Trial of a reduced dose of measles vaccine in Nigerian children*

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To evaluate the effectiveness of measles vaccine in reduced dosage, Schwarz live, further attenuated measles virus vaccine was given in various doses by jet injector to 967 seronegative children aged 7–30 months in rural villages in the Northwest State of Nigeria. For children over 12 months of age, reducing vaccine virus dosage by 40%, 60%, or 80% led to progressive and statistically significant reductions in the seroconversion rates from 89% in children receiving the full dose to a minimum value of 46%. Reducing the volume of the inoculum below the standard of 0.5 ml resulted in a further reduction of seroconversion rates at each antigen dose level. Seroconversion rates in all dosage groups were lower for children below 12 months of age. These data suggest that dose reduction would not be a satisfactory economy measure in measles vaccination campaigns.

Measles is a major cause of disability and death in African children (*9*), apparently because of widespread malnutrition, which alters the host response to the measles virus (*12*). Since 1966, measles immunization campaigns to protect approximately 105 million children in west and central Africa have been carried out through the combined efforts of 19 participating countries, the government of the United States of America, and the World Health Organization (*13*). The high cost of measles vaccine and the fragility of the vaccine under field conditions have often slowed the progress of these campaigns (*2*, *5*).

Efficient and cost-effective use of live measles virus vaccine requires information on the minimum dosage of vaccine virus that is required for immunization, on the variation in the virus titres of various lots, and on the decreases in titre that may occur during vaccine distribution and administration. In the study described here, Nigerian children were given live, further attenuated measles vaccine in standard and in reduced virus doses and in various volumes by jet injector in an attempt to evaluate whether decreases in vaccine virus or in diluent volume could result in acceptable immunization levels. Although there is some disagreement as to what would constitute an effective minimum seroconversion rate for live measles vaccine, most authors would indicate a rate of 85-90% for children aged 12 months or more and would be satisfied with a rate of 70% in children below one year of age.

MATERIALS AND METHODS

Study population

The children under study were residents of nine rural villages in the Emirate of Daura, Northwest State, Nigeria. This area was chosen because a

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Table 1. Composition of experimental groups and results of immunization in initially seronegative children aged 12–30 months

Group	No. in group	Approximate measles vaccine dose ($TCID_{50}$) [a]	Volume of injection (ml)	Percentage seroconverting	Post-vaccination GMTs [b] of seroconverters
0	118	saline placebo	0.5	5.9	97.5
1	105	600	0.5	45.7	162.2
2	118	1200	0.2	64.4	158.3
3	111	1200	0.5	71.2	165.6
4	103	1800	0.3	73.1	173.8
5	105	1800	0.5	79.0	164.1
6	103	3000 (standard)	0.5	89.3	168.7

[a] $TCID_{50}$ = 50 % tissue culture infective dose of virus.
[b] Geometric mean titre; HI titre (reciprocal of dilution) used for both viruses.

preliminary serological survey showed that over 60% of the children there below the age of 2 years did not have measles antibody, this lack of antibody indicating a low level of measles activity in the years immediately preceding the study. In each village, the study was conducted in the dispensary or in a similar central public area. Children were screened for fever and overt illness. Age was judged from historical information supplied by an accompanying adult, and by subjective judgement based on physical stature. Afebrile and apparently healthy children aged 7–30 months were accepted for study. In May 1970, blood samples were taken to test for antibody to measles, and vaccine or placebo was given according to the protocol described below. Each child was given an identification tag that specified the child's vaccination group. Two months later, blood samples were again taken and all the children, regardless of group, were given a standard dose of measles vaccine.

At the time of vaccination, children were randomly assigned to one of seven groups (Table 1). Group 0 received a saline placebo and group 6, the usual recommended dose and volume. The other groups received intermediate doses of antigen at either standard or reduced volumes of injection. All inoculations were given by jet injector (Ped-O-Jet [a]) in the triceps region after alcohol cleansing.

[a] The use of trade names is for identification only and does not imply endorsement by the US Public Health Service or by the US Department of Health, Education, and Welfare.

