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STUDIES ON FURTHER ATTENUATED LIVE MEASLES VACCINE. VIII. ESTIMATED DURATION OF IMMUNITY AFTER VACCINATION WITHOUT NATURAL INFECTION

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SUMMARY A total of 1489 of 2079 children who were vaccinated with further attenuated live measles virus vaccines, CAM original, CAM A4, CAM 70, CAM EX, Moraten and ESC strains between July, 1968 and March, 1972 were followed-up clinically and serologically for 1 to 4 years.

Neutralizing antibody titers of hospitalized children seemed to decrease gradually with time after vaccination following a second order curve. The duration of neutralizing antibody was calculated by a modification of Jensen's equation for the duration of diphtheria antitoxin to be from 6 to 92 years, and mostly more than 10 years in these children without re-exposure to natural measles.

Neutralizing antibodies of children in areas where measles was endemic persisted stably during the observation period, though booster infections without apparent disease were observed in children with low antibody titers.

There were only 13 cases of measles among the 1409 vaccinated children surveyed in measles endemic areas, and in all these cases the disease was milder than usual.

INTRODUCTION

There have been many reports on follow-up studies after measles vaccination. Krugman (1971) showed clearly that HI antibodies persisted well for at least 8 years after vaccination with the Schwarz strain and 10 years with the Enders B strain, suggesting that a single injection with further attenuated or attenuated live measles virus vaccine would confer lifelong immunity against measles. Other reports presented evidence supporting this possibility (Katz, 1965; Brown, Gajdusek and Tsai, 1969; Lepow and Nankervis, 1969; Weibel et al., 1973).

We also reported similar results (Ueda et al., 1970c; Sangkawibha et al., 1971b; Ueda et al., 1971), but our data, especially on further attenuated live measles virus vaccine (FAL), were obtained in a short observation period.

This paper reports results of 1 to 4 year follow-up studies after vaccination mainly with the CAM strain, FAL developed by our group. The durability of immunity after vaccination with FAL is discussed.

MATERIALS AND METHODS

1. *Vaccines and vaccinees*

A total of 2079 children vaccinated with 6 kinds of FAL between July, 1968 and March, 1972 were followed-up clinically and serologically for 1 to 4 years depending on the time when they were vaccinated. The 6 FALs used were the CAM original (Ueda et al., 1970a), CAM A4 (Ueda et al., 1970b), CAM 70, one of the licensed FALs in Japan (Okuno et al., 1971), CAM EX (Ueda et al., 1972), ESC (Chumakov, 1967) and Moraten (Hilleman et al., 1968) strains. Table 1 shows the times of vaccination with the vaccines, the number of children vaccinated and whether the children were home-dwelling or institutionalized. Table 2 shows schematically the data on the clinical reactions and antibody responses of the children to the 6 vaccines reported previously.

2. *Clinical survey*

Parents or guardians of the vaccinees living in their homes were requested to answer postal questionnaires once a year after vaccination. The questions asked were 1) whether their children had contracted measles (if so, the doctor's diagnosis, date of contraction and symptoms in brief), or 2) had

TABLE 1. *Vaccines and vaccinees*

Vaccine	Group	Time of vaccination	No. of children vaccinated	Remarks
CAM original	1	Jul. '68–Jul. '69	301	home-dwelling[a]
CAM A4	2	Dec. '69–Jan. '70	38	hospitalized[c]
	3	Feb. '70	18	institutionalized[d]
	4	Aug. '69–Apr. '70	797	home-dwelling
CAM 70	5	Mar. '70–Aug. '71	448	home-dwelling
CAM EX	6	Jul. '71–Mar. '72	442	home-dwelling[b]
ESC	7	Aug. '69	17	home-dwelling
Moraten	8	Feb. '70	18	institutionalized[d]

[a] Living in or near Osaka unless otherwise stated.
[b] Including 128 children living in Nagano.
[c] Ueda, Okuno and Sakamoto, 1970.
[d] Sangkawibha et al., 1971a.

