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STUDIES ON MEASLES IN THAILAND

III. FIELD TRIALS ON MEASLES VACCINE (continued)¹

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SUMMARY Measles vaccination by the K-L method was again applied to 151 children in Thailand. The clinical reactions and antibody responses of children were the same as those of children in Japan. A one year follow-up of the previous field trial revealed that no measles occurred among the children who were immunized by the K-L method, and 12 of them, whose blood specimens were examined, still showed fairly high antibody levels.

This suggests that measles vaccination by the K-L method is also effective against measles in tropical countries.

INTRODUCTION

We carried out field trials on measles vaccination by the K-L method in Thailand in 1966

(TUCHINDA *et al.*, 1967) and obtained as good results as in our previous field trials in Japan (OKUNO *et al.*, 1965, the Japanese Committee for the Study of Measles Vaccine, 1965).

Accordingly, field trials on measles vaccination by the K-L method on a rather larger scale were undertaken in Thailand.

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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MATERIALS AND METHODS

1. Vaccines

The vaccines used in the field trials were the same lots as those used in previous field trials (TUCHINDA *et al.*, 1967).

1) K vaccine: The potency was 42.4 AED₅₀. The vaccine was kept in a refrigerator (4°C) before use. A dose of 0.5 ml of the vaccine was injected intramuscularly.

2) L vaccine: The lyophilized vaccine in a vial was dissolved in 1.8 ml of distilled water and 0.25 ml (2500 TCID₅₀) was injected subcutaneously, or inhaled for 30 seconds with a special nebulizer. The vaccine was kept in a Revco (−70°C) or in a deep-freezer (−20°C) before use.

2. Vaccination

Vaccination was carried out on children with a negative history of measles by the K-L method in the five field trials, as shown in Table 1.

At the Central Preventorium for Children, the measles vaccines were inoculated simultaneously with live oral poliomyelitis vaccine.

The collection of blood specimens, the method of neutralizing tests and investigation of clinical reactions were as described in the previous paper (TUCHINDA *et al.*, 1967).

RESULTS

1. Clinical Reactions

No side reaction was noted after K vaccination. On the fifth to eighth day after L vaccination, febrile reactions were seen in 7 out of 151 children. One had a maximal temperature of 38.8°C (of 4 days duration) and the other 6 children had temperatures between 37 and 38°C (of 2 days duration). Thus the rate of febrile reaction due to measles vaccination by the K-L method was 4.6%. There were no other clinical reactions.

2. Antibody Responses

Three series of blood specimens (Pre, Post K and Post L) were collected from 101 children and their neutralizing antibody titers were measured. Before K vaccination 90 of them had no neutralizing antibody while 11 had antibody titers of over 2⁰. These antibodies were recognized to be the maternal antibodies.

In the 90 cases who were antibody negative before vaccination, post K antibody titers ranged from <2⁰–2⁴ and in most cases were <2⁰–2² as previously observed (OKUNO *et al.*, 1965, TUCHINDA *et al.*, 1967). After L vaccination, antibody titers increased markedly in 82 cases (Tables 2–6, Fig. 1). The geometric mean titer of post L neutralizing antibodies was 2^{8.25}. The ratio of the “L-take” was 91.1%.

In the 11 cases who had maternal antibodies before vaccination, post K antibody titers were lower than those before vaccination. After L vaccination, antibody titers increased in all

TABLE 1 Number of children immunized with measles vaccine

| Place | Date | K inoc. | K→L inoc. | Blood Specimens | |
|-----------------------------------|--------------------|------------|-----------------|-----------------|----------|
| | | | | 3 series | 4 series |
| Siriraj Hosp. | Oct. '66—Dec. '67 | 67 | 57 | 32 | 12 |
| Siriraj Hosp. | Sept. '67—Jan. '68 | 36 | 35 | 23 | 0 |
| Central Preventorium for Children | Oct. '67—Dec. '67 | 64 | 40 | 39 | 0 |
| Wachira Hosp. | ” | 10 | 9 | 7 | 0 |
| Children Hosp. | ” | 19 | 10 ^a | 0 | 0 |
| Total | | 196 | 151 | 101 | 12 |

