Papers and Originals

Measles Vaccination IV. Responses to Two Different Types of Preparations Given as a Fourth Dose of Vaccine*

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Inactivated measles vaccines give a high rate of serological conversions (Carter *et al.*, 1962 ; Fulginiti *et al.*, 1963 ; Karelitz *et al.*, 1963 ; Norrby *et al.*, 1963, 1965). Concerning the persistence of circulating antibodies, however, different experiences have been reported (Feldman *et al.*, 1963 ; Fulginiti and Kempe, 1963 ; Medoff *et al.*, 1967 ; Norrby *et al.*, 1964). The state of sensitization still remaining after the reduction of antibody titres below detectable levels has been demonstrated to prevent or modify clinical symptoms upon exposure to "wild" virus (Fulginiti and Kempe, 1963 ; Medoff *et al.*, 1964) or to live measles vaccine (Feldman *et al.*, 1962 ; Fulginiti *et al.*, 1963 ; Karelitz *et al.*, 1963 ; Fulginiti and Kempe, 1963 ; Guinee *et al.*, 1963). Combined vaccination, killed vaccine followed by live, has been recommended as a means by which long-lasting immunity can be produced without such reactions as are associated with the use of live vaccine alone.

It has also been suggested (Medoff *et al.*, 1964) that killed vaccine alone might provide a basic immunity sufficient to protect against clinical manifestations after exposures to "wild" virus, which, however, would serve as booster stimuli leading to solid and lifelong immunity.

The general purpose of the series of investigations of which the present study forms a part is to analyse the possible usefulness of killed measles vaccine for elimination of measles and to introduce a measles vaccine consisting of a purified haemagglutinin (Norrby, 1964 ; Norrby *et al.*, 1965).

The immediate aim of the present study was (*a*) to analyse the level of circulating antibodies in children 22 months after vaccination with three monthly doses of a formalin-killed alum-precipitated vaccine, and (*b*) to study the effect of a booster injection of either the same type of vaccine or a vaccine containing purified measles haemagglutinin prepared from fractionated dog-kidney-tissue-culture virus material. Serological and clinical follow-up studies were conducted up to eight months after the time of revaccination.

Material and Methods

Vaccines.—The formalin-killed measles vaccine, lot No. 71A, was kindly supplied by Chas. Pfizer & Co. It was prepared from material of the Edmonston strain of measles virus grown in monkey-kidney-tissue cultures. This was inactivated by formalin and purified by adsorption on aluminium phosphate, which also acts as an adjuvant in the final product. The preparation of purified haemagglutinin was made from material of the Edmonston strain of measles virus propagated in primary dog-kidney-tissue cultures. After disintegration of the material with Tween-ether the haemagglutinin was isolated according to methods previously described (Norrby, 1964 ; Norrby *et al.*, 1965).

The relative potency of the Tween-ether vaccine was three to four times higher than that of the formalin-killed vaccine, as determined by antigenic extinction limit tests in guinea-pigs.

Study Population and Vaccination Procedure.—The group of children vaccinated at the age of ½ to 2 years with three monthly doses of the formalin-killed vaccine (Norrby *et al.*, 1963) and followed up eight to nine months later (Norrby *et al.*, 1964) were submitted to further clinical and serological analyses and injected intramuscularly with 1 ml. of either one of the two vaccines 22 to 23 months after the primary vaccination. Samples of whole blood were collected from the finger-tip and mixed with tissue-culture medium containing heparin. Bleedings were made immediately before the injection of vaccine, and in addition 2 to 4 weeks, 10 weeks, and 8 months later. The erythrocytes were removed by centrifugation, and the samples inactivated at 56° C. for 30 minutes before being used in the tests.

Serological Analyses.—The techniques previously described in detail (Norrby *et al.*, 1963, 1964) were used in the neutralization, haemagglutination-inhibition, and complement-fixation tests. The control titration of the neutralization antigen gave a titre of 40 instead of as calculated 100 $TCID_{50}$. All titres given refer to final dilutions after addition of antigen.

Results

Haemagglutination-inhibition Antibodies Remaining 22 to 23 Months After Vaccination

As in previous reports (Norrby *et al.*, 1963, 1964), the children available for follow-up studies were classified as follows: (1) children without previous or intercurrent exposure to measles, receiving three monthly doses of vaccine ; (2) children receiving two doses only ; and (3) children who were possibly exposed to natural measles in the course of vaccination.