TABLE 2. *Schematic summary of results obtained in clinical studies with several further attenuated live measles virus vaccines*

Vaccine	Year of development of vaccines	% of cases showing febrile reactions	Range of geometric mean antibody titers (log 2)	Seroconversion rate (%)
CAM original	1968	60	7–8	98 or more
CAM A4	1969	50	6–7	,,
ESC	1967	50	6–7	,,
Moraten	1968	50	6–7	,,
CAM 70	1970	30	5–6	,,
CAM EX	1971	10	3–4	,,

been in contact with cases of measles, and whether there had been any cases of measles in their neighbourhood. Answers were collected most recently between January and March, 1973.

3. *Serological examination*

Neutralizing antibody titers of serum specimens collected from the vaccinees at appropriate intervals were measured by the micro-method (Ueda, 1971; Ueda et al., 1972).

RESULTS

1. *Clinical survey*

1) Hospitalized children (group 2)

Twenty seven of 38 vaccinated children were initially seronegative and 24 of the 27 children were followed-up for 3 years. There were no cases of measles during the observation period in the wards where the vaccinated children lived.

2) Institutionalized children (groups 3 and 8)

Of the 36 children in groups 3 and 8, 13 and 15 children, respectively, were followed-up for 2 years. No children in these 2 groups suffered from measles during the period, though in September, 1971, 6 months after the vaccination with FAL in this institution, there were 5 cases of measles among unvaccinated children and children vaccinated by the KL method, as previously reported (Sangkawibha et al., 1971b).

3) Home-dwelling children (groups 1, 4, 5, 6 and 7)

One case of measles in group 1, 7 in group 4, 3 in group 5 and 2 in group 6 were reported 4, 3, 2 and 1 year, respectively after vaccination. The cumulative incidences of measles among the vaccinated children in groups 1, 4, 5 and 6 were 0.6, 1.2, 1.1 and 1.1%, respectively (Table 3). Ten children in group 7 were followed-up for 3 years after vaccination, and none of them contracted measles.

Though in follow-ups 10 to 20% of the vaccinated children were found to come in contact with patients with measles every year, the cumulative incidences of measles were at most 1.2%. In all cases symptoms were milder, and the duration of fever and sporadic rash was shorter than in usual measles. It was not possible to confirm these cases serologically. Some of them may have been diseases similar to measles caused by some other agent, because one case in group 6 was diagnosed clinically as having measles, but this diagnosis could not be confirmed serologically. Anyhow, these incidences coincided well with the seroconversion rates by the vaccines used in these studies.

One of the 2 cases in group 6 is suggestive in discussion of immunity after vaccination. A healthy 4 years old boy was injected with 0.5 ml of the CAM EX strain on February 15, 1972. He did not show any antibody response one month after the vaccination, his neutralizing antibody titer being less than $2^{0.5}$. However,

TABLE 3. *Protective efficacy of "CAM" measles virus vaccine*

Time after vaccination		CAM original	CAM A4	CAM 70	CAM EX
1 year	A	0/229 (0)	3/651 (0.5)	2/354 (0.6)	2/175 (1.1)
	B	31.4	35.3	36.2	35.8
	C	14.0	15.1	9.6	10.8
2 years	A	0/191 (0)	2/612 (0.3)	1/185 (0.5)	
	B	30.9	40.5	34.6	
	C	14.7	20.1	16.2	
3 years	A	1/161 (0.6)	2/474 (0.4)		
	B	37.3	31.4		
	C	18.6	20.9		
4 years	A	0/72 (0)			
	B	44.4			
	C	16.7			
Cumulative incidence of measles cases		(0.6)	(1.2)	(1.1)	(1.1)

Answers to questionnaire:
A: No. of measles cases/No. of answers.
B: Vaccinees with cases of measles in their neighbourhood (%).
C: Vaccinees who came in contact with cases of measles (%).
Figures in parentheses indicate percentages.

just one year later, he suffered from coryza with a slight fever beginning on February 14, 1973. He came in contact with a patient with measles in a hospital 10 days before the onset of the disease when he was taken to receive ophthalmic treatment. A faint rash developed on his face and body on the 4th day of the disease, but it disappeared 3 days later without pigmentation. As shown in Fig. 1, fever was not high and lasted only 4 days. No Koplik's spots were observed and his general condition was good throughout the course of the disease. He played with some of his friends on the 3rd day of the disease, but none of them contracted measles later. His family doctor, a pediatrician, could not diagnose his symptoms as due to measles. However, a serum specimen taken 2 months later showed a marked increase in the measles neutralizing antibody titer to $2^{9.5}$.