Of the 1597 children studied, 1021 were found to have no detectable measles antibody in the preinoculation serum specimen. Of these, 64 (all the participants from one small village) were eliminated from this report when analysis revealed a total breakdown there of the coding and labelling system for the various experimental groups. The remaining 967 children formed the basis for analysis: 204 children aged 7–11 months and 763 aged 12–30 months.

Vaccine and laboratory methods

Schwarz live, further attenuated measles vaccine, supplied in lyophilized form in 50-dose vials, was used in all instances. The vaccine was stored and shipped at −20°C, but was transported to the villages in insulated containers on wet ice. It was reconstituted to the appropriate dilutions with distilled water immediately prior to use. All the vaccine was protected from light and was used within 3 hours of reconstitution. Sample vaccine vials were retained at the Center for Disease Control (CDC) for the determination of virus titres, and samples of vials carried to the study villages, kept on ice, and unreconstituted were returned for similar determination after the study.

Vaccine potency was determined by standard tissue culture techniques then in use at CDC (B. Lourie and J. Nakano, unpublished observations, 1974) and was expressed as the mean tissue culture infective dose ($TCID_{50}$). Blood samples obtained were allowed to clot and, after centrifugation, the serum was stored at −20° until analysis. The presence of

measles haemagglutination inhibition (HAI) antibody was determined by methods previously described (*4*).

Stock measles vaccine averaged 3.40×10^3 $TCID_{50}$ before the start of the study, and vaccine vials returned from the field averaged 3.17×10^3 $TCID_{50}$. Both values were within acceptable limits for vaccine use.

RESULTS

The results in children 12–30 months of age are shown in Table 1. Seroconversion to measles HAI antibody occurred in 5.9% of the placebo group. This was probably due to occasional failure in randomization, identification, or record-keeping procedures rather than to the acquisition of natural illness, because the geometric mean titres were lower in those who seroconverted than in the other vaccine groups. In each of the six groups, the measles HAI antibody geometric mean titres for children who seroconverted were the same. However, the proportion of children who seroconverted decreased with each successive reduction in the inoculating dose while the full inoculating volume of 0.5 ml was maintained. At the full dose (about 3000 $TCID_{50}$) there was 89.3% seroconversion, but dosage reductions of 40%, 60%, and 80% led to seroconversion rates of 79.0%, 71.2%, and 45.7%, respectively. At dosage reduction of 40% and 60%, reduction of the volume of diluted vaccine to 0.3 ml and 0.2 ml, respectively, led to small but significant further reductions in the seroconversion rates.

The results of measles immunization for children aged 7–11 months are shown in Table 2. In all groups the rate of seroconversion was less than in children over one year old. In the group that received the standard dose and volume of vaccine, the seroconversion rate was 63.6%. Reducing the dose of inoculum or the volume of the injection led to further corresponding reductions in the seroconversion rates.

Table 2. Composition of experimental groups and results of immunization in initially seronegative children aged 7–11 months

Group	No. in group	Approximate vaccine dose $TCID_{50}$ [a]	Vaccine volume (ml)	Percentage seroconverting
0	24	saline placebo	0.5	4.2
1	26	600	0.5	26.9
2	20	1200	0.2	50.0
3	28	1200	0.5	39.3
4	34	1800	0.3	44.1
5	39	1800	0.5	53.8
6	33	3000	0.5	63.6

[a] $TCID_{50}$ = 50% tissue culture infective dose of virus.

DISCUSSION

In small clinical trials of the efficacy of live, attenuated measles vaccine, seroconversion has been achieved with antigen inocula far below the usual recommended minimum dose of 1000 $TCID_{50}$. Meyer et al. (*8*), using the Edmonston vaccine, achieved conversions with less than 10 $TCID_{50}$ administered by jet injector. These studies raised the possibility that small doses of the costly measles vaccine might be used effectively in wide-scale vaccination programmes and led to attempts by us and by others to reduce the vaccine dose, using different strains, doses, and methods of inoculation.

