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STUDIES ON FURTHER ATTENUATED LIVE MEASLES VACCINE
VI. CLINICAL AND SEROLOGICAL FOLLOW-UP ONE YEAR AFTER VACCINATION

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SUMMARY Since the development of the new further attenuated live measles virus vaccine " CAM " and immunization tests on it in children, a 2 years clinical, and one year serological follow-up studies have been carried out.

The clinical follow-up revealed that the protective efficacy of CAM measles virus vaccine was nearly complete in over 800 children. The results of the serological follow-up were as follows: 1) Neutralizing antibodies induced by one injection with CAM measles virus vaccine remained stable in home-dwelling children in an area with natural measles, 2) In hospitalized handicapped children who were not exposed to measles, high neutralizing antibody titers one month after vaccination tended to be lower one year later, whereas low antibody titers remained unchanged.

INTRODUCTION

The newly developed, further attenuated live measles virus vaccine, CAM strain showed similar evidence of attenuation to further attenuated strains produced in other countries and induced a good antibody response (Japan Measles Vaccine Research Commission, 1970 ; Ueda et al., 1970c).

The previous reports on follow-up studies in children immunized by the KL method of vaccination showed that measles neutralizing antibodies persisted well and that it might be possible to provide life-long immunity (Sangkawibha et al., 1971 ; Ueda et al., 1969a and 1970a). The KL method, however, has the disadvantage that 2 injections with killed and live virus vaccines are necessary. Recently there has been a demand in Japan for a method of prevention of measles by one injection of live virus vaccine.

The follow-up study reported in this paper was planned to confirm the protective efficacy of one injection of the further attenuated live measles virus vaccine developed by our gorup.

MATERIALS AND METHODS

1. *Postal questionnaires*

Questionnaires were sent to the parents of vaccinees one and 2 years after vaccination to survey the incidence of measles among children who had received CAM measles vaccine, as described previously (Ueda et al., 1969a).

2. *Serological examination*

Blood specimens were collected from a total 148 children one year after vaccination. Neutralizing antibody titers in the paired 148 serum specimens obtained one month and one year after vaccination were measured simultaneously by the micromethod (Ueda, 1971).

3. *Vaccinees*

Follow-ups were made on the following 3 groups of children: Group A; 37 hospitalized handicapped children who received CAM-A4 measles vaccine in December, 1969 and January, 1970 (Ueda et al., 1970d). Ten of these children were immune before the vaccination. All 37 children were examined serologically one year later.

Group B; 688 home-dwelling healthy children who received CAM-A4 measles vaccine in 1969. This group included 57 children who received a combination of CAM-A4 measles virus vaccine and live, attenuated mumps virus vaccine (Ueda et al., 1970c; Yamanishi et al., 1970). Blood specimens from 67 children were available for serological analysis one year later.

Group C; 116 home-dwelling healthy children who received CAM measles virus vaccine in 1968 (Ueda et al., 1970b). Blood specimens from 44 children were available for serological analysis one year later.

RESULTS

1. *Clinical follow-up*

1) Hospitalized children

Handicapped children in Shin-Mukogawa Hospital were vaccinated in December, 1969 and January, 1970. Since then newly admitted children have also been immunized with CAM-A4 measles vaccine and no cases of measles have occurred in the ward where the children are cared for.

2) Home-dwelling children

Questionnaires were sent to the parents of children in group B one year after vaccination (in 1970) and to those of group C one (in 1969) and 2 years (in 1970) after vaccination.

As shown in Table 1, the parents of about 25% of the children in group C reported that there had been cases of measles in their neighbourhood in the 2 years after the vaccination. One and 2 years after vaccination, respectively, 3% and 9% of the parents reported that their children had been in contact with cases of measles, but none of the children contracted measles.

In group B, 37% of the children were in an area where there was an outbreak of measles and 17% of the children came in contact with cases of measles. However, only one of the 688 children developed clinical symptoms of measles and these were in general mild and the

TABLE 1. *Protective efficacy of CAM measles vaccine (Results of questionnaires after 1 and 2 years)*

Group and Vaccine	Vaccination in	Year(s) after vaccination	No. of vaccinees surveyed	No. of answers	No. of measles cases	Measles cases in neighbourhood (yes)	Contact with measles cases (yes)
B CAM-A4	1969	1	955	688 (72.0%)	1 (0.15%)	257 (37.4%)	119 (17.3%)
C CAM	1968	1	128	116 (90.6%)	0 (0%)	26 (22.4%)	4 (3.4%)
C CAM	1968	2	125	98 (78.4%)	0 (0%)	24 (24.5%)	9 (9.2%)

course of the disease was shorter than that of typical measles.

