Comparative Trial of Further Attenuated Measles Vaccines

R. G. HENDRICKSE,* M.D., F.R.C.P.ED. ; D. MONTEFIORE,* M.D., DIP.BACT., M.C.PATH.
P. SHERMAN,* M.B., B.S., D.C.H. ; T. PERADZE,† M.D.

Brit. med. J., 1966, 1, 779–781

There is at present no general agreement about the best method of achieving immunization against measles (Wallgren, 1965). A single injection of a live further-attenuated vaccine usually produces satisfactory immunity, but may be attended by untoward reactions in a small percentage of cases. Reactions to live vaccines can be reduced by prior injection of killed vaccine (Clarke, 1965) or by simultaneous injection of gamma-globulin, but either procedure increases the cost of immunization, and makes greater demands on patient and doctor alike. Because of these considerations, immunization by a single dose of live further-attenuated vaccine recommends itself as the method of choice in developing countries provided that reaction rates are not unacceptably high.

In studies on several new further-attenuated measles vaccines undertaken in Nigeria during 1962–3 Beckenham 20 vaccine proved to be the most satisfactory (Hendrickse *et al.*, 1964). Later this vaccine was subjected to a direct comparative trial with other vaccines, including Schwartz vaccine. Results indicated that the reactogenicity and immunogenicity of Beckenham 20 and the Schwartz vaccines were very similar (Hendrickse *et al.*, 1965). Subsequently, three batches of vaccine, produced at different passage levels from Beckenham 20 vaccine seed, became available for clinical trial. We report here the findings of a study undertaken to compare the reactogenicity and immunogenicity of these three new vaccines and the Schwartz vaccine. One other further-attenuated vaccine, Leningrad 16, was also included in the trial, but findings relating to this vaccine are excluded from this report as the potency of that vaccine was reduced by adverse conditions during transit to Nigeria.

Materials and Methods

The general conduct of the trial was similar to that of our previous comparative trials (Hendrickse *et al.*, 1964).

Healthy Nigerian children aged 6 months to 2 years who had not had measles were accepted for vaccination. Follow-up observations were made on the 5th, 7th, 8th, 10th, 11th, and 12th post-vaccination days ; a final assessment was made on the 21st post-vaccination day. The observers who carried out the clinical examinations were kept unaware of the vaccination status of each child. Findings during the follow-up period were recorded on a standard form.

Vaccine Groups

Children were randomly allocated into one of six groups, as follows: group A, Beckenham 29 ; group B, Beckenham 30 ; group C, placebo (tetanus toxoid) ; group D, Beckenham 31 ; group E, Schwartz vaccine ; group F, Leningrad 16.[1] Beckenham 29, 30, and 31 vaccines were all derived from Beckenham 20 vaccine seed: this has been previously described (Report, 1963). The Schwartz vaccine has been previously described (Report, 1963).

All the vaccines except Beckenham 31 were titrated in Hep-2 tissue cultures. Owing to an error none of the Beckenham 31 vaccine was reserved for subsequent titration : the dosage has therefore been calculated from an earlier titration made by the suppliers, using *Erythrocebus patas* kidney-tissue cultures.

The titration values indicated that the children in the various groups received :

Beckenham 29 vaccine, $10^{3.1}$ $TCID_{50}$ per dose
Beckenham 30 vaccine, $10^{2.8}$ $TCID_{50}$ per dose
Beckenham 31 vaccine, $10^{3.4}$ $TCID_{50}$ per dose
Schwartz vaccine, $10^{3.0}$ $TCID_{50}$ per dose

Serology

Finger-prick blood samples were taken on the day of vaccination and on the 21st post-vaccination day. Children who fell into the control group were not bled : alternate children in the first 400 allocated to the vaccine groups had blood samples taken.

The capillary blood samples were taken on to paper discs cut from Postlip Fluffless Fibrefree paper (Mill 633). Each disc absorbed 0.2 ml. of blood when fully saturated. The samples were stored in individual labelled polyethylene envelopes at −50° C. until required for examination.

When the second blood samples were available the samples were eluted from the paper discs by placing each in a 75 by 12 mm. tube, adding 0.8 ml. of phosphate buffered saline, and shaking for one hour on a Kahn shaker at room temperature. The eluates were then used, without heat-inactivation, for titration of measles antibody by means of the haemagglutination inhibition test. The arbitrary assumption was made that each blood would contain 50% cells and 50% serum : hence the initial dilution after elution of the sample was taken as a 1 : 10 serum dilution.

Each serum was first absorbed with an equal volume of 2.5% *E. patas* red cells. Of the absorbed serum dilutions 0.2 ml. was then allowed to react in the wells of M.R.C. perspex haemagglutination trays, with an equal volume of saline containing 6 H.A. units of measles haemagglutinin, for one hour at room temperature (22° C. approximately). Then 0.2 ml. of a 1.5% suspension of *E. patas* red cells was added, and the trays were placed at 37° C. The results were read by the pattern method when the cells had fully settled, usually after about three hours.

