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A Further Study on Measles Vaccination in Nigerian Children *

R. G. HENDRICKSE,[1] D. MONTEFIORE,[2] P. M. SHERMAN [3] & G. O. SOFOLUWE [4]

Measles is a serious disease in Nigeria, causing severe morbidity and appreciable mortality; it occurs almost exclusively in the pre-school child with a peak incidence in the second year of life. A safe measles vaccine would be of inestimable value both in that country and in other areas where the disease constitutes a grave menace. Studies using vaccines of the Enders Edmonston B type have shown that while these are efficient immunizing agents, severe reactions are too frequent to permit of their wide general use. In the quest for safer vaccines, and in accordance with the recommendations of a WHO Scientific Group, a field trial was undertaken in Western Nigeria in May 1964 to make direct comparisons of the antigenicity and reaction rates of three further-attenuated measles vaccines (Schwarz, Beckenham 20 and Beckenham 20/2) and Enders Edmonston B vaccine plus gamma-globulin. A control group was also included.

Analysis of the clinical responses demonstrated that reactions were similar, and of minimal severity, in all vaccine groups. Neutralizing antibody responses showed that all the vaccines used were effective immunizing agents. From the point of view of ease of administration and expense, however, further-attenuated vaccines seem preferable to Enders Edmonston B administered with gamma-globulin.

In 1963 a WHO Scientific Group that met to discuss measles vaccines recommended that special attention should be given to

" the setting up, in countries with different socio-economic and environmental conditions, of field trials (which should include placebo groups) to make direct comparisons of the antigenicity and reaction rates of the present further-attenuated strains. These trials should also include a group given one injection of inactivated vaccine followed by one injection or an attenuated live vaccine . . . The inclusion of a reference vaccine is essential." [5]

In accordance with this recommendation a study was carried out, under WHO auspices, in a small town in Western Nigeria during the months of May and June 1964. The study was conducted along the lines recommended by the WHO Scientific Group, but practical considerations prevented the inclusion of a group given one injection of inactivated vaccine followed by one injection of attenuated live vaccine. This group was replaced by one that received a further-attenuated vaccine (Beckenham 20/2), which had not been previously subjected to field trial. The results of the study are reported below.

MATERIAL AND METHODS

The general conduct of the trial was similar to that of our previous comparative trials.[6]

Subjects

Healthy children between 6 months and 2 years of age who had no history of a previous attack of measles were invited to attend for vaccination. Most

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[1] Professor and Head of the Department of Paediatrics, and Director of the Institute of Child Health, University of Ibadan, Nigeria.

[2] Department of Bacteriology, University of Ibadan, Nigeria.

[3] Research Fellow, Departments of Paediatrics and Bacteriology, University of Ibadan, Nigeria.

[4] Ibarapa Community Health Project, University of Ibadan, Nigeria.

[5] WHO Scientific Group on Measles Vaccine Studies (1963) *Wld Hlth Org. techn. Rep. Ser.*, 263, 37.

[6] Hendrickse, R. G., Montefiore, D., Sherman, P. M. & Van der Wall, H. M. (1964) *Brit. med. J.*, 1, 470.

of the children were given a curative dose of an antimalarial drug (chloroquine sulfate) prior to vaccination. A few children, however, did not receive their chloroquine owing to a misunderstanding of instructions.

After vaccination, the children were required to attend on the 6th day, 8th-11th days inclusive, 13th day, 21st day and 28th day for follow-up examinations. The observers who carried out the follow-up examinations were kept unaware of the vaccination status of the children. The clinical findings on each child during the follow-up period were recorded on a special record card designed by WHO.

Serum samples were taken on the day of vaccination from alternate children in each vaccine group. Second samples were taken on the 28th post-vaccination day from those children attending who had been previously sampled.

Vaccines

The five vaccine groups were as follows:

Group A	Beckenham 20 vaccine
Group B	Enders Edmonston B vaccine plus gamma-globulin at 0.01 ml/lb (0.45 kg) body-weight (reference vaccine)
Group C	Beckenham 20/2 vaccine
Group D	Placebo (uninfected tissue culture medium)
Group E	Schwarz vaccine

Beckenham 20, Enders Edmonston B and Schwarz vaccines have been described in the report of the WHO Scientific Group on Measles Vaccine Studies quoted above. Beckenham 20/2 vaccine was prepared from the same seed virus as Beckenham 20 vaccine, but differed in having been grown on tissue cultures derived from leucosis-free chick embryos. The control group received an injection of uninfected tissue culture medium.

Vaccines were titrated before the trial in Hep-2 tissue cultures. The dose of each vaccine administered to the children was approximately:

Beckenham 20 vaccine	$10^{2.7}$ $TCID_{50}$
Enders Edmonston B vaccine .	$10^{2.1}$ $TCID_{50}$
Beckenham 20/2 vaccine . . .	$10^{2.1}$ $TCID_{50}$
Schwarz vaccine	$10^{3.4}$ $TCID_{50}$

Assessment of results

At the completion of the trial children known to be immune and those who had defaulted from regular follow-up were excluded from the analysis of results. The clinical records of the remaining children were then carefully scrutinized and an assessment of each child was made to determine whether there had been any evidence of measles and whether the child had remained well or had been unwell during the first 14 days after vaccination, when reactions could have been expected. The vaccination code was only broken after this exercise had been completed.

