Revaccination against measles—a pilot study

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SUMMARY. (1) During the first ten years after primary vaccination with live measles virus vaccine, a slow decline in the level of HAI antibody titres has been demonstrated. The decline after more attenuated vaccines was at the same gradient, but at lower titres.

(2) During the same period after primary vaccination by inactivated (' killed ') followed by live — K + L — measles vaccine, a much steeper decline in the level of HAI antibody titres was demonstrated.

(3) The GMT may not reach the lowest standard titres for over 40 years after the least attenuated vaccine, and 20–25 years after more attenuated vaccines. After K + L vaccine the GMT may be negative after 15 years or less, but this will depend on the frequency of natural boosting.

(4) On revaccination after five to ten years, one out of 20 children (five per cent) who had received live vaccine alone for primary vaccination showed a fourfold or greater rise in titre of HAI antibody, whereas 17 out of 41 children (41%) who had received K + L vaccine showed a significant rise in titre.

(5) With either regime, the age at primary vaccination did not appear to influence the rate of boosting after revaccination except perhaps in children under two years.

(6) Among those who originally received K + L vaccine, the lower the HAI antibody titre before revaccination and the longer the time since primary vaccination, the more likely was a significant rise in titre to occur after revaccination. All should be revaccinated within 10–15 years of primary immunisation.

(7) Children whose primary vaccination was by live ' further attenuated ' vaccine before the age of two years may need to be revaccinated before they leave school, but this requires further study.

(8) A case can be made for using a less attenuated strain of measles virus for revaccination than for primary vaccination.

(9) The eventual need for and timing of revaccination against measles should be examined in a larger group of children.

Introduction

Clinical immunity induced by an attack of natural measles has been found (Panum, 1939) to last for at least 65 years without reinforcement by contact with the disease. A single dose of live measles virus vaccine, when given alone, has been shown (Krugman, 1971) to elicit the production of antibody which, over the first ten years after vaccination, has persisted at levels about as high as that which follows measles itself.

The more the vaccine has been attenuated, the fewer are any adverse or febrile reactions, but the faster the rate at which antibody levels gradually decline (Krugman,

1971). Antibody levels fall still more quickly in those who have received inactivated (' killed ' or K) vaccine before live (L) vaccine and also in those vaccinated before their first birthday. In children vaccinated against measles at the ages of 8 to 11 months, the initial postvaccination titres are lower than in those vaccinated at one year (Linnemann *et al.*, 1972; Schuelderberg *et al.*, 1973). This effect is assumed to be due wholly to persistence of maternal antibody, but there is some evidence (Watson, 1967) to suggest that, throughout the first two and a half years of life, the levels reached by initial postvaccination measles antibody titres rise exponentially with increasing age. These higher titres of antibody reached in children vaccinated over the age of two years are likely to be detectable for longer than the lower titres reached by those vaccinated about their first birthday.

A waning antibody response, originally induced by natural measles or by measles vaccine, can be reinforced with or without symptoms either by subsequent contact with the disease or by revaccination (Krugman, 1971; Linnemann *et al.*, 1972; Watson, 1967; Stokes *et al.*, 1961; Watson and Parry, 1967; Ueda *et al.*, 1969). Serologically confirmed second attacks of natural measles, though rare, have been recorded in those who have lost their immunity (Watson, 1965). Clinical attacks of measles, even with complications, have also been reported in previously vaccinated children, especially if primary vaccination against the disease had been carried out before the first birthday (Krugman, 1971; Linnemann *et al.*, 1972; Watson and Parry, 1967; Krugman *et al.*, 1965) if immune globulin had been given concurrently (Linnemann *et al.*, 1972) or if 'killed' vaccine had been given before the live vaccine (Watson and Parry, 1967; Leedham-Green, 1965). The proportion of vaccinated children who subsequently developed symptomatic, sometimes infectious, attacks of measles increased among those with the lowest antibody titres (Linnemann *et al.*, 1972).

In Britain very few children have received immune globulin at the time of vaccination. A larger but unknown number of children have received a prior dose of ' killed ' vaccine (K + L procedure). Very few children have been vaccinated against measles before their first birthday, but a large proportion were aged between 12 and 18 months when vaccinated.

