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A LONG-TERM FOLLOW-UP STUDY ON THE EFFICACY OF FURTHER ATTENUATED LIVE MEASLES VACCINE, BIKEN CAM VACCINE

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SUMMARY Antibody persistence was measured in 39 chilcren in an open community 12–13 years after immunization against measles with further attenuated live vaccine, Biken CAM. Serum samples of the children taken every two or three years after vaccination had higher, lower, or the same HI antibody titers as those in samples taken 6 weeks after vaccination. These differences reflected a decrease in the titer in some children and subclinical natural reinfection in others. However, all the children still retained detectable antibody in 12 or 13 years after vaccination, indicating long-term persistence of immunity after immunization with Biken CAM vaccine. For evaluation of the protective efficacy of the vaccine, matched controls were studied during the same period. Serological examination revealed that 97.5% of the controls were infected with measles and contracted the disease. In contrast, none of the vaccinees developed clinical infection after close contact with measles patients.

INTRODUCTION

An outstanding attribute of live attenuated measles vaccine is the long-term persistence of antibody and of immunity following its administration to susceptible persons. The protection against the natural disease is due to the presence of circulating antibodies against measles.

Since 1971, a further attenuated live measles vaccine, Biken CAM was licensed and has been used in mass-programs of immunization against measles in Japan. The safety and

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efficacy of the vaccine was well documented in previous papers: Serological examination showed that persistence of circulating antibody was satisfactory during 1 and 4 year periods after vaccination (Ueda et al., 1971, 1974). This paper reports further clinical and serological follow-up studies on the children for 12 and 13 years after a single injection of Biken CAM vaccine. For evaluation of the efficacy of the vaccine, we compared the persistence of circulating antibody among vaccinees with that among nonvaccinated naturally infected control children.

MATERIALS AND METHODS

1. *Vaccine schedules*

Thirty nine seronegative children of 3 to 5 years old were immunized against measles by a single injection of Biken CAM-70 vaccine (Okuno et al., 1971) in 1971 and 1972. Their homes were in various parts of Nagoya City, mainly in urban areas, and their socio-economical backgrounds differed widely. All the vaccinees showed successful seroconversion, as judged by the hemagglutination-inhibition (HI) test, after vaccination.

2. *Clinical follow-up on vaccinees*

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

3. *Nonvaccinated control group*

A total of 40 seronegative, healthy children of matched ages were randomly selected from the same residential area in Nagoya City. They were asked whether they had come in contact with cases of measles and whether they had contracted the disease during the observation period.

4. *Collection and examination of serum samples*

Serum samples were collected from vaccinees at as frequent intervals as possible, at least once every two to three years, during the 12–13 year period. Serum samples from children in the control group were also obtained as frequently as possible during the 10 year period from 1971 to 1981. The HI titers of sera were measured as described previously (Ueda et al., 1971).

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

The extent of exposure to measles 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 who had been in close contact with measles mean those of grade one or grade two. Children who were reported to have been in contact with two or more cases of measles during one epidemic season were classified in the heavy contact group.

RESULTS

1. *Persistence of HI antibody after vaccination with Biken CAM vaccine*

The results of tests for measles HI antibody are shown in Table 1 and Fig. 1. Not all children could be examined throughout the whole 12–13 year period. There was a substantial decrease in the geometric mean HI antibody titer during the studied period, but of 39 vaccinees, 22 showed 4-fold or more increase in antibody titer during the study period, suggesting that they had been reinfected with natural measles during this period. Three vaccinees became seronegative eight and

TABLE 1. *Persistence of measles antibody after vaccination*

Time after vaccination	No.	Measles HI antibody titer	
		Range of titers	GMT[a]
6 weeks	39	×8–×512	$2^{5.1}$
2 years	39	×8–×512	$2^{5.1}$
4 years	39	×8–×512	$2^{4.7}$
6 years	36	×8–×64	$2^{4.3}$
8 years	27	<×8–×64	$2^{3.7}$
10 years	25	<×8–×64	$2^{3.9}$
12–13 years	18	×8–×32	$2^{3.8}$

[a] GMT = Geomtric mean antibody titer.