Serology

Serum samples were tested for the presence of neutralizing antibodies to measles virus using Hep-2 tissue cultures and a challenge dose of 30-300 $TCID_{50}$ of measles virus.

RESULTS

In all, 490 children between the ages of six months and two years attended on the day of vaccination, but 82 were not considered suitable for inclusion in the trial because of concurrent illnesses. The remaining 408 children were randomly allocated to one of the four measles vaccine group or to the control group.

Table 1 shows the number of children in each vaccine group and the number considered suitable for final assessment. As explained earlier, the difference between these totals is accounted for by the exclusion of known immunes and defaulters from the regular follow-up.

TABLE 1
NUMBERS OF CHILDREN VACCINATED AND CLINICALLY ASSESSED

Vaccine group	No. vaccinated	No. assessed
Beckenham 20	81	56
Enders Edmonston B plus gamma-globulin	82	48
Beckenham 20/2	82	43
Placebo	81	56
Schwarz	82	47
Total:	408	250

Clinical assessments were made on a total of 250 children. The clinical findings are summarized in Table 2. While the data given in this table exclude

TABLE 2

CLINICAL RESPONSES AFTER VACCINATION

Observations	Beckenham 20	Enders Edmonston B plus gamma-globulin	Beckenham 20/2	Controls	Schwarz
Number of observations	56	48	43	56	47
Number of males	29	21	25	27	26
Number of females	27	27	18	29	21
Mean age (months)	13.4	12.6	13.1	11.8	12.9
Mean maximum temperature (°F(°C))	100.6 (38,1), SD 1.1	100.5 (38.0), SD 1.3	101.0 (38.3), SD 1.2	100.5 (38.0), SD 1.5	100.5 (38.0), SD 1.6
Mean duration of fever 100°F (37.7°C) or over (days)	1.9, SD 1.1	1.9, SD 1.5	2.5, SD 1.8	1.8, SD 1.1	2.2, SD 1.4
Fever 103°F (39.5°C) or over (%)	7.1	8.3	11.6	8.9	12.8
(?) Malaria [a] (%)	3.6	4.2	11.6	5.4	8.5
With rash (%)	19.6	4.2	27.9	12.5	21.3
With rash and fever over 100°F (37.7°C) (%)	16.1	0	25.6	8.9	17.0
Cough (%)	39.3	39.6	32.5	39.3	36.2
Coryza (%)	58.9	81.2	39.5	58.9	57.4
Conjunctivitis (%)	3.6	2.1	2.3	5.4	2.1
Diarrhoea (%)	28.6	29.1	34.9	25.0	44.7
Tonsillitis (%)	3.6	2.6	0	1.8	0
Faucial inflammation	17.8	14.6	16.3	14.3	14.9
Convulsions (%)	0	2.1	0	1.8	0
"Unwell" (%)	12.6	16.7	13.9	16.1	25.5

[a] Clinical diagnosis only, with response to specific therapy.

children who failed to attend regularly for follow-up, there is no reason to suppose that clinical reactions among the defaulters were significantly different from those occurring among children inincluded in the assessment. It will be seen that there is little difference between the various groups, with the exception of a high incidence of coryza among children given Enders Edmonston B vaccine plus gamma-globulin, and of diarrhoea among the children given Schwarz vaccine. Although the incidence of these findings is significantly higher than among the control group ($P=0.05$), the reasons are not clear, and we feel that further work would be required to ascertain whether or not these effects could be directly attributed to the vaccines.

It will be noted that a small proportion of children in each vaccine group were thought to have had malaria. This diagnosis was made on clinical findings and rapid response to specific antimalarial therapy. Nearly all these children had rectal temperatures of 103°F (39.5°C) or over, and the incidence of severe febrile responses in each group directly attributable to the vaccines may be appreciably lower than that which has actually been recorded.

The incidence of faucial inflammations and tonsillitis in all groups was lower than that found in some of our previous trials.[1] This probably reflects the differing frequencies of intercurrent infections of the upper respiratory tract at different times.

[1] Hendrickse, R. G., Montefiore, D., Sherman, P. M. & Van der Wall, H. M. (1964) *Brit. med. J.*, **1**, 470.

TABLE 3
CRITERIA FOR ASSESSING CHILDREN AS "UNWELL"

Observations	Beckenham 20	Enders Edmonston B plus gamma-globulin	Beckenham 20/2	Controls	Schwarz
Upper respiratory tract infection	1	6	1	3	3
"Bronchitis"	1		1		1
Pneumonia			1		
Otitis media	2				
Diarrhoea			1	1	3
Diarrhoea and tonsillitis	1				
Not eating and dehydrated				1	
"Off colour" (? blood in stools)				1	
Exanthem subitum				1	
Abscess of neck				1	
(?) Malaria [a]	2	2	1		4
"Wild" measles			1		
Died (cause not known)				1	1
Number given specific treatment	6	7	6	6	11

[a] Clinical diagnosis only, with response to specific therapy.

