

# Response of Volta Children to Jet Inoculation of Combined Live Measles, Smallpox and Yellow Fever Vaccines

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*An earlier study established that Upper Volta children respond to vaccination with the Enders live attenuated measles strain in the same general fashion as do children in the USA. The present report describes a second pilot project carried out in Ouagadougou, Upper Volta. During this investigation various mixtures of live measles, smallpox and 17D yellow fever vaccines were introduced into susceptible infants by jet injection. Combining the attenuated virus vaccines did not alter or accentuate the characteristic clinical reactions elicited by the individual components, nor was there evidence of significant immunological interference. From this experience it is concluded that combined vaccination with these agents may be safely and effectively employed in larger programmes as the need dictates.*

Recent experience in the Republic of Upper Volta in the use of Enders live attenuated measles vaccine has been reported in another paper.<sup>4</sup> The results indicated that the clinical and immunological responses of Upper Volta children to the vaccine were comparable with those observed in children in other countries. Therefore, health personnel in the area have chosen to consider practical means by which measles immunization might be carried out within the framework of existing preventive medicine programmes.

Combined vaccines have been in general use for many years and the advantages accruing therefrom are well known (Boué, 1960; Ramon, 1939). For the most part, these combinations have consisted of bacterial vaccines or toxoids, but in West Africa much has been done with a combination of two live, attenuated viral vaccines—those for yellow fever and smallpox (Peltier, 1947).

Elisberg et al. (1956) showed that the cutaneous and serological responses to jet injection of smallpox vaccine were equivalent to those observed following use of the conventional methods of percutaneous

inoculation. Subsequent work by others established that smallpox vaccine prepared in chick embryo and 17D yellow fever vaccine could also be successfully administered to American adults by jet injection.<sup>5</sup> On the basis of this experience our group recently conducted a preliminary investigation in which 24 American infants were vaccinated simultaneously with live measles and smallpox vaccines. The results (unpublished) indicate this to be a safe and effective immunizing procedure. The potential value of administering combined vaccines in field programmes is obvious, and the Minister of Health of Upper Volta wished to undertake a pilot study to evaluate this procedure.

The present report is concerned with a study of the efficacy and safety of various combinations of measles, smallpox and yellow fever vaccines administered by jet injection to Upper Volta children, the majority of whom were less than one year of age and susceptible to infection by all three viruses.

## METHODS AND MATERIAL

Altogether 545 children of Ouagadougou participated in the study; none had a history of previous

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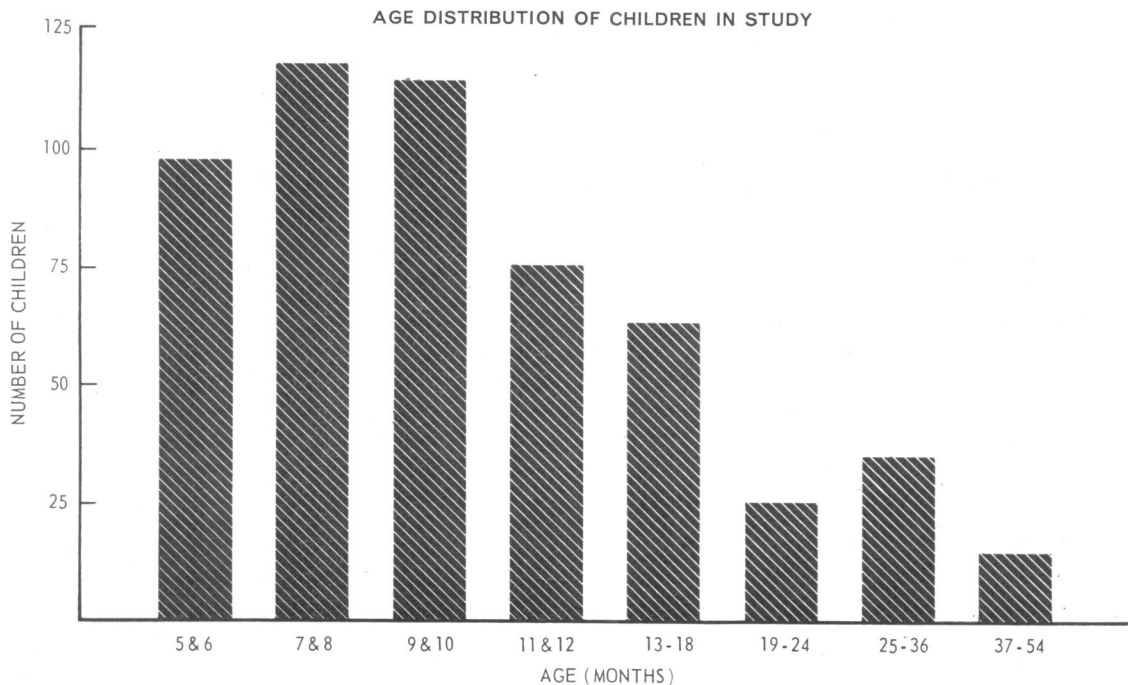
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<sup>4</sup> See the article by Meyer et al. on page 769 of this issue.

<sup>5</sup> Binn, L. N. (1956) *Quarterly progress report, January-March*, Walter Reed Army Institute of Research, Washington, D.C. (unpublished).

