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# STUDIES ON FURTHER ATTENUATED LIVE MEASLES VACCINE

## II. CORRELATION BETWEEN THE TITER OF THE VACCINE, THE ANTIBODY RESPONSE AND CLINICAL REACTIONS<sup>1</sup>

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**S**UMMARY A newly developed, further attenuated live measles vaccine, CAM measles vaccine, was tested clinically and serologically using various virus titers. A dose of 450 or 800 TCID<sub>50</sub> of the vaccine was insufficient to immunize all the children vaccinated. The seroconversion rate reached 100 percent when the vaccine was injected at a dose of over 2500 TCID<sub>50</sub>. The frequency of development of a febrile reaction in children who took the vaccine was unaffected by the titer of the vaccine and ranged between 50 and 60 percent.

### INTRODUCTION

In the previous paper (Ueda et al., 1970), the antibody response and clinical reactions to a newly developed vaccine of virus adapted to the chorioallantoic membrane of chick embryos (CAM) were reported. Preliminary clinical

tests indicated that the CAM-adapted measles virus vaccine (CAM measles vaccine) belonged to the group of further attenuated live measles vaccines. In preliminary studies vaccination was carried out by the inhalation method in children, so it was difficult to determine the exact dose of vaccine inhaled.

To determine the minimal effective dose, the CAM measles vaccine was diluted to a

1. A summary of the results was reported at the First Annual Meeting of the Japan Measles Vaccine Research Commission in Tokyo, March, 1969.

suitable virus titer and injected into healthy children subcutaneously.

The clinical reactions and antibody responses of children to various virus titer of the vaccine are presented in this paper.

## MATERIALS AND METHODS

### 1. CAM Measles Vaccine

The Tanabe strain in the 35th passage in CAM was used as lyophilized vaccine. The original virus titer of the vaccine was  $10^{4.5}$  TCID<sub>50</sub>/0.1 ml in FL cells.

### 2. Vaccination

Vaccination was carried out between September and December, 1968 on children in two groups: Group A, children in two housing sites (in Suita City, Osaka and Nishinomiya City, Hyogo) and group B, those at the out-patient clinic of Hyogo Prefectural Amagasaki Hospital. Healthy children of 9 months to 7 years old living at home with no history of measles were injected subcutaneously with 0.25 ml of suitably diluted vaccine.

Other materials and procedures were as described in the previous paper (Ueda et al., 1970).

## RESULTS

### 1. Antibody Response

When the vaccine was injected at a dose of 450 TCID<sub>50</sub>, 10 of the 14 children in the housing site (Group A) and 62 of the 79 children in the out-patient clinic (Group B) showed a neutralizing antibody response. The seroconversion rates were 71.5% and 78.5%, and the geometric mean titers of neutralizing antibody were  $2^{6.3}$  and  $2^{6.0}$  in groups A and B, respectively.

When the titer of the vaccine was increased to 800 TCID<sub>50</sub>/dose, the seroconversion rate changed to 91.7% among children in group A.

A dose of over 2500 TCID<sub>50</sub> of vaccine induced a neutralizing antibody titer of over  $2^3$  in all the children vaccinated.

The geometric mean neutralizing antibody titers of the children who took the vaccine range between  $2^{6.0}$  and  $2^{7.4}$  (Table 1).

TABLE 1. *Correlation between the vaccine titer and the neutralizing antibody response*

| Vaccine titer<br>(TCID <sub>50</sub> /Dose) | Seroconversion<br>rate<br>(%) | Geometric<br>mean titer<br>(log <sub>2</sub> ) |
|---------------------------------------------|-------------------------------|------------------------------------------------|
| 450 <sup>a</sup>                            | 10/14 (71.5)                  | 6.3                                            |
| 450 <sup>b</sup>                            | 62/79 (78.5)                  | 6.0                                            |
| 800 <sup>a</sup>                            | 22/24 (91.7)                  | 7.1                                            |
| 2500 <sup>a</sup>                           | 13/13 (100)                   | 7.1                                            |
| 5000 <sup>a</sup>                           | 11/11 (100)                   | 7.4                                            |
| 5000 <sup>b</sup>                           | 29/29 (100)                   | 6.4                                            |

<sup>a</sup> group A

<sup>b</sup> group B

### 2. Seroconversion Rate and Age of Children

As shown in Table 2, when the vaccine was injected at a dose of 450 TCID<sub>50</sub> only 7 of 16 babies of 9 to 11 months old, whose neutralizing antibody titers before vaccination were under  $2^2$ , developed an antibody titer of over  $2^3$  and the seroconversion in these babies was only 43.8%. However, in children of over 1 year old the rate was over 80%.

