 2. Duration of NT antibody titers of vaccinees after close contact with mumps.
(○—●), Close contact noticed during the period.
(●—○, ○—○), No contact noticed during the period.

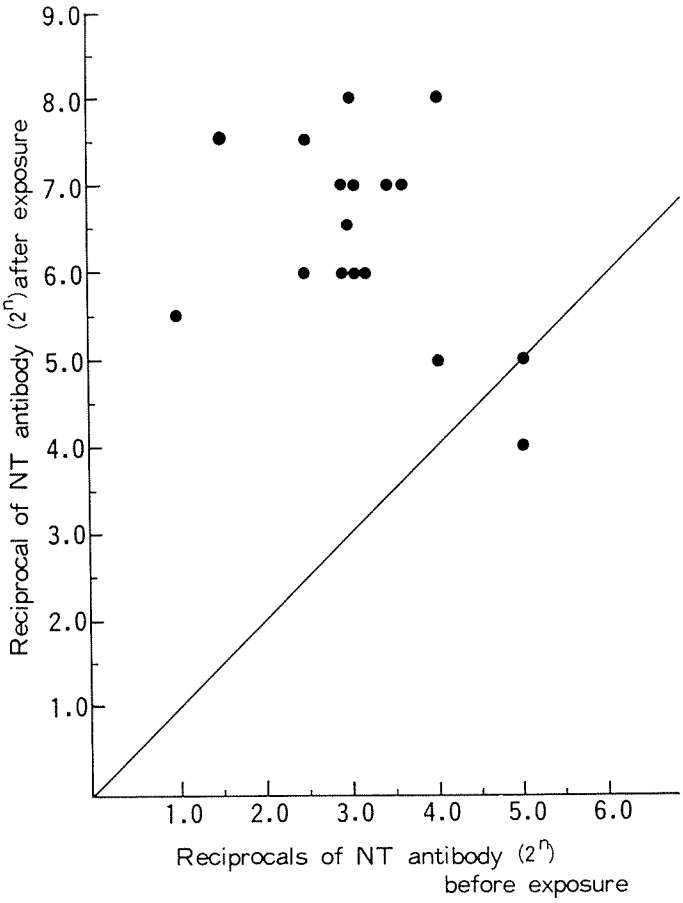

FIGURE 3. NT antibody titers before and after close contact.

came seropositive during the eight year period. Of these seroconverted controls, 16 contracted typical mumps during the period. The other 4 children showed no apparent clinical manifestation of mumps, suggesting that they had experienced subclinical infection with mumps virus during the period. Their antibody levels are shown in Fig. 5, compared with those of vaccinees in the 8th year of the study. There was no significant difference in the geometric mean antibody titers of vaccinees and controls: $2^{2.93}$ in vaccinees, $2^{3.0}$ in controls.

5. *Incidence of mumps among nonvaccinated children*

During the eight year period, 18 of 22 controls came in close contact with mumps patients. All the 18 children showed seroconversion by the 8th year and 15 of them had a history of contraction with mumps during the period. Of four children with mild or no contact with mumps, two showed seroconversion and one contracted the disease (Table 2).

The incidence of mumps after close contact with mumps was 15/18 (83.3%) in controls and 0/14 (0%) in vaccinees (Table 3).

DISCUSSION

The safety and immunogenicity of Biken vaccine have been clearly demonstrated (Yamanishi et al., 1970; Isomura et al., 1973).