Among children submitted to follow-up analyses eight to nine months after vaccination the following numbers were available for further studies: 26 out of 49 in group 1, two out of four in group 2, and four out of four in group 3. Some children who upon exposure contracted clinical symptoms suggesting measles (see Norrby *et al.*, 1964, and below) have been excluded from group 1 in the comparative analyses.

In the 22 to 23 months' post-vaccination serum samples, measles haemagglutination-inhibition antibodies in a titre $\geqslant 10$ were detectable in all sera positive eight to nine months after

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vaccination. Fig. 1 demonstrates the good correlation between the titres on the two occasions. The reduction in geometric mean titres of the 25 positive out of 26 (96%) sera belonging to group 1 was almost exactly one dilution step ($\log_{10}$ 0.312), which can also be seen in Fig. 2. Sera belonging to group 2 behaved similarly to those of group 1, whereas no change in titres was recorded in sera belonging to group 3.

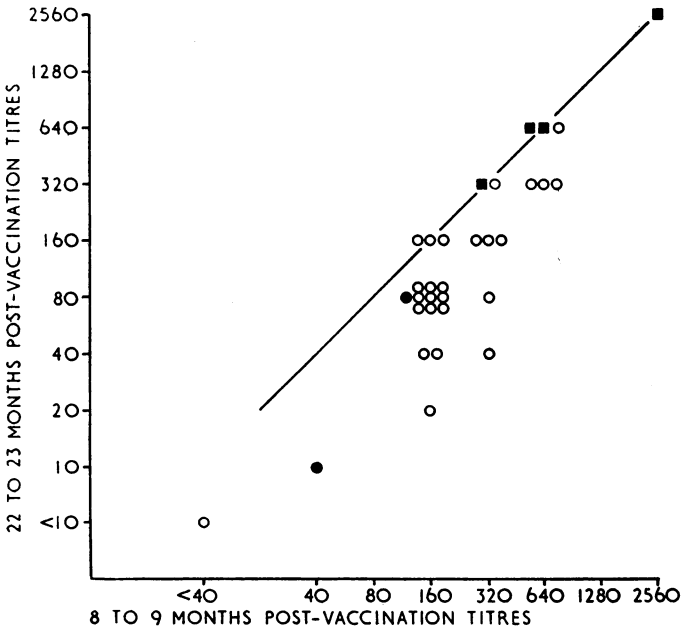

FIG. 1.—Correlation between 8 to 9 months' and 22 to 23 months' post-vaccination haemagglutination-inhibition serum titres. Sera from group (1) = ○, group 2 = ●, and group 3 = ■. The line represents the zone of equivalence.

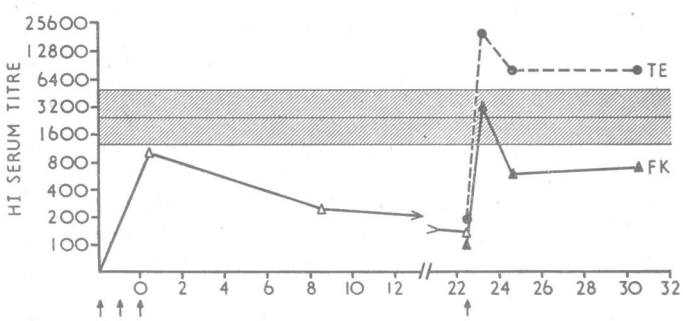

FIG. 2.—Variation in geometric mean haemagglutination-inhibition titres with time in a group of children immunized with four injections (arrows) of killed measles vaccine. Twenty-two to 23 months after three monthly doses of formalin-killed vaccine a booster was given with either formalin-killed (▲——▲) or Tween-ether (● - - - ●) vaccine. The hatched area represents the range within which 90% of the haemagglutination-inhibition titres of early measles convalescent sera fall.