FIG. 1



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measles or of smallpox or yellow fever immunization. Children were placed in five groups of approximately equal size and received vaccines singly or in combination as follows: (1) measles; (2) smallpox;<sup>1</sup> (3) yellow fever;<sup>1</sup> (4) measles and smallpox; and (5) measles, smallpox and yellow fever. Assignments to the vaccine groups were made sequentially as the children registered for vaccination, consideration being given only to equalizing the ages of vaccinees in the groups. Although nutritional deficiencies and infectious and parasitic diseases are unusually common in Volta children,<sup>2</sup> none of those who presented themselves for vaccination were excluded from the study because of intercurrent diseases. Before vaccination each child was given a physical examination and a specimen of blood was obtained for future serological study. All groups were vaccinated during a single week (1-6 October 1962).

The age distribution of the children in the combined vaccine study is indicated in Fig. 1.

<sup>1</sup> Children who did not receive measles vaccine were revaccinated at the completion of the surveillance period.

<sup>2</sup> See the article by Meyer et al. on page 769 of this issue.

### Personnel

Vaccination and surveillance were performed at a centrally located dispensary by a team from the Division of Biologics Standards, National Institutes of Health (NIH), Bethesda, Md., USA, with the assistance of nurses of the Ministry of Health, Upper Volta. Administrative co-ordination of the project was provided through the Ministry of Health. The present study was also planned to serve as training experience for the sixteen Volta nurses who were to participate in a forthcoming mass measles vaccination campaign. With this in view, the Volta nurses performed all the operations associated with vaccination, including surveillance of children, under the immediate supervision of the NIH team.

### Surveillance

Parents were instructed to return with their children to the dispensary for observation every other day for three weeks following vaccination, or daily if the child were ill. On arriving, a Volta nurse gave each child a preliminary examination which included the recording of temperature and determination of the presence or absence of rash and

cutaneous smallpox reaction. Children with fever or other symptoms of illness were examined and treated by the NIH team. All medical records, including those noting the type of vaccine administered, were available to persons conducting the surveillance examinations.

#### *Vaccines*

The following vaccines were employed in the study: (1) Enders B-level live attenuated measles vaccine (Enders et al., 1960) grown in chick-embryo tissue cultures (this vaccine was supplied gratis by Dr M. R. Hilleman, Merck Institute for Therapeutic Research, West Point, Pa., USA); (2) a commercial lot of licensed chick-embryo-type bacteriologically sterile smallpox vaccine (Lederle Laboratories, Pearl River, N.Y., USA; Lot 2096-12A); and (3) a commercial lot of 17D yellow fever vaccine (National Drug Co., Philadelphia, Pa., USA; lot 5312). All three vaccines were supplied in the lyophilized state and were maintained under refrigeration.

#### *Jet injection of vaccines*

In the current study the Automatic Hypodermic Jet Injection Apparatus of the Scientific Equipment Manufacturing Corporation, New York, was employed. For this project the jet nozzle of the apparatus was modified in a simple manner to increase the amount of vaccine deposited intradermally, an important factor for immunization with smallpox vaccine (Elisberg et al., 1956). The modification consisted in the addition of a short sleeve cut from stiff plastic tubing (wall diameter, 3 mm) which slipped over the nozzle and extended 4 mm beyond the jet orifice. The modified jet injector was held against the arm in the usual manner with a pressure of about five pounds. With the sleeve attached, the jet orifice made only light contact against the skin.

In practice, groups of 20-40 children were assembled. Their left upper arms were cleansed with a solution of surgical soap (Phisohex, diluted 1:4 with boiled water) and the surface was wiped dry with surgical gauze. The vaccine was prepared for use at this time, and 0.5-ml amounts were injected into the deltoid region.

Those parts of the jet injector with which the biological materials were in contact were washed and then sterilized in a pressure-cooker prior to each vaccination period, i.e., twice a day. When not in use, the bottle of vaccine was removed from the vaccination gun and refrigerated.

#### *Preparation of vaccines for jet injection*

Each of the three lyophilized vaccines was packaged in multiple-dose containers. Vials contained the following number of human doses: measles vaccine, 25; smallpox vaccine, 100 (on the basis of percutaneous inoculation); and yellow fever vaccine, 20. Immediately before use, measles vaccine was rehydrated with 12.5 ml of sterile distilled water and yellow fever vaccine with 10.0 ml of sterile isotonic saline. Smallpox vaccine was rehydrated with 1 ml of sterile water but further dilution with glycerol solution was omitted. This rehydrated stock of smallpox vaccine was kept refrigerated for as long as one working day and then discarded. Immediately before use the smallpox stock material was diluted 1:100 with sterile isotonic saline. Final vaccines were used promptly; any remnants were discarded within an hour.

Combined vaccines were prepared as follows. For the measles-smallpox mixture, rehydrated measles vaccine was used as the diluent to prepare the 1:100 dilution of rehydrated stock smallpox vaccine. For the measles-smallpox-yellow-fever combination, 10 ml of rehydrated measles vaccine were used to rehydrate one vial of yellow fever vaccine. To this 10-ml volume of bivalent mixture was added 0.1 ml of the stock rehydrated smallpox vaccine. Thus, the bivalent and trivalent mixtures contained the same quantities of attenuated measles, smallpox and yellow fever vaccines as were contained in an equivalent volume of the respective monovalent preparations. Each child, regardless of age, was jet-inoculated with a 0.5-ml volume of the appropriate vaccine. The calculated amounts of the attenuated viruses administered to each recipient under these conditions were: measles, 12 000 median tissue culture infectious doses (TCID<sub>50</sub>); smallpox, 1 500 000 TCID<sub>50</sub>; and yellow fever, 6 300 000 median mouse lethal doses (LD<sub>50</sub>).

