Duration of immunity following immunization with live measles vaccine: 15 years of observation in Zhejiang Province, China

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The duration of immunity following measles vaccination of 2882 immunized children has been investigated in a closed region of China for 15 years. A total of 1002 of the children were treated as primary immunization subjects, and 1547 as reimmunization subjects. These two cohorts were not in contact with known wild measles virus over the whole observation period, and the results obtained probably reflected the antibody responses to measles vaccine alone. The remaining 333 vaccinees came into contact with wild measles virus, and this permitted evaluation of the protective effect of the measles vaccines tested: 4 children experienced very mild clinical measles, and 329 experienced subclinical infection, including 12 who had had undetectable haemagglutination–inhibition antibodies for 9–10 years. These results indicate that the immunity induced by successful primary immunization may persist for at least 15 years. Within this period, a second dose of vaccine only induces low antibody responses which decrease rapidly to their original levels. This provides strong evidence that the immunity produced by primary immunization is long-lasting. However, there were some indications that reimmunization might produce better effects if live attenuated measles virus were used with a longer interval between doses.

Measles used to be a very severe disease before the availability of measles vaccine. In China large outbreaks occurred annually in cities and every 2–3 years in rural areas. Almost every child contracted measles early in life. Morbidity from measles has decreased dramatically in China since the introduction of the vaccine in 1965; however, despite this encouraging trend, and consistent with other countries' experience, an increased incidence among schoolchildren and adolescents has occurred, many of whom have been immunized. It is therefore important to determine the duration of immunity after primary immunization and whether reimmunization is necessary to maintain immunity. Both these concerns have been the subject of the present study over the period 1973–88. Eight papers have previously been published covering earlier stages of the study (*1–8*). Here, we report the level of immunity 14–15 years after initial immunization, evaluate the effect of reimmunizing 1547 children, and analyse the results of an epidemiological study of 333 children who had been successfully immunized and followed up for 12 years before coming into close contact with measles patients.

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Materials and methods

Study area

The study was carried out in Zhuji County (population: 1 million), Zhejiang Province, a closed area in the south of China. To achieve a high level of immunity, about 300 000 children under the age of 15 years were immunized with one dose of live attenuated measles vaccine (two strains) over a 1-month period in 1973, regardless of their past immunization history. Both the immunization rate and the rate of seroconversion for these children were greater than 95%. Subsequently, all children aged 8 months were administered measles vaccine in an effort to protect the closed region from infection with natural measles virus. Because measles may be subclinical and unrecognized, and because there was always the possibility that the virus was being imported from infected areas of China by a variety of age groups, it was impossible to verify that measles virus was absent from the entire study area.

However, the steps that were taken to prevent the spread of measles seem to have been highly successful. An effective surveillance and control network was established, and it was laid down that every suspected case of measles should be notified within 2 days and that clinical investigations of these cases, including collection of blood samples, should be carried out within 24 hours of notification. All reported cases of measles in the county were investigated serologically. In this way, measles morbidity in Zhuji County was kept successfully at a very low level (average morbidity, 1973–84: 1.3 per 100 000).

Study subjects

A total of 3233 children who had neither been infected with measles nor immunized against it before the investigation began in 1973 formed the study subjects in the base area. After primary immunization, the sero-status of the children was determined using haemagglutination–inhibition (HI) tests. In the 15th year of the programme, 2882 children were still under observation and all of them had undergone serological testing. These children could be divided into the following groups.

- Group 1—1002 children who had not received a second dose of vaccine in 15 years—the primary immunization subjects.
- Group 2—1547 children who had received a second dose of vaccine—the reimmunization subjects.
- Group 3—consisting of 333 children who had been infected (4 with clinical and 329 with subclinical infection) during the whole period from 1973–88, mainly in 1985 when measles outbreaks occurred in the base area.

There were 122 cases of measles in the base area (118 nonimmunized persons, while 4 had been immunized). A total of 329 individuals (122 primary and 207 reimmunization subjects) had close contact with a case of measles.