^a KK → L inoculated

TABLE 2 *Antibody Responses of Children to K-L Measles Vaccination*
1. *Siriraj Hospital (1)*

| Code No. | Age | | Neutralizing Antiboby Titer (log ₂) | | | |
|----------|-----|-----|---|--------|--------|--------------|
| | Y | Mo. | Pre | Post K | Post L | 1 year later |
| 15 | 1 | 6 | <1.5 | 0.5 | 9.0 | 7.0 |
| 16 | 1 | 3 | <1.5 | <0.5 | | |
| 17 | 0 | 7 | <1.5 | | | 5.5 |
| 18 | 1 | 0 | <1.5 | 1.0 | >10.5 | 3.0 |
| 19 | 1 | 5 | <1.5 | | | |
| 20 | 0 | 10 | <1.5 | | | |
| 22 | 0 | 5 | <1.5 | 2.5 | <4.5 | |
| 24 | 0 | 7 | <1.5 | 0 | 6.5 | |
| 25 | 0 | 10 | <1.5 | | 10.0 | |
| 26 | 1 | 0 | <1.5 | | 6.0 | |
| 27 | 1 | 7 | <1.5 | <0 | | |
| 28 | 1 | 8 | <1.5 | <0 | >10.0 | 5.0 |
| 29 | 1 | 10 | <1.5 | 3.0 | 10.0 | |
| 30 | 1 | 5 | <1.5 | 1.5 | >10.0 | |
| 31 | 0 | 6 | <1.5 | <0 | 8.0 | |
| 33 | 0 | 8 | <1.5 | 2.0 | >10.5 | |
| 34 | 0 | 10 | <1.5 | 0 | 9.5 | |
| 35 | 0 | 11 | <1.5 | | | |
| 37 | 0 | 9 | <1.5 | 3.5 | <4.5 | |
| 38 | 1 | 3 | <1.5 | | | |
| 39 | 1 | 2 | <1.5 | 0 | | |
| 40 | 1 | 5 | <1.5 | | | |
| 41 | | | <1.5 | | | |
| 42 | 2 | 2 | <1.5 | 0.5 | <4.5 | |
| 45 | 0 | 6 | <1.5 | 0.5 | 6.5 | 5.0 |
| 46 | 1 | 6 | <1.5 | 0.5 | 8.5 | |
| 47 | 1 | 8 | <1.5 | <0 | 8.5 | |
| 49 | 1 | 2 | <1.5 | 0 | 7.0 | 7.0 |
| 50 | 0 | 7 | <1.5 | | | |
| 52 | 2 | 2 | <1.5 | <0 | 9.0 | |
| 53 | 0 | 5 | 1.5 | <0 | 2.5 | 4.0 |
| 54 | 1 | 7 | <1.5 | 1.5 | 6.5 | 5.0 |
| 55 | 0 | 6 | <1.5 | | | |
| 56 | 1 | 0 | <0 | <0 | 5.0 | 6.5 |
| 57 | 1 | 10 | <0 | 0.5 | 5.5 | 4.5 |
| 58 | 0 | 6 | 2.5 | <2.5 | 7.0 | 2.5 |
| 59 | 0 | 4 | 3.0 | 2.0 | 4.0 | 4.5 |
| 60 | 0 | 4 | 0 | 0 | 1.5 | |
| 61 | 0 | 9 | 2.5 | 0.5 | 6.5 | 5.5 |
| 62 | 0 | 4 | 0.5 | 0 | 4.0 | |
| 63 | 0 | 4 | <0 | 1.5 | 4.5 | |
| 65 | 1 | 1 | <1.5 | | | |
| 66 | 0 | 4 | 2.5 | 1.5 | <0.5 | |
| 67 | 0 | 4 | <0 | 0.5 | 5.5 | |
| 68 | 0 | 3 | <1.5 | | | |
| 69 | 1 | 6 | <0 | 2.0 | 6.0 | |
| 70 | 0 | 5 | | | | 3.0 |
| 71 | 0 | 4 | 3.0 | 1.0 | 6.5 | |
| 72 | 0 | 4 | 2.5 | 1.5 | | |
| 73 | 0 | 6 | <1.5 | 0.5 | | |
| 74 | 0 | 4 | 2.5 | | 7.0 | |
| 75 | 0 | 4 | 2.5 | <2.5 | | |
| 76 | 0 | 5 | <1.5 | 0.5 | 7.0 | |
| 78 | 0 | 5 | | 0.5 | 6.0 | |

31-42 : L, inhaled.
70-78 : K-L interval, 3 months.