#### *Serum collection*

Blood specimens were collected from all children before vaccination, and from the majority a second sample was obtained three weeks after vaccination. Sera were promptly separated aseptically from the clots, then stored and shipped in the frozen state to the NIH for detailed examination.

#### *Antibody determinations*

Haemagglutination-inhibition (HAI) techniques were employed for the determination of antibodies for measles and smallpox (Elisberg et al., 1956;

TABLE 1  
PREVACCINATION SUSCEPTIBILITY OF CHILDREN IN STUDY TO MEASLES,  
SMALLPOX AND YELLOW FEVER

Vaccination group	Prevaccination serological results					
	Measles		Smallpox		Yellow fever	
	No. neg./ No. tested	% neg.	No. neg./ No. tested	% neg.	No. neg./ No. tested	% neg.
Measles	118/124	95	—	—	—	—
Smallpox	—	—	88/101	87	—	—
Yellow fever	—	—	—	—	94/102	92
Measles-smallpox	109/117	93	105/117	90	—	—
Measles-smallpox-yellow-fever	91/101	90	92/101	91	93/101	92
Total	318/342	93	285/319	89	187/203	92

Rosen, 1961). Smallpox HAI tests were begun at an initial serum dilution of 1 : 10, and those for measles at 1 : 8. When both specimens of paired sera were negative for measles antibodies they were retested at an initial dilution of 1 : 2. Seroconversion was considered to have occurred if the prevaccination serum of a child contained no demonstrable measles or smallpox antibodies while the post-vaccination serum gave positive results.

The mouse neutralization test was used for detection of yellow fever neutralizing antibodies. Inoculated mice were observed for 18 days; results were calculated by several methods including the conventional LD<sub>50</sub> test (Lennette, 1959) and a variation of the survival time method (Smith & Westgarth, 1957).

When the results of the yellow fever neutralization tests were calculated on the basis of a lethal endpoint, the following criteria were employed.

Seroconversion: prevaccination serum neutralizing less than 25 LD<sub>50</sub> of virus but post-vaccination serum neutralizing 25 or more LD<sub>50</sub> and at least 10-fold more than the prevaccination specimen.

No conversion: neither serum capable of neutralizing 25 or more LD<sub>50</sub> of virus.

Equivocal: (a) Prevaccination serum neutralizing 25 or more LD<sub>50</sub> of virus but post-vaccination serum neutralizing 10-fold more than the prevaccination serum; or (b) prevaccination serum neutralizing less than 25 LD<sub>50</sub> of virus and post-vaccination serum neutralizing 25 LD<sub>50</sub> or more but with less than a 10-fold difference between the two.

Previous immunity: both sera neutralizing 25 or more LD<sub>50</sub> of virus with less than a 10-fold difference between the two.

After completing analysis of the yellow fever data as described above, the raw data were re-examined on the basis of the survival time of mice. By this method seroconversion was demonstrated in all the paired samples that had previously been interpreted as positive, as well as in most of those that had formerly been considered equivocal and a few of those previously classified as negative.

The criteria used for defining seroconversion or no conversion by the survival time method were as follows.

Seroconversion: average survival time of mice inoculated with post-vaccination-serum and virus mixture at least eight days longer than mice receiving prevaccination-serum and virus mixture.

No conversion: serum pairs giving less than eight days difference in average survival time.

## RESULTS

### *Prevaccination status of children in study group*

Clinical observation of the vaccinees indicated that their health status was similar to that of children examined the previous year.<sup>1</sup> Although members of the present study were selected on the basis of no history of measles infection or vaccination against smallpox or yellow fever, serological studies revealed that some of the children had evidence of previous

<sup>1</sup> See the article by Meyer et al. on page 769 of this issue.

TABLE 2  
SEROCONVERSION OF SUSCEPTIBLE CHILDREN AFTER ADMINISTRATION OF VACCINES  
SINGLY OR IN COMBINATION

Type of vaccine	Children developing antibody against:					
	Measles <sup>a</sup>		Smallpox		Yellow fever <sup>b</sup>	
	No. pos./ No. tested	% pos.	No. pos./ No. tested	% pos.	No. pos./ No. tested	% pos.
Measles	65/67	97	—	—	—	—
Smallpox	—	—	67/67	100	—	—
Yellow fever	—	—	—	—	70/72	97
Measles-smallpox	56/56	100	89/90	99	—	—
Measles-smallpox-yellow-fever	61/62	98	80/80	100	69/81	85
Total	182/185	98.4	236/237	99.6	139/153	90.8

<sup>a</sup> Measles seroconversion calculated on children 8 months of age or older.

<sup>b</sup> Yellow fever seroconversion calculated by survival-time method.

experience with one or another of the viruses under discussion, as shown in Table 1.

The occurrence of immunity to measles in about 7% of these children who were without a history of the disease is similar to our earlier experience.<sup>1</sup> A number of those with precedent antibodies against smallpox were re-examined for evidence of smallpox vaccination scars, and their mothers were again questioned about prior vaccination. In the majority of these instances it was evident that the child had previously been vaccinated against smallpox. Some 8% of the children were designated as having had pre-existing antibodies against yellow fever; the interpretation of these positive results is difficult. Yellow fever vaccination had not been practised in Ouagadougou in children of this age for several years. Furthermore, the disease had not been recognized in the area during the lifetime of these young Voltans. It is possible that in some of the younger children the yellow fever antibody detected was the remnant of transplacentally transferred antibody from vaccinated mothers. This explanation does not suffice, however, in the older children. Some of the positive results attributed to yellow fever might have been the result of infections with other members of Casals' Group B arthropod-borne viruses (Casals, 1957).

