

A survey of measles antibodies in different populations

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In previous studies of measles (Black, 1959; Bech, 1960; Snyder, McCrumb, Bigbee, Schluederberg & Togo, 1962) an interesting feature has been the presence of complement-fixing as well as neutralizing antibody in sera from populations of all ages. Both types of antibody persist long after the illness, which is essentially one of childhood. Further, measles is uncommon in the first 6 months of life mainly owing to passive immunity from maternal antibody. Mortality is highest in 6- to 11-month-old children (Langmuir, 1962), a very susceptible group, in whom maternal antibody no longer exerts a protective influence.

For this investigation, samples of serum obtained from persons of different ages were tested for measles complement-fixing antibody. The following groups were included:

(1) Twenty-two sera from infants under 1 year of age who had taken part in a study of live poliovirus vaccine (Report, 1961).

(2) 243 sera submitted to the Diagnostic Laboratory, Colindale, from patients of all ages in the London area, for anti-streptolysin 'O' (ASO) estimations.

(3) Twenty-seven pairs of sera from mothers shortly before childbirth and from the umbilical cord blood of their infants immediately after birth.

(4) Twenty-eight sera from mothers whose infants contracted measles before they were 10 months old.

(5) Eight sera from persons stating they had not had measles.

Additionally, measles virus neutralization tests were done on the sera from groups 3, 4 and 5.

MATERIALS AND METHODS

Measles antigen for the complement-fixation tests was prepared in HeLa cell cultures infected with the Edmonston strain of measles virus. The cells were grown in a medium of 0.5% lactalbumin hydrolysate in Hanks's balanced salt solution with 12% calf serum, 3% Hartley's infusion broth, 36.5 mg. NaHCO₃ per 100 ml. (0.83 ml. of a 4.4% NaHCO₃ solution), 200 units penicillin and 200 µg. streptomycin per ml. For maintenance, synthetic medium 199 (Morgan, Morton & Parker, 1950) with 2% inactivated horse serum, and 220 mg. NaHCO₃ per 100 ml. was used. The cells were inoculated with a dose of virus calculated to infect the entire cell sheet, which was harvested when the characteristic measles cytopathic changes were well advanced. The antigen consisted of the cells and tissue culture

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fluid harvested after freezing and thawing twice. This fluid was titrated as a chess-board in a WHO plastic plate with a serum from a hyperimmunized monkey and used at its optimal titre. The antigen was stored at -70°C . Its specificity was checked against a measles-positive and measles-negative monkey serum.

The complement-fixation test was done by the method of Bradstreet & Taylor (1962) with two units of complement (2HC 50). Sera were inactivated at 60°C . for 20 min. immediately before use.

Virus suspensions for neutralization tests were prepared in a similar manner to the complement-fixing antigen. High titres were obtained by inoculating large amounts of virus and harvesting as soon as cytopathic changes were well evident in the HeLa cells. The harvested suspension was immediately dispensed in 3 ml. quantities in bijoux bottles and stored at -70°C . It was titrated in serial half-log dilutions, duplicate HeLa tubes being inoculated with 0.1 ml. amounts. The highest dilution showing cytopathic change was the end point as calculated by the method of Reed & Muench (1938). Such a dilution represented one tissue culture dose (TC₅₀) of virus per 0.1 ml. of suspension. In the neutralization tests, 500 TC₅₀ of virus contained in this volume were employed.

Neutralization tests were done in roller cultures of HeLa cells used within 48 hr. because it was found that their sensitivity to measles virus decreased if older cultures were used. Sera were not inactivated. They were diluted in twofold steps in Hanks's balanced salt solution over a range from 1/10 to 1/1280. Equal volumes (0.3 ml.) of the serum dilutions and virus suspension were mixed and left at 4°C . for 1 hr. Each mixture was then inoculated in 0.2 ml. amounts into duplicate tubes. The cultures were incubated at 37°C . for 6 days when they were examined for cytopathic changes. The fluid in each tube was replaced with fresh maintenance medium and a final reading made after re-incubation for a further 24 hr. This was done because with measles and other syncytial viruses such as respiratory syncytial virus the cytopathic effect may be partly masked until the fluid is changed.

RESULTS

All results are presented in the form of histograms with the antibody titres in both the complement-fixation and the neutralization tests first subdivided broadly as shown in Table 1.