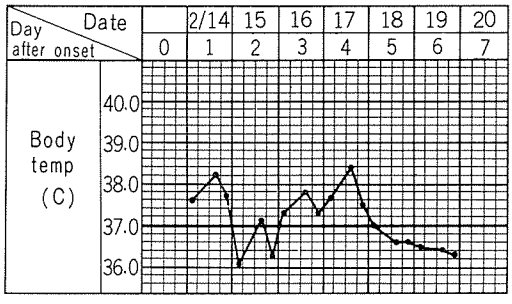

FIGURE 1. *Body temp of a 5-year old boy who contracted measles one year after receiving CAM EX measles virus vaccines.*

2. *Serological examination*

1) Hospitalized children (group 2)

Serum specimens from 24 children were collected at one year intervals for 3 years. High neutralizing antibody titers one month after vaccination tended to decrease more than

low ones. This tendency was observed in a one-year follow-up study (Ueda et al., 1971), and even more clearly in this study (Table 4).

TABLE 4. *Decrease of measles neutralizing antibody titers in hospitalized handicapped children 3 years after vaccination with CAM A4 strain*

Antibody titer after 1 month	Under $2^{6.0}$	Over $2^{6.5}$
Rate of 4 fold or more decrease	3/7 (42.9%)	16/17 (94.1%)
(a) G.M. titer after 1 month	$2^{5.1}$	$2^{7.5}$
(b) G.M. titer after 3 years	$2^{3.3}$	$2^{3.9}$
(a)/(b)	$2^{1.8}$	$2^{3.6}$

Namely only 3 of 7 children with initial neutralizing antibody titers of $2^{6.0}$ or lower showed 4-fold or more decrease in neutralizing antibody titers, while 16 of 17 children with titers of $2^{6.5}$ or higher showed such decreases 3 years after vaccination. The geometric mean titers of children in the former and latter groups after 3 years were $2^{3.3}$ and $2^{3.9}$, respectively.

The patterns of persistence of neutralizing antibody titers or the curves of their decrease seem to follow a curve for a second-order reaction, a typical example being the curve of decrease in the geometric mean titer shown in Fig. 2. Jensen (1933) proposed an equation for estimation of the duration and degree of diphtheria antitoxic immunity. We modified this equation as follows for use in estimation of the duration of measles immunity after vaccination:

$$kt = \frac{x}{a(a-x)}$$

where a is the neutralizing antibody titer one month after vaccination, x is the lost neutralizing antibody titer at time t, and k is a constant.

On secondary infection with measles virus, a neutralizing antibody titer of $2^{1.0}$ is sufficient to prevent apparent disease, though it allows inapparent infection (Stokes et al., 1961;

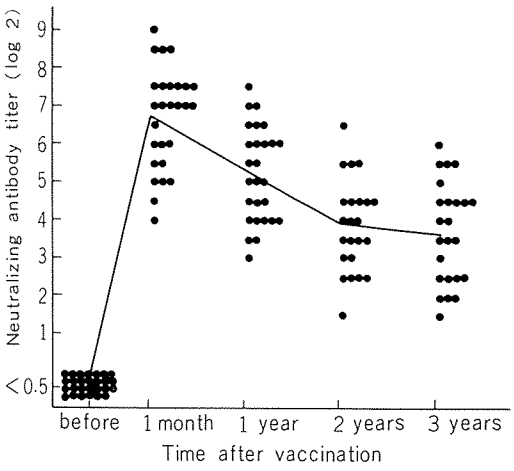

FIGURE 2. *Patterns of neutralizing antibody persistence in hospitalized handicapped children vaccinated with CAM A4 measles virus vaccine in the absence of natural virus.* ———, *geometric mean titer.*

TABLE 5. *Estimation of the duration of meales neutralizing antibody after vaccination with CAM A4 strain in hospitalized handicapped children in the absence of natural measles*