#### *Seroconversion of susceptible children*

Pertinent information on the seroconversion of susceptible children following inoculation with live

measles, smallpox and yellow fever vaccine given singly or in combination is summarized in Table 2. Not included in Table 2 are children from whom paired sera were not available, those with antecedent immunity, and finally, children under eight months of age who received measles vaccine. Thus, the numbers of children in the different groups in Table 2 varied from 56 to 90 as compared with the 101 to 124 persons originally included in each group (Table 1).

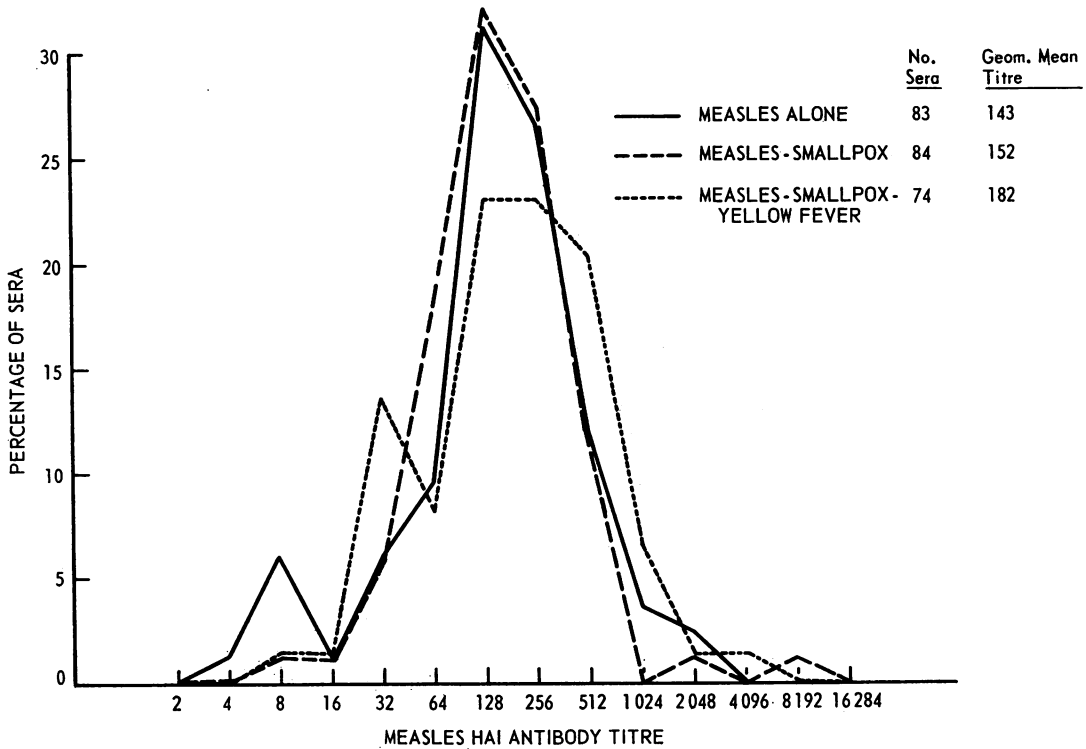
It is apparent from Table 2 that practically all the members of the three groups who received measles vaccine developed measles antibody. The conversion rate varied from 97% to 100%. Similarly, the susceptible children who received smallpox inoculations showed evidence of seroconversion in almost 100% of instances. Finally, most of the children who received yellow fever vaccine developed significant levels of antibodies against yellow fever virus.

The distribution of post-immunization measles antibody titres is summarized in Fig. 2. Results are plotted only for children who converted from negative to positive. It is apparent that the antibody responses displayed by members of the three groups were essentially the same. Furthermore, the geometric mean titres did not vary appreciably.

Measles vaccination in early infancy presents a special problem. An appraisal of the efficacy of measles immunization in very young children can be made in Table 3. Here, seroconversion data are presented for vaccinees 5, 6, 7 and 8 months of age compared with those 9 months and over.

<sup>1</sup> See the article by Meyer et al. on page 769 of this issue.