TABLE 2. *Correlation between age and seroconversion rate in children receiving 450 TCID<sub>50</sub> of CAM vaccine*

| Age                                     | 9-11 m         | 1 y             | 2 y             | ≥ 3 y           | Total           |
|-----------------------------------------|----------------|-----------------|-----------------|-----------------|-----------------|
| Seroconversion <sup>a</sup><br>rate (%) | 7/16<br>(43.8) | 36/44<br>(81.8) | 13/14<br>(92.8) | 12/15<br>(80.0) | 68/89<br>(76.4) |

<sup>a</sup> 1 : 8 or greater rise in neutralizing antibody titer

### 3. Clinical Reactions

The main clinical reactions of children who received the CAM measles vaccine were a febrile reaction and rash, as reported previously (Ueda et al., 1970).

The percentages of children with a fever of over 37.5°C during days 5 to 12 after vaccination were between 40.0 and 75.8. There was no correlation between the vaccine titer and the frequency of incidence of a febrile reaction.

The mean incubation period was between 6.6 and 9.5 days. The mean maximal temperature of children with fever was  $38.7 \pm 0.2^\circ\text{C}$ . The mean duration of a fever of over  $37.5^\circ\text{C}$  was between 2.2 and 2.6 days except with a dose of 450 TCID<sub>50</sub> in group A when it was 0.9 days. The mean maximal temperature and mean duration of fever were not affected by varying the titer of the vaccine.

Between 0 and 19.4 percent of the children developed a mild rash on the face and chest following febrile reaction.

Convulsions due to the febrile reaction occurred in only 2 of the 161 children (Table 3).

#### 4. Vaccine Titer, Seroconversion Rate and Frequency of Febrile Reaction

The correlations between the vaccine titer (TCID<sub>50</sub>/dose), the seroconversion rate and the frequency of febrile reaction are shown in Fig. 1. The seroconversion rate increased rapidly to 100% with increase in the titer of the vaccine, while the mean frequency of incidence of the febrile reaction was consistently between 50 and 60 percent.

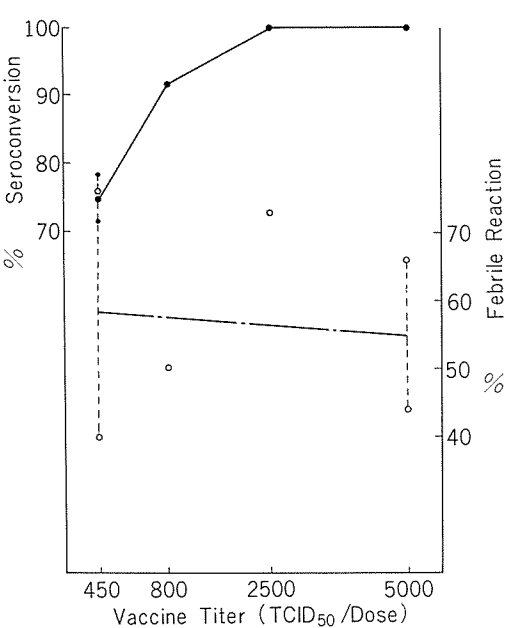


FIGURE 1. Correlation among vaccine titer, seroconversion rate and frequency of febrile reaction.  
 ●—● seroconversion rate  
 ---○--- and open circles % incidence of a febrile reaction