Vaccine

For primary immunization, the following live attenuated (virus titre $\geq 2.5 \log/0.1$ ml) measles vaccines were used: two domestic (Hu_{191} and $Chang_{47}$) and two foreign strains (Schwarz (USA) and Leningrad-16 (L-16) (USSR)). Limited use was made also of the Hang-M_{13} strain, which had a better immunogenicity but high fever rate (16.1%). For reimmunization, two other vaccines were used: formalin-killed Hu_{191} measles vaccine, and primary attenuated measles vaccine—a measles virus adapted through four passages in chick embryo tissue culture. All the vaccines were prepared in chick embryo tissue culture except the L-16, which was cultured in guinea-pig kidney cells.

Routes of administration

For primary immunization, the vaccine was administered subcutaneously or by aerosol, while for reimmunization it was administered subcutaneously, intradermally, or by aerosol.

Serological tests

HI tests were used to test for antibody in all samples of serum (about 3000 each year for 15 years). The sera were first inactivated at 56 °C for 30 minutes and then allowed to absorb unspecific agglutinins from monkey red blood cells. Serum diluted twofold from 1 : 2 was regarded as negative. Some samples were screened using neutralization (NT) and haemolysis-inhibition (HLI) tests (*2, 16*).

Observation period

The 15-year observation period can be divided into the two parts shown below.

- 1973–83. During this time, the main activity was the continued and systematic observation of serological dynamics.
- 1984–88. Over this 5-year period, the study of serological dynamics was continued and an epidemiological study of the immunity of children was carried out. An outbreak of 122 cases of measles occurred in the base area in 1985. A total of 333 children who had close contact with the cases were also infected.

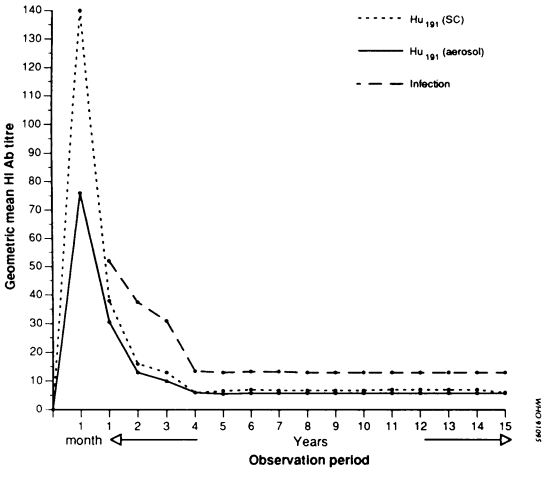
Results

Duration of immunity after primary immunization

Children in China are routinely injected subcutaneously with 0.2 ml of measles vaccine. However, some children receive the vaccine as an aerosol, dispensed using a JM-2 aerosol gun. Blood samples were taken from the study children every March for the 15 years of the investigation. The HI antibody titre declined markedly in the first year, continued to decrease gradually from the second to the fourth year, and thereafter remained steady at a low level (Fig. 1).

Undetected antibody levels were recorded in slowly increasing numbers, even among children who had been infected naturally. In the closed area, four patients lost detectable HI antibody within 15 years. The pattern of the HI antibody decay was similar among different groups (Table 1).

Fig. 1. **Plots showing the duration of immunity up to 15 years after immunization with Hu_{191} measles vaccine (SC = subcutaneous; HI Ab = haemagglutination-inhibition antibody).**



Duration of immunity provided by the domestic versus the imported vaccines

A total of 449 children aged 8–16 months were given a single 0.5 ml dose of one of the domestic or imported vaccines. Since the routine dose of measles vaccine used in China is 0.2 ml, we compared the effects of the two doses for the $Chang_{47}$ and L-16 vaccines.

In order to investigate the effect of immunization age on the duration of immunity, we compared the rate of conversion to seronegative over a 14-year period among children whose age at primary immunization was 8–12 months or 13–16 months. At the end of the 14-year period, the following were the rates for conversion to seronegative: 12.8% and 8.1% (Hu_{191}), $U = 0.87$; 11.1% and 10.2% ($Chang_{47}$), $U = 0.14$; 15.4% and 9.7% (Schwarz), $U = 0.85$; 12.7% and 20% (L-16), $U = 1.07$. No significant differences between the vaccines were found ($P > 0.05$).

It can therefore be concluded that the duration of immunity produced by the Hu_{191} and $Chang_{47}$ vaccines is similar to that of the Schwarz vaccine, and is better than that induced by the L-16 vaccine under these circumstances (Table 2).