Two questions remain: will ' second ' attacks of measles be more common among adequately vaccinated children than among those immunised by the natural disease? What constitutes adequate vaccination? We should make a distinction here between symptomatic and serological evidence of re-invasion whether by wild measles or vaccine virus. As the proportion of children protected against measles by vaccination increases, opportunities for natural re-infection will become less frequent, so that an increasing proportion of those vaccinated in early childhood will eventually have very low or undetectable antibody titres. Under such circumstances will there be a place for routine revaccination?

Opinion is divided whether one dose of measles vaccine can provide the same lifelong immunity to a second attack of the disease as does a natural infection. Krugman (1971) holds that the height of antibody titre is of no practical importance and that, for the great majority, one dose of potent vaccine will provide durable immunity to clinical measles. On the other hand Linnemann (1972) records that, although children vaccinated at about one year of age show a high rate of symptomless boosting, a few have developed infectious measles. He foresees that, once the epidemic spread of measles have been significantly interrupted, revaccination may be needed 10–15 years after primary vaccination.

When epidemic measles does become less frequent, a postponement of primary vaccination until the age of 2–2½ years would achieve maximal post vaccination antibody titres (Watson, 1967) with minimal rates for CNS complications.

Aims

The aims of this investigation were:

(1) To study the persistence of haemagglutination inhibiting (HAI) antibody elicited by various types and doses of measles vaccines,

(2) To seek further evidence of natural boosting by ' wild ' measles,

(3) To study antibody responses after revaccination with a live ' further attenuated ' measles vaccine,

(4) To attempt to correlate antibody responses after revaccination with the type and dose of the primary immunising vaccine, the interval since primary vaccination, and the antibody titre immediately before revaccination.

Method

There were 72 children from volunteer families in a rural group practice, who received various doses and types of measles vaccine between 1962 and 1967, who took part in this study. Nearly all the children were over the age of three years at the time of primary vaccination. The vaccines and schedules employed are shown in table 1.

TABLE 1
TYPE OF INITIAL VACCINE AGAINST MEASLES AND NUMBER OF CHILDREN IN EACH GROUP

Live vaccine only				*Inactivated (killed=K) followed by live virus*				
MV 16	MV 20	MV 27	MV 31	K. 1·0 ml x3 then MV 16	K. 1·0 ml x1 then MV 16 or 16a	K. 1·0 ml x1 then MV 31	K. 0·5 ml x1 then MV 16a	K. 0·5 ml x1 then MV 31
11	6	5	5	8	20	4	8	5
27 children				45 children				

Passage histories of the various Wellcome measles vaccines are as follows. All originated from Enders B strain:

MV 16=Enders B passed 36 times in chick embryo tissue culture (cetc)

MV 20=Enders B passed 77 times in cetc.

MV 27=Enders B passed 83 times in cetc.

MV 31 (the Beckenham 31 strain or ' Wellcovax ')=Enders B passed 85 times in cetc.

Inactivated (' killed ') vaccine was supplied by Eli Lilly. This was the Enders virus cultured in chick embryo tissue, inactivated by formaldehyde and adsorbed on to aluminium phosphate.

The live ' further attenuated ' vaccine used for revaccination was Glaxo's Schwartz strain=Enders B passed 77 times in cetc.

Serology

From most subjects blood samples had been collected before and after primary vaccination and on at least one occasion during the following five to ten years. During 1971–73 further samples were collected and 61 subjects were revaccinated with live ' further attenuated ' Schwartz strain vaccine. Samples of blood were collected on one or more occasions between four weeks and two years after revaccination. Measles HAI antibody titrations were carried out at the Wellcome Research Laboratories, using the method described in *Diagnostic Procedures for Viral and Rickettsial Infections*, fourth

edition, 1969, American Public Health Association. Neutralising antibody titrations had been carried out on most of the blood samples taken before and after primary vaccination, but sera from many of these children had been retained at —20°C. These sera were re-titrated for HAI antibodies in parallel with recent samples. Sera collected before and after revaccination were also tested in parallel.

