

The clinical reaction of Nigerian children to measles vaccine with and without gamma globulin

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In earlier papers (Morley, 1962; Morley, Woodland & Martin, 1963) the manifestations of measles in Nigerian children were described and it was shown that measles in these children was outstanding among the acute infectious diseases as a cause of death. The prevalence and seriousness of the disease prompted a trial of live attenuated measles vaccine in which advantage was taken of the experience with measles vaccine gained in the U.S.A. by two of the authors (S.L.K. and S.K.). In this paper the clinical reaction of 500 children to the attenuated vaccine will be reported. Among the purposes of the trial was to ascertain whether the reaction of the African child, who is often malnourished, differs from that of the American child.

A more limited trial of measles vaccine in Ibadan, Nigeria, has been reported by Collard and his associates (1961).

RESULTS

The trial was made in the village of Imesi, and among out-patients attending the Ilesha Hospital. It was divided into three stages as follows:

Stage 1. Preliminary observations on the effect of vaccine†

Twenty-six children were given Enders 'B' liquid measles vaccine (Merck, U.S.A. Lot no. 15) which was flown to Nigeria in solid carbon dioxide. A similar control group were given pertussis/tetanus vaccine.

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† The vaccines and gamma globulin were supplied by Dr Maurice Hilleman, Director, Merck Institute for Therapeutic Research.

Stage 2. Effect of dry vaccine alone

Lyophilized vaccine (Merck, Lot no. 22) was given to 120 children; this was expected to give them permanent immunity to measles. A similar control group of children was given an injection of gamma globulin together with some inert material; this was expected to give them a temporary immunity from the severe effects of measles.

Stage 3. Effect of dry vaccine modified by gamma globulin

Dry vaccine (Lot no. 22) was given to over 800 children with a simultaneous injection of gamma globulin. A control group received gamma globulin plus inert material. This stage was similar to stage 2 except that an attempt was made to modify the reaction to the vaccine by the use of gamma globulin. The observations on the reaction to the inoculation were confined to 378 vaccinated children, and 367 children in the control group.

The inoculations in stage 1 were given in the village of Imesi where a 'longitudinal' health study of a group of children is in progress. The children were seen twice daily at the local clinic from the 5th to 14th day after inoculation. The co-operation of the mothers was good and a remarkable attendance of 100% was achieved. Blood specimens were taken immediately before inoculation and again 3 weeks later. It was found, however, that because of local beliefs the parents disliked having blood taken from their children. Because of this attitude, and also because of shortage of staff, specimens of blood were not taken in the later two stages of the trial.

The preliminary first stage was undertaken in November 1960. Measles was not present in Imesi at that time. The second and third stages were undertaken from February 1961 onwards in Ilesha, when measles was becoming increasingly common. A number of children receiving gamma globulin had a mild attenuated attack but were spared serious or fatal illness. The occurrence of mild measles in these children made the interpretation of the results more difficult.

The children given the inoculations were between the ages of 6 months and 2 years. As the last epidemic had subsided only 6 months previously, the records of all the inoculated children, particularly those over a year old, had to be examined, and the mothers questioned, to discover whether measles had occurred previously.

Age and weight of vaccinated and control children

The mean age and weight of the boys and girls in the vaccinated and control groups are shown in Table 1. It will be seen that there was no statistical difference between the two groups in respect of age and weight.

Inoculation and follow-up techniques

On the day the child was registered, an injection of gamma globulin (0.02 ml. per pound of body weight containing 40 measles antibody units per ml.) was given into the left buttock, and either 0.50 ml. of the vaccine or 0.50 ml. of inert material into the right buttock. A system of random numbers was used, but it was arranged

at all children attending on 1 day should receive the same inoculation to make cording errors less likely. The mothers were told and understood that only half the children would be fully protected. The above relates to stage 3. The procedure followed in stage 2 was similar, except that no gamma globulin was given to the children receiving vaccine.