The results shown in Table 3 indicate that the duration of immunity induced in children who received a 0.5 ml dose of $Chang_{47}$ or L-16 strains was better than that induced by a 0.2 ml dose, although the differences were not statistically significant.

Duration of immunity following reimmunization at various intervals

A total of 1547 subjects were involved in this aspect of the study, all of whom had undergone successful primary immunization as confirmed serologically in 1973–74. Three groups were immunized at different intervals between primary and secondary injection as outlined below.

- Group A: 420 children whose HI antibody titre decreased 2–3 years after primary immunization by $\leq 1:16$. Group B (519 children) and group C (608 children) were reimmunized after 5–7 years and 10–11 years, respectively.

The results in Table 4 show that the increase in HI antibody titre after reimmunization was low, regardless of the interval between doses and the antibody level before the booster dose was given. However, for children with the same HI antibody titre before reimmunization the proportion who became seronegative was markedly dependent on the interval between doses. For example, the HI antibody titres of children in group A were more likely to become seronegative, especially those with HI antibody titres $< 1:2$. The increased antibody

Table 1: **Antibody levels and negative conversion rates among the children following primary immunization with measles vaccine (0.2 ml) or natural infection with measles virus over the 15 year study period**

Measles vaccine	Route	No. of children	HI Ab GMT[a]		Negative conversion rate (%) after:						
			1 month	1 year	3 years	5 years	7 years	9 years	11 years	13 years	15 years
Hu_{191}	SC[b]	109	140	38	1.8	6.4	7.3	9.2	12.0	18.3	18.3
	Aerosol	58	76	31	0	1.7	3.4	5.2	5.2	15.5	15.5
$Chang_{47}$	Aerosol	77	67	34	3.9	7.8	10.4	10.4	11.7	16.9	18.2
Hang-M_{13}	SC	154	246	74	1.3	4.5	5.8	6.5	7.8	10.4	10.4
Natural infection		27	NT[c]	54	0	3.7	3.7	7.4	11.1	14.8	14.8

[a] Haemagglutination-inhibition antibody geometric mean titre.
[b] SC = subcutaneous injection.
[c] NT = not tested.

Table 2: **Comparison of the duration of immunity produced by primary immunization with 0.5 ml of measles vaccine over a 14-year follow-up period**

Vaccine	Age at vaccination (months)	No. of children	HI Ab GMT[a] (1 month)	Negative conversion rate (%) after: 2 years	4 years	6 years	8 years	10 years	12 years	14 years
Hu_{191}	8–12	47	71	0	2.1	6.4	6.4	10.6	12.8	12.8
	13–16	86	78	0	1.2	2.3	2.3	5.8	8.1	8.1
$Chang_{47}$	8–12	36	114	0	0	0	2.8	2.8	8.3	11.1
	13–16	59	85	0	0	1.7	1.7	1.7	10.2	10.2
Schwarz	8–12	39	113	0	5.1	5.1	5.1	5.1	12.8	15.4
	13–16	62	88	0	3.2	3.2	3.2	3.2	9.7	9.7
L-16	8–12	55	76	1.8	5.5	5.5	9.1	9.1	12.7	12.7
	13–16	65	68	1.5	3.1	4.6	4.6	9.2	20.0	20.0

[a] Haemagglutination–inhibition antibody geometric mean titre.

Table 3: **Comparison of the duration of immunity produced by primary immunization with different doses of the $Chang_{47}$ or L-16 measles vaccine over a 14-year follow-up period**

Vaccine	Dose (ml)[a]	No. of children	HI Ab GMT[b] (1 month)	Negative conversion rate (%) after: 2 years	4 years	6 years	8 years	10 years	12 years	14 years
$Chang_{47}$	0.5	95	95	0	0	1.1	2.1	2.1	9.5	10.5
	0.2	56	53	0	5.4	8.9	10.7	12.5	14.3	14.3
L-16	0.5	120	71	1.7	4.2	5.0	6.7	9.2	16.7	16.7
	0.2	72	70	0	11.1	12.5	12.5	16.7	20.8	23.6

[a] The following doses were used: $Chang_{47}$: 3.5 log $TCID_{50}$ per 0.1 ml; L-16: 3.25 log $TCID_{50}$ per 0.1 ml.
[b] Haemagglutination-inhibition antibody geometric mean titre.

levels dropped to approximately their original levels within 1–2 years. Although the antibody titres 3 weeks after reimmunization of all subjects in the three groups were very low, the HI levels for groups B and C were less variable than those for group A.