Table 1. *Range of antibody titres in complement-fixation and neutralization tests*

Antibody titre	Complement-fixation test	Neutralization test
Negative	< 8	≤ 10
Low	8-16	20-40
Intermediate	32-128	80-160
High	> 128	> 160

The figures given as titres are the reciprocals of the initial dilutions of serum. The sera composing the first two groups came from persons whose age varied from less than 1 year to more than 40 years. The results of investigations have been set

out in steps as follows: 1, 0-1 year—22 sera; 2(a) 1-4 years—45 sera; 2(b) 5-11 years—51 sera; 2(c) 12-20 years—48 sera; 2(d) 21-40 years—49 sera; 2(e) over 40 years—50 sera.

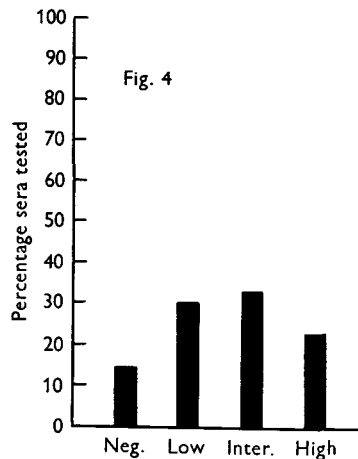
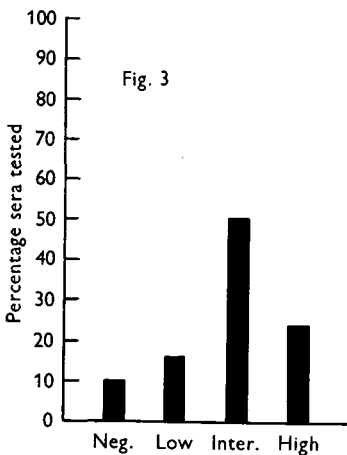
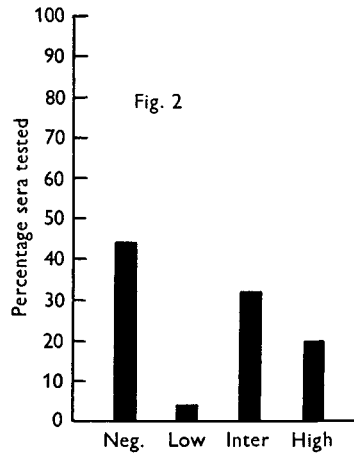
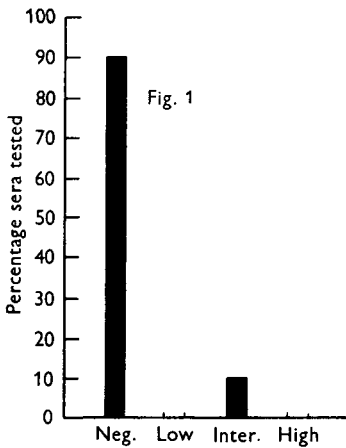


Fig. 1. Complement-fixing antibody titres in group 1.

Fig. 2. Complement-fixing antibody titres in group 2(a).

Fig. 3. Complement-fixing antibody titres in group 2(b).

Fig. 4. Complement-fixing antibody titres in group 2(c).

In group 1 complement-fixing antibody was present in only 10% of the sera, with the titres mainly in the intermediate range (Fig. 1). In group 2(a) the percentage of sera with complement-fixing antibody had risen to 56. Despite the fact that the sera were collected during a so-called non-epidemic period more than 50% showed intermediate or high titres (Fig. 2). In group 2(b) 90% of the sera had complement-fixing antibody. Those which were negative all came from 5- to 6-year-old children and those positive showed a scatter in their titres which was indicative of past infection at different times. The picture showed little further variation in antibody distribution for groups 2(c-e). Most persons had had measles

at some stage (Figs. 3–6). In those over 40 years of age, the antibody titres were intermediate or low suggesting little recent effective contact with the virus.