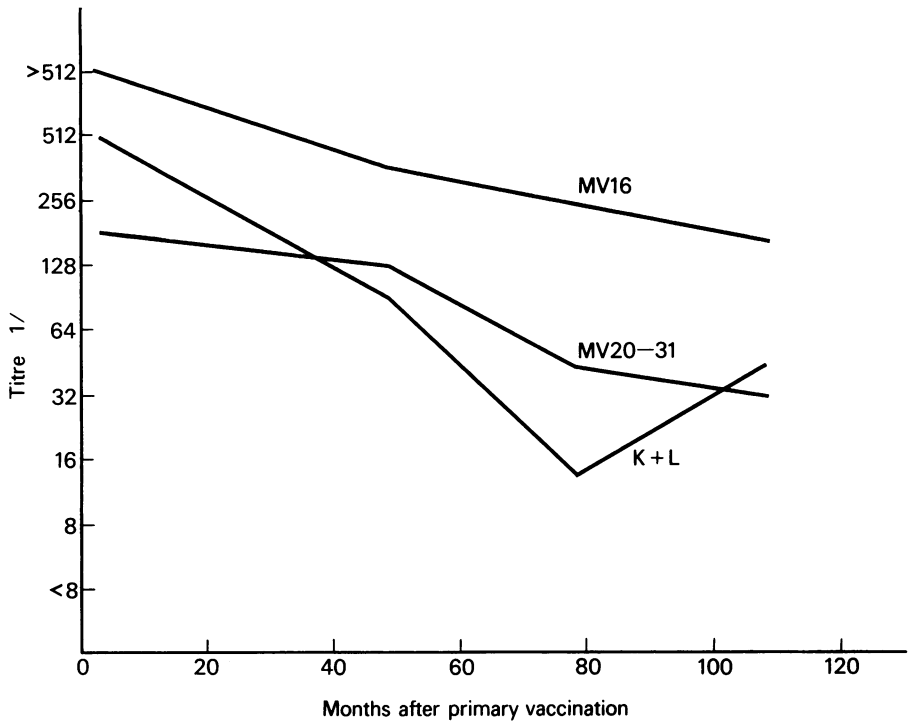

Figure 1

Persistence of measles HAI antibody: geometric mean titres: after live measles vaccines MV16 and MV20–31 and 'killed' + live measles vaccine.

TABLE 2

HAI ANTIBODY DECAY AFTER VACCINATION WITH MV 16
(NUMBER OF CHILDREN STUDIED—11)

HAI antibody titres	*Interval since primary vaccination*			
	one month	3–5 years	6–7 years	8–10 years
>1/512	6	3	—	1
1/512	2	1	—	—
1/256—320	—	3	—	1
1/128—160	—	1	—	6
1/64 — 80	—	1	1	2
1/32 — 40	—	—	—	1
1/16 — 20	—	—	1	—
1/8 — 10	—	—	—	—
<1/8	—	—	—	—
Not tested	3	2	9	0

Results

(1) *Persistence of HAI antibody*

The rate of decay of HAI antibodies was faster in those who had received 'killed' followed by live vaccine than in those who were given live vaccines alone (figure 1). In the latter groups those who were given MV 16 showed higher titres throughout the first eight to ten years (table 2) than those who received MV/20, 21 or 31 (table 3). In the killed plus live group, titres were even lower and four out of 45 were less than one in eight within less than ten years (table 4). No differences were found between children treated with different dosages of 'killed' vaccine; their results are therefore reported in one group.

TABLE 3

HAI ANTIBODY DECAY AFTER VACCINATION WITH MV 20, 27, AND 31 (NUMBER OF CHILDREN STUDIED—16)

HAI antibody titres	*Interval since primary vaccination*			
	one month	3–5 years	6–7 years	8–10 years
>1/512	2	—	—	—
1/512	1	—	—	—
1/256—320	3	3	—	—
1/128—160	3	2	3	—
1/64 — 80	2	3	1	2
1/32 — 40	2	1	3	2
1/16 — 20	—	—	—	2
1/8 — 10	—	—	1	—
<1/8	—	—	—	—
Not tested (or already revaccinated)	3	7	8	10