FIG. 2  
MEASLES ANTIBODY RESPONSE OF VACCINATED CHILDREN



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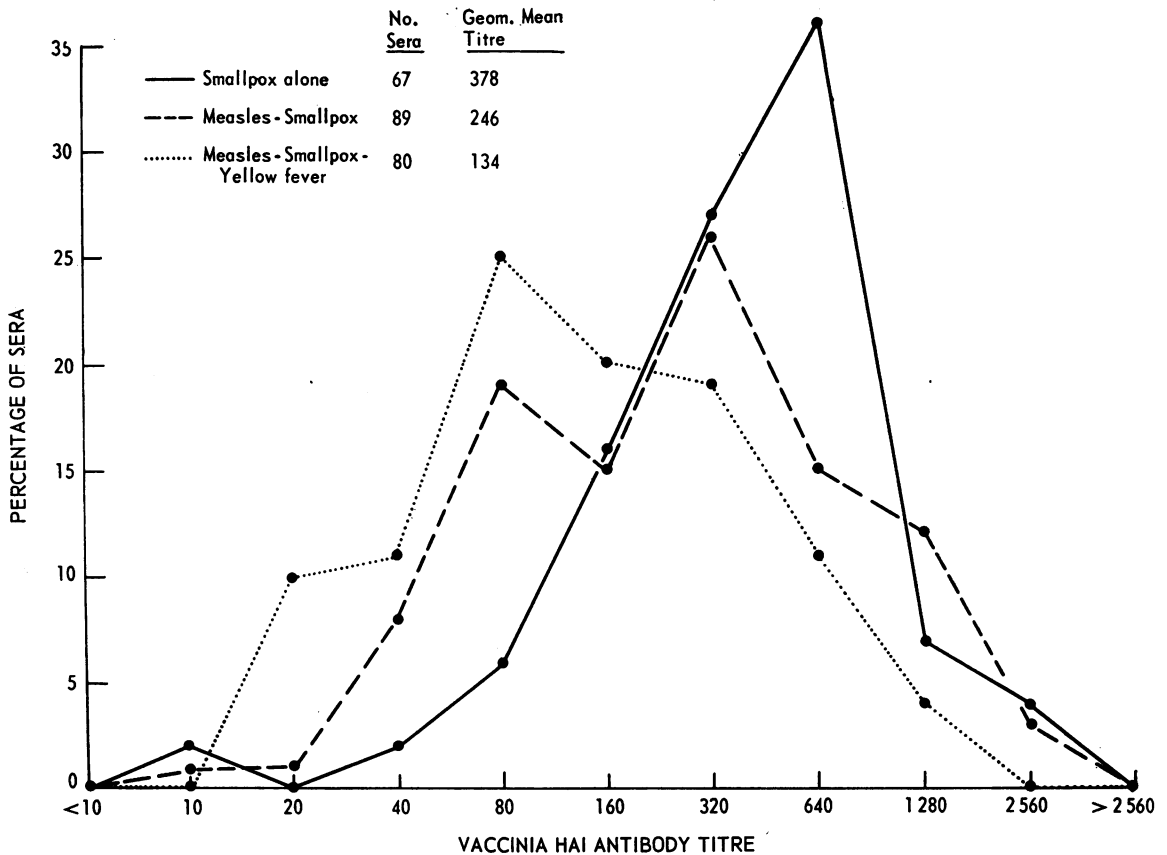
TABLE 3  
RELATION OF AGE TO MEASLES SEROCONVERSION<sup>a</sup> AFTER JET INJECTION  
OF LIVE MEASLES VACCINE

Type of vaccine	Age (months) <sup>b</sup>				
	5	6	7	8	9 and over
Measles alone	1/3	9/11	8/10	11/12	54/56
Measles-smallpox	1/2	12/17	15/15	16/16	40/40
Measles-smallpox-yellow-fever	1/1	8/10	4/5	10/10	51/52
Total	3/6	29/38	27/30	37/38	145/148
% seroconversion	50	76	90	97	98

<sup>a</sup> Expressed as number of serum pairs evidencing seroconversion over number of serum pairs tested.

<sup>b</sup> Pre vaccination sera of children negative at a 1:8 dilution for measles HAI antibody.

FIG. 3  
SMALLPOX ANTIBODY RESPONSE OF VACCINATED CHILDREN



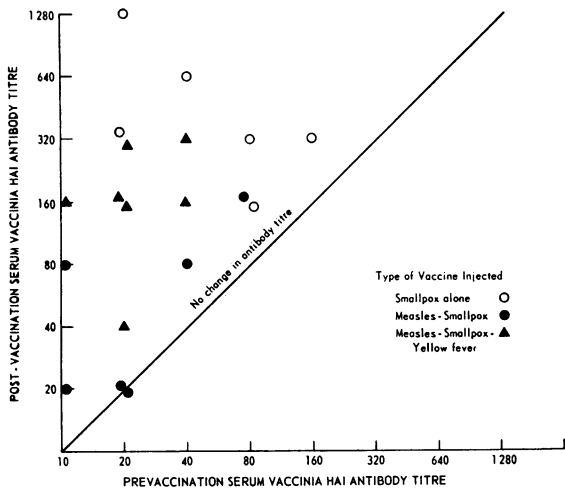
It is clear that in children less than eight or nine months of age there are many more vaccine failures, these increasing as the age decreases. This phenomenon of the relative resistance of younger children both to live measles virus vaccination and to natural measles is well known and apparently related to the presence of minimal amounts of transplacentally transferred passive antibody (Reilly et al, 1961). Indeed, when the prevaccination sera of these apparent vaccine failures were re-examined at lower starting dilutions—i.e., 1:2 and 1:4—seven of those from children eight months of age or younger were found to contain measles antibodies. Apparently, still others had antibody below the level detectable by present serological techniques yet capable of rendering the vaccine ineffective.

The antibody levels elicited by smallpox vaccine are summarized in Fig. 3. Here again, it is evident that the distribution of antibody levels is about the same. However, high antibody titres occurred most frequently in the group receiving monovalent vaccine and the titres in the bivalent group were generally higher than those in the trivalent group. Using an analysis-of-variance test, these differences among the three preparations were found to be significant at the level  $P > 0.005$ .<sup>1</sup>

It may be noted that, although mixing of the vaccines resulted in up to a threefold reduction in the smallpox antibody response, no effect on the

<sup>1</sup> All statistical analyses were performed by Dr Clifford J. Maloney and Mrs Dorothy F. Berg, Biometrics Section, Division of Biologics Standards, National Institutes of Health, Bethesda, Md., USA.

FIG. 4  
 SEROLOGICAL RESPONSE OF CHILDREN WITH PRE-EXISTING SMALLPOX ANTIBODY TO JET INJECTION OF SMALLPOX VACCINE ALONE OR IN COMBINATION WITH MEASLES OR MEASLES PLUS YELLOW FEVER VACCINES



incidence of primary cutaneous vaccinal reactions or rate of seroconversion could be shown.

