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STUDIES ON THE COMBINED USE OF KILLED AND LIVE MEASLES VACCINES

III. CONDITIONS FOR THE "TAKE" OF LIVE VACCINE

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SUMMARY For the combined use of killed and live measles vaccines, the advantage of the inhalation method over the injection method of live measles vaccine was reported previously. In the present study the advantage and reproducibility of the inhalation method was confirmed in a field trial on over 70 children who provided three consecutive blood specimens. The upper limit of the post-killed vaccine antibody titer which permitted the live vaccine to "take" was also defined.

INTRODUCTION

In the previous papers, it was reported that the combined use of killed and live measles vaccines was the best method for mass immunization against measles, and that the inhalation method of live vaccine was better than the injection method (OKUNO *et al.*, 1965 b). Thus, when a high antibody titer was present due to previous inoculation with killed vaccine, no increase of antibody titer was observed on injection of live vaccine ("no take" of live vaccine), whereas an apparent further increase of antibody titer was obtained on inhalation ("take" of live vaccine). In the present study, the advantage and reproducibility of the inhalation method was confirmed by an additional field trial. However, a limit to the applicability of the inhalation method was also found. Thus, "no take" of live vaccine was observed when too high an antibody titer was already present due to vaccination with killed vaccine.

MATERIALS AND METHODS

1. *Vaccine*

1) Killed vaccine

Plain and adjuvant (precipitated with aluminium phosphate) vaccines, with potencies of ED_{50} $4^{3.4}$ in mice, were used.

2) Live vaccine

Biken vaccine Lot 21 was used.

The details of these vaccines have been reported (OKUNO *et al.*, 1965 a).

2. *Method of administration and vaccination schedule*

The method of administration and the vaccination schedule are given in Table 1. Killed vaccine was injected in the doses shown in the Table 1. Live vaccine was given either by the inhalation method for 30 seconds using a routine type compressor (Nissho-type) with a nebulizer or by subcutaneous

TABLE 1 *Vaccination schedule*

Group \ Date	Dec. 16, 1964	Jan. 13, 1965	Feb. 3	Mar. 3
1	Ⓚ (Plain 0.5 ml)	K (Pl. 0.5)	Ⓛ$_H$	○
2	Ⓚ (,,)	K (,,)	Ⓛ$_J$	○
3	Ⓚ (Adjuvant 0.25)	K (Adj. 0.25)	Ⓛ$_H$	○
4	Ⓚ (,,)	K (,,)	Ⓛ$_J$	○

K : Killed vaccine L : Live vaccine (Hamakoshien 3rd trial in 1964–1965)
○ : Blood specimens taken H : Inhalation J : Injection

TABLE 2 *Inhalation and injection of L after plain K measles vaccine*

Group	No.	Name	Age	Body weight	NT titer			Clinical reactions			
					Pre-K	Post-K	Post-L	Inc.	Max.F.	Dur. F.	Rash
PPH	1	K. W.	1Y 6M	11.0 Kg	<0	4.5	6.5	—			
	5	M. M.	1 0	10.0	<0	≤0.5	11.0	12	37.5	0.5	+
	9	A. T.	5 8	18.2	<0	<0	11.0	7	39.5	3.0	+
	13	Y. M.	2 1	11.3	<0	4.5	10.5	—			
	21	Y. S.	3 0	11.0	<0	0.5	8.5	—			
	25	N. B.	3 6	17.0	<0	4.0	9.5	—			
	29	Y. K.	6 10	22.5	<0	0.5	8.0	8	38.5	2.5	—
	37	R. A.	5 5	15.0	<0	5.5	12.5	—			
	45	S. K.	7 2	17.0	<0	≤0.5	6.5	—			
	49	H. F.	4 0	15.5	<0	3.5	9.0	—			
	77	K. T.	1 8	10.9	<0	2.5	6.5	—			
	89	T. Y.	1 1	8.4	<0	3.5	9.0	—			+
	101	M. S.	1 3	10.0	<0	7.5	6.5	—			
PPJ	3	T. S.	1 6	11.0	<0	5.5	7.0	—			
	7	K. I.	2 11	13.5	<0	6.5	6.0	—			
	11	M. S.	2 5	14.0	<0	1.5	5.0	—			
	31	T. U.	3 0	13.5	<0	3.5	6.5	—			
	39	J. K.	4 3	17.0	<0	1.5	8.5	8	37.5	0.5	—
	75	M. Y.	4 6	16.5	<0	1.5	5.5	—			