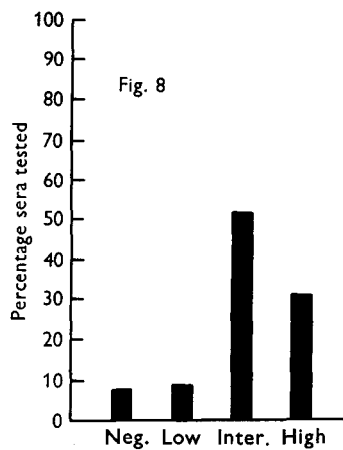
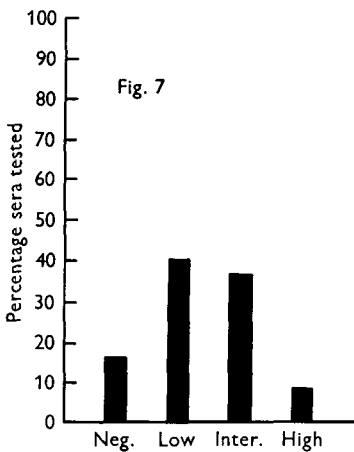
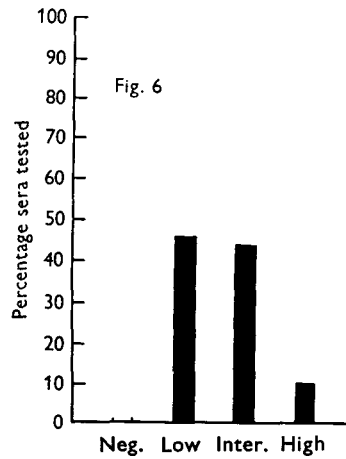
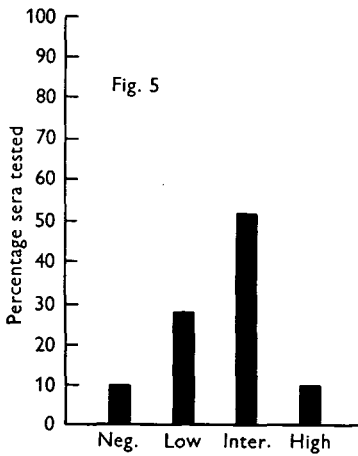


Fig. 5. Complement-fixing antibody titres in group 2 (*d*).

Fig. 6. Complement-fixing antibody titres in group 2 (*e*).

Fig. 7. Complement-fixing antibody titres in group 3 maternal sera.

Fig. 8. Complement-fixing antibody titres in group 3 cord sera.

In group 3—the study of maternal and cord sera—the antibody titres in the mothers' sera (Fig. 7) showed a similar pattern to that in group 2 (*d*) which was composed of persons of both sexes aged 21–40 years. When antibody was present in the maternal circulation, it was passively transferred to the infant across the placental barrier. It was further shown that in most instances a fourfold or occasionally greater concentration of antibody took place in the cord blood (Fig. 8). Neutralization tests (Figs. 9 and 10) with these sera showed the same pattern. Again the antibody in the cord sera was concentrated and in addition only two maternal sera were completely negative. This may have been due to non-specific inhibition of the formation of the antibody-antigen complex or to the amount of

specific antibody present in the maternal serum being too low to be measured easily.

In group 4, the distribution of antibody in mothers whose infants developed measles by the age of 10 months did not differ from the earlier groups (Figs. 11, 12). The passive antibody derived from the mothers disappears in 3–6 months and

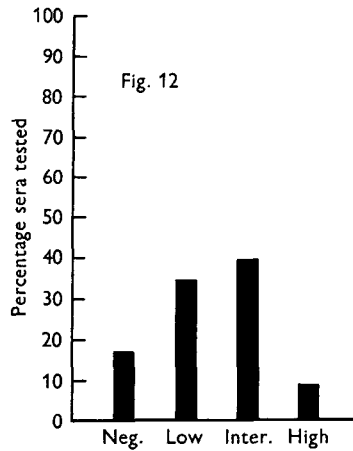
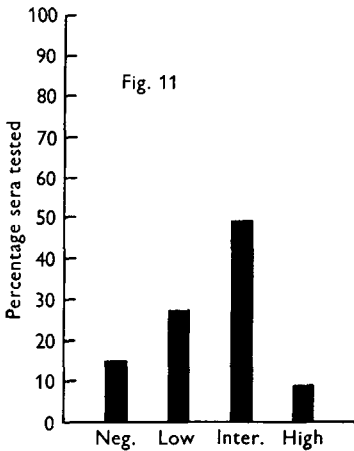
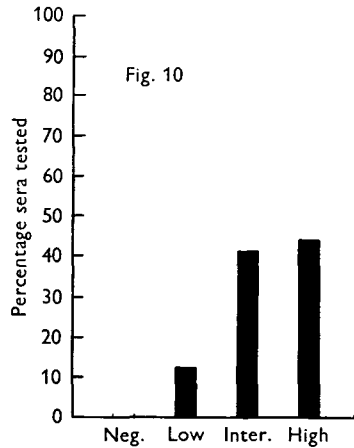
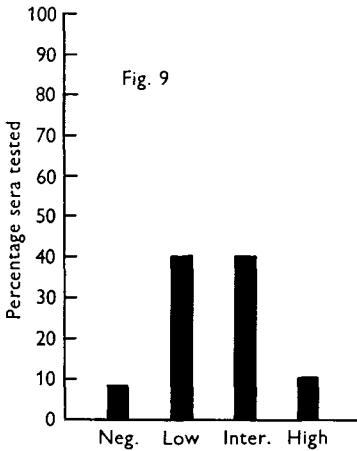


Fig. 9. Neutralizing antibody titres in group 3 maternal sera.