TABLE 3 *Antibody Responses of Children to K-L Measles Vaccination*
2. *Siriraj Hospital (2)*

| Code No. | Age | | Neutralizing Antibody Titer (\log_2) | | |
|----------|-----|-----|--|--------|--------|
| | Y | Mo. | Pre | Post K | Post L |
| 101 | 0 | 6 | <1.5 | 0 | 7.5 |
| 102 | 0 | 6 | <1.5 | <0 | 7.0 |
| 103 | 0 | 6 | <1.5 | 0 | 6.0 |
| 104 | 0 | 5 | 2.5 | 1.0 | >8.5 |
| 105 | 0 | 5 | <1.5 | 0.5 | 6.5 |
| 106 | 2 | 0 | <1.5 | | |
| 108 | 1 | 0 | <1.5 | | |
| 110 | 1 | 1 | <1.5 | 2.0 | 8.5 |
| 112 | 0 | 6 | <1.5 | <0 | 5.0 |
| 113 | 0 | 6 | <1.5 | 1.5 | 9.0 |
| 114 | 0 | 7 | <1.5 | 0.5 | >10.5 |
| 115 | 0 | 6 | <1.5 | <0 | 8.0 |
| 116 | 0 | 10 | <1.5 | 3.5 | 9.5 |
| 117 | 3 | 0 | <1.5 | 2.5 | 8.0 |
| 118 | 0 | 8 | <1.5 | <0 | 8.5 |
| 119 | 0 | 6 | <1.5 | <0 | |
| 120 | 1 | 1 | <1.5 | 2.5 | 9.5 |
| 121 | 0 | 8 | <1.5 | <0 | 7.0 |
| 122 | 1 | 3 | <1.5 | 2.5 | |
| 123 | 2 | 4 | <1.5 | 0 | |
| 124 | 0 | 6 | <1.5 | 2.5 | >10.5 |
| 125 | 0 | 6 | <1.5 | <0 | >10.5 |
| 127 | 0 | 10 | <1.5 | | |
| 128 | 0 | 5 | <1.5 | | |
| 129 | 0 | 6 | <1.5 | 0 | 9.5 |
| 130 | 0 | 9 | <1.5 | <0 | 7.5 |
| 131 | 0 | 6 | <1.5 | 0.5 | 7.0 |
| 132 | 0 | 7 | | 0.5 | 7.5 |
| 133 | 0 | 5 | 3.0 | 2.5 | 5.5 |
| 134 | 1 | 1 | <1.5 | 2.5 | 10.0 |
| 135 | 0 | 7 | <1.5 | | |
| 136 | 0 | 7 | <1.5 | 0.5 | 9.5 |

except one case, but the mean titer was lower than that of the group with no antibody before vaccination (Fig. 2).

3. *One Year Follow-up of Children Vaccinated by the K-L Method.*

No case of measles was confirmed among

children who received measles vaccines by the K-L method one year previously.

Blood specimens were collected from 12 children one year after vaccination by the K-L method at Siriraj Hospital. As shown in Fig. 3, in some cases the antibody titers decreased rapidly, and in some cases slowly. Though

TABLE 4 *Antibody Responses of Children to K-L Measles Vaccination*
3. *Central Preventrium for Children*