2. *Serological follow-up*

1) Hospitalized children

A comparison of the neutralizing antibody titers one month and one year after vaccination is shown in Fig. 1. No child had a neutralizing antibody titer one year after vaccination which increased 4-fold or more than that one month after vaccination. The figure shows that high antibody titers one month after vaccination decreased in one year more than lower ones. This is shown more clearly in Table 2. The children were divided into two groups with antibody titers of under $2^{6.0}$ and over $2^{6.5}$ after one month. A decrease in the antibody titer of 4-fold or more was seen in 20% of children in the first group and in 59% of those in the second group. Moreover, the decrease in the geometric mean antibody titer of children in the second group was about 3 fold that of children in the first group.

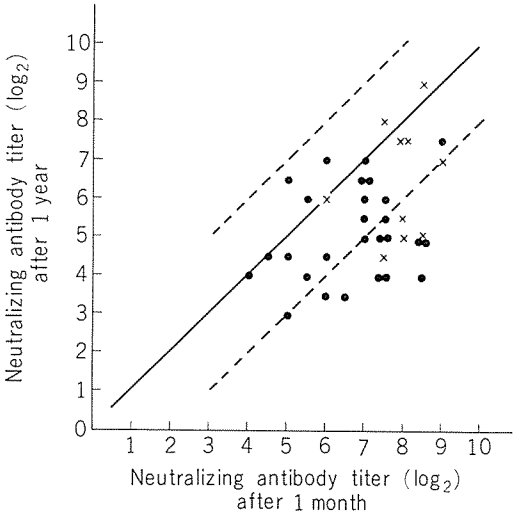

FIGURE 1. *Comparison of measles neutralizing antibody titers in hospitalized handicapped children 1 month and 1 year after immunization with CAM-A4 measles vaccine in 1969.*

●=*children immunized with CAM-A4 measles vaccine.*

×=*immune children before vaccination.*

TABLE 2. *Decrease of neutralizing antibody titers in hospitalized handicapped children one year after immunization with CAM-A4 measles vaccine*

Antibody titer after 1 month	under $2^{6.0}$	over $2^{6.5}$
Rate of 4 fold or greater decrease	2/10 (20.0%)	10/17 (58.8%)
(a) G. M. titer after 1 month	$2^{5.3}$	$2^{7.5}$
(b) G. M. titer after 1 year	$2^{4.8}$	$2^{5.5}$
(a) / (b)	$2^{0.5}$	$2^{2.0}$

Children who were immune before vaccination had high neutralizing antibody titers at the time of vaccination. Half of them showed 4 fold or more decrease in the antibody titer, like the vaccinated children.

2) *Home-dwelling children*

The neutralizing antibody titers of children in group C one month and one year after vaccination are compared in Fig. 2, and those of children in group B are shown in Fig. 3.

Fig. 2 and 3 show that children who had a low antibody titer after one month tended to show 4-fold or more increase in antibody titer one year later, while those who had a high antibody titer tended to show a decrease of antibody titer one year later. However, in most children there was no difference in the antibody titers one month and one year after vaccination. This increase in antibody titer one year after vaccination may be due to inappearent re-infection with wild virus.

Fig. 3 also shows that the antibodies induced by one injection of a combination of measles and mumps live virus vaccines persisted as well as on injection of measles virus vaccine alone.

Children who received the ESC strain, a further attenuated live measles virus vaccine produced in the U. S. S. R. (Chumakov, 1967) as a control in the clinical test in 1969 (Takaku et al., 1970) showed a similar persistence of anti-