Effect of Exposures up till 22 to 23 Months After Vaccination

In one previous paper (Norrby *et al.*, 1964) the effect of clear-cut exposures through siblings and close playmates during a period of 17 months after vaccinations was described. Four out of 14 exposed children in group 1 reacted. One contracted normal measles, whereas three appeared as mild cases. The specific character of the former case was confirmed serologically. Among the remaining three children one (J.-C. D.) contributed with a 22-months serum sample. This exhibited a neutralization and haemagglutination-inhibition titre of 2,560 and 10,240, respectively, which must be considered to settle the diagnosis as measles. One child belonging to group 3 was also reported at the previous interview (Norrby *et al.*, 1964) to have displayed mild symptoms (fever only) after exposure to measles. The significance of this reaction, however, is somewhat doubtful, since there was a reduction in haemagglutination-inhibition serum titre from 2,560 directly after vaccination to 320 22 months later. A similar, about eightfold, reduction in titres was also seen in sera from other children belonging to group 3.

At the interviews made 22 to 23 months after vaccination one additional suspected case of measles (M.d.H.) was reported to have occurred during the 17 months after vaccination. Between 17 and 22 months another four children had been exposed and one of these (L. J.) displayed clinical symptoms.

Case M.d.H.—This child was exposed 12 months after vaccination through a brother who had contracted natural measles. Ten days after this exposure the vaccinee became ill with symptoms from the respiratory tract and increasing fever. Three days later a consulting physician diagnosed the case as bronchopneumonia and prescribed broad-spectrum antibiotics. A faint unspecific rash was seen but no Koplik's spots. The fever, which at the visit of the physician was 40.6° C., persisted on a somewhat lower level during the next four days, after which the child recovered. Serological analysis of sera collected four months before and 10 months after the incident showed haemagglutination-inhibition serum titres of 80 and 10,240, respectively.

This demonstrates without doubt that a measles infection had occurred, but whether this in itself had the character of pneumonia (giant-cell pneumonia ?), or provided suitable conditions for a superinfecting micro-organism, or was only coincidental with a pneumonia are questions that have to be left open. Another child (Case L. J.) also had been exposed through a brother with typical measles. The vaccinee ran a fever for four days with a maximum of 39.4° C., and exhibited a finely dotted rash that never became confluent. No blood sample was available to confirm the presumed diagnosis serologically.

Effect of a Booster Injection with Two Different Types of Vaccine

Twenty-two to 23 months after the full course of three injections with formalin-killed vaccine a booster injection was given to 15 children with the formalin-killed vaccine and to 14 children with the Tween-ether vaccine. Post-booster serum samples were collected two to four weeks later. Impressive secondary responses were elicited in all the children, as can be seen from Table I and in Figs. 2 and 3. The figures given in Table I and Fig. 2 do not include titres of the child that exhibited a pre-booster titre of <1 : 10 and whose post-booster titre was 1 : 1,280. The increase in geometric mean haemagglutination-inhibition titres of the remaining children was 35-fold in the group given formalin-killed vaccine, and 100-fold in the group that received Tween-ether vaccine. The mean titre in the latter group was about seven times higher than titres recorded in early measles convalescent sera (Fig. 2). There was a good correlation between haemagglutination-inhibition and neutralization titres (Fig. 4) ; the difference in geometric mean titres was about five times in both groups. Complement-

TABLE I.—*Geometric Mean Titres in Children Vaccinated with Three Monthly Doses of Formalin-killed Vaccine and Revaccinated 22 Months Later with Formalin-killed or Tween-ether Vaccine. Pre-booster Serum Samples were Collected Immediately Before the Injection and Post-booster Samples 2–4 Weeks Later. All Sera Analysed Contained Measurable Amounts of Pre-booster Haemagglutination-inhibition Antibodies (≥ 1 : 10) and Post-booster Neutralization (≥ 1 : 20) and Haemagglutination-inhibition (≥ 1 : 40) Antibodies*

Type of vaccine	Formalin-killed	Tween-ether
No. of children	14	14
Pre-booster titres:		
Haemagglutination-inhibition	88	180
Post-booster titres:		
Neutralization	630	3,600
Haemagglutination-inhibition	3,100	18,100
Complement-fixation	(67)*	540
Increase in Haemagglutination titres	35 ×	100 ×

* The figure is calculated on values from 11 out of 14 sera that had a titre ≥ 1: 40 the lowest dilution tested.

fixation antibodies were demonstrable on a serum dilution of ⩾1:40 in 11 out of 14 sera from children immunized with formalin-killed vaccine and in all sera from children given Tween-ether vaccine. Five of the sera in the latter group exhibited a titre of 1:1,280, which also is higher than what has been recorded after natural measles in this laboratory. The ratio of haemagglutination-inhibition to complement-fixation antibody titres amounted to 35 to 50, which is of the same order of magnitude as the difference seen after primary vaccination with killed vaccine (Norrby *et al.*, 1963).

