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STUDIES ON THE COMBINED USE OF KILLED AND LIVE MEASLES VACCINES

V. FIVE YEAR FOLLOW-UP

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SUMMARY A serological and clinical follow-up was made for 5 years on 230 children vaccinated by the combined use of killed and live measles vaccines. Neutralizing antibody titers persisted well during this period, though booster responses by natural infection occurred in children whose antibody titers decreased to relatively low levels between 3 and 5 years after vaccination. Three mild cases of measles occurred among the vaccinees 2 and 3 years after vaccination but no further cases have occurred since then although there have been measles epidemics in the area.

INTRODUCTION

The previous paper of this series reported the results of a 3 year serological and 4 year clinical follow-up on children who were immunized by the combined use of killed (K) and live (L) measles vaccines (Ueda et al., 1969a). Measles neutralizing antibodies were detected in all the vaccinees who were tested serologically. Antibody persisted at a higher level in the KL-inhalation group (immunized with a single dose of K followed by L inhalation a month later) than in the other groups, namely, the KL-injection group (L was injected instead of inhaled) and the KKL and KKK-L groups (2 or 3 doses of K were injected before L administration). Three mild cases of measles occurred among the vaccinees 2 and 3 years after vaccination.

The present paper describes results of additional serological and clinical follow-up studies on the children immunized with killed and live measles vaccines.

MATERIALS AND METHODS

Serological Examination

Fifty five blood specimens were collected from the vaccinees in Muyuen Kindergarten and in Hamakoshien housing site in January, 1970. Antibody titration was done following an overnight neutralizing test (Toyoshima et al., 1965). To obtain comparable results and to correct for experimental fluctuation in the antibody titers, diluted rabbit hyperimmune serum with a mean neutralizing antibody titer of $2^{8.5}$ was included in each antibody titration.

Other materials and methods were as described in the previous paper (Ueda et al., 1969a).

RESULTS

1. *Contraction of measles after vaccination*

As reported previously (Ueda et al., 1969a) and as shown in Table 1, cases of measles only occurred in 1966 and 1967 and there were no cases in 1965, 1968 or 1969 although there were measles epidemics in the area in these years. All 3 children who contracted measles had received injections of killed vaccine 2 or 3 years previously, but their symptoms were milder than usual.

2. *Serological analysis*

The neutralizing antibody titers of 122 vaccinees at intervals after vaccination are shown in Fig. 1. After administration of live vaccine all the children tested had antibody titers of over $2^{1.5}$ after 3 years and of over $2^{3.5}$ after 5 years.

The geometric mean neutralizing antibody titers of children in the different groups (KL-inhalation, KL-injection, KKL-inhalation, KKL-injection and KKK-L-inhalation groups) are shown in Fig. 2. The geometric mean antibody titers decreased 4 to 8 fold in 3 years from their values one month after vaccination.

In the period between 3 and 5 years after vaccination, the geometric mean titers increased 2 to 4 fold over those 3 years after vaccination in all the groups. The patterns of persistence of neutralizing antibody were similar in all the groups, though the increase in titer was greater in children vaccinated by injection of live vaccine than in those vaccinated by inhalation of live vaccine.

Fourteen of the 122 vaccinees were available for continuous serological follow-up for 5 years after vaccination. The patterns and persistence of the neutralizing antibody responses after vaccination in individual children are shown in Fig. 3. The antibody titers decreased in the first 3 years after vaccination in all but one child whose antibody titer a month after injection of live vaccine was lower than that before the injection. In the next 2 years, the antibody titers of half the children increased again, though these children showed no symptoms of measles. Three of the children with increased antibody titers had no contact with cases of measles during this period. The two children indicated by arrows in the figure inhaled live vaccine 3 years after vaccination. A child whose antibody titer was at the low level of $2^{2.0}$ showed a marked increase in antibody titer a month after challenge with live vaccine but developed no clinical reactions.

TABLE 1. *Protective efficacy of combination of killed and live measles vaccines (Results of 5 years postal inquiry in the Hamakoshien housing site)*

Vaccine	No. surveyed in 1965	Year of inquiry				
		1965	1966	1967	1968	1969
KL	149	0/114 ^b (0) ^c	0/108 (0)	1/ 91 (1.1)	0/ 73 (0)	0/53 (0)
KKL ^a	49	0/ 37 (0)	1/ 32 (3.1)	0/ 29 (0)	0/ 20 (0)	0/19 (0)
KKK	8	0/ 6 (0)	0/ 6 (0)	1/ 5 (20.0)	0/ 2 (0)	0/ 1 (0)
KL-L	7	0/ 5 (0)	0/ 5 (0)	0/ 4 (0)	0/ 1 (0)	0/ 1 (0)
KKK-L	17	0/ 12 (0)	0/ 10 (0)	0/ 9 (0)	0/ 7 (0)	0/ 9 (0)
Total	230	0/174 (0)	1/161 (0.6)	2/138 (1.4)	0/103 (0)	0/83 (0)