N.B. P : Plain killed vaccine H : Inhalation (Hamakoshien 3rd trial '64. 12–'65. 3)
J : Injection of live vaccine
Three specimens were taken from each child.

injection of 0.25 ml per child.

killed vaccine was injected with an interval of 28 days between injections. Twenty eight days after the second injection, live vaccine was given. Blood specimens were taken on the day of first inoculation with killed vaccine (pre-K), on the day of inoculation with live vaccine (post-K), and four weeks after inoculation with live vaccine (post-L).

3. *Antibody titration*

Neutralizing antibody was determined by the overnight method (TOYOSHIMA *et al.*, 1965).

RESULTS

The field trial was carried out at Hamakoshien housing site, Nishinomiya, from Dec. 16, 1964 to Mar. 3, 1965. In all 101 children with no history of measles received inoculations. These children were divided into 4 groups, each consisting of about 25 children. Thirty eight series of three consecutive blood specimens were obtained from these 4 groups. Tables 2 and 3 show the detailed results of neutralization tests on the blood specimens and the clinical reactions of the children in these 4 groups. Table 4 summarizes these results.

From these results it is apparent that adjuvant vaccine evoked a better antibody response than plain vaccine. Furthermore, as in the previous work (OKUNO *et al.*, 1965 b), the group which inhaled vaccine showed a higher rate of " take " of live vaccine than the group which received injections.

The results of the previous field trial (OKUNO *et al.*, 1965 a, b) on 40 children who supplied three series of blood specimens were combined with the results of the present field trial. The combined results are given in Fig. 1, which shows the relationship between the post K and post L antibody titers of 78 children.

When the post K antibody titer was less than 2^3, the " take " of live vaccine was satisfactory either on injection or on inhalation and there was a marked increase in antibody titer. When the post K antibody titer was 2^3–2^6, on injection of live vaccine there was " no take " in many children, whereas on inhalation almost all children showed a " take ". The post L

TABLE 3 *Inhalation and injection of L after adjuvant K measles vaccine*

Group	No.	Name	Age	Body weight	NT titer			Clinical reactions			
					Pre-K	Post-K	Post-L	Inc.	Max. F.	Dur.	Rash
AAH	2	M. T.	1Y 9M	11.0 Kg	<0	≧9.5	9.0	—			
	6	H. I.	4 5	13.5	<0	4.5	9.5	—			
	10	M. T.	3 11	13.0	<0	6.5	6.5	—			
	14	K. S.	2 8	14.0	<0	6.5	5.5	—			
	18	M. T.	1 2	7.9	<0	6.5	5.0	—			
	30	H. U.	1 3	9.5	<0	7.5	7.0	—			
	34	N. S.	1 9	12.5	<0	7.5	4.0	5	38.0	2.0	—
	50	H. F.	1 9	11.6	<0	3.5	9.5	—			
	58	K. N.	3 3	15.0	<0	4.5	9.5	11	37.8	1.5	—
	66	W. O.	3 1	13.5	<0	4.5	6.5	—			
	90	K. U.	1 3	9.4	<0	4.5	9.0	12	38.0	0.5	—
AAJ	4	Y. O.	3 2	13.5	<0	5.5	6.0	—			
	20	T. W.	2 11	16.5	<0	7.0	5.5	—			
	28	Y. F.	2 6	13.0	<0	8.5	6.5	8	38.6	1.0	—
	36	M. O.	5 2	16.0	<0	6.5	6.5	—			
	44	K. S.	4 4	15.0	<0	4.5	6.0	—			
	52	Y. I.	4 10	14.5	<0	7.0	5.5	—			
	92	M. O.	1 2	11.0	<0	5.5	7.0	—			
	100	K. H.	4 6	16.5	<0	<0	7.5	—			

N.B. A : Adjuvant killed vaccine
H : Inhalation J : Injection of live vaccine
Three specimens were taken from each child.