Children in group A exhibited poor immune responses both after primary immunization and reimmunization. Also, the increase in antibody titre caused by reimmunization does not appear to produce lasting immunity. The effects of reimmunization therefore appear to be simply an anamnestic reaction to a booster dose.

Duration of immunity according to vaccines and administration route

A total of 519 children in group B were reimmunized as follows: 344 children were injected with the live attenuated vaccine by subcutaneous, intracutaneous, or aerosol routes; 127 received the killed vaccine (subcutaneously); and 48 primary attenuated vaccine (subcutaneously).

The results in Table 5 show that 3 weeks after reimmunization the geometric mean HI antibody titres were similar and low. Also, there were no significant differences between the titres 8 years after reimmunization or between the rates of those becoming seronegative.

Duration of immunity: primary immunization versus reimmunization

One way to determine whether reimmunization can produce high levels of immunity is to compare the duration of immunity among children who have a similar history of immunization. A total of 755 children had HI antibody titres $\leq 1:16$ at 2–3 years after primary immunization. Of these, 420 children received a second dose of vaccine, while the remaining 335 received only the first dose.

The rates of conversion to seronegative for these two groups of children 4, 8 and 12 years after reimmunization (Table 6) indicate that the duration of immunity for children who received a second dose was no longer than for those receiving one dose.

Duration of immunity following successful or unsuccessful reimmunization

The antibody levels produced by successful reimmunization were compared with those produced by unsuccessful immunization.

Table 4: **Comparison of the duration of immunity following reimmunization at different intervals**

Group	Reimmunization interval (years)	No. of children	HI Ab GMT[a] Before revaccination	HI Ab GMT[a] 3 weeks after reimmunization	Negative conversion rate (%) after: 1 year	4 years	8 years
A	2–3	25		13	40.0	48.0	76.0
B	5–7	5	< 2	23	0	20.0	20.0
C	10–11	5		28	0	0	NT[b]
A	2–3	60		11	8.3	31.7	46.7
B	5–7	27	2	21	0	3.7	14.8
C	10–11	74		18	1.4	8.1	NT
A	2–3	189		14	1.6	3.2	16.9
B	5–7	98	4	21	0	0	6.1
C	10–11	230		19	0	1.7	NT
A	2–3	101		18	0	1.0	5.9
B	5–7	246	8	25	0	0	0
C	10–11	216		21	0	0	NT
A	2–3	45		23	0	0	2.2
B	5–7	143	16	34	0	0	0
C	10–11	83		28	0	0	NT

[a] Haemagglutination–inhibition antibody geometric mean titre.
[b] NT = not tested.

Table 5: **Results obtained following revaccination with different measles vaccines and routes of administration**

Vaccine	Route[a]	No. of children	HI Ab GMT[a] 3 weeks after reimmunization	HI Ab GMT after:[b] 2 years	4 years	6 years	8 years
Live (Hu_{191})	SC	211	24	9.2	7.5 (0.9)[c]	7.6 (3.8)	7.4 (3.8)
	IC	65	23	9.3	7.9	7.3 (1.5)	7.7 (1.5)
	Aerosol	68	28	8.9	7.9	7.9 (1.5)	7.2 (1.5)
Killed	SC	127	32	11.0	8.1	8.2 (0.8)	7.2 (0.8)
Primary attenuated	SC	48	23	10.0	8.0	7.4	7.6

[a] SC = subcutaneous; IC = intracutaneous.
[b] HI Ab GMT = haemagglutination–inhibition antibody geometric mean titre.
[c] Figures in parentheses are the % who became seronegative.

Table 7 shows that the rates of conversion to seronegative for the successful vaccinees 4, 8 and 12 years after reimmunization were unexpectedly slightly higher than those for whom reimmunization was unsuccessful. This perhaps arose because before reimmunization, successful vaccinees had lower antibody titres than those who were unsuccessful.

Duration of immunity following natural infection and reimmunization

Wild measles virus can stimulate an increase in antibody titres both after infection or immunization. It might be asked whether there is any difference between the booster effect produced by the wild virus and that stimulated by measles vaccine, and whether patients who are clinically infected experience a greater immune response than that induced in patients with subclinical infections. During the 1985 epidemic, blood samples were collected from 53 children 1 month after infection with wild measles virus.

