PN-AAA 2-470
ISN = 55342

FINAL REPORT

MEASLES ANTIBODY STUDY

CONGO

A Report Prepared by PRITECH Consultant
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During the Period
August 22 - September 6, 1986

TECHNOLOGIES FOR PRIMARY HEALTH CARE (PRITECH) PROJECT
Supported by The:
U.S. Agency for International Development
AID/DPE - 5927-C-00-3083-00

AUTHORIZATION:
AID/S&T/HEA: 12/21/87
ASSGN. NO.: SS 156

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FINAL REPORT

A. INTRODUCTION

At the request of the CCCD-Congo project, a CCCD/PRITECH mission was carried out in Brazzaville from August 22 to September 9, 1986. The mission had two objectives: to conduct a serologic study of the dynamics of maternal measles antibodies in infants less than 10 months of age, and to review Oral Rehydration (ORT) activities in the hospital environment in Brazzaville.

The preliminary report* of the consultant (Dr. F. Dabis), dated September 19, 1986, presented the ORT results and recommendations. The present final report gives the principal results of the serologic investigation. These results were presented during the Third International Seminar on Vaccinations in Africa, which was held in Niamey, Niger from January 29 to 31, 1987 (see Proceeding of the Seminar, in press).

B. MATERIALS AND METHODS

The detailed protocol for this study is presented in Appendix 1 of this document. The subjects of the study were infants from two to nine months of age who were brought to the consulting services for healthy children at the city's eight major clinics for Maternal and Child Protection during the period extending from August 25 to September 4, 1986. The objective was to include the first 30 infants from each one-month age group that presented at the clinic.

The following information was collected for each infant by using the questionnaire presented in Appendix 2: date of birth, sex, weight and height, (measured on site with calibrated instruments by investigators who had been received prior training), previous history of measles and measles vaccination, nursing modalities, birth weight, age of the mother, and child's rank in the family.

A capillary blood sample was taken on each child. The blood was centrifuged within 12 hours and the serum maintained at +4° Co. The measles antibody titration was carried out at the London School of Tropical Medicine (G. Mann and associates). The titration technique used was that of plaque inhibition, derived from a trial technique on the Schwartz vaccinal strain. Results were converted into International milliUnits of Reference, with seronegativity defined as 40 International milliUnits (mlU) or less per milliliter (ml) of serum.

C. RESULTS

1. Description of the Sample

There were 264 infants enrolled in the study; of these, 12 were subsequently excluded from the analysis for the following reasons:

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* see Appendix III.

- 11 of the 12 presented with a highly elevated antibody titer (i.e., 2,000 International milliUnits or more per ml of serum) suggesting a recent infection, a fact that was later confirmed from the medical record in 4 cases. Of these 11 infants, 10 were seven to nine months of age and one was three months old.

- Of the 264 infants, only one was not being, and had never been, breast-fed. This infant was likewise excluded from the analysis even though his antibody titer was considered protective (i.e., 119 International milliUnits per ml of serum at 15 weeks of age.

Comparison of the total initial sample of 264 infants with the 252 on whom the analysis of the serologic data was based showed no difference in terms of age (see Tables 1 and 2), nutritional status (see Tables 3 and 4), birth weight (see Tables 5 and 6), or maternal characteristics (see Tables 7 and 8). However, it should be noted that 4 (21%) of the 19 children in the initial sample who were suffering from chronic malnutrition (see Tables 3 and 4) had had measles.

2. Serologic Results

The laboratory conducted a blind analysis of the sera. Two specimens were taken from 24 infants, 3 in each one-month age group (see Table 1), and these specimens were subjected to separate analyses. In 15 cases the serology for both specimens was negative. In 9 cases the serology was positive, but only showed, on average, a 17 percent difference between the specimens. Moreover, the sera of five young adults, who had an a priori acquired immunity against the measles virus, were added at random. All were strongly positive. The same test conducted on the serum of five laboratory rabbits was consistently negative.

If the proportion of seropositive infants is studied by age (see Figure 1), it can be noted that 96 percent of the children have protective antibodies at two months of age; however, this proportion drops sharply below 50 percent beginning with four months of age and reaches less than 10 percent at seven months of age.