Nineteen children in the study had pre-existing smallpox antibodies; their serological responses are shown in Fig. 4. In 11 of these 19 instances a significant (fourfold or greater) increase in antibody

occurred subsequent to vaccination. These findings, which are in accord with the observations of Elisberg et al. (1956) in studies involving previously vaccinated adults, indicate that even partially immune individuals may respond immunologically to jet injection of vaccine.

As described earlier, yellow fever seroconversion was calculated by two methods:  $LD_{50}$  and survival time. In Table 2, summarizing the serological responses of all vaccinated groups, the yellow fever data included were those obtained by the survival time method. Table 4 presents the results obtained by both methods. The apparent differences in yellow fever seroconversion between the monovalent and trivalent vaccine groups, as shown by each method of calculation, are of borderline statistical significance. These observations suggest that the presence of the other two attenuated viruses may interfere somewhat with the expected immunological expression of yellow fever vaccine.

#### Clinical response to vaccination

No unusual or excessively severe reaction to vaccination occurred in any child. Measles and smallpox vaccination elicited the expected febrile and cutaneous responses, while 17D yellow fever immunization produced no clearly discernible clinical reaction other than an occasional febrile episode. Fig. 5 shows the average daily temperature for all the children in the study during the 21-day surveillance period. The data in this figure are of

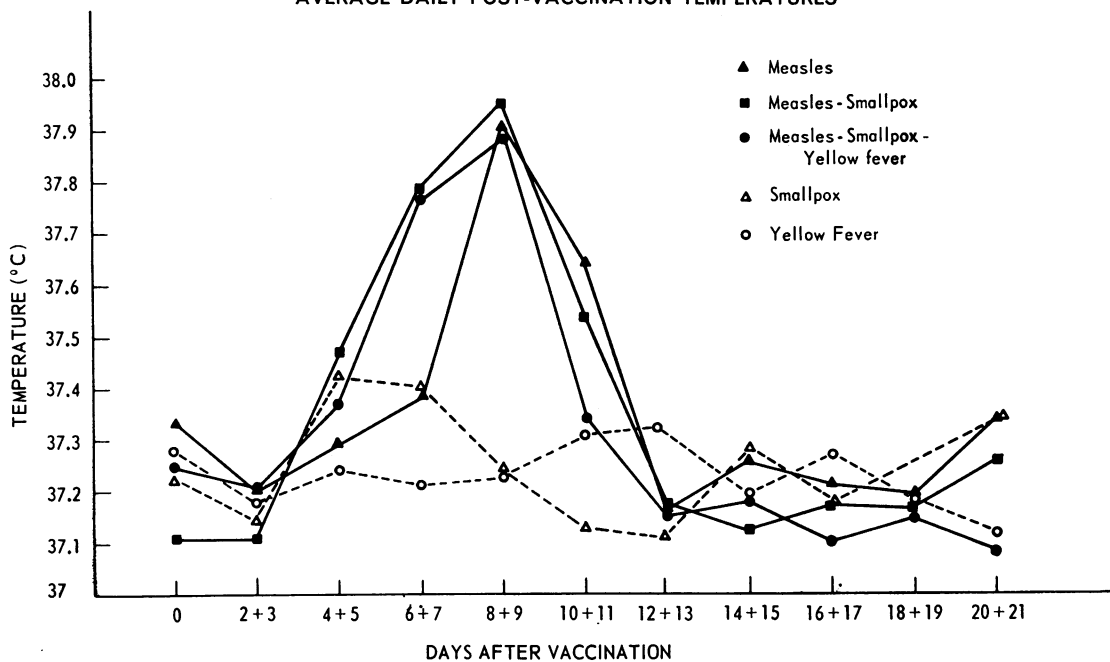
TABLE 4  
 SEROCONVERSION FOLLOWING YELLOW FEVER VACCINE GIVEN ALONE OR WITH SMALLPOX AND MEASLES VACCINES

Method of calculation <sup>a</sup>	Group	Number of vaccinees	Seroconversion					
			Positive		Equivocal		Negative	
			No.	%	No.	%	No.	%
$LD_{50}$	Yellow fever	72	47	65	20	28	5	7
	Yellow-fever-measles-smallpox	81	51	63	15	19	15	19
Survival time	Yellow fever	72	70	97	—	—	2	3
	Yellow-fever-measles-smallpox	81	69	85	—	—	12	14

<sup>a</sup> See text for details regarding methods of calculation of seroconversion. With the  $LD_{50}$  method, three groups were designated; with the survival time method only two groups were designated—positive or negative.