The reasons for assessing children as "unwell" are given in Table 3. It will be noted that two children died during the period of follow-up: one of these had received the Schwarz vaccine and the other was in the control group. Autopsies were not performed, but there was no evidence to suggest that vaccination had played any part in these fatalities.

Thirteen children were not seen at all after the day of vaccination, but all other defaulters were visited or reports were obtained within the period of 28 days after vaccination. The reasons for failure to attend were generally that the child was well, and the mother, being busy or away on her farm, had no incentive to bring the child to the clinic. From the reports obtained there is no reason to suppose that the children failing to attend the follow-up fared any worse than the others.

Serology

Blood samples were taken from a total of 200 children on the day of vaccination; 30 of these children proved to be immune to measles.

The occurrence of neutralizing antibody increased with age. As is shown in Table 4, there was a sharp increase in the proportion of children immune to measles after the age of 20 months.

TABLE 4
INFLUENCE OF AGE ON IMMUNITY TO MEASLES

Age-group (months)	Number of children [a]	Total immune
6-8	49	2 (4.1 %)
9-12	62	6 (9.7 %)
13-16	34	4 (11.8 %)
17-20	30	6 (20.0 %)
21-24	24	11 (45.8 %)

[a] The age of one immune male was not recorded.

Altogether 102 paired serum samples were obtained from initially non-immune children. The results of antibody determinations are given in Table 5. Although the numbers in each group are

TABLE 5

NEUTRALIZING ANTIBODY RESPONSE IN INITIALLY SUSCEPTIBLE CHILDREN

Observations	Beckenham 20	Enders Edmonston B plus gamma-globulin	Beckenham 20/2	Control	Schwarz
Number of paired sera tested	23	17	19	23	20
Nu mber showing fourfold or greater increase in antibodies	20	16	18	1	19
% Seroconversion	87	94	95	4	95
Geometric mean titre of post-vaccination serum	23	38	34	0.5	27

too small for any differences to be statistically significant, there is some suggestion that the batch of Beckenham 20 vaccines used may be a less effective antigen than the other vaccines employed in this trial.

CONCLUSIONS

There was little difference in clinical response between any of the vaccine groups and the control group. The only significant differences were, as already noted, a higher incidence of coryza among children given Enders Edmonston B Vaccine plus gamma-globulin and of diarrhoea among children given Schwarz vaccine. It would therefore appear that the reactions following the administration of any of the further-attenuated vaccines, or the Enders Edmonston B vaccine plus gamma-globulin, are of minimal severity. However, from the point of view of ease of administration and expense the further-attenuated vaccines are preferable to Enders Edmonston B vaccine plus gamma-globulin. Neutralizing antibody responses showed that all the vaccines used were effective immunizing agents.

We consider that the time has now come when large-scale immunization with a further-attenuated vaccine could justifiably be undertaken, especially in developing countries where measles is a serious disease.

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RÉSUMÉ

Cette enquête, menée au Nigéria occidental en 1964, avait pour but d'évaluer l'antigénicité et les taux de réaction respectifs de différents vaccins antirougeoleux suratténués et du vaccin Enders de souche Edmonston B, servant de préparation de référence.

Au total, 408 enfants de 6 mois à 2 ans, répartis en cinq groupes, ont reçu l'une des préparations suivantes: vaccin Beckenham 20, vaccin Beckenham 20/2 (préparé à partir de la même souche que le vaccin Beckenham 20, mais cultivé sur cellules d'embryon de poulet exempt de leucose aviaire), vaccin Schwarz, placebo et vaccin de référence. La surveillance clinique a porté sur 250 enfants, et un examen sérologique a été effectué chez 102 vaccinés, au moment de la vaccination et 28 jours après.

Le coryza a été fréquent chez les enfants ayant reçu le vaccin Enders, cependant que la vaccination par le vaccin Schwarz provoquait un grand nombre de diarrhées. Il y eut, dans tous les groupes de vaccinés, moins de cas de laryngite et d'amygdalite que lors d'essais antérieurs. Le fait qu'un certain nombre d'enfants souffraient de paludisme n'a pas permis de préciser l'influence exacte de la vaccination dans l'apparition des réactions fébriles post-vaccinales. Deux décès ont été enregistrés: l'un des enfants avait reçu le vaccin Schwarz, l'autre du placebo. L'autopsie n'a pas été pratiquée, mais une influence éventuelle de la vaccination n'a pu être démontrée.

L'examen sérologique a montré que tous les vaccins déterminaient une immunisation très satisfaisante. Cependant, au cours de cette enquête limitée, il semble que le pouvoir antigénique du vaccin Beckenham 20 ait été inférieur à celui des autres préparations.