The antibody titer was positive in 90 (36%) of the 252 observations. As can be seen from Table 9 and Figure 2, it is clear that the average antibody titer, represented for each age group by its geometric mean, likewise drops with age. The apparent rise in the antibody titer in the nine-month age group is probably due to the small sample size in this age group (n=2).

Table 10 and Figure 3 are designed to show the existence of a linear relationship between the rate of measles antibodies and age expressed in months. When variables other than age are taken into account in the model, especially sex of the child, birth weight, and maternal age, these variables do not change the

relationship (see Table 11). However, it is difficult to interpret this model because the titration method used gives a value of zero to each titration less than or equal to 40 International milliUnits. In order to clarify the existence of this correlation, the observations were regrouped into four-week age groups, and the median age for each group was correlated with the percentage of seronegative subjects (see Table 12). The linear relationship between the proportion of seronegative subjects and age then appears very clear (see Figure 4): the correlation coefficient is 0.92, and the proportion of seronegative subjects increases to 3.3 percent per week beginning with the second month of life. According to this model, only one out of two children would have protective antibodies at four and a half months of age, and none would have them at eight months.

D. DISCUSSION

Our serologic study shows that in a sample of healthy infants in Brazzaville, passive immunity to measles does not last as long as one would be led to believe from the African studies on which are based the recommendations on measles vaccination of the Expanded Program on Immunization (EPI). (See Bull WHO 1977; 55:21-31.)

Several studies have recently been published in this area. Halsey and associates (N Engl J Med 1985; 313:544-9) showed that in Haiti, the optimum age for measles vaccination seemed to be eight months of age. Black and associates (Am J Epidemiol 1986; 124:442-52) recently reported results of several studies confirming that there are important geographic differences in terms of both passive measles immunity of maternal origin and of vaccinal seroconversion. Unfortunately, only one of these studies was conducted in Africa, at Lagos in Nigeria. In addition, all these serologic studies used the measles antibody titration technique called hemagglutination inhibition. All the authors agree that although this method is a good early detection method, it is inadequate for producing quantitative results. Mann and associates were able to compare this method with that of plaque inhibition. This latter method, which was used in our study, proved to be four times more sensitive than hemagglutination inhibition. Finally, in the course of their work, Burgess and associates were able to discover a linear drop in the rate of maternal antibodies very similar to that observed in the Congo: 100 percent of the children tested were seronegative at 7.6 months of age. (See Burgess W., Tomkin A., Garelick H, and Mann G. Measles immunization trials in Mbeya, Tanzania. Manuscript in preparation.)

Several of our results still need to be validated. It is probable that the antibody titer observed in an infant depends on that of the mother. We have simply been able to note that neither maternal age nor parity is an intervening factor in decreasing the antibody rate in the infant. Therefore, it would be important to complete our work by conducting a comparative mother-child study.

There are two possible approaches we could take: one approach consists of repeating our work on another group of two to eight month old infants, while systematically taking blood samples from the mothers and measuring their anthropometric parameters (i.e., weight, height, and age); the other approach, which complements the first, involves taking a maternal blood and cord sample at the time of birth in order to study the transplacental transfer of antibodies. In both cases, the plaque inhibition technique is the only viable serologic method to use because it gives quantitative results with sufficient precision.

It is more logical to consider repeating this study in a rural population and also in a group where the prevalence of malnutrition is higher than it was in our present study (6.0 % in our sample).

Taking into account the preliminary results observed in the Congo, it seems justifiable to propose that some vaccinal seroconversion trials, beginning at three months of age, be conducted in that geographic area. This would be a difficult undertaking and would require a rigorous scientific protocol so as to avoid the dangers of not being able to conclude the trial or of creating serious ethical problems. As far as possible, such trials should be conducted by using the most recently developed vaccines, indeed even those in the course of being developed.

It is important to conduct all or part of these complementary studies <u>before the end of 1987</u>. If possible, they should also take place in the Congo where the preliminary studies have already been undertaken. In the interim, the Congolese EPI objective must be retained, i.e., vaccination against measles <u>at nine months of age</u> for 90 percent or more of the children. In this way, a substantial reduction in mortality and in mortality caused by measles can be assured.