Table 1. *Age and weight of children in stage 2 and 3 of the measles vaccine trial*

	Age (months)		Weight (lb.)	
	Vaccine	Control	Vaccine	Control
Boys	13.50 ± 0.32	13.92 ± 0.31	18.30 ± 0.22	18.67 ± 0.19
Girls	12.91 ± 0.28	13.15 ± 0.30	17.03 ± 0.20	17.47 ± 0.18

The children should have been seen on the 8th, 10th and 12th day after inoculation. This was in fact done in the third stage. In the second stage, however, owing to a misunderstanding, the children were brought back on the 7th, 9th and 11th day. In this stage they were brought to the hospital at 4 p.m. (16.00 hours), but an afternoon visit was found to be difficult, and in the third stage they were seen at 7 a.m. (07.00 hours). Because of these differences, together with the fact that the third stage took place when there was more infection in the community, the second and third stages cannot be directly compared.

Only a very simple follow-up examination for children in stage 2 and 3 was possible. Rectal temperatures were taken by a nurse, and the children were then briefly seen in bright daylight by the paediatrician. At the same time the mother was asked if the child was well, and any complaints were recorded. The paediatrician did not know whether the children were in the vaccine or control group.

Sterile disposable syringes were used. One of the children developed a small injection abscess that required incision. One mother also said that the site of injection was painful.

Results of the first stage

Serological investigations undertaken in Dr Enders' laboratories in Boston revealed the following: of the 26 children, 7 showed evidence of previous measles, with a low titre of complement fixing antibodies in the first specimen taken and no rise in the second. In the remaining children there was a strong response to vaccination, with titres in the second specimen equal to or greater than 1:512. This is a higher titre than usually observed among American children, using an identical technique in the same laboratory.

The clinical reactions are set out in Table 2. There was a high incidence of minor reactions in the vaccinated group, but reactions were also high in the children who were already immune, and also in the control group. Over half the inoculated children had a rash and diarrhoea: in many children the distinction between a vaccine and a 'sweat' rash was difficult, and was not attempted. None of the children was, however, seriously upset, and their reaction resembled that seen by two of us (S.L.K. and S.K.) in American children receiving measles vaccine. On the basis of the results, it was considered safe to proceed with the next stages.

Results of the second and third stages

In stage 2 the reaction of children given vaccine was compared with that of children given gamma globulin and inert material. In stage 3 the comparison was between children given vaccine and gamma globulin together, and children given gamma globulin and inert material together. The results were transferred to punch cards and mechanically analysed.

Table 2. *Clinical reactions of children receiving live attenuated measles vaccine, stage 1 of the trial*

	Children receiving vaccine		Controls receiving pertussis/tetanus (26)
	Non-immunes (19)	Immunes (7)	
Fever (101° F.-105° F. 38.3° C-40.6° C.)	19	4	11
Catarrh	14	6	10
Loose stools	11	3	7
Restlessness	6	3	5
Refused solid food	15	3	13
Refused breast	0	0	0
Rash	10	4	5

Fever

The incidence of fever is shown diagrammatically in Fig. 1. It will be seen that 38% of the African children given the vaccine alone developed temperatures between 101° F. (38.3° C.) and 102° F. (38.9° C.), and 19% temperatures of 103° F. (39.4° C.) and over. Less fever occurred in the group given vaccine plus gamma globulin, the corresponding percentages being 20 and 6. Data relating to American children are included in Fig. 1 for purposes of comparison. Less fever was recorded among the African than the American children. The difference is, however, probably due to the fact that the American children had their temperatures taken twice daily for 18 days, while the African children were available on only 3 days for temperature recordings. In a few instances, the temperatures of the African children were taken more often, because their mothers considered them unwell and brought them specially to the clinic. In general African mothers do not regard fever in their children as anything very unusual, and few showed concern about the febrile reaction produced by the vaccine.