(Hamakoshien 3rd trial '64. 12–'65. 3)

TABLE 4 *Summarized results of inhalation and injection of live vaccine after injection of killed vaccine*

Vaccine	Potency mouse ED_{50}	Case No.	Post-K NT Ab. titers		Method of L administration	Average post L NT titers	Case No. NT rise by L (over 4 fold)
			Range	M±σ			
Plain	$4^{3.4}$	19	<0 ~ 7.5	3.1±2.3	Inhalation	8.8	12/13
					Injection	6.4	4/6
Adjuvant	$4^{3.4}$	19	<0~≧9.5	5.8±2.1	Inhalation	7.4	5/11
					Injection	6.3	1/8

(Results of 3rd trial in Hamakoshien)

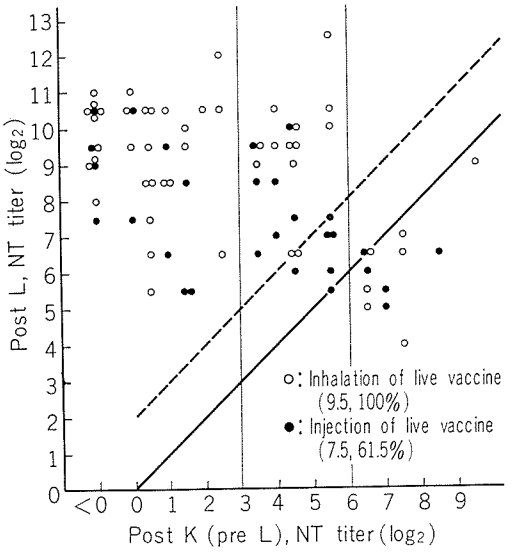

FIGURE 1 Combined use of K & L measles vaccines. Comparison of inhalation & injection of L vaccine.
(H Housing site, 1964).

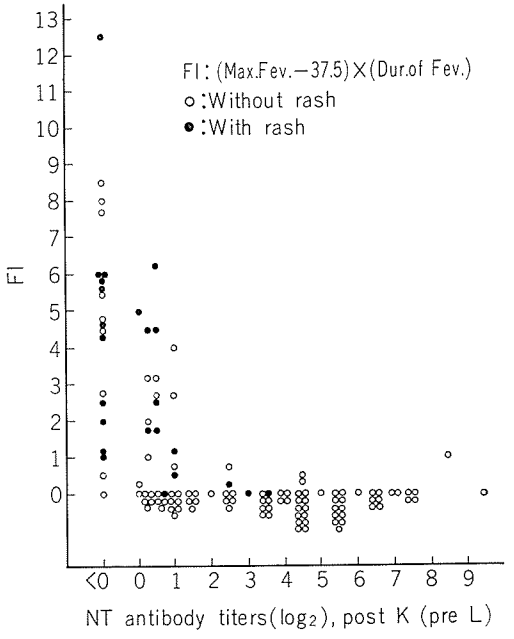

FIGURE 2 Combined use of K and L measles vaccines. Relation between post K titers and clinical reactions due to L
(H Housing site, 1964).

antibody titer was higher after inhalation than after injection of live vaccine.

However, when the post K antibody titer was over 2^6, there was " no take " even on inhalation. Therefore the upper limit of the post K NT antibody titer for a " take " of live vaccine seems to be around 2^6.

It should be mentioned that there was a correlation between the post K antibody titer and the severity of subsequent clinical reactions due to inoculation of live vaccine (Fig. 2). Thus, when children with a post K NT antibody titer of 2^1 or less were inoculated with live vaccine, they showed considerable clinical reactions. However those with an NT titer of more than 2^2 were almost free from clinical reactions.

DISCUSSION

From the results of the present study, together with previous results (OKUNO *et al.*, 1965 a, b) the following conclusions are drawn.

So far as the combined use of killed and live measles vaccine is concerned, the ideal method is a single injection of potent killed vaccine followed by inhalation of live vaccine.

This method can be most favorably applied to mass immunization against measles since it shows a high rate of " take " of live vaccine with a good antibody response and few clinical reactions.

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