The results obtained (Table 8) indicate that the four cases of clinical measles had high antibody responses 1 month after infection and greater duration of immunity for 1–3 years afterwards, even though 4–8 years before infection their HI antibody titres were all $< 1:2$. This contrasts with the situation following reimmunization. For subclinically infected children the antibody response and duration of immunity were intermediate between those caused by clinical infection and reimmunization (Fig. 2).

Because it is simple and specific and can be used to screen the antibody titres for large-scale field trials, the HI antibody test is widely used all over the

Table 6: **Comparison of the duration of immunity of children following primary and secondary immunization with measles vaccine at the same HI antibody titre**

HI Ab GMT[a] 2–3 years after primary immunization	Dose	No. of children	Negative conversion rate (%) after: 1 year	4 years	8 years	12 years
< 2	Primary	13	100.0	100.0	100.0	100.0
	Secondary	25	40.0	48.0	76.0	80.0
2	Primary	20	15.0	45.0	55.0	75.0
	Secondary	60	8.3	31.7	46.7	65.0
4	Primary	83	3.6	15.7	24.1	46.7
	Secondary	189	1.6	3.2	16.9	40.2
8	Primary	123	0	0	1.6	12.8
	Secondary	101	0	1.0	5.9	9.9
16	Primary	96	0	0	1.0	2.7
	Secondary	45	0	0	2.2	4.4

[a] Haemagglutination–inhibition antibody geometric mean titre.

Table 7: **Comparison of the duration of immunity following successful or unsuccessful reimmunization with measles vaccine**

Years after reimmunization	No. of children	No. of negative conversions	Successful immunization: *n*	Successful immunization: No. of negative conversions	Unsuccessful immunization: *n*	Unsuccessful immunization: No. of negative conversions
12	420	147	228	91 (39.9)[a]	192	56 (29.2)
8	519	11	340	8 (2.4)	179	3 (1.7)
4	608	10	358	7 (2.0)	250	3 (1.2)

[a] Figures in parentheses are percentages.

Table 8: **Comparison of the duration of immunity induced by natural infection with measles virus or by reimmunization among the study children**

		No. of children	HI Ab GMT[a]: S_1[b]	S_2[c]	1 year	2 years	3 years
Infection	Clinical	4	<2 (100.0)[d]	128	38	27	23
	Subclinical	49	2.7 (24.5)	51	26	18	16
Reimmunization		608	5.7 (0.8)	21	7.7 (0.2)	7.6 (1.2)	7.7 (1.2)

[a] Haemagglutination–inhibition antibody geometric mean titre.
[b] Sera taken before infection or reimmunization.
[c] Sera taken 1 month after infection or reimmunization.
[d] Figures in parentheses are the negative conversion rate (%).

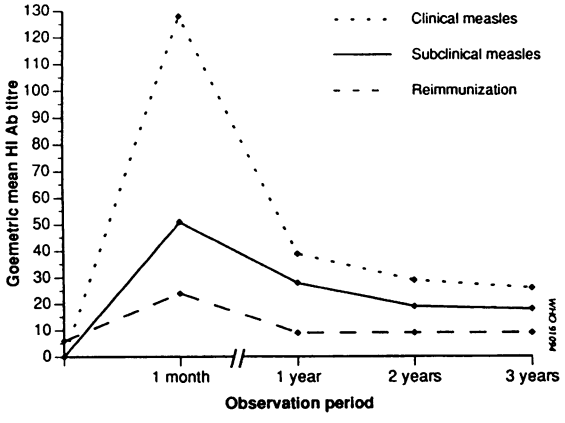
world to detect immunity to measles. The test is, however, not very sensitive; it therefore does not imply that an individual whose HI antibody titre is undetectable (< 1 : 2) is not immune. In the present study 333 children had been exposed to wild measles virus and became infected. Of these, 78 with an HI antibody titre < 1 : 2 had close contact with measles cases, but only four subjects exhibited clinical infection; the remaining 74 children experienced subclinical infections, and no clinical symptoms were observed after careful medical examination.