Previous experiments had shown that the results obtained by the above method were closely comparable to those obtained with serum separated from samples of venous blood.

Assessment of Results

After completion of the daily follow-up the clinical records were carefully examined. The records of those children who

* From the Departments of Paediatrics and Bacteriology, and the Institute of Child Health, University of Ibadan.
† On secondment by W.H.O. from Pasteur Institute, Leningrad.
[1] The Leningrad 16 vaccine arrived only on the day of vaccination: children who had been originally allocated to group A were subdivided so that a proportion of them received Leningrad 16 vaccine. Hence the numbers of children in group A and group F are smaller than in the other groups.

had failed to attend regularly were excluded. An assessment was then made on the remaining records of the degree of reaction shown to vaccination, and whether the child had been well or unwell during the period when vaccination reactions were expected. The vaccination code was broken only after this exercise had been completed.

Later, when the serological results were available, records of known immune children were also excluded from analysis of the results.

Results

A total of 496 children were included in the trial. Table I shows the numbers of children in each vaccine group and the numbers on which final assessments were made. The differences between these totals are accounted for by exclusion of known immunes and defaulters.

The clinical findings in the 360 children finally assessed are summarized in Table II.

TABLE I.—*Numbers of Children Vaccinated and Clinically Assessed*

	Beckenham 29	Beckenham 30	Control	Beckenham 31	Schwartz	Leningrad 16
No. vaccinated	55	97	97	97	90	60
No. assessed ..	46	71	89	80	74	Not assessed

TABLE II.—*Clinical Responses After Vaccination*

	Beckenham 29	Beckenham 30	Control	Beckenham 31	Schwartz
No. observed	46	71	89	80	74
Mean age (months)	13·3	13·6	14·3	14·0	12·6
Mean max. temp. (°F. rectal)	100·8 S.D. 1·2	100·5 S.D. 1·1	100·1 S.D. 0·6	100·8 S.D. 1·05	100·3 S.D. 1·03
Mean duration fever 100° F. and over	3·1 S.D. 2·02	3·0 S.D. 1·66	2·1 S.D. 1·5	3·2 S.D. 1·9	2·8 S.D. 1·7
% fever 100° F. and over	84·8	83·1	70·8	87·5	81·1
% fever 103° F. and over	6·5	2·8	0	6·25	2·7
% with rash	17·4	22·5	5·6	27·5	9·5
% with rash and fever: 100° F. and over	17·4	13·3	4·5	26·25	6·7
% cough	54·3	57·7	50·6	58·7	55·4
% coryza	56·5	54·9	56·2	63·7	66·2
% conjunctivitis	2·2	2·8	9·0	6·25	6·7
*% diarrhoea	23·9	22·5	29·2	31·25	35·1
% tonsillitis	4·3	0	0	0	0
% faucial inflam.	8·7	12·7	3·4	7·5	4·1
% wild measles	0	1·4	0	0	0
% unwell	17·4	14·1	5·6	10·0	10·8

* Complaints made by parents. S.D. = Standard deviation.

The following points are worthy of note :

1. Less than 3% of children receiving either Beckenham 30 vaccine or Schwartz vaccine developed fevers higher than 103° F. (39.4° C.) (rectal), while over 6% of those receiving Beckenham 29 or Beckenham 31 vaccines developed fevers of this degree. These differences are, however, not statistically significant ($P>0.01$).

2. There is evidence that the Beckenham vaccines give rise to rashes more often than does the Schwartz vaccine ($P<0.01$).

3. Children receiving Beckenham 29 vaccine were more frequently "unwell" than those receiving the other vaccines. The proportion of unwell children in the Beckenham 29 group is significantly higher than in the control group ($P<0.05$). There is no significant difference at this level of confidence between the proportion of unwell children in the other vaccine groups and the control group. The findings do suggest, however, that between 8 and 10% of children receiving Beckenham 30, Beckenham 31, or Schwartz vaccines develop some degree of illness attributable to the administration of the vaccines.

4. The reasons for assessing children as unwell are given in Table III. Despite the small numbers, the figures suggest, as has been reported in previous trials, that administration of measles vaccine may predispose towards the development of tonsillitis and diarrhoea (Hendrickse *et al.*, 1964 ; Milovanović, 1965). None of the children recorded as unwell was seriously ill, and certain conditions (abscess, ulcerative stomatitis, and impetigo) were clearly unrelated to vaccination. The abscesses were not at the site of vaccination.