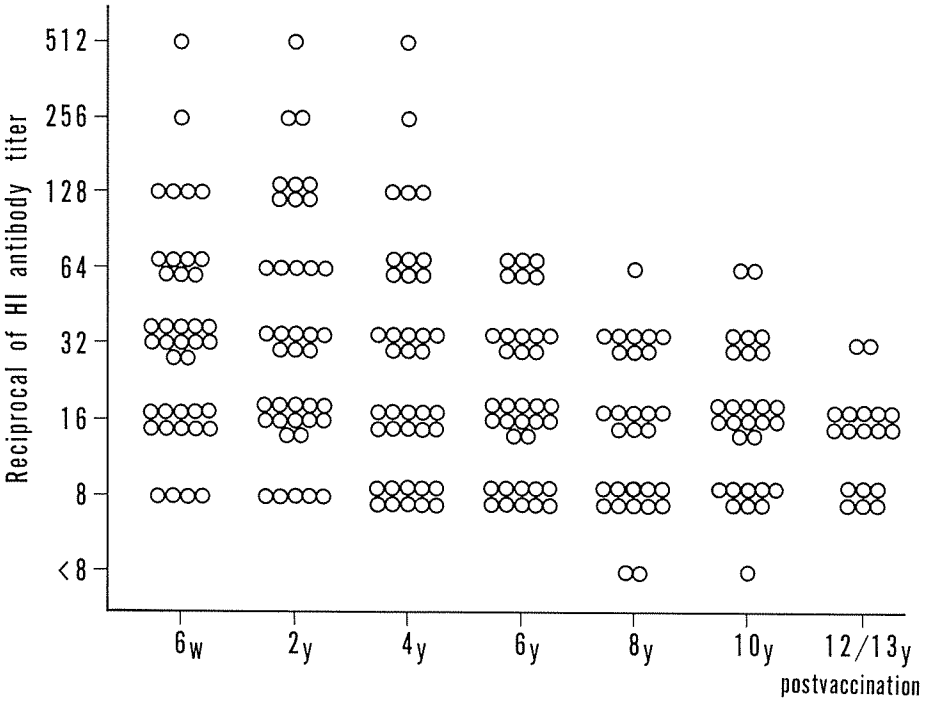

FIGURE 1. *Distribution of HI antibody titers in vaccinees.*

ten years after vaccination, but later became seropositive again. Significantly, none of vaccinated children were seronegative 12–13 years after vaccination.

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

Thirty vaccinees came into household and/or indoor contact with measles patients once or twice during the study period, but none of them developed measles. The HI antibody titers of these 30 children during the period are shown in Figs. 2 and 3. After close contact with measles patients, a serological booster effect was observed in children whose antibody level had been as low as $\times 16$ before exposure (Fig. 4).

3. *Persistence of HI antibody in children with mild or no contact with measles*

The HI antibody levels in 9 children with mild or no contact with measles during the study period are shown in Fig. 5. Individual titers rose, fell or remained the same. However, none became seronegative during the studied period.

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

Of 40 nonvaccinated control children, 39 became seropositive during the ten year period. Of these seroconverted controls, 37 contracted typical measles during the period, and two others developed mildly modified measles after treatment with human gamma-globulin during the incubation period. There was no subclinical infection with measles virus during the period. The interval between contraction of the disease and blood sampling ranged from 8 weeks to 10 years. Their antibody titers in relation to the intervals between the onset of measles and serum