In the Nigerian community in which the trials were made, there is always a proportion of children with marasmus, or in danger of developing kwashiorkor. It was felt possible that such children might react differently to measles vaccine than children in a better stage of nutrition. To test this possibility, the temperature records were separated by sex and age in months and then divided by weight into percentiles. The temperatures in the percentile groups are shown in Fig. 2. The children of below the local average weight in the left hand column (10 and 25 percentile groups) fared no worse than those with a relatively good weight in the 90 and 75 percentile groups.

The incidence of fever following vaccination is of considerable importance, since high fever from any cause is likely to cause convulsions, a serious event which tends to disturb both the parent and the doctor more than most other illnesses. In the present trials no children with convulsions were seen, but eight mothers gave

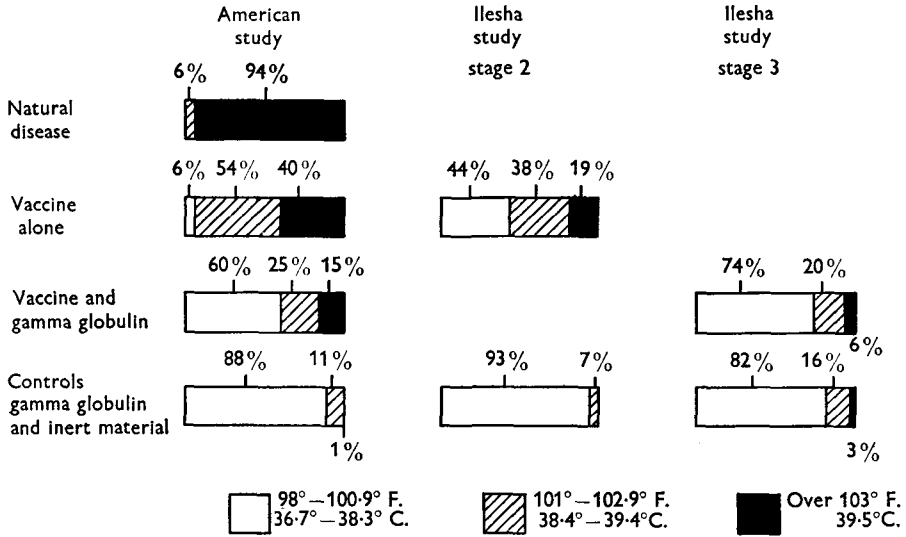


Fig. 1. Immunization with live attenuated measles virus vaccine. Incidence of fever in American and African children. The incidence of fever following measles virus vaccination is similar in American and Nigerian children. The American children (Krugman, Giles, Milton Jacobs & Friedman, 1962) had their temperatures recorded more frequently which may account for a slightly higher recorded incidence of fever.

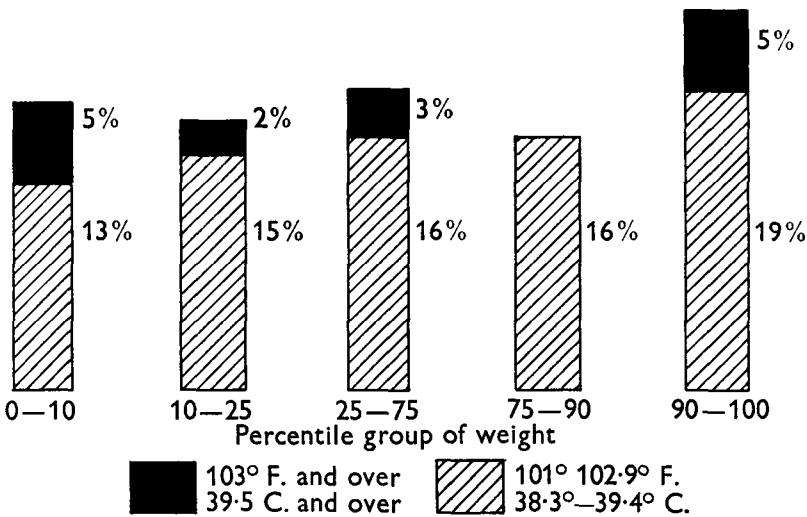


Fig. 2. 441 Nigerian children, standardized by age and sex, receiving measles vaccine. Percentage distribution of fever (over 100.9° F., 38.3° C.) by weight percentile. In this figure is set out the incidence of febrile reaction in each weight group. There is no evidence that children in the low percentile group, who are below average weight for this community have more fever than children of above average weight.

suggestive histories; these related to five children given vaccine and three given gamma globulin and inert material. There was nothing to suggest that the vaccine had any specific effect in producing convulsions.