TABLE III.—*Reasons for Assessing Children as "Unwell"*

	No. of Children				
	Beckenham 29	Beckenham 30	Control	Beckenham 31	Schwartz
U.R.T.I.	1	3	2	1	1
L.R.T.I.	1			1	
Tonsillitis	2	1		1	
Otitis media	1			1	
Diarrhoea		1		3	2
D. & V.	1				1
D. & V. and dehydration		1			
D. & V. and otitis media					1
Diarrhoea and U.R.T.I.				1	1
Dysentery		1	1		1
"Wild" measles					
General ill-health; no specific cause	1	2	1		
Ulcerative stomatitis			1		
Abscess	1	1			
Impetigo					1

U.R.T.I. = Upper respiratory tract infections, including faucial inflammation.
L.R.T.I. = Lower respiratory tract infections.
D. & V. = Diarrhoea and vomiting.

5. One child who had been given Beckenham 29 vaccine died. She had had recurrent diarrhoea before vaccination, but this was not mentioned by the mother, and at the initial examination on the day of vaccination she was considered fit to receive the vaccine. Three days after vaccination the diarrhoea recurred, and she was thereafter cared for at the University College Hospital, Ibadan, and did not attend any follow-up clinics. She died as a result of the diarrhoea on the 15th post-vaccination day.

Serology.—The serological findings are shown in Table IV. There is no difference between the conversion rates, at the 95% level of confidence, between the Beckenham and Schwartz vaccines.

TABLE IV.—*Antibody Response in Initially Susceptible Children*

	Beckenham 29	Beckenham 30	Control	Beckenham 31	Schwartz	Leningrad* 16
No. paired sera tested	13	30	—	26	23	18
No. with fourfold or greater increase in antibodies	13	28	—	23	21	14
% seroconversion	100	93·3	—	88·4	91·3	77·7
Geometric mean titre after vaccination	144	157	—	96	94	25

* It is of interest that despite the low titre of this vaccine ($10^{1.3}$ $TCID_{50}$ per dose) a 77·7% seroconversion rate was achieved. There was clinical evidence of natural measles in only one of the children given this vaccine.

Summary and Conclusions

A comparative trial of five different further-attenuated measles vaccines matched against a control group of children given tetanus toxoid is reported. Findings based on the clinical assessments of 360 children showed that there is little difference in the reactogenicity of Beckenham 30, Beckenham 31, and Schwartz vaccines. Children receiving these vaccines were more often "unwell" than children in the control group, but in no cases were any serious complications observed. Beckenham 29 vaccine showed the highest unwell rate and also the highest sero-conversion rate. There is some evidence, therefore, that this vaccine may be the least attenuated of those included in the present trial.

One child who received Beckenham 29 vaccine died, but the nature of the illness and the time of onset indicate that there is no reason to ascribe her death to the measles vaccination.

We would like to thank Dr. S. O. Franklin and Dr. M. P. Otolorin, Ministry of Health and Social Welfare, Western Region ; Dr. G. S. Sethi, Medical Officer of Health, Ibadan ; and the sister in charge of the Maternity Centre, Inalende, Ibadan, for their

assistance. We are grateful to members of the medical and nursing staff at University College Hospital, Ibadan, who volunteered their assistance during the trial. We would also like to thank the Western Nigerian Broadcasting Service for help in publicizing the trial.

The vaccines were kindly supplied by the Wellcome Research Laboratories and by Professor A. A. Smorodintzev, Pasteur Institute, Leningrad.

REFERENCES

Clarke, M. (1965). *Arch. ges. Virusforsch.*, **16**, 351.
Hendrickse, R. G., Montefiore, D., Sherman, P. M., and Van Der Wall, H. M. (1964). *Brit. med. J.*, **1**, 470.
—— —— —— and Sofoluwe, G. O. (1965). *Bull. Wld Hlth Org.*, **32**, 803.
Milovanović, M. V. (1965). *Arch. ges. Virusforsch.*, **16**, 231.
Report (1963). *Wld Hlth Org. techn. Rep. Ser.*, No. 263.
Wallgren, A. (1965). *Arch. ges. Virusforsch.*, **16**, 367.

Medical Memoranda

Survival After High-tension Electrical Burns Complicated by Acute Tubular Necrosis

Brit. med. J., 1966, **1**, 781–782

Recovery from acute tubular necrosis resulting from high-tension electrocution is unusual (Alwall, 1958). This paper therefore presents the characteristic features shown by two victims of such accidents seen by us in the last 18 months. The management of the second patient was facilitated by the local application of a cream containing organic acids (Aserbine), which obviated the need for surgical desloughing.

