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STUDIES ON MEASLES IN THAILAND

II. FIELD TRIALS OF MEASLES VACCINE, WITH SPECIAL REFERENCE TO THE K-L METHOD¹

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SUMMARY The K-L method of measles vaccination was applied to 40 hospitalized children and 99 home dwelling children in Thailand. The clinical reactions of all the children and the neutralizing antibody responses of 58 of them were examined.

Clinical reactions occurred in less than 6% of vaccinated children, and all the blood specimens showed a striking antibody response as comparable to that given with L vaccine alone.

All the 40 children in hospital were feeble or sick, but the clinical reactions observed in this group were as few as in healthy groups. This suggests that the K-L method is suitable for mass immunization and that it is also the safest way of measles vaccination.

1 This study was carried out as part of the plan for Technical Cooperation between Japan and Thailand, based on the Colombo Plan.

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INTRODUCTION

Our experience in measles vaccination suggests that the combined use of killed (K) vaccine and live (L) vaccine (OKUNO *et al.*, 1965) is the most favorable method for mass immunization.

The Japanese Committee for the Study of Measles Vaccine (1965) has also come to the same conclusion.

Accordingly, anticipating the same effect of a high antibody response and few side-reactions, we carried out field trials on measles vaccination in Thailand.

MATERIALS

The following two kinds of killed (K) and live (L) vaccines were used in the field trials.

K vaccine: Inactivated measles vaccine (Biken) was prepared by the following method. The Tanabe strain of measles virus was propagated in monkey kidney tissue culture cells. After clarifying the harvested virus fluid, the virus was inactivated with formaldehyde and was adsorbed on aluminum phosphate.

The potency of this K vaccine was indicated by the antigen extinction method in mice, having an AED₅₀ value of 4^{2.4}.

L vaccine: Live, attenuated measles virus vaccine (Biken) was prepared from the attenuated Toyoshima strain of measles virus developed by OKUNO *et al.*, (1960). This virus was propagated in the amniotic membrane of developing chick embryos, and virus fluids were mixed with stabilizer and lyophilized.

The L vaccine from this strain has received extensive official field trials by the Japanese Committee for the Study of Measles Vaccine (1963), and its safety, potency and efficacy were confirmed by them.

The infective titer of this L vaccine in FL cells is 10^{3.0} TCID₅₀/0.1 ml. Both K and L vaccines have been prepared in accordance with the requirement of Killed and Live Attenuated Measles Virus Vaccine (Note 466, 467, issued by the Ministry of Health and Welfare of Japan, 1965). Their safety, potency and efficacy against measles have been proved by tests carried out in the Kannonji laboratory of the Osaka Microbial Diseases Research Foundation.

METHODS

VACCINATION SCHEDULE

In the four field trials, vaccination was carried

out on children with a negative history of measles by the K-L method. Administration of inactivated vaccine was followed by that of live vaccine three weeks later. Blood specimens were collected as follows:

1. *Pre-K serum*

A dose of 0.5 ml of K vaccine was injected intramuscularly and a blood sample was taken at the same time.

2. *Post-K or Pre-L serum*

Three weeks after K vaccine injection, 0.25 ml of L vaccine was injected subcutaneously and a blood sample was taken at the same time.

3. *Post-L serum*

Three weeks after L vaccine injection, blood was taken.

The following four groups of children were vaccinated between September and October, 1966 (Tables 1-4).

1. Siriraj Hospital, 14 hospitalized orphans
2. Children's Hospital, 16 hospitalized children
3. Vajira Municipal Hospital, 10 hospitalized children
4. Japanese children in their homes, 99 children were vaccinated, and blood samples were collected from 18 of them.

METHOD FOR SERUM TEST

The neutralization test was carried out as described in the previous paper (UEDA *et al.*, 1967). The antibody titer was examined by serum dilution in this study.

INVESTIGATION OF CLINICAL REACTION

Children in hospital were carefully observed by doctors and nurses for one month after L vaccination. Their temperature was checked 4 times a day. Parents of children at home were asked to observe clinical reactions, if any, and fill in a questionnaire paper.