Vaccination; between May and Oct., 1964 (a: between Dec., 1964 and Feb., 1965)

b: No. of measles cases/No. of answers

c: percent of cases of measles among vaccinees

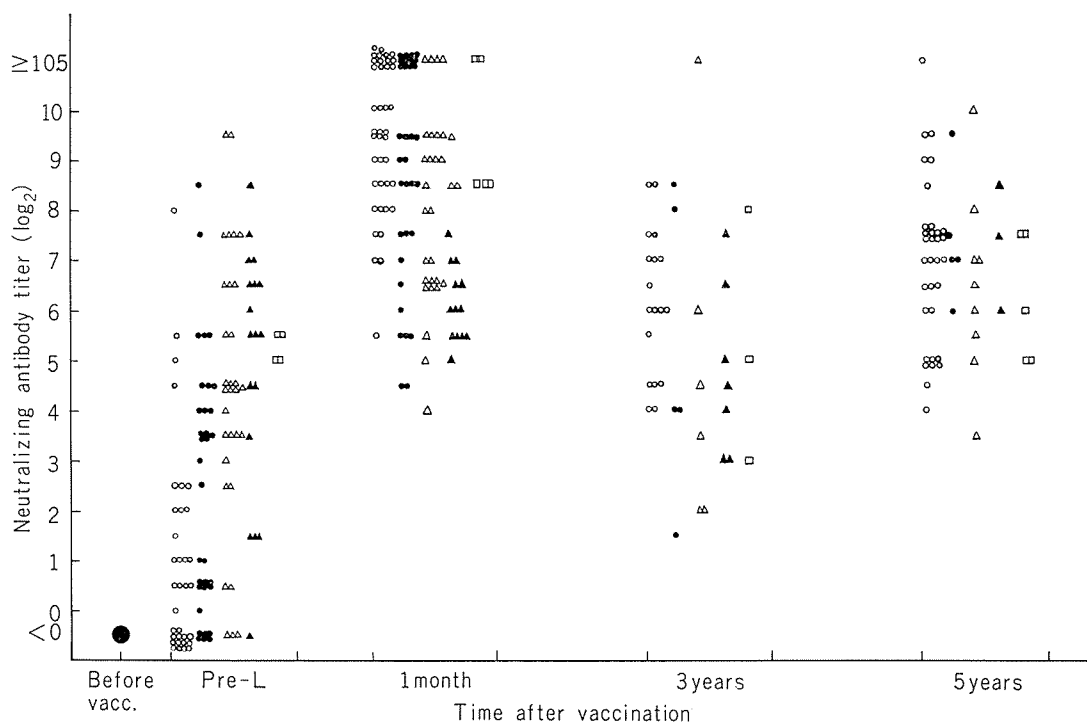


FIGURE 1. Measles neutralizing antibody titers at intervals after vaccination by the combined use of K and L.

- KL-inhalation (a single dose of K followed by L inhalation a month later)
- KL-injection (a single dose of K followed by L injection a month later)
- △ KKL-inhalation (2 doses of K followed by L inhalation at monthly intervals)
- ▲ KKL-injection (2 doses of K followed by L injection at monthly intervals)
- KKK-L (3 doses of K at intervals of 2 weeks followed by L inhalation 4 months later)

Another child whose antibody titer was very high ($2^{6.5}$) did not respond to challenge with live vaccine.

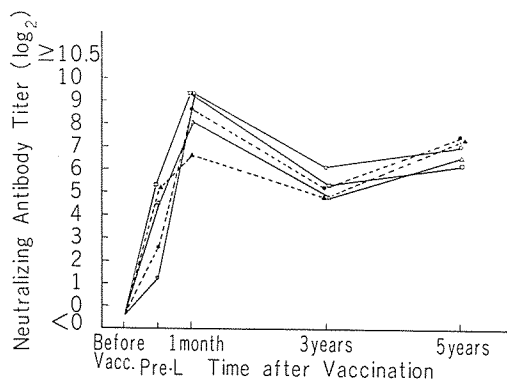


FIGURE 2. Geometric mean measles neutralizing antibody titers in different vaccine groups at intervals after vaccination by the combined use of K and L. For explanation of symbols see legend to Fig. 1.