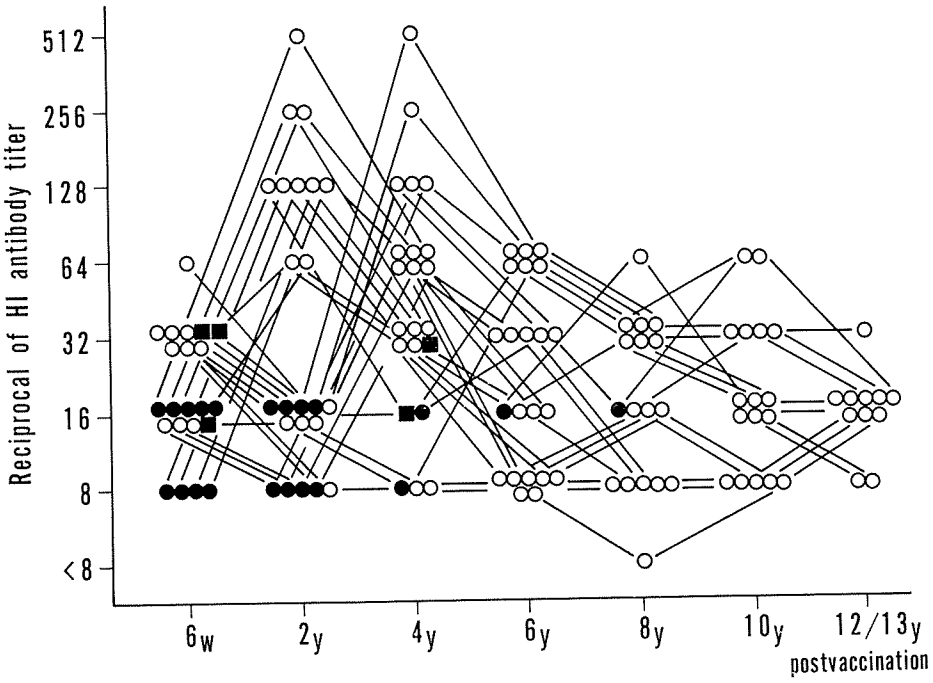

FIGURE 2. *HI antibody titers of vaccinees whose antibody titers showed 4-fold or more increase in the period studied.*
(●—○) Serological booster effect noticed after close contact with measles during the period.
(■—○) No serological booster effect after close contact with measles during the period.
(○—○) No close contact noticed during the period.

samplings are shown in Table 2 and Fig. 6. The geometric mean antibody titers were higher in children with natural infection than in vaccinated children in the period shortly after infection or vaccination; $2^{7.0}$ in controls, $2^{5.1}$ in vaccinees. However, during the ten year period, the difference between these groups became small; $2^{4.5}$ in controls, $2^{3.9}$ in vaccinees.

5. *Clinical efficacy of Biken CAM vaccine after close contact with measles patients*

During the ten year period, 28 of 40 controls came in close contact with measles patients, and all the 28 children contracted measles after exposure, followed by seroconversion. Of the other 12 children, 11 contracted measles during the ten year period after mild or no apparent contact with measles patients (Table 3).

The incidence of measles after close contact with measles was 28/28 in controls and 0/30 in vaccinees (Table 4).

DISCUSSION

The safety and immunogenicity of Biken CAM vaccine has been clearly demonstrated (Ueda et al., 1971, Okuno et al., 1971). The preceding papers reported short term follow-up studies on vaccinees for 1 to 4 years (Ueda et al., 1971, Ueda et al., 1974). Results showed that (1) serologically, neutralizing antibodies induced by one injection of the vaccine remained stable for 1 to 4 years after vaccination, and (2) the clinical protective efficacy was nearly complete in over 800 vaccinees. These findings were in good

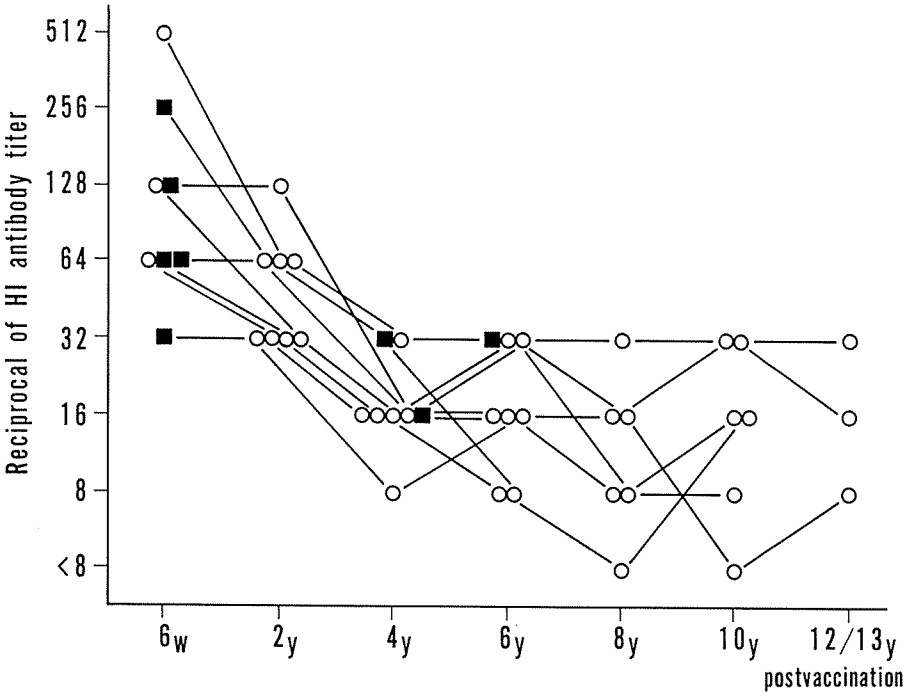

FIGURE 3. *HI antibody titers of vaccinees whose antibody titers showed no serological booster effect after close contact with measles in the period studied.*
(■—○) No booster effect noticed after close contact during the period.
(○—○) No close contact noticed during the period.

agreement with reports on long term surveillance conducted by the Japan Measles Vaccine Research Commission (Shishido et al., 1978): The protection rate against infection resulting from close contact within families was as high as 97% in children who received the live attenuated virus or the further attenuated virus including the Biken CAM strain.