TABLE 4

HAI ANTIBODY DECAY AFTER VACCINATION WITH K + L VACCINES (NUMBER OF CHILDREN STUDIED—45)

HAI antibody titres	*Interval since live vaccine*			
	one month	3–5 years	6–7 years	8–10 years
>1/512	22	1	—	—
1/512	5	4	1	—
1/256—320	5	6	1	1
1/128—160	4	4	5	2
1/64 — 80	1	5	6	2
1/32 — 40	1	4	5	1
1/16 — 20	1	6	4	—
1/8 — 10	—	1	6	—
<1/8	1	—*	2†	2‡
Not tested (or already revaccinated)	5	14	15	37

* One subject, aged 1 year at time of primary vaccination, showed decay of HAI antibody titre to <1/10 two and a half years later, and then a rise in HAI titre to 1/80, presumed due to contact with measles.
† One of these two aged 2½ years at the time of primary vaccination.
‡ One of these two aged 1½ years at the time of primary vaccination.

Apart from two children who were immunised with K + L vaccine under the age of two years, no relationship could be found between the age at primary vaccination and the rate of decay of HAI antibodies (see footnote to table 4).

(2) *Evidence of natural boosting*

The rate of natural boosting by ' wild ' measles is difficult to estimate. No boosting was recognised among those who received live vaccine only.

In 1967 among 20 children who had received K + L vaccine three or four years previously (many of whom are included in the present study), the level of HAI antibody in six out of nine (70 per cent) appeared to have been boosted to titres of 1/128 or greater by known contact with measles at home or in school, whereas in 11 others without a history of contact all the titres were 1/64 or less and four were 1/8 or less (Watson and Parry, 1967).

In the present study, after a known or presumed contact with natural measles a second significant rise in titre of HAI antibody was recorded in four out of 45 children included in table 4, whose primary immunisation was with K + L vaccine. It is probable, however, that several other subjects also, who showed no change of HAI antibody titre after revaccination, had already sustained an unrecorded, symptomless ' natural boost ' as a result of previous contact with live measles. This boost is reflected in figure 1.

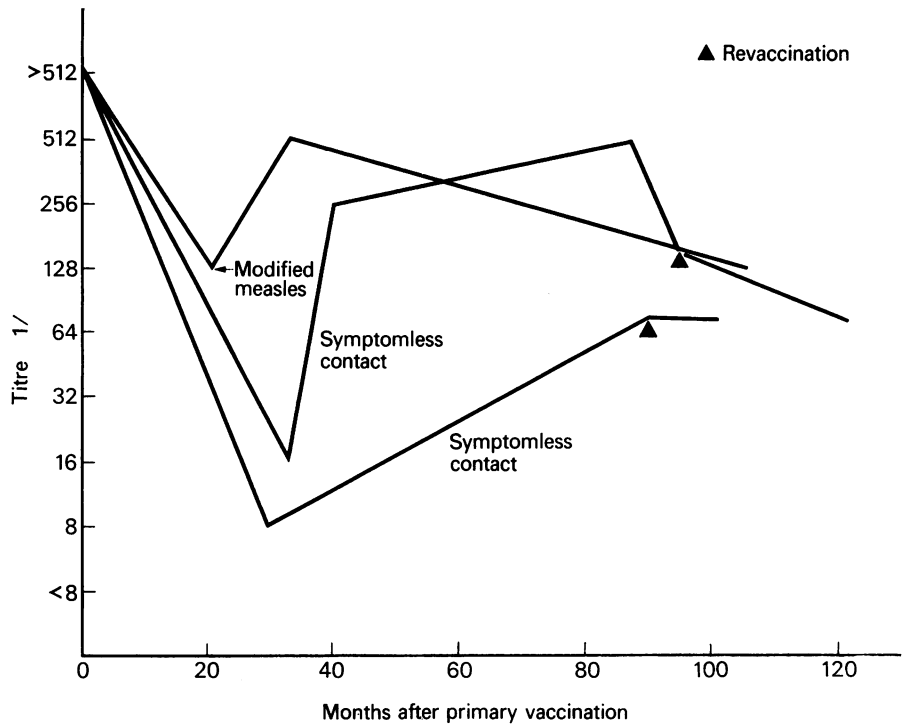

Figure 2

Persistence of measles HAI antibody after ' killed ' + live measles vaccine showing effect of contact and revaccination.