The results in Table 9 show that 4–8 years after immunization the HI antibody titres for the four clinical cases were < 1 : 2, while 12 children had lost their HI antibody titre after 9–10 years but still had immunity to wild measles virus.

Discussion

In China the same live attenuated measles vaccine and the recommended age for immunization have been used since 1965, and the Hu_{191} and $Chang_{47}$ vaccines have been widely used from the very beginning. From 1965 to 1984 a major concern was vaccine failure caused by use of the heat-labile liquid products. The occurrence of measles cases among

Fig. 2. **Comparison of geometric mean haemagglutination-inhibition antibody (HI Ab) titre between infection and reimmunization.**



previously immunized children arose because either the protection produced by the vaccine was of short duration or seroconversion did not occur after immunization, often because impotent vaccine was used. Clinical disease did occur in some children who had previously received measles vaccine, but antibodies were detected in few of them after primary immunization or before the development of clinical disease. It is therefore difficult to determine whether waning immunity or failure to seroconvert after immunization was the real cause of measles among children who had been immunized. Reimmunization may overcome the problems of failure to seroconvert. Since lyophilized vaccine completely replaced liquid measles vaccines in 1985 in China, and the cold chain has been progressively improved, administration of impotent vaccine has become less of a problem.

The duration of immunity induced by measles vaccine was investigated in the study not only by using the results of serological tests and the persistence of immunity following primary and second immunizations in a closed geographical region, but also by epidemiological study of 333 vaccinees who had been infected with wild measles virus.

While it is possible that no wild measles virus entered the study population during the 15 years of the study period, it must be accepted realistically that at least some of the study population contracted the wild virus infection. Circumstantial evidence suggests this number was not high, and presumably does not alter the validity of the overall conclusions significantly. In a normal field situation, it would be reasonable to expect that any circulating wild virus was producing a natural boosting effect on primary immunization. In such circumstances, the duration of immunity could be expected to be even longer than the 15 years studied in this trial. Our observations warrant the conclusions outlined below.

- About 85% of the vaccinees still had detectable HI antibody titres 15 years after primary immunization. However, even when the HI titres decreased to undetectable levels this did not imply that they had lost immunity to wild measles virus. A total of 82% of the children who had no measurable HI antibody 1–5 years later, still had detectable levels of neutralizing antibody (*9*). Epidemiological investigations corroborated this evidence, since of 78 children with undetectable HI antibody titres 1–10 years later who had close contact with measles patients only four (HI antibody titre $< 1 : 2$ for 4–8 years) experienced mild clinical measles. The remaining 74 children suffered only subclinical infections, even the 12 children who had had undetectable HI antibody levels for 9–10 years.
- There have been several reports about the duration of immunity provided by measles vaccine (*10–13*). One of these studies consisted only of an assessment of an epidemic without any systematic serological confirmation of the findings (*11*); another was restricted to an investigation of wild measles virus (*12*); and a third was carried out in an open community (*13*). In contrast, in our study all 1002 primary vaccinees lived in the closed region and had annual serological tests.
- In the context of our study, reimmunization was

Table 9: **Correlation between haemagglutination-inhibition antibody titres and measles infection among children exposed to wild measles virus in the study**

Type of infection	No. of children	No. with HI Ab[a] titres $< 1 : 2$ for:				
		1–2 years	3–4 years	5–6 years	7–8 years	9–10 years
Clinical	4	–	1	2	1	–
Subclinical	74	30	15	10	7	12

[a] Haemagglutination-inhibition antibody.

taken to be the administration of a second dose to subjects who had had a serologically confirmed response to a primary measles immunization. This definition differs from that used by Linnemann et al. (*14*) and Black et al. (*15*), *inter alia*, who defined reimmunization as a second dose given to children who, for various reasons, were immunization failures.