Clinical and serological long term follow-up studies were carried out for 12–13 years after vaccination with Biken CAM vaccine. Serologically, the initial level of antibody after vaccination was rather low. Increase in antibody titers were frequently observed after close contact with cases of measles, and this high frequency of a booster effect may be due to the relatively low antibody titers developed after vaccination (Fig. 2, 5). Though the booster effect suggests that natural reinfection took place during the study period, no clinical illness was observed. Thus, a measles HI antibody level of ×8 or more may confer solid immunity against natural infection.

To confirm this excellent protective efficacy of the vaccine, we examined the incidence of measles among vaccinated and nonvaccinated children after exposure to the disease. As seen in Table 3, 28 of 40 nonvaccinated controls came in close contact with measles, mostly in the early 1970s when measles was endemic in the urban area studied. The acceptance rate of vaccination against measles in Nagoya City had been very low in these years. All the 28 children subsequently developed measles. In contrast, no vaccinees developed clinical infection after close contact. Thus, Biken CAM vaccine had a clear protective effect in these children.

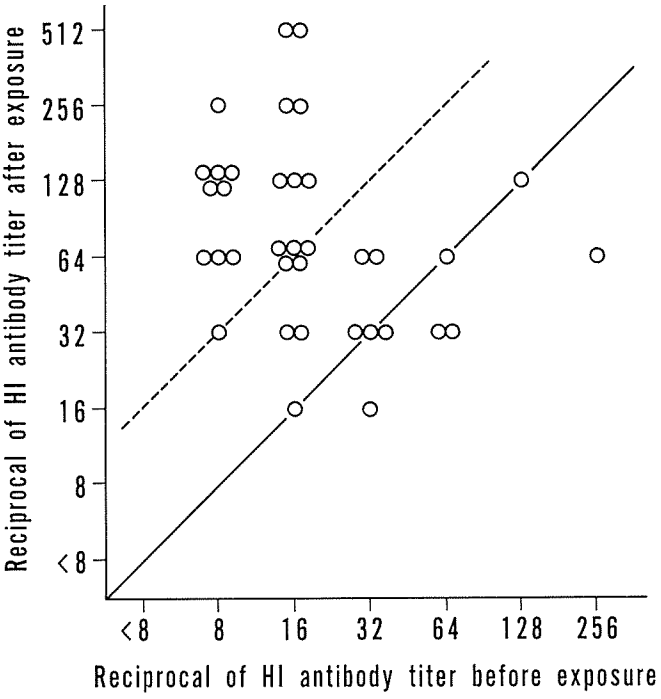

FIGURE 4. *HI antibody titers before and after close contcat.*

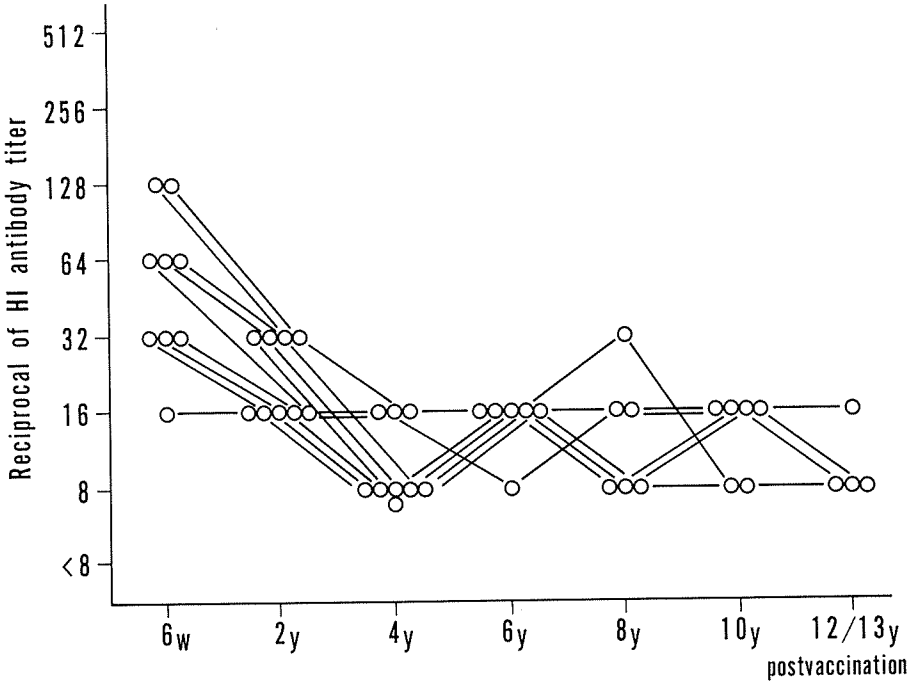

FIGURE 5. *HI antibody titers of vaccinees who had mild or no contact with measles during observation period.*

TABLE 2. *Persistence of measles antibody after natural infection.*