FIG. 5  
AVERAGE DAILY POST-VACCINATION TEMPERATURES



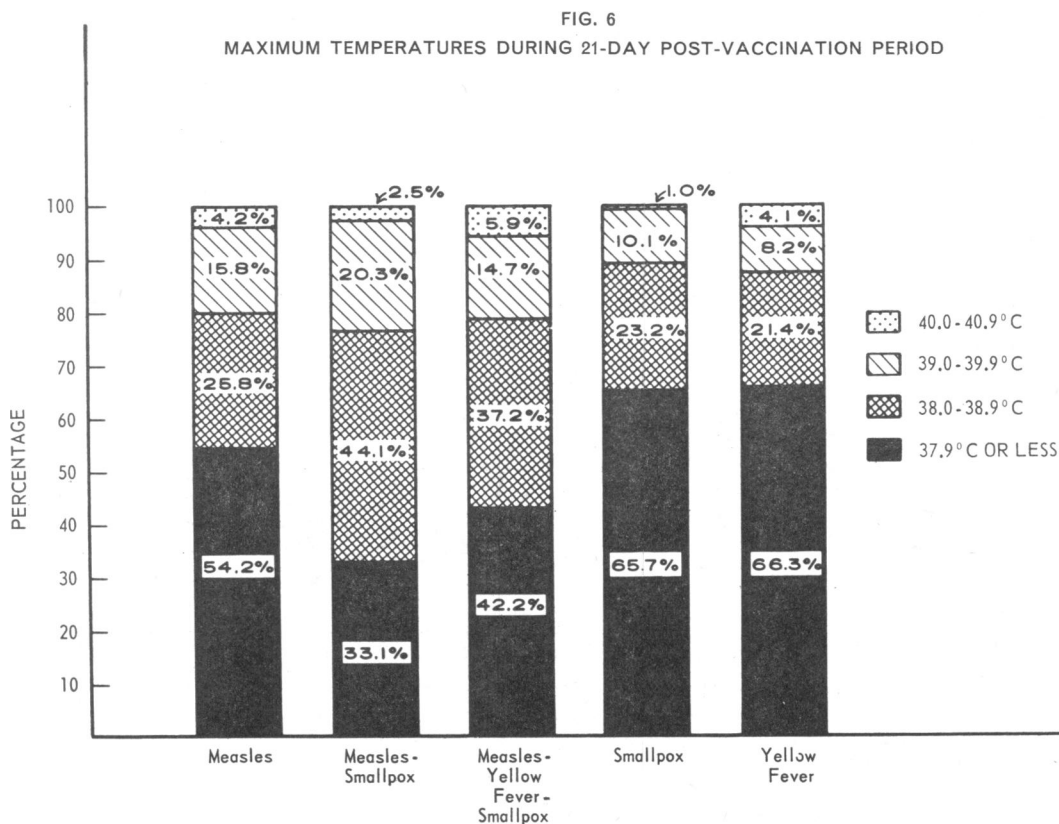
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value primarily in delineating the periods during which the individual vaccines can be expected to elicit fever in recipients. Fevers associated with measles vaccination were first detected on the sixth and seventh post-inoculation days. The height of these responses was greatest on the eighth and ninth days, and they generally terminated before day 12. Smallpox vaccination was commonly associated with fever occurring four to seven days after inoculation. Recipients of 17D yellow fever vaccine exhibited no characteristic period of temperature elevation. The two groups jet-inoculated with combined vaccines tended to have an onset of fever by the fourth and fifth days, reflecting the inclusion of smallpox vaccine in the mixture which they received. These children experienced maximum temperatures on days 8 or 9 with termination of fever by day 12, as was observed in the group receiving measles vaccine alone. The peaks of the febrile responses on days 8 and 9 were comparable in all three groups receiving measles vaccine.

In Fig. 6 data pertaining to febrile reactions are assembled to indicate the percentage of children in each group experiencing a maximum temperature within certain defined ranges. As indicated in the

figure, children receiving measles vaccine developed fever more frequently than those inoculated with either smallpox or yellow fever vaccines singly. However, in each of the two latter groups, 34% of vaccinees developed a temperature of 38°C or more on at least one occasion. Fevers of 39°C or more were equally common (20.0%-22.8%) among groups receiving measles vaccine but considerably less common (11.1%-12.3%) in groups not vaccinated against measles. Among children vaccinated against yellow fever alone only nine individuals (12.3%) experienced fevers of 39°C or more; all were less than one year of age. It was interesting to note that with the other vaccines fevers were not similarly restricted to the very young. High fevers, i.e., 40°C or more, were rare irrespective of the vaccine administered, ranging from 1% to 5.9% in the five groups. It should be borne in mind that the definitive association of fevers with one or another type of vaccine poses certain problems since, in our preceding study,<sup>1</sup> we found that about one-fourth of the Voltans in a control group (given gamma-globulin alone) developed fever of 38°C or greater during a two-week surveillance period.

<sup>1</sup> See the article by Meyer et al. on page 769 of this issue.



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A maculopapular rash was detected between the ninth and fifteenth post-vaccination days in about 50% of children in each group who received measles vaccine (measles alone, 45%; measles-smallpox, 50%; and measles-smallpox-yellow-fever, 52%). These rashes assumed a generalized distribution in about half the children involved and were only rarely of sufficient severity to mimic the cutaneous manifestations of natural measles.

Smallpox vaccination was followed by the development of the typical primary cutaneous vaccinal reaction in 99% of susceptible Voltans. The character of the skin lesion was unaltered by the addition of measles or measles and yellow fever viruses to the vaccine.

During the course of surveillance many children manifested symptoms or signs of one or another infectious or parasitic disease. Common complaints were of diarrhoea, respiratory illness, otitis, purulent conjunctivitis and skin infection. These problems were about equally distributed through the five

vaccine groups and bore no apparent relation to the type of vaccine administered.

Central nervous system involvement has been reported as an occasional grave complication of both smallpox (Stuart, 1947) and yellow fever (Macnamara, 1953) vaccination and of natural measles (Litvak et al., 1943). It is noteworthy, therefore, that no child in the present study experienced any illness suggestive of encephalitis.