- In the present study, reimmunization using different vaccines, routes, and intervals (see Table 5) unexpectedly produced very similar antibody response profiles, i.e., 3 weeks after the booster dose the HI antibody titres were much lower and decreased rapidly compared with the HI antibody titres after primary inoculation. The HLI antibody did not increase as much as the HI antibody in those who were successfully reimmunized (*16*). The second dose of measles vaccine therefore does not appear to produce lasting augmentation of immunity, even with a 10–11-year interval between the primary and second doses, and with subjects who exhibited undetectable HI antibody titres over many years. Other workers have reported similar results (*17–19*). For example, Krugmann found that reimmunization of seven children who had been observed for 14 years after primary immunization boosted their HI antibody titre from $< 1 : 2$ to $1 : 16$ at 2 weeks, while 8 weeks after reimmunization the titres had dropped to $1 : 4$ (*17*). In a 6-month follow-up study of 19 children after reimmunization, Bass et al. reported that the neutralizing antibody titres of nine of the children decreased to pre-reimmunization levels (*18*). Finally, Desada-Tous et al. reported that 14 children who had no detectable SIgM after immunization (regarded as reimmunization) exhibited an HI antibody geometric mean titre of $1 : 28$, three weeks after immunization, and that 10 months later in 11 samples of serum the titre had decreased to $1 : 9$ (*19*).
- The results of the present study suggest that measles reimmunization produces an anamnestic reaction. This provides strong evidence that effective immunity is provided by one dose of measles vaccine and demonstrates that a booster dose is not necessary for persons who had successful primary immunization against measles up to 15 years previously. The presence of a low HI antibody titre does not necessarily indicate the need for reimmunization, since children with low antibody titres were not susceptible to clinical infection with measles.

The points outlined below should nevertheless be considered carefully.

- The proportion of those who became seronegative increased with the interval after primary immunization.
- Clinical cases of measles occurred among some successful vaccinees, although such cases were rare and of mild severity.
- Neutralizing antibody was not found in sera from 10 primary vaccinees in whom HI antibody was undetectable for more than 10 years.
- The immunity resulting from natural infection with measles virus differed from that produced by immunization (as indicated by NT and HLI antibody responses) although the HI antibody patterns were similar in both cases.

The above points indicate that primary immunization can produce long-term immunity against measles, but not necessarily life-long protection. The results shown in Table 8 indicate that there were differences in the duration of immunity among children depending on whether they were infected clinically, subclinically, or were reimmunized. After clinical infection, the antibody levels were higher and more persistent than after reimmunization. Four clinically infected patients not only had high HI antibody responses but also had very high HLI antibody titres (512–4096) 1 month after infection. This pattern of antibody reaction was not a simple anamnestic reaction but a profound immuno-transformation, and is probably an important indication of measles immunity. It might be expected to produce longer-lasting effects if better antigenic strains of measles vaccine are used.

The overall results of the study indicate that the immunogenicity of the two Chinese vaccines (Hu_{191} and $Chang_{47}$) was comparable with that of the Schwarz strain. Altogether, 10.5%, 9.8% and 11.9%, respectively, of patients became seronegative following administration of the Hu_{191}, $Chang_{47}$, and Schwarz vaccines 14 years after primary immunization, with the HI antibody titres beginning to convert to negative between the 3rd and 6th years after immunization. For L-16 vaccine the rate at which patients became seronegative increased to 16.7% after 14 years. The HI antibody titre of children who received primary immunization with the L-16 vaccine became seronegative from the second year after immunization.

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Résumé

Durée de l'immunité après vaccination antirougeoleuse par un vaccin vivant: 15 ans d'observation dans la province de Zhejiang, Chine

La durée de l'immunité après vaccination antirougeoleuse de 2882 enfants a été étudiée pendant 15 ans dans une région fermée de la Chine. Pour 1002 de ces enfants, il s'agissait d'une primovaccination, et pour 1547 autres d'une revaccination. Ces deux cohortes n'ont eu aucun contact avec un virus rougeoleux vivant connu pendant toute la durée de la période d'observation, et les résultats obtenus reflètent probablement les réponses en anticorps au seul vaccin antirougeoleux. Les 333 sujets restants sont entrés en contact avec le virus rougeoleux sauvage, ce qui a permis d'évaluer l'effet protecteur du vaccin utilisé: 4 enfants ont eu une rougeole très légère, et 329 une infection infraclinique, dont 12 cas qui pendant 9 à 10 ans n'ont eu aucun anticorps décelable par inhibition de l'hémaglutination. Ces résultats indiquent que l'immunité induite par une primovaccination réussie peut durer au moins 15 ans. Pendant cette période, l'administration d'une deuxième dose de vaccin n'induit que de faibles réponses en anticorps, qui retombent rapidement à leur taux d'origine. Cela confirme la durabilité de l'immunité due à la primovaccination. Toutefois, quelques observations semblent indiquer que la revaccination pourrait avoir un effet plus sensible si on utilisait un vaccin antirougeoleux vivant atténué, en espaçant davantage les doses.