Fig. 10. Neutralizing antibody titres in group 3 cord sera.

Fig. 11. Complement-fixing antibody titres in group 4.

Fig. 12. Neutralizing antibody titres in group 4.

the development of measles in these infants is the result of their exposure to other patients with the disease.

In group 5, only two out of eight sera from persons with no history of measles failed to show the presence of both complement-fixing and neutralizing antibody.

DISCUSSION

The results of complement-fixation tests on the first two groups of sera showed the presence of antibody in 10 % of the samples from children up to 1 year of age. Thereafter, the proportion positive increased rapidly to reach a plateau of about 90 % in children between 5 and 11 years of age, and this proportion remained virtually unchanged throughout the age groups studied. Apart from indicating the widespread prevalence of measles, the results are noteworthy in that for most virus infections, complement-fixing antibody reaches its peak during the convalescent stage of illness and then often declines to an amount too small to detect within 9 to 12 months. With measles, however, after an initial reduction both complement-fixing and neutralizing antibody remain at a fairly constant titre after infection. It is uncertain whether this is due to frequent repeated exposure to measles virus or to the persistence of viral antigen in the body after the infection has subsided. No demonstration of latent virus has so far been made. Black (1962) showed that members of isolated communities might retain their complement-fixing antibody long after an epidemic had subsided. In Tahiti, for example, antibody titres decreased only twofold in 8½ years during which time there was no measles in the community and no likelihood of any specific stimulus to measles antibody having occurred.

In the youngest infants studied, antibody titres were low although the infections must have been comparatively recent. This may be because in the first few months of life the antibody-producing mechanism is still immature. In the group of children under 5 years of age 44 % were without antibody. These sera had been collected in an inter-epidemic period during which a sufficiently large number of susceptible children is built up to provide material for the next epidemic.

In group 3, twenty-four out of twenty-seven samples of cord serum contained an increased amount of antibody compared with their own maternal serum. This discrepancy, which was observed in both complement-fixation and neutralization tests, is in agreement with the report of Ruckle & Rogers (1957) who found a two-fold concentration in five cord sera although, in the present series, the concentration for the most part appeared to be fourfold or even greater. The amount of γ -globulin in cord serum has been reported (Oberman, Gregory, Burke, Ross & Rice, 1956) to be the same as in the maternal serum but the serum albumins are considerably higher. It may be interesting to speculate whether any protein fraction in the cord serum other than γ -globulin contains measles antibody.

Of the twenty-eight sera tested in group 4, six were from mothers who were doubtful whether they had had measles but five of these contained antibody; three were from mothers who denied having had measles but two contained antibody. On the other hand, sera from two mothers who claimed that they had had measles contained no antibody. These, together with the additional results in group 5, are in keeping with the extensive morbidity of measles but suggest that in a few instances inapparent or very mild infection can occur.

SUMMARY

A survey of serum samples from all age groups in the population has shown a rapid acquisition of antibody between the ages of 1 and 6 years which reaches a plateau in concentration and does not disappear later.

The concentration of antibody in cord serum may be four or more times greater than that in the mother's serum.

Presence or absence of a record of past infection by measles is not necessarily reflected by the titre of antibody in the serum.

Low antibody titres in very young infants may be due to an imperfectly developed antibody producing mechanism.

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Participating doctors

Dr J. Alexander	Dr C. R. Kenchington	Dr K. Scott
Dr D. S. Ball	Dr J. D. E. Knox	Dr H. Shire
Dr A. P. Barker	Dr G. S. K. Little	Dr R. Simpson-White
Dr F. V. A. Bose	Dr H. Z. Lewinska	Dr G. Stow
Dr M. H. Butler	Dr J. McAlister Williams	Dr W. Symonds
Dr M. P. Carter	Dr J. O. Newman	Dr J. Walker
Dr G. G. M. Edelsten	Dr R. H. Sandiford	Dr G. I. Watson
Dr S. Griffiths	Dr E. Sawdon	Dr W. O. Williams
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