RESULTS

CLINICAL REACTIONS

No appreciable clinical reaction was noted after K vaccination. After L vaccination, clinical reactions were observed in some of the vaccinated children. A temperature of over 37°C

TABLE 1 *Results of field trials of measles vaccine (K-L) in Bangkok Siriraj Hospital*

Code No.	Name	Age		Body Weight (kg)	Sex	Antibody Titer (NT, log ₂)			Clinical Reactions Fever			Rash
		Yr.	mo.			Pre K	Post K	Post L	Inc. (day)	Max. (°C)	Dur. (day)	
1	Dang	1	6	9.0	F	<1.5	0	5.5	none			
2	Thonsookmak	1	8	9.5	M	<1.5	2.5	7.5	none			
3	Tabskul	1	6	6.3	F	<1.5	3.0	10.5	none			
4	Prayoon	0	8	6.5	M	<1.5	1.5	8.0-8.5	none			
5	Dang	2	0	8.5	M	<1.5	<0	9.5	none			
6	Lui	0	6		M	<1.5	0.5	—	—			
7	Uey	0	5	4.5	F	>2.5	—	—	—			
8	Sangsri	1	11	8.5	M	<1.5	—	11.0	none			
9	Chai	1	0	9.5	M	<1.5	2.5	8.5	none			
10	Siang	2	2	8.0	M	<1.5	0	7.5	none			
11	Noi	8		12.5	F	<1.5	<0	9.5	7	38.6	2.0	none
12	Sangwan	3	5	11.5	F	<1.5	<0	9.5	8	39.4	3.5	none
13	Chanthra	0	4	4.7	F	<1.5	0	8.5	none			
14	Dang	2		12.0	M	>2.5	—	—	—			

(1966 Sept.—Nov.)

TABLE 2 *Results of field trials of measles vaccine (K-L) in Bangkok Children's Hospital*

Code No.	Name	Age		Body Weight (kg)	Sex	Antibody Titer (NT, log ₂)			Clinical Reactions Fever			Rash
		Yr.	mo.			Pre K	Post K	Post L	Inc. (day)	Max. (°C)	Dur. (day)	
1	Sopa	1	2	9	F	<2.5	0	6.5	none			
2	Vichai	2	1	10	M	<1.5	<0	9.0	none			
3	Charoemak	2	11	9	M	≥2.5	—	—	none			
4	Sakda	0	11	7.7	M	<1.5	<0	8.0	none			
5	Roonarm	2	3	6	F	≥2.5	—	—	8	38.1	2	none
6	Dang	2		11	M	<1.5	≥4.5	9.5	none			
7	Bang-on	3		8	F	<1.5	<0	6.5	none			
8	Anong	1	9	9	M	<1.5	<0	7.5	8	38.1	2	none
9	Toe-Charoen	1	1	6.2	M	<1.5	<0	10.0	8	39.5	2	none
10	Klomwong	0	8	5.7	M	<2.5	≤0.5	5.0	none			
11	Kampoey	1	1	6	F	<1.5	<0	9.0	9	39.5	2	none
12	Dang	3	1	10	F	≥2.5	—	—	none			
13	Parncharoen	0	11	7.2	F	<1.5	<0	≤4.5	none			
14	Buppa	1	2	5.5	M	<1.5	0.5	7.5	10	37.5	0.5	none
15	Chairat	0	8	7.2	M	<1.5	<0	—	—			
17	Vibooncharoen	0	6	4.9	M	<1.5	0.5	8.0	none			

(1966 Sept.—Nov.)

TABLE 3 *Results of field trials of measles vaccine (K-L) in Bangkok Vajira Municipal Hospital*

Code No.	Name	Age		Body Weight (kg)	Sex	Antibody Titer (NT, log ₂)			Clinical Reaction Fever			Rash
		Yr.	mo.			Pre K	Post K	Post L	Inc. (day)	Max. (°C)	Dur. (day)	
1	Fanta	2	0	10.7	F	<1.5	0	9.0	none			
2	Sonit	1	5	5.5	M	<1.5	1.5	≥11.5	none			
3	Prom	1	0	7.7	F	<1.5	<0	9.5	none			
4	Soodjal	0	9	5.8	F	<1.5	<0	9.0	none			
5	Tawil	1	9	7.2	F	<1.5	1.5	7.5	none			
6	Boo-rong	0	6	4.5	F	<1.5	2.0	—	none			
7	Changchit	0	6	4.7	M	<1.5	0.5	—	none			
8	Sutin	0	6	4.5	F	<1.5	—	—	—			
9	Cha-on	0	5	4.5	M	<1.5	—	—	—			
10	Surin	0	10	5.1	F	<1.5	1.0	9.0	none			

(1966 Sept.—Nov.)