References

1. **Zhuji Collaborating Unit for the Observation of the Duration of Immunity Provided by Measles Live Vaccine.** [Studies on the duration of immunity provided by attenuated measles live vaccine I: results of antibody responses 5 years after primary vaccination]. *National medical journal of China,* **60**: 1–4 (1980) (in Chinese).
2. **Zhuji Collaborative Unit for the Observation of the Duration of Immunity Provided by Measles Live Vaccine.** [Observation on the clinical reaction and immunities produced by four strains of measles live vaccine]. *National medical journal of China,* **60**: 4–9 (1980) (in Chinese).
3. **Zhuji Collaborative Unit for the Observation of the Duration of Immunity Provided by Measles Live Vaccine.** [Observations on the results of revaccination of measles live vaccine]. *National medical journal of China,* **60**: 9–13 (1980) (in Chinese).
4. **Zhuji Collaborative Unit for the Observation of the Duration of Immunity Provided by Measles Live Vaccine.** [Results of 9 years since primary inoculation]. *National medical journal of China,* **63**: 423–425 (1983) (in Chinese).
5. **Zhuji Collaborative Unit for the Observation of the Duration of Immunity Provided by Measles Live Vaccine.** [The persistence of immunity after primary immunization with four strains of measles live vaccine]. *National medical journal of China,* **63**: 490–492 (1983) (in Chinese).
6. **Zhuji Collaborative Unit for the Observation of the Duration of Immunity Provided by Measles Live Vaccine.** [Observations on the results of revaccination with different vaccines and by different routes]. *National medical journal of China,* **63**: 541–545 (1983) (in Chinese).
7. **Zhuji Collaborative Unit for the Observation of the Duration of Immunity Provided by Measles Live Vaccine.** [Epidemiological examination of the duration of immunity of measles vaccine]. *National medical journal of China,* **67**: 19–22 (1987) (in Chinese).
8. **Zhuji Collaborative Unit for the Observation of the Duration of Immunity Provided by Measles Live Vaccine.** [An investigation on measles epidemic condition in Zhuji County: the group investigation of measles vaccine immunity duration]. *Chinese journal of epidemiology,* **8**: 92–95 (1987) (in Chinese).
9. **Fang Hanhua.** Comparison between HI and NT antibody after vaccination. *Journal of biologicals,* **3**(1): 37–40 (1990).
10. **Krugman, S. et al.** Further attenuated measles vaccine: characteristics and use. *Reviews of infectious diseases,* **5**: 477–481 (1983).
11. **Miller, C.** Live measles vaccine: a 21 year follow-up. *British medical journal,* **295**: 22–24 (1987).
12. **Pedersen, I.R. et al.** Long-term antibody response after measles vaccination in an isolated Arctic society in Greenland. *Vaccine,* **4**: 173–178 (1986).
13. **Isomura, S. et al.** A long-term follow-up study on the efficacy of further attenuated live measles vaccine: Biken CAM vaccine. *Biken journal,* **29**: 19–26 (1986).
14. **Linnemann, C.C. et al.** Measles immunity after revaccination: results in children vaccinated before 10 months of age. *Pediatrics,* **69**: 332–335 (1982).
15. **Black, F.L. et al.** Inadequate immunity to measles in children vaccinated at an early age: effect of revaccination. *Bulletin of the World Health Organization,* **62**: 315–319 (1984).
16. **Dai Bin, et al.** [Study on the hemolysis-inhibition antibody produced after immunization of live measles vaccine]. *Chinese journal of microbiology and immunology,* **2**: 80–85 (1982) (in Chinese).
17. **Krugmann, S.** Present status of measles and rubella immunization in the United States: a medical progress report. *Journal of pediatrics,* **90**: 1–12 (1987).
18. **Bass, J.W. et al.** Booster vaccination with further live attenuated measles vaccine. *Journal of the American Medical Association,* **235**: 31–34 (1976).
19. **Desada-Tous, J. et al.** Measles revaccination persistence and degree of antibody titre by type of immune response. *American journal of diseases of children,* **132**: 287–290 (1978).