Figure 2 shows the antibody response in three children in whom a second rise in HAI antibody was recorded. In two, both school children, a history of exposure to natural measles was lacking. The third subject had developed non-infectious ' modified measles ' from a home contact two years after primary vaccination (Watson, 1965); six years later his HAI antibody titre had fallen from 1/512 after contact to 1/160.

A schoolgirl who was not included in the original serological study (Watson, 1965) of children vaccinated against measles had received K + L vaccine at the age of five years.

In 1973 at the age of ten she developed a mild morbilliform illness (fever, cough, and rash) two weeks after contact with measles at school. After a further two weeks her unvaccinated brother, aged three years, developed classical measles. The girl's illness was not seen by a doctor, but her grandmother considered the rash to have been typical of measles. Two weeks after her rash had faded, when her brother was ill, her HAI antibody titre was 1/160. These facts suggest that her primary course of K + L measles vaccine had not prevented her from developing an infectious morbilliform illness five years later.

(3) *Revaccination*

(i) *Type and dose of primary vaccine.* Sixty one subjects were revaccinated with live 'further attenuated' measles vaccine (table 5). In 20 of these, primary vaccination had been with live vaccine only; the remaining 41 had received various dosage regimes of K + L vaccine. No differences were found between children treated with different dosages of 'killed' vaccine; their results are therefore reported in one group. Among children whose primary immunisation was with K + L vaccine, significantly more showed a fourfold or greater rise in titre after revaccination and significantly fewer showed no change than amongst children who received live vaccine only. Only one subject (five per cent) from the 'live only' group developed a significant symptomless rise in HAI antibody titre after revaccination; he had received MV 16 at the age of 19 months. Of the K + L group 17 (41 per cent) developed a significant symptomless rise in HAI antibody titre after revaccination.

TABLE 5
EFFECT OF REVACCINATION ACCORDING TO TYPE OF PRIMARY VACCINE USED

Change in HAI antibody titre after revaccination	*Type of primary vaccine*			
	Live only	*%*	*'Killed' followed by live*	*%*
No change	19	*95*	24	*59*
Fourfold or greater rise	1	*5*	17	*41*
Total revaccinated	20		41	
Not revaccinated	7		4	

TABLE 6
PROPORTION IN K + L GROUP SHOWING SIGNIFICANT CHANGE IN HAI ANTIBODY TITRE IN RELATION TO TITRE BEFORE REVACCINATION

HAI antibody titre before revaccination	*Change in HAI antibody titre with revaccination*		
	Number showing significant rise after revaccination ('boost')	*Number showing no significant change after revaccination*	*Percentage boosting after revaccination*
1/320	—	2	*0*
1/160	1	6	*14*
1/80	3	7	*30*
1/40	2	5	*29*
1/20	1	2	*33*
1/10	5	2	*71*
<1/10	5	—	*100*
Total	17	24	

In two cases from the ' live only ' group and three from the K + L group fourfold falls in HAI antibody titres were found to have occurred when next tested after revaccination; all five of these subjects had titres of 1/160 or higher before revaccination, and the interval between revaccination and taking the follow-up serum was seven to nine months.

(ii) *Antibody titres after revaccination.* In the K + L group the proportion showing a significant increase in titre after revaccination was inversely proportional to the pre-booster HAI antibody titre (table 6). When the titre before revaccination was 1/10 or less, ten out of 12 (83 per cent) of patients developed a significant rise. At titres from 1/20 to 1/80 six out of 20 (30 per cent) showed a rise, while above 1/80 only one out of nine 11 per cent showed a significant rise in titre. No such correlation was observed in the ' live only ' group.