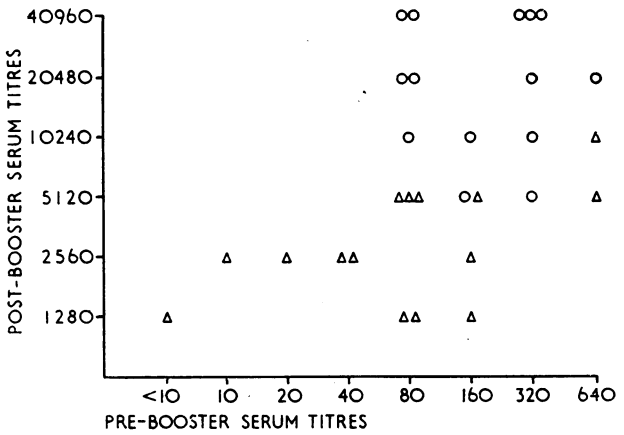

FIG. 3.—Correlation between haemagglutination-inhibition titres in serum samples collected immediately before the booster injection of formalin-killed (△) or Tween-ether (O) vaccine and two to four weeks later.

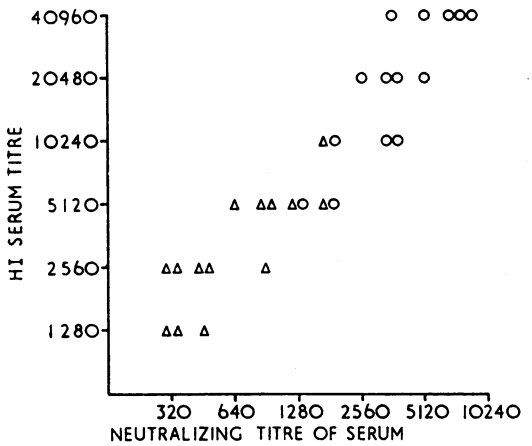

FIG. 4.—Correlation between haemagglutination-inhibition and neutralization titres in sera collected from children two to four weeks after the injection of a booster of formalin-killed (△) or Tween-ether (O) vaccine.

Clinical Reactions in Connexion with Administration of Booster Injections

No local or general reactions were recorded except in one girl given the formalin-killed vaccine. This child developed a strong local reaction at the site of inoculation, increasing during the first 24 hours after vaccination. The reaction consisted of redness and infiltration covering a circular area 10 cm. in diameter. In addition the child complained of some headache and dizziness, and the temperature rose to 39.5° C. After 48 hours the child had recovered completely from the reaction.

Changes in Antibody Titres over a Period of Eight Months After Booster Injection

Serum samples were collected 10 weeks and eight months after the fourth dose of vaccine in order to determine the persistence of antibody titres. On the two occasions 19 and 26, respectively, out of the 28 children included were available for bleeding. All blood samples were analysed for haemagglutination-inhibition antibodies, and the eight months post-booster samples also for complement-fixation antibodies.

The results of the haemagglutination-inhibition tests are summarized in Table II and illustrated diagrammatically in Fig. 2. Between the 2–4 weeks and 10 weeks post-booster samples the reduction in geometric mean titres was 2.4-fold and 5.5-fold in the groups of children given Tween-ether and formalin-killed vaccine, respectively. However, after that the haemagglutination-inhibition titres were stabilized and no further decrease was demonstrable after another six months. Thus the geometric mean titres eight months after the booster shots were 7,800 and 600 for the Tween-ether and formalin-killed group of children, respectively. It might be worth mentioning that the former mean titre is in excess of maximum titres after a natural measles infection.

TABLE II.—*Geometric Mean Haemagglutination-inhibition Titres in Sera 2–4 Weeks, 10 Weeks, and 8 Months After a Booster Injection of Tween-ether or Formalin-killed Vaccine. The Relative Decrease in Titres of Samples From the Early to the Two Late Post-booster Bleedings Are Also Given*

Type of Vaccine		Time After Booster Injections		
		2–4 Weeks	10 Weeks	8 Months
Tween-ether	No. of children	14	8	14
	Geometric mean HI titre	18,100	7,700	7,800
	Relative decrease in titre*	—	2·4	2·3
Formalin-killed	No. of children	14	11	12
	Geometric mean HI titre	3,100	520	600
	Relative decrease in titre*	—	5·5	4·5

* For calculation of relative decrease in titre only paired sera from vaccinees were compared.