| Code No. | Age | | Neutralizing Antibody Titer (log ₂) | | |
|----------|-----|-----|---|--------|--------|
| | Y | Mo. | Pre | Post K | Post L |
| 1 | 0 | 11 | <1.5 | <0 | 9.5 |
| 2 | 1 | 1 | <1.5 | 0.5 | 8.0 |
| 3 | 0 | 11 | <1.5 | <0 | <4.5 |
| 4 | 1 | 3 | <1.5 | <0 | 9.0 |
| 5 | 0 | 9 | <1.5 | <0 | >10.5 |
| 6 | 0 | 11 | <1.5 | 2.0 | 7.5 |
| 7 | 0 | 10 | <1.5 | <0 | 8.5 |
| 8 | 1 | 5 | <1.5 | <0 | 9.0 |
| 9 | 0 | 11 | <1.5 | <0 | 9.0 |
| 11 | 1 | 1 | <1.5 | <0 | 10.0 |
| 12 | 1 | 1 | <1.5 | 0 | 10.0 |
| 13 | 1 | 1 | <1.5 | 2.0 | 8.0 |
| 26 | 0 | 7 | <1.5 | 1.0 | 7.0 |
| 29 | 1 | 5 | <1.5 | 0.5 | 8.0 |
| 30 | 1 | 5 | <1.5 | <0.5 | >10.5 |
| 31 | 1 | 1 | <1.5 | 0.5 | 8.5 |
| 32 | 1 | 4 | <1.5 | 0.5 | <4.5 |
| 33 | 1 | 3 | <1.5 | 0.5 | 9.5 |
| 34 | 1 | 4 | <1.5 | | 7.5 |
| 35 | 1 | 1 | <1.5 | 0.5 | 6.5 |
| 36 | 1 | 4 | <1.5 | <0 | 9.0 |
| 37 | 1 | 3 | <1.5 | 0.5 | 6.5 |
| 38 | 1 | 3 | <1.5 | <0 | 9.5 |
| 39 | 1 | 5 | <1.5 | 0 | 8.5 |
| 40 | 1 | 1 | <1.5 | 0.5 | 8.5 |
| 41 | 1 | 6 | <1.5 | 0.5 | 8.5 |
| 42 | 1 | 4 | <1.5 | <0 | 7.0 |
| 43 | 1 | 5 | <1.5 | 1.5 | 7.5 |
| 44 | 1 | 2 | <1.5 | <0 | 7.5 |
| 45 | 1 | 9 | <1.5 | 0.5 | 6.0 |
| 46 | 1 | 4 | <1.5 | 0.5 | <4.5 |
| 47 | 1 | 1 | <1.5 | <0 | 6.5 |
| 49 | 1 | 7 | <1.5 | 2.5 | 9.5 |
| 50 | 1 | 10 | <1.5 | 0.5 | >10.5 |
| 52 | 1 | 4 | <1.5 | 0.5 | 9.5 |
| 53 | 1 | 9 | <1.5 | 4.0 | 6.5 |
| 54 | 1 | 7 | <1.5 | <0 | <4.5 |
| 56 | 1 | 6 | <1.5 | <0 | <4.5 |
| 58 | 1 | 4 | <1.5 | <0 | 8.5 |
| 59 | 1 | 5 | <1.5 | <0 | 9.5 |

TABLE 5 *Antibody Responses of Children to K-L Measles Vaccination*
4. *Wachira Hospital*

| Code No. | Age | | Neutralizing Antibody Titer (\log_2) | | |
|----------|-----|-----|--|--------|--------|
| | Y | Mo. | Pre | Post K | Post L |
| 1 | 0 | 8 | 4.5 | 3.5 | 7.5 |
| 2 | | | <1.5 | <0 | |
| 3 | | | <1.5 | | |
| 4 | | | <1.5 | <0 | 10.0 |
| 5 | 0 | 6 | <1.5 | <0 | 6.5 |
| 6 | 1 | 2 | <1.5 | 1.5 | |
| 7 | 1 | 0 | <1.5 | <0 | 9.0 |
| 8 | 1 | 4 | <1.5 | <0 | 9.5 |
| 9 | 0 | 6 | <1.5 | <0 | 8.0 |
| 10 | 0 | 7 | <1.5 | <0 | >10.5 |

TABLE 6 *Antibody Responses of Children to KKL Measles Vaccination*
5. *Children's Hospital*

| Code No. | Age | | Neutralizing Antibody Titer (\log_2) | | | |
|----------|-----|-----|--|--------|---------|--------|
| | Y | Mo. | Pre | Post K | Post KK | Post L |
| 1 | 0 | 10 | <1.5 | 0.5 | 5.0 | |
| 2 | 0 | 10 | <1.5 | <1.5 | | <4.5 |
| 3 | 0 | 11 | <1.5 | | | |
| 4 | 0 | 10 | <1.5 | <0 | 2.0 | |
| 5 | 0 | 7 | <1.5 | | | |
| 6 | 0 | 10 | <1.5 | | | |
| 7 | 1 | 1 | <1.5 | <0 | | |
| 8 | 0 | 7 | <1.5 | | | |
| 9 | 0 | 11 | <1.5 | | | |
| 10 | 0 | 7 | <1.5 | <0 | | |
| 11 | 0 | 8 | <1.5 | | | |
| 12 | 0 | 10 | <1.5 | | 5.0 | |
| 13 | 0 | 9 | <1.5 | 1.5 | | |
| 14 | 0 | 11 | <1.5 | 0 | | 8.0 |
| 15 | 0 | 8 | <1.5 | | | |
| 16 | 0 | 11 | <1.5 | | <0.5 | |
| 17 | 0 | 8 | <1.5 | | | |
| 18 | 1 | 0 | <1.5 | | | |
| 19 | 0 | 7 | <1.5 | | | |