TABLE 1

AGE DISTRIBUTION OF CHILDREN INCLUDED IN THE BRAZZAVILLE STUDY AUGUST - SEPTEMBER, 1986

N=264

Age Group	Children (%)	Samples
2 months	24 (9.1%)	27
3 months	33 (12.5%)	36
4 months	33 (12.5%)	36
5 months	33 (12.5%)	36
6 months	33 (12.5%)	36
7 months	38 (14.4%)	41
8 months	37 (14.0%)	40
9 months	33 (12.5%)	36
TOTAL	264 (100%)	288

TABLE 2

AGE DISTRIBUTION OF CHILDREN RETAINED FOR ANALYSIS IN THE BRAZZAVILLE STUDY AUGUST - SEPTEMBER, 1986

N=252

Age Group	Children (%)	Samples
2 months	24 (9.5%)	27
3 months	31 (12.3%)	34
4 months	33 (13.1%)	36
5 months	33 (13.1%)	36
6 months	33 (13.1%)	36
7 months	35 (13.9%)	38
8 months	34 (13.5%)	37
9 months	29 (11.5%)	32
TOTAL	252 (100%)	276

TABLE 3

NUTRITIONAL STATUS OF 263 CHILDREN[1] INCLUDED IN THE BRAZZAVILLE STUDY AUGUST - SEPTEMBER, 1986

Weight/age relationship < 80% of the median

Age Group	n	%
2-3 months	2	3.5%
4-5 months	2	3.0%
6-7 months	5	7.0%
8-9 months	10	14.3%
TOTAL	19	7.2%

1 Weight not available for one child

TABLE 4

NUTRITIONAL STATUS OF 251 CHILDREN[1] RETAINED FOR ANALYSIS IN THE BRAZZAVILLE STUDY AUGUST - SEPTEMBER, 1986

Weight/age relationship < 80% of the median

Age Group	n	%
2-3 months	2	3.6%
4-5 months	2	3.0%
6-7 months	4	5.9%
8-9 months	7	11.1%
TOTAL	15	6.0%

1 Weight not available for one child

TABLE 5

BIRTH WEIGHT OF 263 CHILDREN[1] INCLUDED IN THE BRAZZAVILLE STUDY AUGUST - SEPTEMBER, 1986

Birth Weight	n	%
1.5-1.99 kg	6	2.3%
2.0-2.49 kgs	20	7.6%
2.5-2.99 kgs	99	37.6%
3.0-3.49 kgs	94	35.7%
3.5-3.99 kgs	38	14.5%
4.0-4.49 kgs	6	2.3%
TOTAL	263	100 %

1 Birth weight not available for one child

TABLE 6

BIRTH WEIGHT OF 251 CHILDREN[1] RETAINED FOR ANALYSIS IN THE BRAZZAVILLE STUDY AUGUST - SEPTEMBER, 1986

Birth Weight	n	%
1.5-1.99 kg	6	2.4%
2.0-2.49 kg	20	8.0%
2.5-2.99 kg	96	38.2%
3.0-3.49 kg	87	34.7%
3.5-3.99 kg	36	14.3%
4.0-4.49 kg	6	2.4%
TOTAL	251	100 %

1 Birth weight not available for one child

TABLE 7

CHARACTERISTICS OF 262 MOTHERS[1] OF CHILDREN INCLUDED IN THE BRAZZAVILLE STUDY AUGUST - SEPTEMBER, 1986

Total Number of Pregnancies	Age (in years)					
	<20	20-29	30-39	40-49	Unknown	Total
1	56	36	0	0	0	92 (35.1%)
2-3	10	80	3	0	4	97 (37.0%)
4-5	0	33	16	0	1	50 (19.1%)
≥6	0	1	16	3	3	23 (8.8%)
TOTAL	66 (25.2%)	150 (57.2%)	35 (13.3%)	3 (1.1%)	8 (3.0%)	262 (100%)

[1] Two mothers had twins.