In the eight months post-booster samples complement-fixation antibodies were detectable at a serum dilution of ⩾1:20 in 5 out of 12 sera from children given formalin-killed vaccine and in all 14 sera from children given Tween-ether vaccine. There

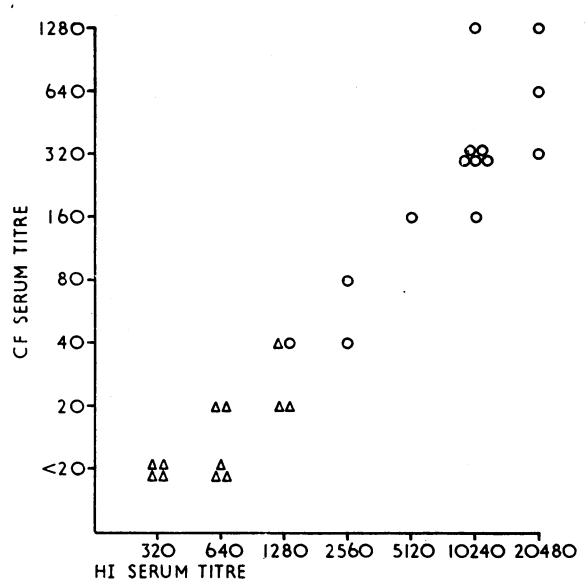

FIG. 5.—Correlation between haemagglutination-inhibition and complement-fixation titres in sera from children given a booster eight months previously with formalin-killed (△) or Tween-ether (O) vaccine.

was a high degree of correlation between haemagglutination-inhibition and complement-fixation titres, as can be seen in Fig. 5. The ratio of geometric mean haemagglutination-inhibition to complement-fixation titres was 32 and 42, respectively, for sera from children given Tween-ether and formalin-killed vaccine.

Effect of Measles Exposure During Eight Months After Fourth Dose of Vaccine

During the eight months that elapsed between the booster injection and the last blood samples collected 4 out of the 26 children interviewed had been in close contact with measles. None of these displayed clinical symptoms.

Discussion

An attack of natural measles is assumed to confer a lifelong immunity, although the possible importance of booster effects caused by re-exposure is still a matter of discussion. Accumulated evidence indicates that the immunity appearing after vaccination with attenuated measles vaccine is equivalent to that obtained after natural measles (Stokes *et al.*, 1962 ; W.H.O., 1963) and therefore should be of similar duration. On the other hand, the killed measles vaccines are generally supposed to give an immunity quantitatively and qualitatively inferior to that after natural measles (W.H.O., 1963). For this reason they are usually recommended for use only in combination with live vaccine.

Similar arguments were raised against inactivated and for live poliovirus vaccines. However, the excellent results achieved in the Scandinavian countries with inactivated poliovirus vaccine appear to invalidate those arguments, and for this reason it would seem unwise to discount inactivated measles vaccines before they have been given a fair trial.

Their effect and usefulness will depend upon two conditions: (*a*) whether circulating antibodies alone provide satisfactory protection and, if so, (*b*) whether sufficiently high antibody levels can be maintained over a sufficiently long period.

It has been found in cases of agammaglobulinaemia that recovery from an attack of measles confers apparently lifelong immunity to reinfection (Janeway and Gitlin, 1957). Since, in fact, complete lack of capacity to produce gamma-globulin is extremely rare, it cannot be excluded that the immune state in the cases observed is in fact attributable to low levels of circulating antibody. The protective or modifying effect of passively administered gamma-globulin seems actually to furnish conclusive evidence that no other mechanism besides classical serological immunity is required for protection. In accordance herewith a protective effect of immunization with inactivated vaccine has indeed been demonstrated.

The main problem, therefore, is the duration of immunity. As an explanation for the long-lasting serological immunity following certain virus infections it has been assumed that virus antigen somehow persists in the organism, providing a continued stimulation of the antibody-producing system. However, whatever the underlying mechanism, lifeless antigens also may produce at least certain types of immunity of extremely long duration, as, for instance, a state of hypersensitivity.