TABLE 3. Summary of clinical reactions with various vaccine titers

| Vaccine titer<br>(TCID <sub>50</sub> /Dose) | Clinical reactions |                             |                             |                                |                 |                    |
|---------------------------------------------|--------------------|-----------------------------|-----------------------------|--------------------------------|-----------------|--------------------|
|                                             | Febrile reaction   |                             |                             |                                | Rash<br>(%)     | Convulsions<br>(%) |
|                                             | ≥ 37.5 C<br>(%)    | Inc. <sup>c</sup><br>(days) | Max. T. <sup>d</sup><br>(C) | Dur. F. <sup>e</sup><br>(days) |                 |                    |
| 450 <sup>a</sup>                            | 4/10<br>(40.0)     | 9.0                         | 38.5                        | 0.9                            | 0/10<br>(0)     | 0/10<br>(0)        |
| 450 <sup>b</sup>                            | 47/62<br>(75.8)    | 9.5                         | 38.7                        | 2.6                            | 12/62<br>(19.4) | 1/62<br>(1.6)      |
| 800 <sup>a</sup>                            | 11/22<br>(50.0)    | 8.7                         | 38.7                        | 2.2                            | 1/22<br>(4.5)   | 0/22<br>(0)        |
| 2500 <sup>a</sup>                           | 16/22<br>(72.7)    | 6.6                         | 38.9                        | 2.5                            | 4/22<br>(18.2)  | 1/22<br>(4.5)      |
| 5000 <sup>a</sup>                           | 7/16<br>(43.8)     | 7.2                         | 38.9                        | 2.4                            | 1/16<br>(6.3)   | 0/16<br>(0)        |
| 5000 <sup>b</sup>                           | 19/29<br>(65.6)    | 8.2                         | 38.8                        | 2.5                            | 4/29<br>(13.8)  | 0/29<br>(0)        |

<sup>a</sup> group A  
<sup>b</sup> group B  
<sup>c</sup> mean incubation period  
<sup>d</sup> mean maximal temperature  
<sup>e</sup> mean duration of fever of over 37.5 C

## DISCUSSION

Our newly developed live measles vaccine (CAM measles vaccine) differed in several points from our former Am-adapted live measles virus vaccine.

First, a dose of 450 and 800 TCID<sub>50</sub> of CAM vaccine was not sufficient to immunize all of the children receiving the vaccine, and this was confirmed by the Japan Measles Vaccine Research Commission (Shishido, 1969), while a dose of 100 TCID<sub>50</sub> of Am-adapted vaccine was sufficient (Okuno and Ueda, 1969). This difference is thought to be because the CAM vaccine virus became more attenuated than the Am-adapted vaccine during passages in the chorioallantoic membrane of chick embryos, and its rate of multiplication in the human body became less than that of the Am-adapted vaccine virus.

Buynak et al. (1969) reported that a dose of only 20 TCID<sub>50</sub> of their further attenuated, Moraten measles vaccine virus was sufficient to immunize all the children tested. This difference cannot be explained at present.

Second, when the CAM vaccine was injected at a dose of 450 TCID<sub>50</sub>, the seroconversion rate in babies of 9 to 11 months old was half that among children of over 1 year old. This difference is suspected to be because there

might be a little maternal antibody in some babies whose neutralizing antibody titers before vaccination were under 2<sup>2</sup>, and this small amount of antibody might suppress multiplication of the CAM vaccine virus and prevent induction of detectable antibody, whereas 100 TCID<sub>50</sub> of Am-adapted vaccine virus was sufficient to induce antibody even in young babies who had maternal antibodies. This phenomenon may be also due to the greater attenuation of the CAM vaccine virus than the Am-adapted vaccine virus.

Third, the febrile reaction due to the CAM vaccine was much milder than that due to the Am-adapted vaccine.

The mean frequency of febrile reaction was within a range of 50 to 60%, but in clinical tests individual values ranged between 40 and 76%. Chiang (1966) reported that measles virus was detected in the amniotic membrane when inoculated into the chorioallantoic cavity of chick embryos. The CAM vaccine virus when inoculated onto the chorioallantoic membrane probably passed through the amniotic membrane acquiring the character of less attenuated Am-adapted vaccine virus. The variation in the frequency of incidence of the febrile reaction may be due to contamination of the CAM vaccine material with back mutated virus.

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