TABLE 4 *Results of field trials of measles vaccine (K-L) in Bangkok Japanese Children*

Code No.	Name	Age		Body Weight (kg)	Sex	Antibody Titer (NT, log ₂)			Clinical Reaction Fever			Rash
		Yr.	mo.			Pre K	Post K	Post L	Inc. (day)	Max. (°C)	Dur. (day)	
1	K. S.	5	6	20	M	<1.5	0.5	8.5	none			
2	Y. Y.	5	4	19	M	<1.5	0.5-1.0	9.0	none			
3	A. T.	7	6		F	≥2.5	—	—	none			
4	T. C.	4	0	13	M	≥2.5	—	—	none			
5	K. E.	3	2	14	F	<1.5	—	—	none			
6	H. Y.	3	2	15	F	<1.5	—	8.5	none			
7	K. W.	9	5	27	F	≥2.5	—	—	none			
8	H. K.	4	8	17	F	<1.5	—	—	none			
9	N. T.	2	6	12.5	F	<1.5	—	10.5	none			
10	T. K.	12	7	38.5	M	<1.5	1.0	4.5	none			
11	H. A.	5	8	15.5	M	<1.5	2.0	9.5	none			
12	K. M.	4	0	14.5	M	<1.5	—	—	none			
13	N. S.	5	5	17	F	<1.5	1.0	—	none			
14	Y. F.	13	2	33.5	M	<1.5	0.5	8.0	none			
15	H. F.	12	1	30.8	M	<1.5	<0	9.0	none			
16	M. K.	11	5	41	F	<1.5	1.0	11.0	none			
17	T. D.	1	3	10.5	M	<1.5	<0	8.5	none			
18	T. K.	6	4	23	M	<1.5	≥4.5	8.0	none			

(1966 Sept — Nov.)

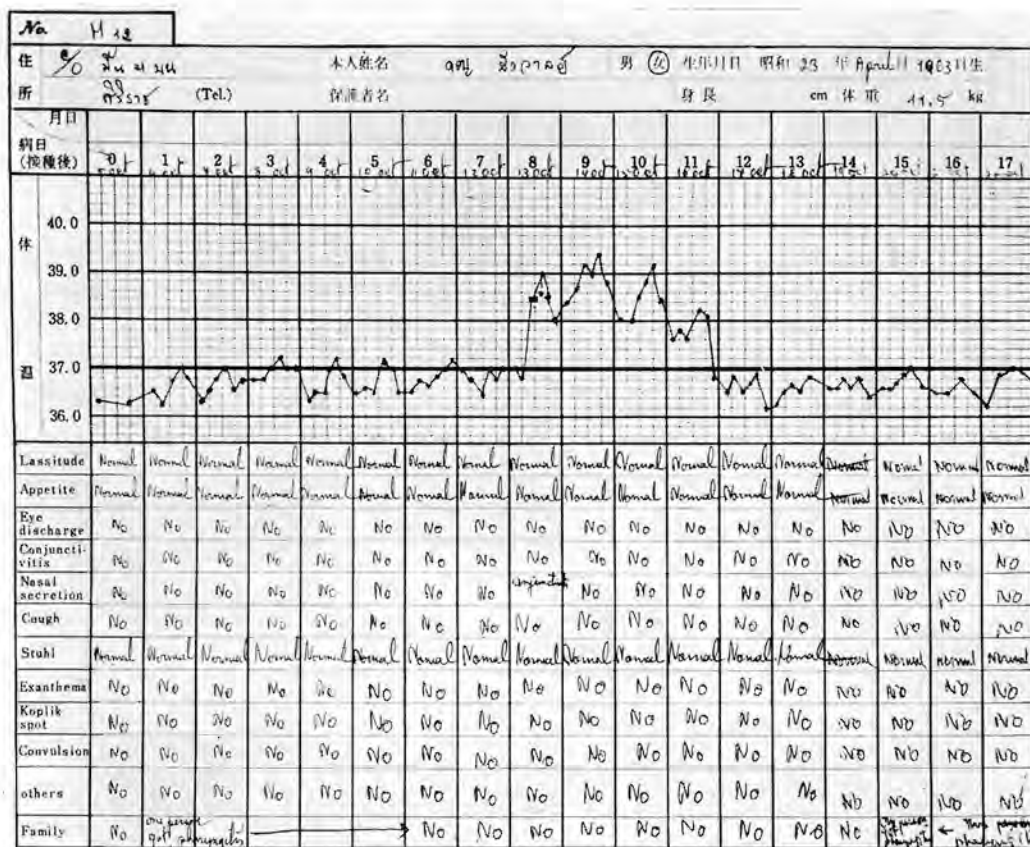


FIGURE 1 A sample of record of clinical signs after L vaccination.

developed in 7 of 40 children in hospital (Tables 1-3), and 2 of 99 children in their homes (Table 4). In all, 9 out of the 139 vaccinated children (6%) developed a temperature 6 to 14 days after L vaccination. No rash, convulsions or other complications were observed in vaccinated children. The feverish reaction was only observed in children whose post K antibody titer was very low. Fig. 1 is the clinical record card of the child whose clinical reaction was the most severe in the Siriraj Hospital.