Cough

Respiratory infections were prevalent among the children in the community at the time when the trials were being made. In stage 2, complaints of cough in their children were made by 47 and 39 mothers in the two groups respectively, while in stage 3 the incidence of cough so reported was also approximately the same in both groups.

Diarrhoea

In a previous paper one of the authors (Morley, 1962) reported that diarrhoea is frequently associated with the acute stages of measles and that the child is apparently more susceptible to diarrhoea in the ensuing months. In the trials diarrhoea was more frequent among the children who received vaccine alone; 31 % of the mothers complained of abnormally watery and frequent stools in their children, and among the controls only 19 %. In no case was the diarrhoea severe. Among the 356 children who had vaccine and gamma globulin and were followed up, 22 % had diarrhoea, and of 335 controls, 21 %. Possibly diarrhoea is part of the reaction to measles vaccine that is suppressed by gamma globulin.

Rash

Among the vaccinated children in stage 2 who did not have gamma globulin the rash was recognized in 25 %. American workers have observed rash in 50–60 % of white children given the vaccine without gamma globulin. This difference may be due to the fact that the African children were seen only on alternate days, and the measles vaccine rash may appear for only a brief period and is not easily detected on a dark skin. The incidence of rash in stage 3 amongst the children given vaccine and gamma globulin was similar to that in the control group.

Comparison of the incidence of cough, diarrhoea and rash in the various weight groups showed no higher incidence among underweight children in the 10 and 25 percentile groups than in children of greater weight in the 90 and 75 percentile groups.

Treatment of conditions appearing during the trials

Coughs were treated with a simple cough mixture. For fever, chloroquin was given as a routine, and an aspirin mixture in many cases. Children who apparently had true measles were given sulphonamide, with penicillin if there were respiratory signs. Diarrhoea was treated with a routine mixture containing sodium and potassium chloride, which the mothers were instructed to add to the child's drinking water. The two children with rectal temperatures over 106° F. were both admitted to the ward for a few hours. Neither seemed to be ill, and after tepid sponging and observation the mothers were allowed to take them home. Both were well when seen on the following day.

DISCUSSION

The trials described here are open to criticism on the following grounds: the children were routinely seen only on 3 of the days on which they were likely to have reactions: the examination they were given could not be more than cursory; 40–50 children had to be seen each morning in addition to the routine work of a heavy paediatric unit. However, they were seen in a very good light, fully stripped, on their mother's knees. The authors are confident that any major abnormality would have been noticed.

SUMMARY

1. The severity of measles in infants and young children in Ilesha in Nigeria suggested this as a suitable centre for a trial of measles vaccine.

2. The trial was divided into three stages. In the first the vaccine was given to a group of 26 children who could be kept under close observation and were seen twice daily. In the second the vaccine was given to 120 children, a similar group receiving gamma globulin and an inert material. In the third stage the effect of vaccine and gamma globulin given as separate injections to 378 children, was compared with that of gamma globulin and inert material given to another control group. The second and third stages were run on the 'double blind' principle.

3. The children receiving vaccine alone showed fairly severe reactions but none were disabled by them; for example, 19% had fever over 103° F. The reactions were similar to those observed in American children, with the one exception that diarrhoea was seen amongst African children receiving vaccine without gamma globulin. Those receiving vaccine and gamma globulin had only minor reactions. In the vaccinated children there was a notable absence of the severe complications seen with the natural disease in Nigeria.

4. Children who were well below the average weight for their age and sex in this community did not show more severe reactions than those above the average weight.

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