Figure 3 illustrates the rise in HAI antibody titre after revaccination in three patients with low titres after K + L vaccine. In figure 4 neither contact with measles nor revaccination altered the level of HAI antibody in two people with high titres after live

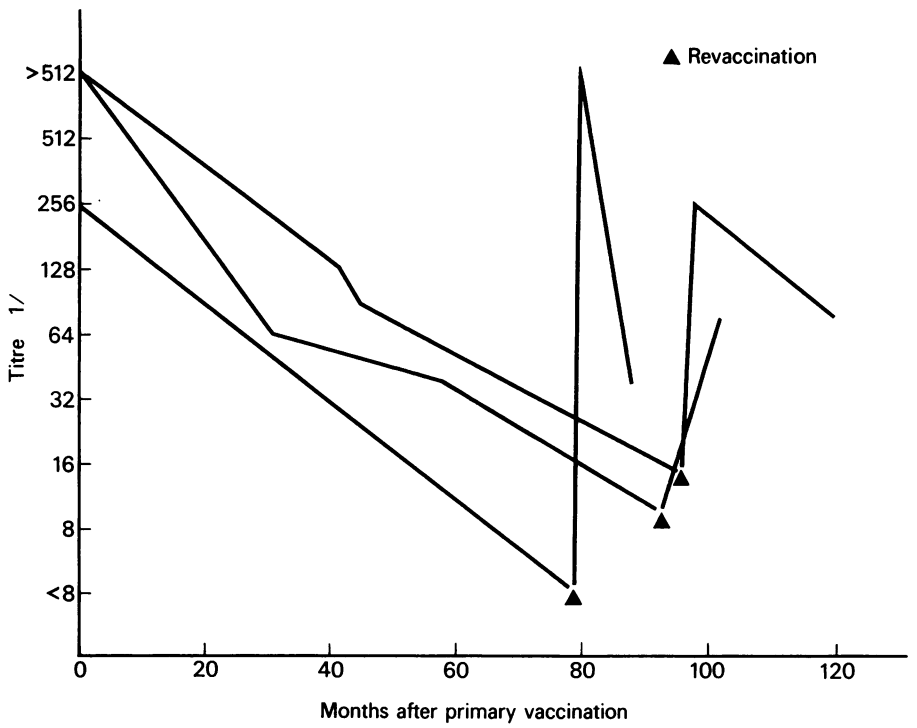

Figure 3

Persistence of measles HAI antibody after ' killed ' + live measles vaccine showing effect of revaccination.

vaccines only. In the third patient primary immunisation had been by a mild and atypical attack of natural measles at the age of four years; 33 months later he received MV/16 after which his HAI antibody titre rose from 1/80 to 1/256 or higher.

(iii) *Time interval since primary vaccination in K + L group.* There was a positive correlation between the time since primary vaccination with K + L vaccine and the proportion of subjects developing a significant increase in HAI antibody titre after revaccination (table 7).

TABLE 7

PROPORTION IN K + L GROUP SHOWING SIGNIFICANT RISE IN HAI ANTIBODY TITRE AFTER REVACCINATION IN RELATION TO TIME SINCE PRIMARY VACCINATION

Changes in HAI antibody titre after revaccination	*Number of years since primary vaccination*		
	Under 6½ years	*6½–8½ years*	*Over 8½ years*
Number showing fourfold or greater rise	2	10	5
Number showing no significant rise	9	13	2
Proportion boosted—%	*18*	*43*	*71*

By 6½ years after primary K + L vaccination about one fifth of the subjects showed a significant rise in titre after revaccination; between 6½ and 8½ years one half of those revaccinated showed a rise; and after more than 8½ years, threequarters of those revaccinated showed a significant rise in titre. The four subjects in table 6 who showed fourfold or greater rises from titres of 1/80 or above had all received their primary vaccination more than seven years before revaccination.

(iv) *Age at primary vaccination.* The age at primary vaccination with K + L vaccine or with live vaccine alone did not appear to affect the rate of boosting except perhaps in the youngest age group. The only subject from the ' live only' group to develop a fourfold increase in HAI antibody titre (table 5) received his primary vaccination at the age of 19 months, younger than any other in the ' live only ' group (two others had received primary vaccination at 22 months; the remainder were all over two years old.)