The level of circulating antibody is obviously determined by the rates of production and elimination ; the rate of production in turn must be a function of the size of the population of antibody-producing cells. Duration of immunity should therefore be mainly dependent upon to what extent this cell population maintains its size and activity. For the time being little is known about the mechanisms regulating the activity of the gamma-globulin-producing system. It would seem, however, that present knowledge does not rule out the possibility that long-lasting immunity might be achieved by immunization with lifeless antigens. The nature of the antigen probably is of importance, but the provisions most likely to prove crucial are that large-enough quantities of antigen be administered and that an optimal time schedule for the immunization be applied.

The present observations indicate that an interval between inoculations of one month is too short to condition the vaccinees for true booster responses. The series of three primary inoculations, used in the present study, are in effect to be considered as a protracted primary stimulus. Each additional dose induces a rise in titre, but each time the increase seems to be smaller than that obtained with the preceding inoculations (Norrby *et al.*, 1965). There is actually reason to believe that there exists an upper limit for what can be achieved by such a procedure, a ceiling that can be approached asymptotically but cannot be broken through (see also Peck, 1965). Under such conditions—with repeated doses at relatively short intervals—sensitization or hyperreactivity probably does not develop. Only if antigen administration is interrupted for a longer period of time—presumably to permit complete breakdown and elimination of the antigen—conditioning for a secondary response in the classical sense may take place.

With consideration of the actual titres observed it is reasonable to assume that the immunity following natural measles infection also represents a response to a protracted primary stimulus. When we take into account the large quantities of antigen produced and released in the course of infection it appears likely that the post-infection titre levels correspond to the upper limit attainable under such conditions. Furthermore, as immune seropositive individuals can react with booster responses upon parenteral administration of either live (Martin *et al.*, 1963) or particularly inactivated virus, a state of sensitization can apparently develop, which would indicate that antigenic stimulation after infection is of limited duration. This fact is not compatible with the assumption of persistence in the organism of the virus or its antigen.

Since in a protracted primary reaction each additional dose of antigen seems to have proportionately less effect than the preceding one, little is to be gained by increasing the amount of antigen above a certain level (Peck, 1965). A true booster response, on the other hand, seems to be largely proportional to the dose administered. Thus although in antigenic extinction limit titrations the Tween-ether vaccine showed about three times higher potency than the formalin-killed vaccine, results of primary immunization with the three doses used showed no significant difference in effect between the two vaccines (Norrby *et al.*, 1965). However, when the same amounts were given in a single booster dose a clear-cut difference in responses was observed.

After primary immunization as well as after a booster inoculation a drop in titres is observed which is relatively rapid during the first months but later slows down considerably. In the group now under study the initial mean drop in titre amounted to (in decadic logarithms) 0.8 after primary immunization, and to 0.75 and 0.38 after booster with formalin-killed and Tween-ether vaccine respectively. The further long-range slow decline after primary immunization was 0.31 over a period of 14 months, whereas no change was demonstrable during six months after booster.

As anticipated, the post-booster titres thus tend to be more stable than those after primary immunization. It may be too early to draw any definite conclusions, but the present observations seem to justify a decided optimism as regards the possibility of producing long-lasting immunity with inactivated vaccine alone.

For several reasons, discussed in previous communications (Norrby, 1964 ; Norrby *et al.*, 1965), a purified non-infectious antigen as a vaccine would seem to have distinct advantages over a live attenuated virus. Inclusion in the vaccine of aluminium phosphate, presumably acting as an adjuvant, did not seem to improve the results in the present study. Instead, certain untoward reactions, mainly infiltration, and sometimes abscess-formation, could be attributed to the aluminium content of the formalin-killed vaccine. The single case of what might have been an allergic reaction after a booster injection of this vaccine deserves attention. It is not known at present whether this child had developed hypersensitivity to any component of the vaccine. It may be worth mentioning that the lot of formalin-killed vaccine used was produced in monkey-kidney cells and was not purified beyond a simple adsorption process.

Finally, it may be of interest to note that the ratio of complement-fixation to haemagglutination-inhibition or neutralization titres seemed to remain stable over the eight-month period studied, unlike what has been reported after natural measles (Stokes *et al.*, 1961), or after immunization with live vaccine (Stokes *et al.*, 1962), in which cases a drop in complement-fixation titres relative to neutralization titres were observed. Whether or not this apparent difference is significant will be elucidated by further follow-up studies.