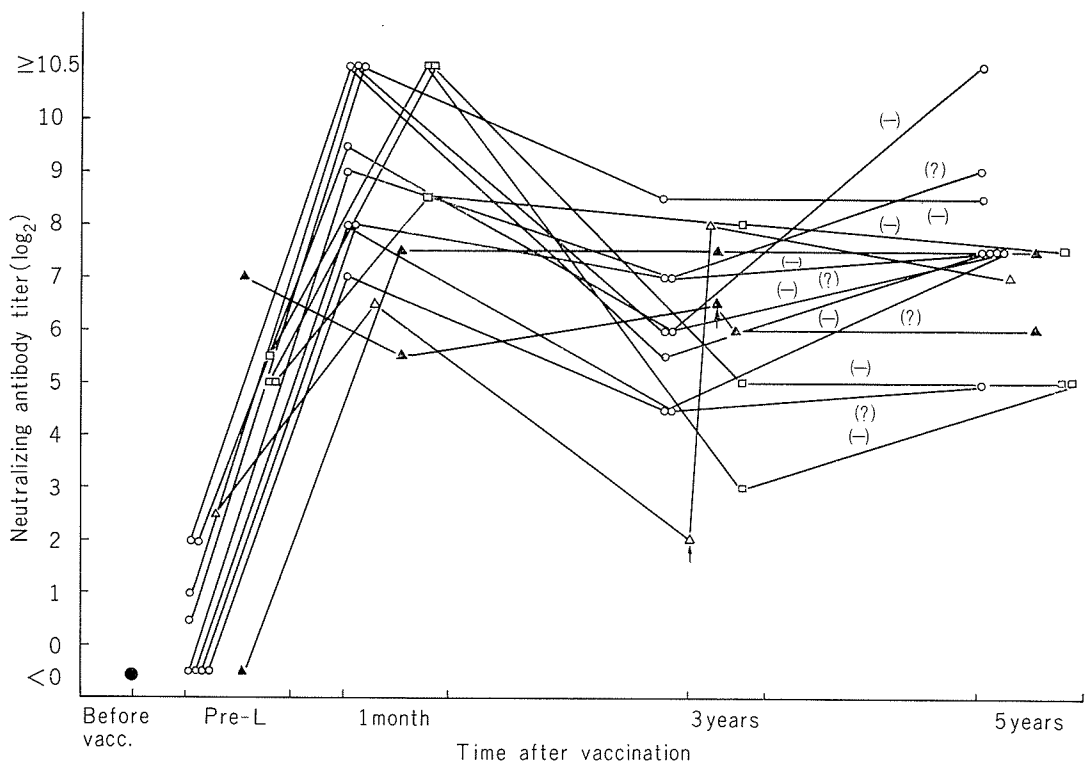


FIGURE 3. Pattern and persistence of measles neutralizing antibodies in 14 children vaccinated by the combined use of K and L. Arrows indicate L inhalation.

—: no contact with cases of measles.

?: contact with cases of measles uncertain.

DISCUSSION

Panum (1939) reported that measles immunity after natural infection persisted for more than 60 years on isolated islands. Antibodies after natural infection and vaccination with attenuated virus persisted at fairly high titers for at least 5 to 8 years even without re-exposure or re-infection (Bech, 1960; Black and Rosen, 1962; Krugman et al., 1965; Lepow and Nankervis, 1969).

However, as reported previously, booster infections or reinfections without symptoms were observed in mothers when their children had measles (Ueda et al., 1969b). Thus in areas of measles epidemics booster infections

probably occur when the antibody titer decreases to a low level.

The present results also show the persistence of immunity conferred by the combined use of K and L. The neutralizing antibody titers of children immunized by the combined use of K and L were still high 5 years after vaccination, though when the antibody titers decreased to relatively low levels 3 to 5 years after vaccination booster responses occurred in children even when they did not come into contact with cases of measles.

These observations may account for the results of the clinical follow-up of vaccinees;

3 cases of measles occurred 2 and 3 years after vaccination but there have been no further cases since then. Altered reactions to measles virus were reported in recipients of killed vaccine (Fulginiti et al., 1967), but all 3 cases were milder than in cases of regular measles.

Almost all vaccinees received immunity to live virus by the K-L method (a single dose of K followed by L inhalation or injection),

and vaccination in this way caused no serious side reactions. The incidence of a febrile reaction due to K-L vaccination was much lower than that with attenuated virus vaccine with gammaglobulin or with further attenuated virus vaccine alone (Okuno et al., 1965; Ueda et al., 1966). Thus the K-L method seems to be the method of choice for mass vaccination to eradicate measles in a short period.

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