Discussion

Protection against clinical measles is the critical yardstick by which to judge the success of any vaccine schedule. By this criterion there was only one partial failure among the 70 children from our original series (Watson, 1965) and his attack was not infectious; he had received K + L vaccine .However, the other girl reported here, who developed what seems to have been a mild but infectious attack of measles five years after receiving K + L vaccine, must be counted as another failure for this schedule, although she was not studied serologically at the time of primary vaccination.

Those subjects who received a single dose of live measles vaccine have maintained a high, but slowly falling, titre of HAI antibody over a period of eight to ten years. The geometric mean titre (GMT) of those who received MV/16 has fallen from $>$ 1/512 to 1/160, while the GMT of those given MV/20–31 has fallen at about the same gradient from 1/192 to 1/32 over the same period.

The gradients in these children vaccinated mainly at or over three years of age are similar to those reported by Krugman (1971) for children aged one to two years when vaccinated but our GMT are, age for age, about two dilutions higher than his for MV/20–31 and four dilutions higher for MV/16. By projection, the GMT of HAI antibody generated in our group by MV/16 is likely to remain at $>$ 1/10 for over 40 years, while that resulting from MV/20–31 will remain detectable at the same level for 20–25 years.

During the same period after primary vaccination by ' killed ' followed by live measles vaccine a much steeper initial decline in HAI antibody titre occurred, so that after six or seven years two out of 30 (six per cent) patients had no detectable HAI antibody at 1/8 dilution and after eight to ten years this proportion had risen to two out of eight

(25 per cent). On the other hand exposure to natural measles had evidently still been frequent enough for titres of 1/128 or higher to be present in seven out of thirty (20 per cent) children after six to seven years and three out of eight (40 per cent) between 8–10 years after primary vaccination.

Our data conform with the view that, whatever schedule or type of vaccine is used, primary vaccination under the age of two years provides detectable immunity for a shorter period than when performed in older children (Linnemann *et al.*, 1972; Schuelberger *et al.*, 1973).

We confirm that natural boosting of HAI antibody occurs after contact with measles, particularly in children who received K + L vaccine, but the frequency of such boosting by contact with epidemic measles may already be falling. Not all such boosts are symptomless and the reaction in a few children may be infectious.

Measles HAI antibody, generated either by the natural disease or by primary vaccination, can be boosted by revaccination. Whether a significant rise in titre is evoked will depend upon the type of primary stimulus and the level of HAI antibody before revaccination, which in turn will depend upon the interval since primary immunisation and probably on the age at primary vaccination. The degree of attenuation of the booster vaccine is probably another variable.

Our observation that in the K + L group revaccination can produce significant rises in HAI antibody titre from pre-booster levels as high as 1/80 and 1/160 and the boy recorded by Watson and Parry (1967), whose titre of 1/128 was boosted by home contact with measles within two years of primary vaccination, suggest that K + L vaccine generates HAI antibody which differs in some way from that generated by natural measles or live vaccines alone.