#### DISCUSSION

The data presented here indicate that live measles, smallpox and 17D yellow fever vaccines, singly or in combination, can be administered safely and effectively by jet inoculation into susceptible children. There was no indication that any of these combinations potentiated the characteristic clinical reactions elicited by the individual attenuated viruses. Also, there was little evidence that viral

interference substantially diminished the immunological response to the combined vaccines. Measles and smallpox seroconversions were uniformly excellent, occurring in 97%-100% of all groups receiving these vaccines. The smallpox HAI antibody response tended to be slightly lower in Voltans receiving the mixtures. However, the geometric mean antibody titres of each of the three groups receiving smallpox inoculations were of a high order and comparable to those observed by others in persons responding to primary vaccination with either the calf-lymph or the chick-embryo type of vaccine (Elisberg et al., 1956; McCarthy & Downie, 1958).

Only a few children evidenced antecedent immunity at the time of smallpox vaccination; these frequently experienced an increase in antibody subsequent to vaccination (Fig. 4). Theoretically, jet-inoculated vaccine might be more immunogenic than similar material administered in the traditional manner, since an antigenic mass has been introduced which might stimulate antibody formation, even in the absence of virus multiplication. Yellow fever seroconversion was observed more frequently in the group that received only yellow fever vaccine, but the over-all conversion rate of 90.8% for groups given 17D virus was considered satisfactory and in keeping with the general experience in the use of 17D-type vaccine (Stuart, 1956).

Regarding the use of jet injectors, several general comments are in order. These devices operate on the principle that vaccine, when forced through a minute orifice under high pressure, emerges as a high-speed jet capable of penetrating the skin (Hingson et al., 1963; Warren et al., 1955). The character of penetration is dependent upon several factors such as orifice diameter, pressure and proximity of the orifice to the skin surface. As described earlier, slight modifications may be made to increase the intradermal inoculum; however, even with such changes, significant amounts of vaccine are deposited in the subcutaneous and intramuscular layers. These comments have been made to call attention to two practical considerations. Because of the depth of penetration, material selected for jet injection should be bacteriologically sterile or at least pathogen-free. Furthermore, the dynamics of mechanical operation are such that viscous fluids,

i.e., vaccines suspended in glycerol or gum arabic, are poorly handled in jet guns.

Those seeking to carry out preventive medicine programmes in West Africa are beset by many problems. The population is widely dispersed, residing for the most part in rural areas which are often difficult to reach and sometimes inaccessible during portions of the rainy season. Moreover, funds and personnel available for health work are frequently limited. Nevertheless, Upper Volta and her neighbours are plagued by a number of major endemic diseases (Sénécal et al., 1962). Two of these, smallpox and yellow fever, are controlled by mass vaccination (Peltier, 1947). Measles, another of these endemic threats, has been described as one of the greatest hazards to child health in West Africa today (Armengaud & Frament, 1960; Morley et al., 1963; Sénécal et al., 1962). The Enders live attenuated measles vaccine, by conferring long-term immunity to recipients following a single inoculation, offers a practical solution to this grave problem. As the West African infant emerges from the shelter of maternal antibodies, he enters a period of high risk to measles. To counter this hazard, protective immunization should be instituted at the earliest practical age. Live measles vaccine can be given with full effectiveness by the eighth or ninth month of life and may, if indicated, be employed with a predictable reduction of efficiency in younger children (see Table 3).

Looking to the future, one hopes it will be possible to extend the current anti-smallpox and anti-yellow fever programmes to include measles immunization. This could be most simply accomplished if existing mobile health teams could simultaneously vaccinate against measles as well as smallpox and yellow fever. Unfortunately, live measles vaccine shows little activity by the traditional inoculation route (Kempe et al., 1960; and unpublished observations of the present authors), which is widely used in West Africa for both smallpox and yellow fever inoculation. Measles vaccination with syringe and needle would pose several technical and financial problems for large field programmes. Many of these difficulties could be overcome by the use of jet injectors which, as demonstrated in this study, can be successfully employed to deliver any of these three vaccines, either alone or in combination.

#### ACKNOWLEDGEMENTS

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## RÉSUMÉ

Une première étude de vaccination contre la rougeole, effectuée en Haute-Volta, avait montré que la réponse clinique et immunologique des enfants de ce pays était semblable à celle des enfants d'autres continents. Les autorités sanitaires de Haute-Volta ont alors décidé d'entreprendre une nouvelle étude, comportant une vaccination mixte, ajoutant la rougeole au vaccin associé déjà en usage contre la variole et la fièvre jaune, afin de protéger les nourrissons contre cette maladie qui est l'une des plus graves de l'enfance, dans le cadre du programme de médecine préventive.

Un total de 545 enfants, la plupart de moins d'un an, et tous séronégatifs, ont été répartis en cinq groupes, qui ont reçu respectivement: du vaccin anti-rougeole; du vaccin antivariolique; du vaccin antiamaril; un vaccin mixte variole-rougeole; un vaccin mixte variole-fièvre jaune-rougeole. Tous les enfants ont été examinés avant vaccination et suivis pendant trois semaines après. Des

échantillons de sérums couplés ont été prélevés avant et après vaccination. Cette dernière a été effectuée par injections sous pression sans aiguille.

Les réactions consécutives à la vaccination (fièvre, rash) se sont manifestées comme on l'attendait. L'association de virus atténués semble n'avoir ni modifié ni potentialisé les réactions cliniques, provoquées par chacun des virus composant le mélange.

Le virage sérologique a été observé chez 97-100% des enfants vaccinés contre la rougeole, chez 99-100% des vaccinés contre la variole, et 87-90% des vaccinés contre la fièvre jaune. Aucune interférence immunologique appréciable n'a été notée chez les enfants ayant reçu les vaccins mixtes.

Les auteurs concluent que le vaccin mixte (variole-fièvre jaune-rougeole) peut être administré, selon la technique particulière indiquée, avec efficacité et sécurité.

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