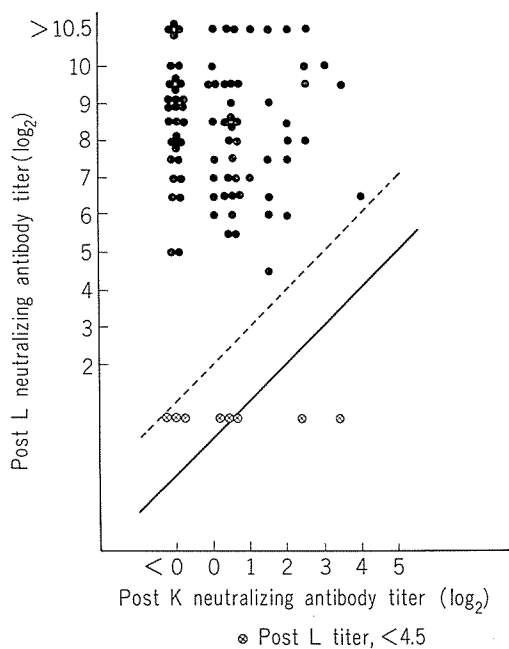
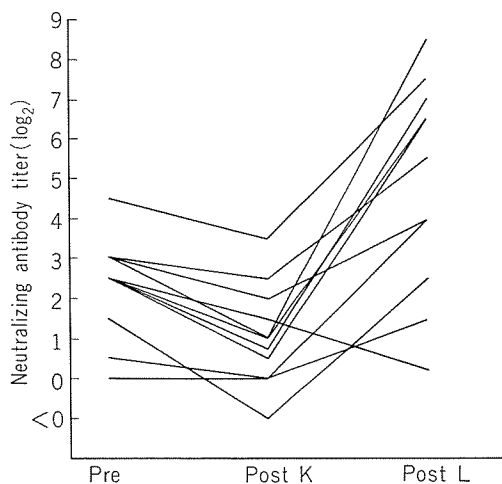


FIGURE 1 Antibody responses of pre vaccination antibody negative 90 cases to K-L measles vaccination.



*The 11 babies were 4–9 months old.

FIGURE 2 Antibody responses of maternal antibody positive 11 cases* to K-L measles vaccination.

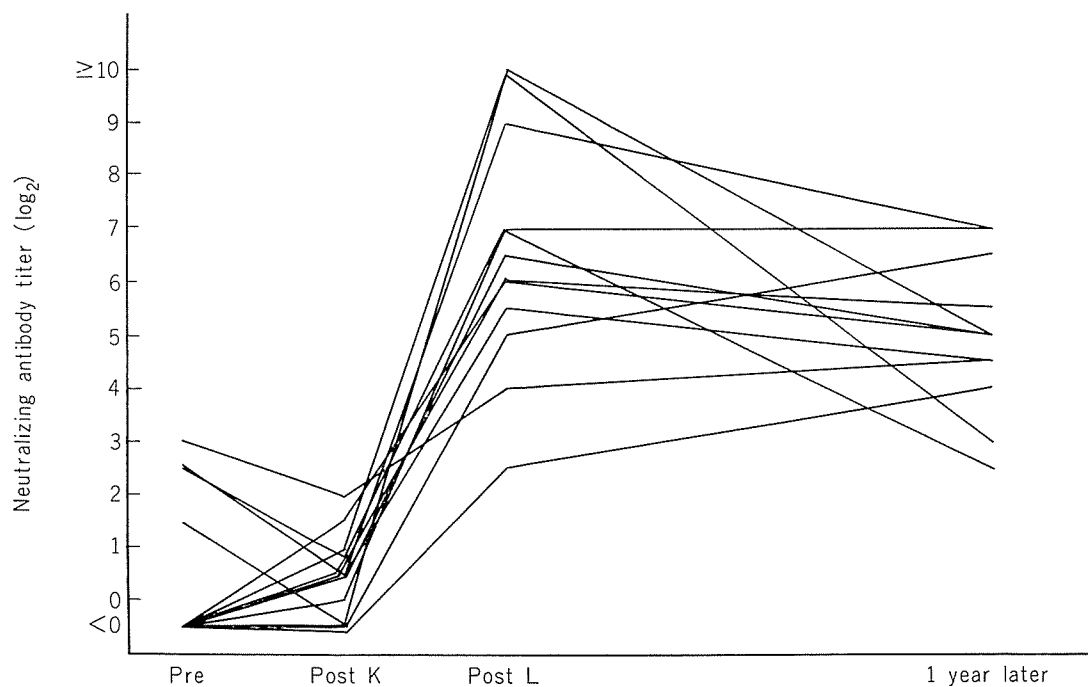


FIGURE 3 Antibody levels of K-L measles vaccinees after 1 year.