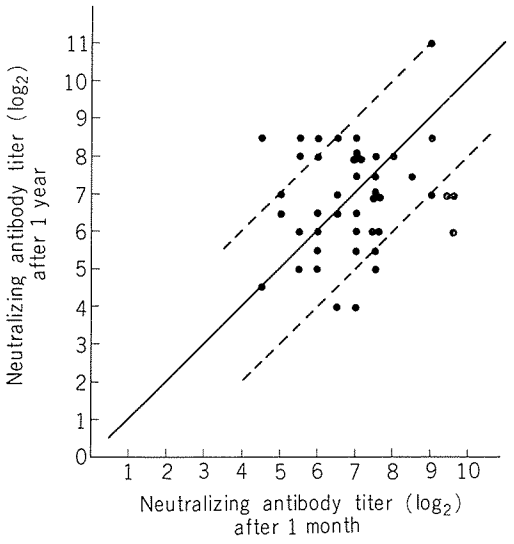

FIGURE 2. *Comparison of measles neutralizing antibody titers of home-dwelling children 1 month and 1 year after immunization with CAM measles vaccine in 1968.*

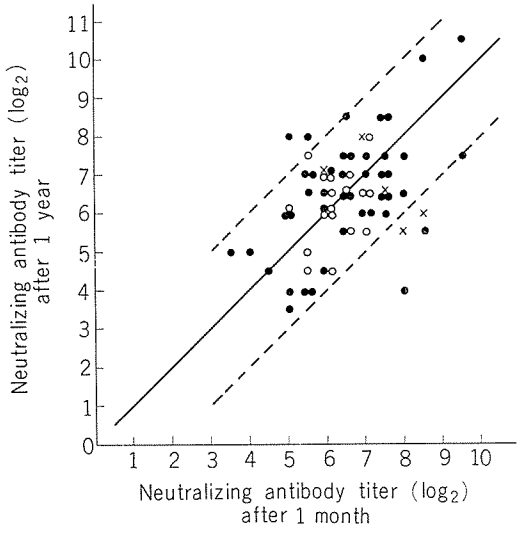

FIGURE 3. *Comparison of measles neutralizing antibody titers of home-dwelling children 1 month and 1 year after immunization with CAM-A4 measles vaccine in 1969.*

●=*immunized with CAM-A4 measles vaccine.*

○=*immunized with CAM-A4 measles and live mumps vaccine.*

×=*immunized with ESC measles vaccine.*

bodies to those of children who received CAM-A4 measles virus vaccine (Fig. 3).

DISCUSSION

The symptoms or clinical reactions to further attenuated live measles virus vaccines are milder than those to attenuated live measles virus vaccines. However, the antibody titers induced by the former are lower than those induced by the latter, and it was uncertain whether the antibodies induced by further attenuated live measles virus vaccine persisted.

The protective efficacy of the further attenuated live measles virus vaccine " CAM " shown in this report was nearly complete in enviroments where 20 to 40% of the vaccinated children were exposed to natural measles in the one or 2 year period of observation after vaccination.

On analysis of the neutralizing antibody titers, it was found that, in general, those of home-dwelling children persisted well. Booster antibody responses without clinical evidence of measles were observed in children with relatively low antibody titers, as reported previously in children who had been vaccinated by the KL method (Ueda et al., 1969a and 1970a) and in the mothers of children with natural measles (Ueda et al., 1969b). Krugman also reported this phenomenon (Krugman et al., 1965). In children in the hospital who were not exposed to natural measles, the pattern of antibody persistence was rather different from that of home-dwelling children with a chance of exposure to natural measles. As shown in Fig. 1 and Table 2, antibody titers which were above $2^{6.5}$ one month after vaccination decreased more rapidly than those which were below $2^{6.0}$. Moreover, 50% of the children who had natural measles before vaccination also showed 4 fold or more decrease in antibody titer in one year.

This follow-up period is still only one year, but these data suggest that the antibodies induced by immunization with further attenuated vaccine will persist for a long time even when

the vaccinees are not exposed to natural measles. Sangkawibha et al. (1971) reported similar findings that the neutralizing antibody titers after KL vaccination declined rapidly in the year following vaccination to a level which was subsequently maintained with scarcely any further decline. In the recent report by Krugman (1971), the geometric mean HI antibody titer of institutionalized children who received the Schwarz strain of measles vaccine declined rather rapidly than that of children who contracted natural measles or who received Edmonston B vaccine, but these antibodies persisted well for at least 8 years after vaccination.

Thus, it seems that a high antibody titer after vaccination is not necessary and long-term prevention of measles is achieved providing the antibody titer exceeds a certain level of around 2^4 after one injection with live virus vaccine. This suggests that it may be possible to develope a more attenuated live measles virus vaccine which will induce antibodies at a lower level but will cause fewer clinical reactions.

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