Initals	Neutralizing antibody titer 1 month after vaccination (log 2)	Constant (K)	Calculated duration of antibody (years)
E. T.	7.0	0.0093	92
M. Y.	7.0	0.0150	57
N. U.	7.0	0.0257	33
K. T.	9.0	0.0271	33
S. M.	7.0	0.0300	29
T. M.	8.5	0.0342	26
A. K.	5.0	0.0326	25
S. I.	7.5	0.0408	21
S. Y.	7.5	0.0667	13
Y. M.	5.5	0.0720	11
T. Y.	7.5	0.0773	11
M. T.	7.5	0.0812	11
T. M.	7.5	0.1019	9
T. I.	6.5	0.1044	8
T. K.	6.0	0.1045	8
T. A.	8.5	0.1300	7
K. O.	5.0	0.1445	6

Krugman et al., 1965; Ueda, Toyoshima and Kurose, 1969a; Ueda et al., 1969b). So, we calculated the durations of measles immunity after vaccination until the neutralizing antibody titers decreased to $2^{1.0}$ ($a-x=1.0$) from the neutralizing antibody titers of 17 of 24 children for whom the calculation was possible. As shown in Table 5, the duration of neutralizing antibodies of the 17 children ranged from 92 years, lifelong, to 6 years, showing great individual variations. As also seen in the Table, a high titer after vaccination does not necessarily ensure retention of immunity for a long term, and the duration of immunity depends greatly on the K value. However, for two thirds of the children the duration of measles immunity after a single injection of live virus vaccine without re-exposure to natural measles was estimated as over 10 years.

2) Institutionalized children (groups 3 and 8)

Twenty eight of 36 vaccinated children could be followed-up serologically for 2 years after vaccination. There was one case with booster infection among the children who received Moraten strain when 5 cases of measles occurred in this institution 6 months after the vaccination. Other children were not affected. The patterns of persistence of neutralizing antibody of the children are shown in Fig. 3. The tendency in the neutralizing antibody titers to decrease was the same as that seen in Fig. 2, though the titers were rather high in these groups. No difference observed between the persistences of antibody in children who received the CAM and Moraten strains.

3) Home-dwelling children (groups 1, 4, 5 and 7)

The patterns of persistence of neutralizing antibody in children in groups 1, 4 and 7, and 5 are shown in Figs. 4, 5 and 6, respectively.

As shown schematically in Table 2, the vaccines used in these groups differed in attenuation level. However, there were no striking differences in the patterns of persistence of neutralizing antibody.

All the children who were examined serologically had neutralizing antibody titers of at least $2^{1.5}$ for 2 to 4 years after vaccination.

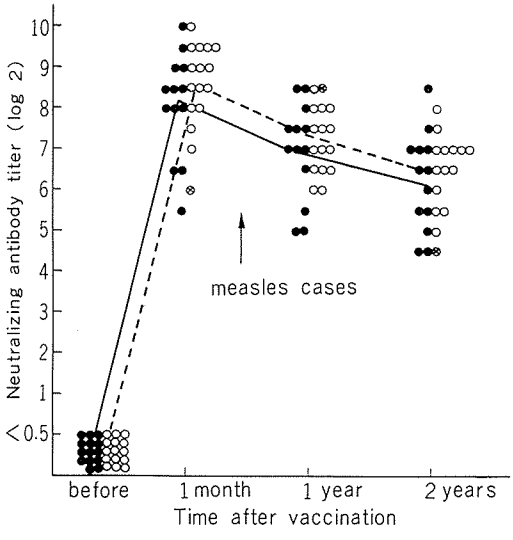

FIGURE 3. *Patterns of neutralizing antibody persistence in the children vaccinated with CAM A4 or Moraten measles virus vaccine in an institution in Bangkok, Thailand.* ●, *CAM A4;* ○, *Moraten;* ⊗, *booster infection;* ———, *geometric mean titer with CAM A4;* - - - -, *geometric mean titer with Moraten.*

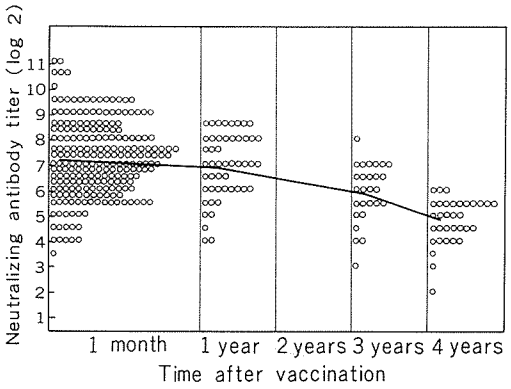

FIGURE 4. *Patterns of neutralizing antibody persistence in home-dwelling children vaccinated with CAM original measles virus vaccine.* ———, *geometric mean titer.*