Time after infection	No.	Measles HI antibody titer	
		Range of titers	GMT[a]
8 weeks	27	×32–×1024	$2^{7.0}$
2 years	40	×16–×1024	$2^{7.0}$
4 years	27	×16–×512	$2^{6.5}$
6 years	26	×8–×256	$2^{5.6}$
8 years	31	×8–×256	$2^{4.7}$
10 years	22	×8–×256	$2^{4.5}$

[a] GMT=Geometric mean antibody titer.

After increase of antibody titers in response to vaccination or natural reinfection, the antibody levels of vaccinees decreased gradually (Fig. 2, 3, 5). However, an important finding was that all the vaccinees retained detectable antibody during the 12–13 year observation period. These findings are in good agreement with previous reports on other strains of further attenuated measles virus: The immunity induced as a result of effective immunization with the further attenuated strains lasted at least 14 years and may, in fact, be permanent (Buynak et al., 1976, Weibel et al., 1980). Further follow-up studies on the vaccinees are now in progress.

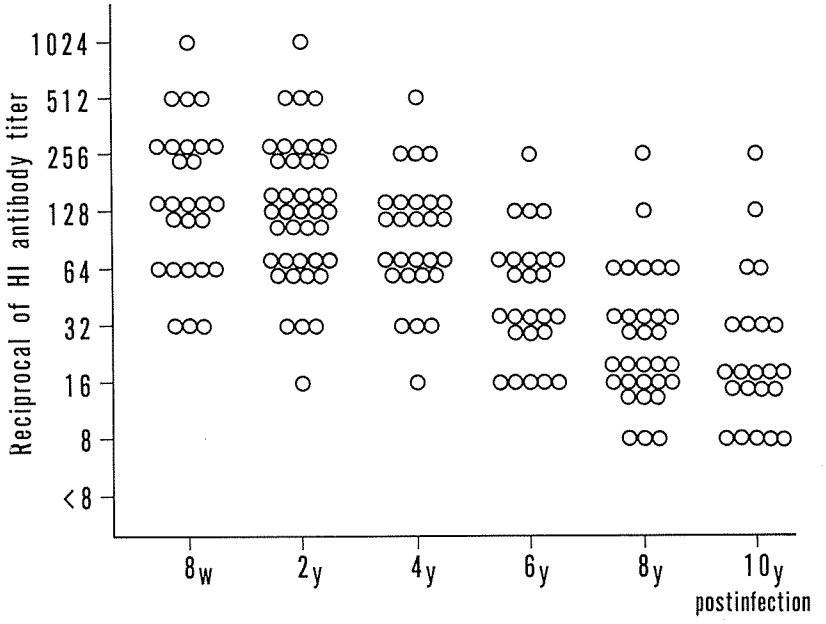

FIGURE 6. *Distribution of HI antibody titers after natural infection.*

TABLE 3. *Extent of exposure, seroconversion and contraction of measles among nonvaccinated controls.*

Total	40
No. with close contacts	28
Seroconversion	28/28
Contraction(+)/Seroconversion(+)	28/28
No. with mild or no contact	12
Seroconversion	11/12
Contraction(+)/Seroconversion(+)	11/11
Total seroconversion	39/40
Total contraction/Total seroconversion	39/39

TABLE 4. *Incidence of measles after close contact with measles measles among vaccinees and controls.*

	Clinically infected/ No. with close contact
Vaccinees	0/30
Not vaccinated	28/28

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