Calafiore et al. (*1*) found a significant reduction in seroconversion to Schwarz vaccine when one-fifth of the standard dose was given in a 0.1 ml volume by a jet injector with either a subcutaneous or an intradermal nozzle. They suggested that this finding may have resulted from the inability of the jet injector to deliver this reduced volume effectively. Rey et al. (*10*) reported 95% seroconversion with 100 $TCID_{50}$ of the Schwarz strain given by jet injector in two injections. Rosenbloom et al. (*11*) were able to attain seroconversion in 22 of 26 children (84.6%) in Cameroon by giving 53 $TCID_{50}$ of Schwarz vaccine in the standard 0.5 ml volume by jet injector.

With 200 $TCID_{50}$ of Beckenham 31 measles vaccine administered in a 0.5 ml volume by jet injector, Hendrickse & Montefiore (*7*) achieved seroconversion in 90.2% of children studied in Kwara State, Nigeria. Hayden (*6*), with the same strain, also achieved over 90% seroconversion with one-fifth of the standard dose.

In the present study, unlike most of those cited, any reduction in the dose of the Schwarz strain or in the volume in which it was administered resulted in a reduction in the proportion of seroconverters. As seen in Table 1, this progressive failure rate was dose-related, even for the 1800 and 1200 $TCID_{50}$ doses of virus, which are above the recommended minimum potency standard of 1000 $TCID_{50}$. The reason for the disparate result is unclear. No specific lapses in vaccine handling or equipment failures were detected. The adequate maintenance of

vaccine viability under field conditions was demonstrated.

The reason for the lower seroconversion rates in children aged 7–11 months is unclear. This relative failure was not observed by Hayden (*6*) in a similar age group. It is possible that persistent measles antibody of maternal origin, not detected by the HAI system, was partly responsible (*13*). However, the 63.6% seroconversion rate in infants who received full doses should not deter mass vaccination in that age group in the developing countries, because of the high morbidity and mortality from measles that children of that age experience there.

At two dosages (1200 and 1800 $TCID_{50}$), reduction in the volume of the inoculum given by jet injector resulted in further diminished seroconversion rates. It has already been shown that alteration of the dose volume to 0.1 ml may lead to variable delivery of fluid into the tissue (*1*). The present study also suggests that, when vaccine is given in volumes of 0.2 and 0.3 ml by jet injector, delivery may be inadequate and that, even if vaccine dosage is reduced, the 0.5 ml injection volume should be maintained.

It remains to be shown whether a reduced dose of live, attenuated measles vaccine can maintain its efficacy when administered with other live and killed vaccine antigens—a procedure that is gaining popularity in immunization programmes (*2*).

RÉSUMÉ

ESSAI DE DOSES RÉDUITES DE VACCIN ANTIROUGEOLEUX CHEZ LES ENFANTS AU NIGÉRIA

Pour évaluer l'efficacité du vaccin antirougeoleux à posologie réduite, on a administré du virus vaccin vivant, souche Schwarz, hyperatténué, à diverses doses, à l'aide d'un injecteur sans aiguille, à 967 enfants séronégatifs, de 7 à 30 mois, dans des villages d'une zone rurale de l'Etat du Nord-ouest du Nigéria. Chez les enfants de plus de 12 mois, lorsqu'on réduisait la dose de virus vaccin de 40%, 60% ou 80%, on observait des réductions progressives et statistiquement significatives des taux de séroconversion qui ont été ainsi compris entre 89% chez les enfants ayant reçu la dose complète, et une valeur minimale de 46%. La diminution du volume de l'inoculum au-dessous du volume standard de 0,5 ml a provoqué une réduction encore plus poussée des taux de conversion pour chaque posologie de l'antigène. Dans tous les groupes constitués en fonction de la posologie, les taux de conversion ont été plus bas chez les enfants de moins de 12 mois. D'après ces données, il semble que la réduction des doses dans les campagnes de vaccination antirougeoleuse ne serait pas une mesure d'économie satisfaisante.

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