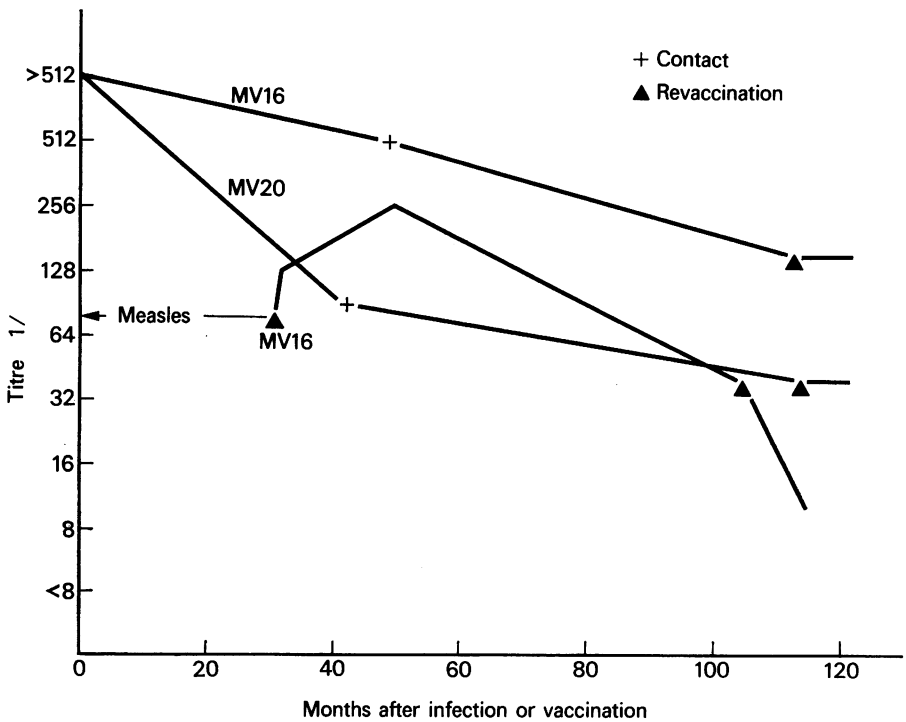

Figure 4
Persistence of HAI antibody after measles or live measles vaccine showing effect of contact and revaccination.

In addition to the patient recorded in figure 4, one of us (Watson, 1963) has reported another patient whose low residual titre of neutralising antibody after natural measles was boosted by the relatively unattenuated vaccine MV/16. Since a second attack of measles may occur clinically or sub-clinically and since many subjects with a waning immunity, originally induced by vaccine, may be boosted without symptoms by contact with natural measles, it would seem logical to administer a relatively unattenuated vaccine as the booster if and when this is required.

Primary immunisation against measles might then be achieved with a highly attenuated vaccine, perhaps free from the risks of febrile convulsions and encephilitis, even when administered before the age of two years. This would elicit enough response to protect the child from measles during its earliest years when any complications of measles are relatively serious. Revaccination would be needed earlier than at present and use of the least attenuated vaccine for this purpose could be expected to provide prolonged immunity.

Our data on the persistence of HAI antibody evoked by live measles vaccines, the boosting effect of exposure to measles and the high degree of protection afforded against clinical illness all support Krugman's expectation that a " single dose of vaccine should provide long-term immunity against measles for approximately 98 per cent of inoculated children " (Krugman, 1971).

Against that should be set the low titre reached by children vaccinated under the age of two years, the steep decline in GMT of HAI antibody among those who received the K + L schedule at any age, and the diminishing opportunity in future for booster contacts with natural measles.

We suggest that further epidemiological and serological studies are needed particularly on those children who received the K + L schedule (now withdrawn), since they may be the first group to require revaccination. About those children who are notified as developing measles at present in spite of vaccination, we need to discover immediately their ages at primary immunisation and the types of vaccines used. As epidemics of measles become less frequent, the chances of collecting this relevant information will grow less. Those initially vaccinated between 12 and 18 months of age may be the next group to require and benefit from revaccination.

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REFERENCES

Krugman, S., Giles, J. P., Friedman, H. & Stone, S. (1965). *Journal of Pediatrics*, **66**, 471–488.
Krugman, S. (1971). *Journal of Pediatrics*, **78**, 1–16.
Leedham-Green, J. C. (1965). *Journal of the College of General Practitioners*, **10**, 244–246.
Linnemann, C. C., Jr., Dine, M. S., Bloom, J. E. & Schiff, G. M. (1972). *American Journal of Diseases of Children*, **124**, 53–57.
Panum, P. L. (1939). *M.Classics*, **3**, 829.
Schuelderberg, A., Lamm, S. H., Landrigan, P. J. & Black, F. L. (1973). *American Journal of Epidemiology*, **97**, 402–409.
Stokes, J., Jr., Reilly, C. M., Buynack, E. B. & Hilleman, M. R. (1961). *American Journal of Hygiene*, **74**, 293–303.
Ueda, S., Toyoshima, K. & Kurose, T. (1969). *Biken Journal*, **12**, 127–128.
Watson, G. I. (1963). *British Medical Journal*, **1**, 860–861.
Watson, G. I. (1965). *British Medical Journal*, **2**, 13–16.
Watson, G. I. (1965). *Lancet*, **1**, 80–81.
Watson, G. I. (1967). *Royal Society of Health Journal*, **87**, 266–271.
Watson, G. I. & Parry, J. M. (1967). *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service*, **26**, 146–153.