we were not able to confirm the occurrence of measles clinically, antibody titers of 3 cases whose post L antibody titers were low had increased one year later.

4. *Clinical and Serological Reactions to Measles Vaccines inoculated simultaneously with Live Oral Poliomyelitis Vaccine.*

At the Central Preventorium for Children, 40 children of over 7 months of age were injected with measles K and L vaccines at 6 weeks intervals at the same time as an oral dose of live poliomyelitis vaccine. No child showed any clinical symptoms. The antibody responses of these children were as great as those of children who were given measles or live poliomyelitis vaccine alone.

5. *Survey of History of Measles at the Central Preventorium for Children.*

At the beginning of 1967 there was an epidemic of measles at the Central Preventorium for Children. In October 1967, at the time of K vaccination, 67 out of 80 children of over 2 years old with clinical histories of measles and 13 of those with no clinical history had measles antibody titers of over 2^2 . Four out of 7 children of one year 9 months old (one with a clinical history of measles and 6 with none) had antibodies. One of 2 children of one year 10 months of age with no clinical history of measles had antibody. Forty children of 7 months to one year 8 months old had neither a clinical history of measles nor antibody.

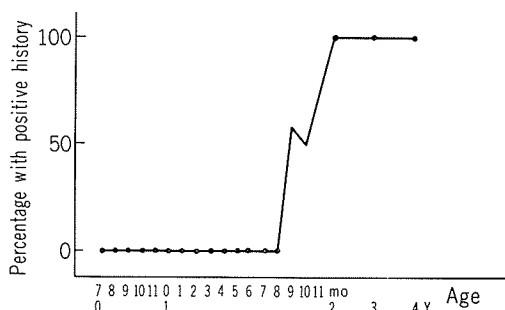


FIGURE 4 Correlation between age and history of measles at the Central Preventorium for Children.

Fig. 4 shows the clinically or serologically positive history curve of measles in the institute. The data on the epidemiological status in this small institute are rather different from our previous data (UEDA *et al.*, 1967).

DISCUSSION

Clinical symptoms due to L vaccination—vaccination measles (OKUNO *et al.*, 1960) were almost completely suppressed by K vaccination 3 to 6 weeks previously, and the antibody response to L vaccine was striking. Although Thailand is tropical and children in Thailand differ from those in Japan in nutritional and living conditions, they showed the same response to measles vaccines. Children inoculated with measles vaccines at the same time as oral poliomyelitis vaccination showed a striking antibody response without any clinical symptoms. This suggests that measles vaccines are safe and effective even when inoculated with oral poliomyelitis vaccine in a tropical country.

K vaccine was not effective in babies who had maternal antibodies. But after L vaccination babies showed antibody responses, though post L antibody titers were lower than those of children with no antibody before vaccination. This phenomenon suggests that the primary immune response of babies was suppressed by passively transferred maternal antibody. Two of the 4 babies vaccinated by the K-L method, however, retained high antibody levels for at least one year. Antibody titers of the other two increased a little one year after vaccination. Though these raised antibody titers may be due to a booster effect of natural measles, we did not confirm the occurrence of measles in these two babies. So, in a highly endemic area of measles, measles vaccination would also be effective to protecting young babies against measles.

Twelve children vaccinated by the K-L method were examined serologically one year later. Their antibody levels were the same as those of children examined 3 years after K-L

vaccination in Japan (OKUNO *et al.*, 1967). Compared with the results of BECH (1960) who surveyed the antibody levels after natural measles in Greenland, the antibody levels after either natural measles or measles vaccination by the K-L method seem to decrease rather rapidly for the first year, but thereafter decrease very slowly. So the immune state of children vaccinated by the K-L method in Thailand will persist for as many years as that of Japanese

children.

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