CASE 1

A 44-year-old man accidentally touched a high-tension cable (33,000 volts) while descending an iron ladder. On admission shortly afterwards he was conscious but unable to move either arm. The coins in his pocket had been partially melted and he had sustained full-thickness burns on both arms and a partial-thickness burn on the right leg—in all about 10% of the body surface area. Within 48 hours both arms became very swollen and hard, but the radial pulses remained good. The left arm was totally anaesthetic and the right arm was anaesthetic below the level of the insertion of the deltoid. Both arms remained completely paralysed apart from slight movements of the shoulders.

His systolic blood-pressure never fell below 100 mm. Hg, yet during the first 48 hours he passed only 400 ml. of brown urine, which showed a strong absorption band characteristic of methaemoglobin. By the second day his plasma urea was 208 mg./100 ml., potassium 7.9 mEq/l., and bicarbonate 10 mEq/l. Eight haemodialyses were required to control the hyperkalaemia and uraemia during his 30 days of oliguria.

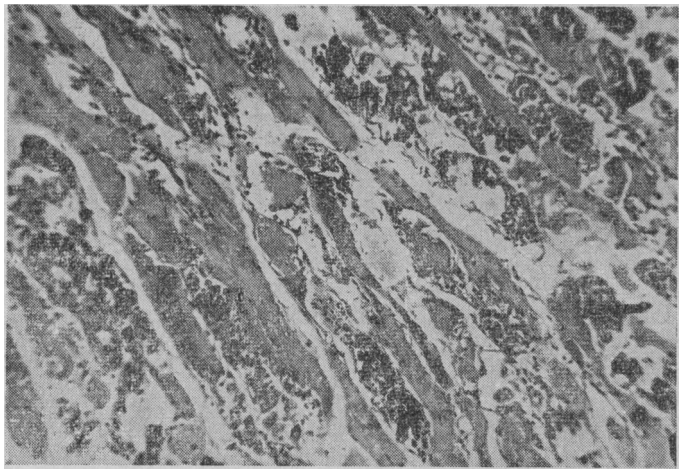

FIG. 1.—Section of latissimus dorsi from Case 1 stained with haematoxylin and eosin to show necrotic muscle as dark patches.

The dressings were removed for the first time on the eleventh day because of a copious discharge of pus containing penicillin-resistant staphylococci from a deep wound in the left axilla. Though the infection responded to fusidic acid, a haemorrhage of about 250 ml. from the left axillary vein necessitated amputation of the arm on the eighteenth day. The left latissimus dorsi (Fig. 1) and all the muscle groups in the arm were stippled by pale necrotic muscle bundles despite the complete patency of all the arteries.

After the operation his general condition immediately began to improve and 13 days later his 24-hour urine volume exceeded 500 ml. for the first time. By the fifth week the amputation wound and the burn on the leg had healed, the paralysis and anaesthesia of the right arm had not improved, and areas of necrosis had become demarcated over the elbow and ulnar side of the forearm.

When these wounds were desloughed surgically on the forty-third day it was apparent that the distal one-third of the biceps and 3 in. (7.6 cm.) of the median and ulnar nerves had been destroyed in the antecubital fossa. The radial nerve was swollen, soft, and haemorrhagic, but as it was in continuity it was left *in situ*. Two weeks later the forearm had to be desloughed again because of necrosis of tissue which had initially appeared viable. On the sixty-seventh day the skin defects in front of the elbow and on the forearm were grafted and by the fifteenth week the arm had healed completely.

By October 1965 normal sensation had returned in the distribution of the radial nerve and the patient had some active, albeit weak, extension at the elbow, wrist, and metacarpophalangeal joints. His general health was excellent and his blood urea was 35 mg./100 ml.

CASE 2

A 39-year-old schizophrenic man attempted suicide by grasping a high-tension wire (33,000 volts). He sustained small full-thickness burns on the palm of the left hand, the right buttock, and sole of the left foot, and extensive, partial, and full-thickness burns on the right side of the body, totalling about 20% of the body surface. Two pints (1.1 litre) of blood and 5 pints (2.8 litres) of plasma were required in the first three days. He became oliguric almost immediately, and his plasma urea had risen to 141 mg./100 ml. and plasma potassium to 7.1 mEq/l. by the second day.

The whole of the right arm became indurated and swollen to a circumference of 35.5 cm. at the mid-humeral level—that is, about 10 cm. more than the unaffected arm. The dorsum of the right hand was anaesthetic for two days, but all movements were present at about half normal strength and have remained so.

The burns were initially treated by exposure, but from the eighth day Aserbine cream was applied to the burns daily. By the thirtieth day the sloughs had separated to reveal either healed areas or healthy granulations (Fig. 2), and to expose the pectoralis major tendon in the right axilla. A little pus drained from this wound but otherwise there were no signs of infection. The patient's temperature rose to 100° F. (37.8° C.) each day during the first and third weeks of this treatment but the fever seemed to respond to antibiotics. Despite the oliguria no other toxic effects due to Aserbine were detected. No desloughing operation was required and the wounds