TABLE 8

CHARACTERISTICS OF 250 MOTHERS[1] OF CHILDREN RETAINED FOR ANALYSIS IN THE BRAZZAVILLE STUDY AUGUST - SEPTEMBER, 1986

Total Number of Pregnancies	Age (in years)					
	<20	20-29	30-39	40-49	Unknown	Total
1	54	36	0	0	0	90 (36.0%)
2-3	10	76	3	0	4	93 (37.2%)
4-5	0	30	15	0	1	46 (18.4%)
≥6	0	1	15	3	2	21 (8.4%)
TOTAL	64 (25.6%)	143 (57.2%)	33 (13.2%)	3 (1.2%)	7 (2.8%)	250 (100%)

[1] Two mothers had twins.

FIGURE 1

MATERNAL MEASLES ANTIBODIES BY AGE
252 INFANTS
BRAZZAVILLE STUDY
SEPTEMBER, 1986

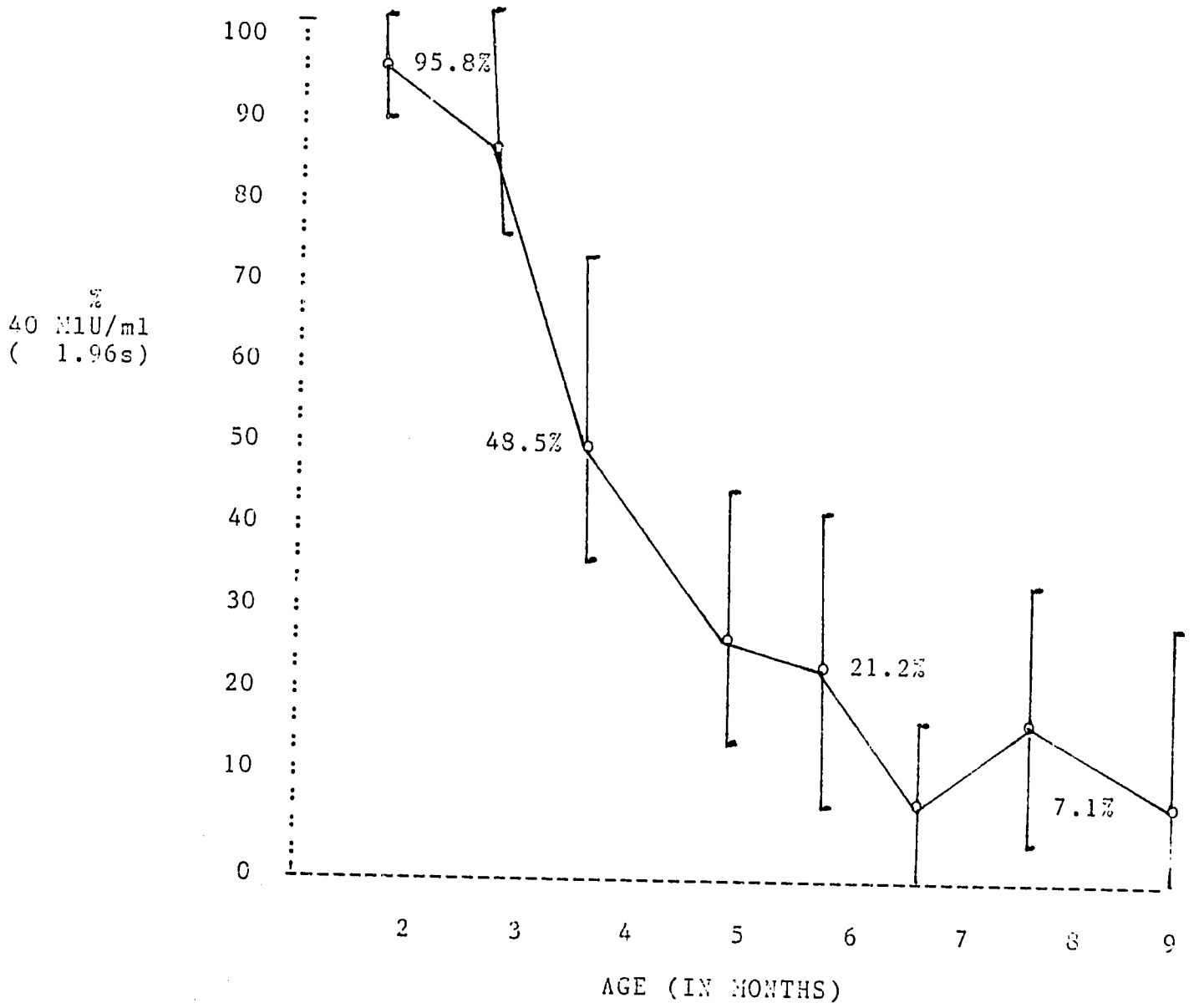


TABLE 9

RATE OF MEASLES ANTIBODIES BY AGE
BRAZZAVILLE STUDY
AUGUST - SEPTEMBER, 1986

N=252

2 Months
AB2

Mean:	Std. Dev.:	Std.Error:	Variance:	Coef.Var.:	Count:
334.783	320.73	66.877	102867.451	95.802	23
Minimum:	**Maximum:**	**Range:**	**Sum:**	**Sum Squared:**	*
56	1152	1096	7700	4840910	1
Median:	**Mode:**	**Geo. Mean:**			
237	•	219.284			

3 Months
AB2

Mean:	Std. Dev.:	Std.Error:	Variance:	Coef.Var.:	Count:
211.963	222.268	42.776	49403.191	104.862	27
Minimum:	**Maximum:**	**Range:**	**Sum:**	**Sum Squared:**	*
41	988	947	5723	2497547	4
Median:	**Mode:**	**Geo. Mean:**			
123	•	145.944			

4 Months
AB2

Mean:	Std. Dev.:	Std.Error:	Variance:	Coef.Var.:	Count:
196.438	241.314	60.328	58232.262	122.845	16
Minimum:	**Maximum:**	**Range:**	**Sum:**	**Sum Squared:**	*
43	933	890	3143	1490887	17
Median:	**Mode:**	**Geo. Mean:**			
92.5	•	123.309			

* = Number missing

TABLE 9 (CONTINUED)

RATE OF MEASLES ANTIBODIES BY AGE
BRAZZAVILLE STUDY