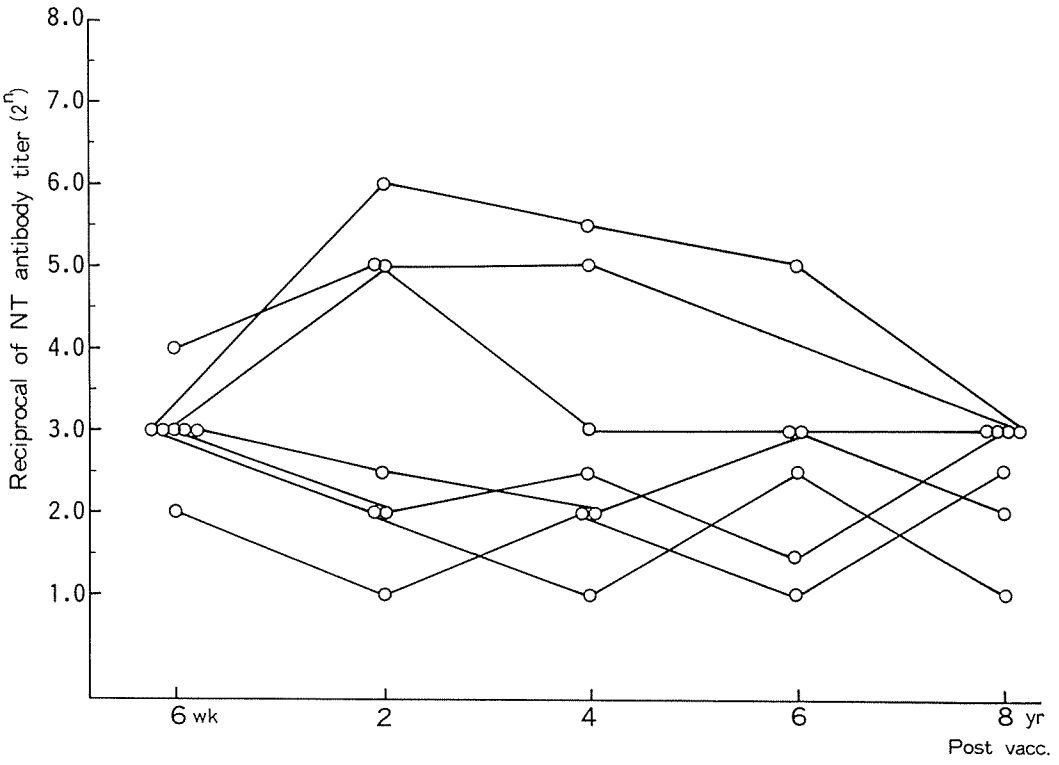

FIGURE 4. Duration of NT antibody titers of vaccinees after mild or no contact with mumps.

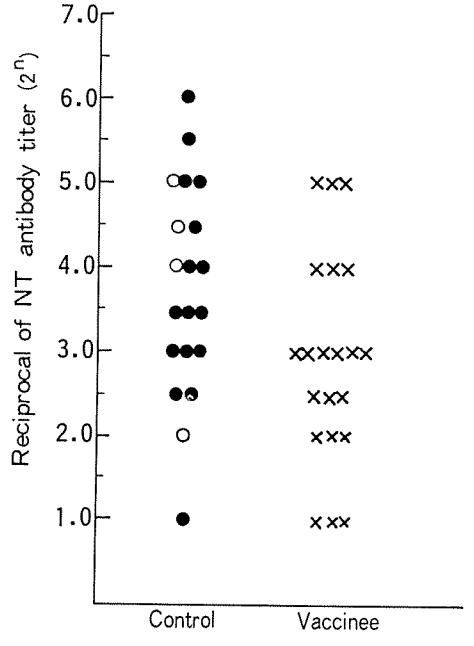

TABLE 2. *Extent of exposure, seroconversion and contraction with mumps among nonvaccinated controls.*

Total	22
No. with close contacts	18
seroconversion	18/18
Contraction(+)/Seroconversion(+)	15/18
No. with mild or no contact	4
Seroconversion	2/4
Contraction(+)/Seroconversion(+)	1/2
Total seroconversion	20/22
Total contraction/Total seroconversion	16/20

←

FIGURE 5. NT antibody titers of seroconverted controls in 8th year of the study, compared with those of vaccinees.

●, controls that contracted mumps; ○, controls, with no history of mumps during the period; ×, vaccinees.

TABLE 3. *Incidence of mumps after close contact with mumps among vaccinees and controls*

	Clinically infected/ Serologically infected[a]
Vaccinees	0/14
Not vaccinated	15/18

[a] Two-fold or more increase of antibody rise in vaccinees and seroconversion in controls after exposure.

The preceding paper reported short term follow-up studies on vaccinees (Isomura et al., 1976). Results showed that (1) serologically, there was no substantial decrease in the neutralizing antibody titers in 3 and 4 years after vaccination, and (2) the protective efficacy of the vaccine was high; none of the vaccinees contracted mumps after close exposure to the disease. These findings were in good agreement with a previous report on the vaccine (Yamanishi et al., 1971).

Long term follow-up studies were carried out for 8 years after Biken vaccine. Serologically, the initial level of antibody reached after vaccination was rather low. Increases in antibody titers were frequently observed after close contact with cases of mumps, and this high frequency of a booster effect may be due to the relatively low antibody titers developed after vaccination (Fig. 2, 3). Though the booster effect suggests that natural reinfection took place during the study period, no clinical illness was observed. Thus a mumps neutralizing antibody level of $2^{1.0}$ or greater may confer solid immunity against natural infection.

To confirm this excellent protective efficacy of the vaccine, we examined the incidences of mumps among vaccinated and nonvaccinated children after exposure to the disease. As seen in Table 2, all the nonvaccinated susceptible children became seropositive after close contact with mumps patients and 83.3% of them subsequently developed regular mumps. This high communicability and high incidence after heavy exposure to the disease are in good agreement with previous reports (Mayer, 1962; Isomura et al., 1975). In contrast, no vaccinees developed clinical infection after close contact (Table 3). Thus, Biken vaccine had a clear protective effect in these children.

After the increases of antibody titers in response to natural reinfection, antibody levels of vaccinees decreased rapidly (Fig. 2). However, they remained at almost the same level as those of controls after natural mumps (Fig. 5). No elevation of the antibody titers during the period was observed in 7 vaccinees. Of these 7 vaccinees, 5 did not come in contact with case of mumps in the eight year period after vaccination. Serologically, their antibody activities remained at the same level as those 6 weeks after vaccination. Persistence of the circulating antibody level seemed as good as after the natural disease.

Maintenance of antibody titers and low incidences of clinical mumps among vaccinees were also observed by other investigators, with other strains of attenuated mumps viruses (Weibel et al., 1975; Weibel et al., 1979). Further follow-up studies on the children are now in progress.

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