Summary

A group of children vaccinated with three monthly doses of a formalin-killed vaccine at the age of ½ to 2 years were (*a*) submitted to clinical and serological follow-up analyses 22 to 23 months after vaccination, (*b*) given a fourth dose of either formalin-killed vaccine or purified haemagglutinin prepared from Tween-ether-treated material, and (*c*) followed during an additional period of eight months.

In addition to the previously reported four cases of mainly mild measles among 15 children exposed to natural measles two more cases appeared among five children exposed during 22 to 23 months after vaccination. One case was associated with pneumonia of doubtful aetiology, and one was a mild case with slight fever and a faint rash.

In 25 out of 26 children (96%) haemagglutination-inhibition antibodies in a titre ⩾10 were detectable 22 to 23 months after vaccination, and there was a twofold decrease in titre since the nearest previous follow-up analysis, 14 months earlier.

Two to four weeks after revaccination the geometric mean haemagglutination-inhibition titre of the group of 14 children given formalin-killed vaccine had increased 35 times, whereas the corresponding figure for a group of 14 children given Tween-ether vaccine was 100. There was a good correlation with neutralizing and complement-fixation titres. Six weeks later the mean haemagglutination-inhibition titre had been reduced 5.5-fold in the formalin-killed group and 2.4-fold in the Tween-ether group. No further reduction in titres could be detected during the next six months. The mean haemagglutination-inhibition titre eight months after revaccination was 600 in the group of children given formalin-killed vaccine, and 7,800 in the group given Tween-ether vaccine.

The excellent technical assistance of Miss Ulla Arfwidsson, Miss Birgitta Norén, Miss Britt Åkestad, and Miss Britt-Marie Andersson is gratefully acknowledged.

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Vaccination Against Measles: a Study of Clinical Reactions and Serological Responses of Young Children

A Report to the Medical Research Council by the Measles Vaccines Committee*

Brit. med. J., 1965, **1**, 817–823

In 1954 Enders and Peebles reported the isolation of measles virus in human and monkey kidney cell cultures. The first strain to be isolated was from a boy named Edmonston and was attenuated by serial passage in human amnion cultures and whole chick embryos (Milovanović *et al.*, 1957) and finally serially propagated in chick embryo fibroblast cultures (Katz *et al.*, 1958). The attenuated strain (Enders–Edmonston) no longer gave clinical signs of the disease when inoculated into monkeys (Enders *et al.*, 1960). Live vaccine prepared from it was tried in children (Katz and Enders, 1959 ; Krugman *et al.*, 1962), and although it gave good measles antibody responses it caused febrile reactions with rash in more than half the children. Such reactions were greatly reduced by giving a simultaneous dose of gamma-globulin (Stokes *et al.*, 1961).

In order to obtain a vaccine free from reactions there are two possibilities. Either the virus may be further attenuated for use in a live vaccine or an inactivated vaccine may be prepared, and both possibilities have been investigated. In the U.S.A. Schwarz (1962) further attenuated the Enders–Edmonston strain by passage in chick embryo fibroblast cultures, and live vaccine produced from it gave good antibody titres in children without causing the comparatively severe reactions which occurred after vaccine from the original strain (Krugman *et al.*, 1963 ; Andelman *et al.*, 1963). A similar further-attenuated strain (Goffe strain) has also been produced in this country from the Enders–Edmonston strain, and live vaccine prepared from this was also shown to give good antibody responses with fewer reactions than the original strain (Hendrickse *et al.*, 1964 ; Benson *et al.*, 1964). Inactivated vaccine has been prepared by Warren and Gallian (1962) by inactivating the Enders–Edmonston strain with formaldehyde

* Professor Wilson Smith (chairman), Professor D. G. Evans, Professor W. Gaisford, Professor C. H. Stuart Harris, Dr. J. Stevenson Logan, Dr. K. McCarthy, Dr. C. L. Miller, Professor Sir Alan Moncrieff, Dr. Ian Sutherland, Dr. D. Thomson, Dr. G. I. Watson, Sir Graham Wilson, and Dr. F. T. Perkins (secretary).

The trials were co-ordinated by Dr. C. L. Miller, of the M.R.C. Laboratories, and the serological tests were done by Dr. M. Clarke, of the M.R.C. Division of Immunological Products Control. The results were analysed by Miss N. Seyd, of the M.R.C. Statistical Research Unit.

The report was prepared by Dr. Ian Sutherland, Dr. F. T. Perkins, and Professor D. G. Evans.