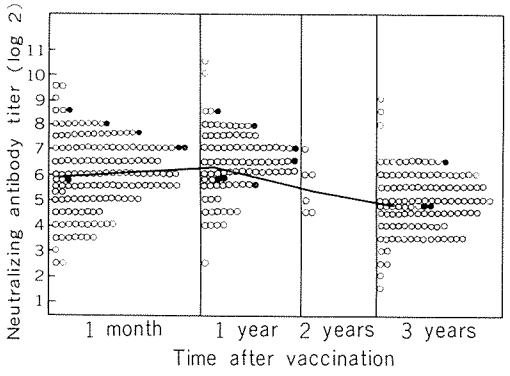

FIGURE 5. *Patterns of neutralizing antibody persistence in home-dwelling children vaccinated with CAM A4 or ESC measles virus vaccine.* ○, *CAM A4;* ●, *ESC;* ———, *geometric mean titer with CAM A4.*

Some of the children had booster infections during the observation period when their neutralizing antibody titers decreased, as previously reported (Ueda et al., 1970c; Ueda et al., 1971).

4) Home-dwelling children (group 6)

Children in this group received the most attenuated live virus vaccine, CAM EX. So, their neutralizing antibody titers one month after vaccination were lower than those of children in other groups. Among 133 children examined, 14 children (10.5%) showed 4-fold or more increase in neutralizing antibody titers one year later, suggesting inapparent booster infections, and 18 children (13.5%) showed decrease in the titers. Four of the latter showed decrease in neutralizing antibody titers to less than $2^{0.5}$. Three of these children were re-vaccinated, 2 with CAM EX and one with CAM 70, resulting in increase in neutralizing antibody titers to $2^{6.0}$ and $2^{5.0}$, respectively. The neutralizing antibody titers of most other children remained unchanged during the one year observation period, despite their initial low titers (Fig. 7).

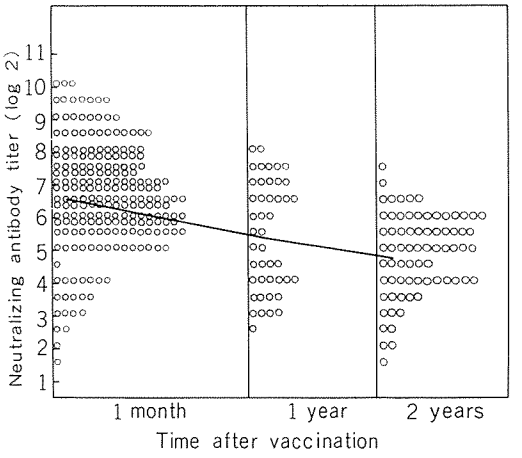

FIGURE 6. *Patterns of neutralizing antibody persistence in home-dwelling children vaccinated with CAM 70 measles virus vaccine.* ———, *geometric mean titer.*

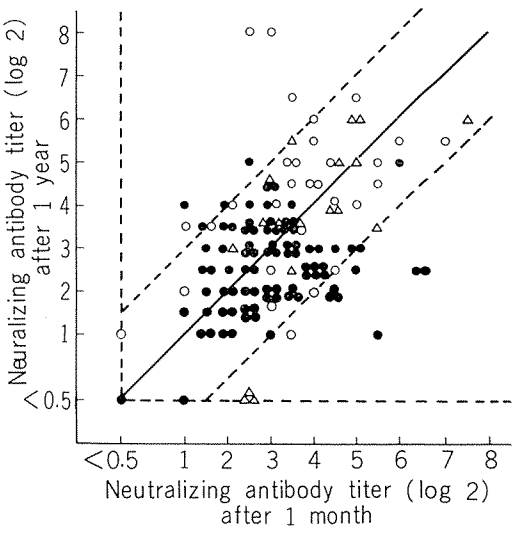

FIGURE 7. *Comparison of neutralizing antibody titers of home-dwelling children 1 month and 1 year after vaccination with CAM EX measles virus vaccine.* ●, *children living in Nagano;* ○, *in Hyogo;* △, *in Osaka.*

DISCUSSION

Immunity after vaccination with live, attenuated measles virus vaccine seems to be as good as that after natural infection (Katz, 1965; Brown et al., 1969; Lepow and Nanker-

vis, 1969; Krugman, 1971). That after vaccination with live, further attenuated measles virus vaccine can also be expected to be satisfactory (Krugman, 1971; Ueda et al., 1971; Weibel et al., 1973).