ANTIBODY RESPONSE

Blood specimens from 58 cases were examined. Great variations in the post-K antibody titer were observed between different children

as previously observed (OKUNO *et al.*, 1965): most cases were 2^0 - 2^2 , some were undetectable, and 2 cases were over 2^4 . However, a striking increase in the post-L antibody titer was observed in all cases (Tables 1-4, Figs. 2-5).

DISCUSSION

It was previously reported that the clinical reaction caused by L vaccine was strikingly alleviated by preinoculation of the K vaccine, and the extent of alleviation was related to the post-K neutralizing antibody titer (UEDA *et al.*, 1966). This was again confirmed in the present study. Those who developed clinical reactions were found to have had a low post-K antibody titer of below $2^{0.5}$ which was usually

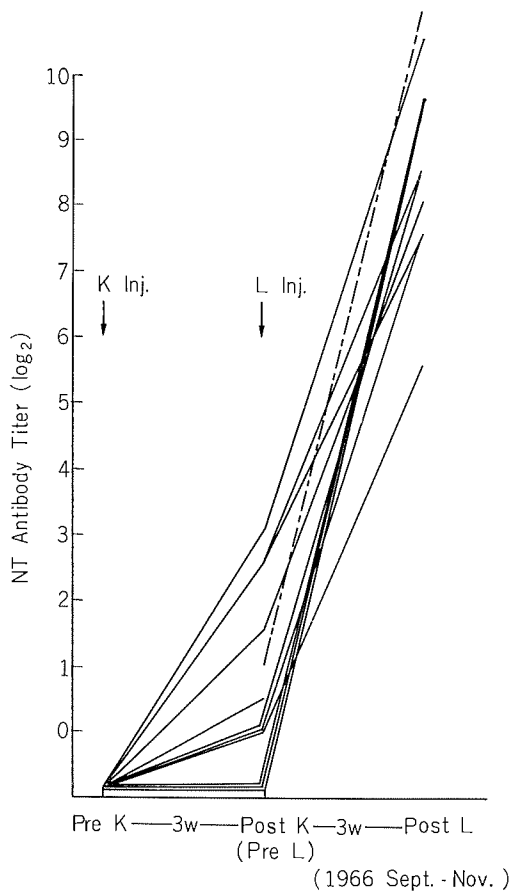


FIGURE 2 Antibody Response in Measles Vaccine Field Trials in Bangkok 1. Siriraj Hospital

undetectable. This is exemplified in Fig. 2. A feverish reaction occurred in 2 of the 3 children who had undetectable post-K antibody.

A feverish reaction occurred in 6% of the vaccinated children between 6 and 14 days after vaccination. However, the true percentage was probably lower than this, as a feverish reaction is often observed in children for various other cases. The severity of this feverish reaction was far milder than that of the typical natural infection, and yet a striking antibody response was observed in all cases whose

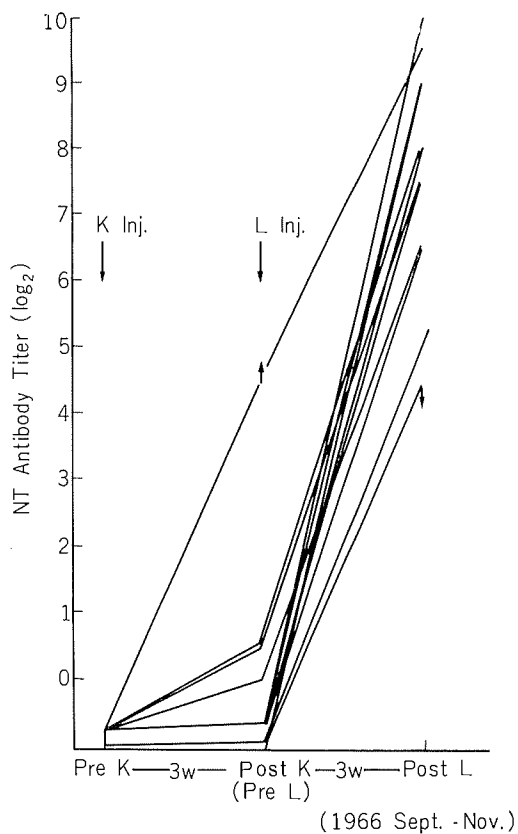


FIGURE 3 Antibody Response in Measles Vaccine Field Trials in Bangkok 2. Children's Hospital

blood specimens were examined. This indicates that the K vaccine used in the present study had satisfactory potency for the K-L combined method.