On the other hand, there are several reports of cases of measles among children previously vaccinated with live measles virus vaccines (Baratta et al., 1970; Lerman and Gold, 1971; Wyll and Witte, 1971; Cherry et al., 1972; Currier, Hardy and Conrad, 1972; Linnemann et al., 1972). These cases were not due to decrease in immunity after vaccination, but mostly to 1) vaccination at less than 12 months of age, 2) simultaneous injection of γ-globulin, or 3) improper handling or storage of the vaccine.

So, it seems probable that once a child is conferred with immunity from attenuated or further attenuated live measles virus vaccine, his immunity will last a long time. In this connection, the data presented here agree well with those of other workers, though different strains were used for preparation of vaccines.

We roughly estimated the duration of persistence of neutralizing antibody in hospitalized handicapped children who had been vaccinated with the CAM A4 strain and were protected from natural measles infection. Using a modification of Jensen's equation, the duration of neutralizing antibody was estimated as more than 10 years at a titer of $2^{1.0}$, that is in more than two-thirds of the children vaccinated, and as more than 20 years in half the children. In some children the duration of antibody was estimated as less than 10 years, but at least 6 years. Six years seems a short duration. However, as shown in the text (Table 4 and Fig. 7), lower titers did not decrease appreciably. Moreover, it was observed that booster antibody responses in secondary infections were very rapid (Krugman et al., 1965). It was also observed that a very small amount of antibody was enough to prevent apparent disease (Stokes et al., 1961; Ueda et al., 1966; Ueda, et al., 1969a). So, the duration of immunity may be longer than that estimated.

The case of a 5 year old boy who received the CAM EX strain and contracted measles one year later is very interesting in considering what will occur when the neutralizing antibody titer decreases to an undetectable level. We usually regard a child who did not show an antibody response after vaccination as a " non-taker " of live virus vaccine, who is still susceptible to measles. This case, however, did not develop typical symptoms of measles. Moreover, he seemed not to excrete measles virus. Burnet (1968) claimed that cellular immunity was of primary importance in immunity against measles virus infection. Toyoshima (1971) proposed the preventive roles of both humoral and cellular immune levels against spread of measles virus in the human body and virus excretion in secondary infection (Fig. 8). The slight cellular immunity which might be left by CAM EX strain and/or a secondarily provoked rapid antibody response seemed to prevent development of typical disease and

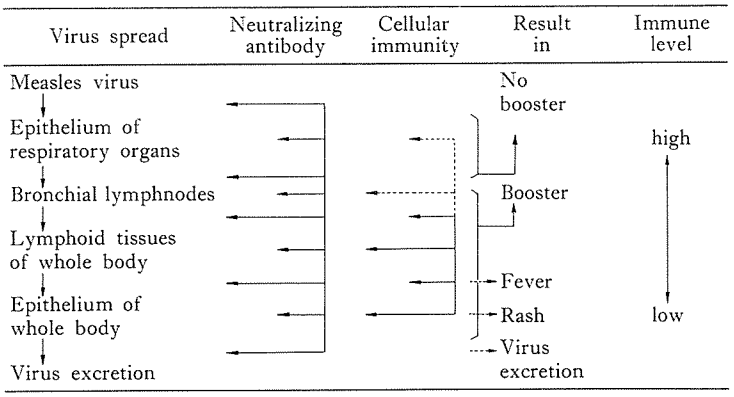

FIGURE 8. *Preventive roles of both humoral and cellular immune levels against spread of measles virus in the human body and virus excretion in secondary infection.* ←——, ←—, *blocking site and degree;* ←·····, ←····, *uncertain* (*by courtesy of Prof. K. Toyoshima*).

virus excretion in this case.

So, we may expect that a positive antibody response in children vaccinated with live measles virus vaccine means that they had sufficient positive cellular immunity to prevent the disease for a long time except in rare cases with immunodeficiencies. In this regard, immunity induced by live measles virus vaccine seems to be very different from that induced by killed measles virus vaccine.

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