These results are consistent with those obtained in the previous field trials (OKUNO *et al.*, 1965). One noteworthy feature of this study was that the safety of vaccination by the K-L method was further confirmed. Most children who were vaccinated in hospital were feeble or sick, and were understandard level of weight (Table 1-3). Nevertheless, as satisfactory result as those with healthy children

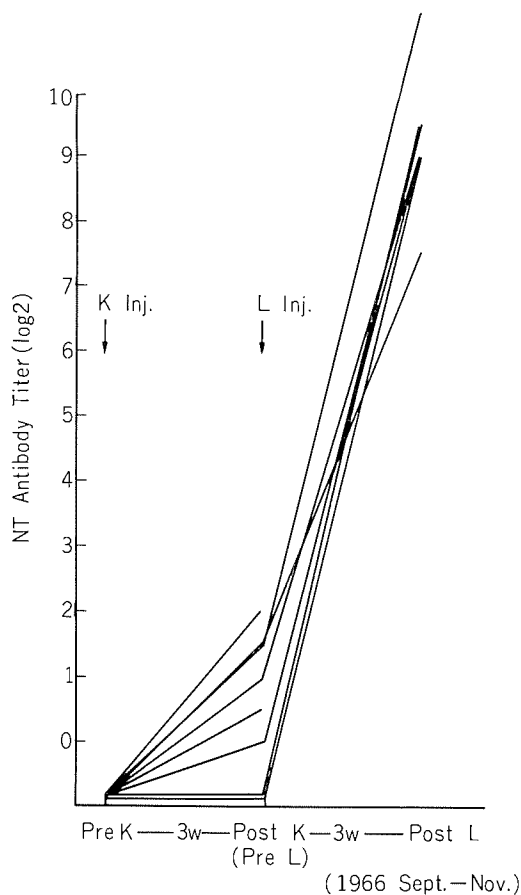


FIGURE 4 Antibody Response in Measles Vaccine Field Trials in Bangkok.

3. Vajira Municipal Hospital

were obtained. This seems sufficient proof of the safety of this vaccination method.

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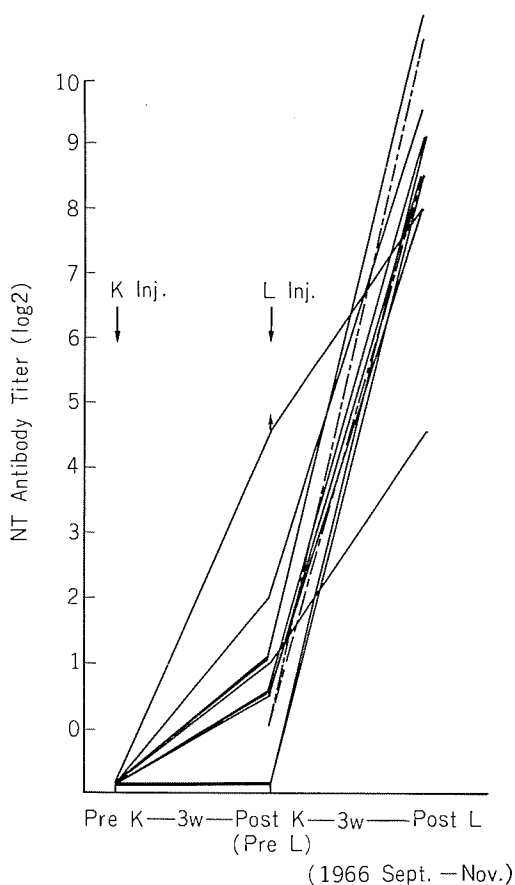


FIGURE 5 Antibody Response in Measles Vaccine Field Trials in Bangkok.

4. Japanese Children

of the Research Foundation for Microbial Diseases of Osaka University for providing measles vaccines, and to the Thailand Government and OTCA (Overseas Technical Cooperation Agency) of Japan for financing this research.

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