AUGUST - SEPTEMBER, 1986

N=252

5 Months
AB2

Mean:	Std. Dev.:	Std.Error:	Variance:	Coef.Var.:	Count:
137.375	138.606	49.005	19211.696	100.896	8
Minimum:	**Maximum:**	**Range:**	**Sum:**	**Sum Squared:**	*
44	428	384	1099	285457	25
Median:	**Mode:**	**Geo. Mean:**			
70.5	•	96.291			

6 Months
AB2

Mean:	Std. Dev.:	Std.Error:	Variance:	Coef.Var.:	Count:
105.429	83.664	31.622	6999.619	79.356	7
Minimum:	**Maximum:**	**Range:**	**Sum:**	**Sum Squared:**	*
41	284	243	738	119804	26
Median:	**Mode:**	**Geo. Mean:**			
88	•	85.999			

7 Months
AB2

Mean:	Std. Dev.:	Std.Error:	Variance:	Coef.Var.:	Count:
79.5	28.991	20.5	840.5	36.467	2
Minimum:	**Maximum:**	**Range:**	**Sum:**	**Sum Squared:**	*
59	100	41	159	13481	33
Median:	**Mode:**	**Geo. Mean:**			
79.5	•	76.811			

* = Number missing

TABLE 9 (CONTINUED)

RATE OF MEASLES ANTIBODIES BY AGE
BRAZZAVILLE STUDY
AUGUST - SEPTEMBER, 1986

N=252

3 Months
AB2

Mean:	Std. Dev.:	Std.Error:	Variance:	Coef.Var.:	Count:
70.8	52.742	23.587	2781.7	74.494	5
Minimum:	**Maximum:**	**Range:**	**Sum:**	**Sum Squared:**	*
43	165	122	354	36190	30
Median:	**Mode:**	**Geo. Mean:**			
50	50	60.58			

9 Months
AB2

Mean:	Std. Dev.:	Std.Error:	Variance:	Coef.Var.:	Count:
210	209.304	148	43808	99.668	2
Minimum:	**Maximum:**	**Range:**	**Sum:**	**Sum Squared:**	*
62	358	296	420	132008	26
Median:	**Mode:**	**Geo. Mean:**			
210	•	148.983			

* = Number missing

FIGURE 2

MATERNAL MEASLES ANTIBODIES BY AGE
90 SEROPOSITIVE INFANTS
BRAZZAVILLE STUDY
SEPTEMBER, 1986

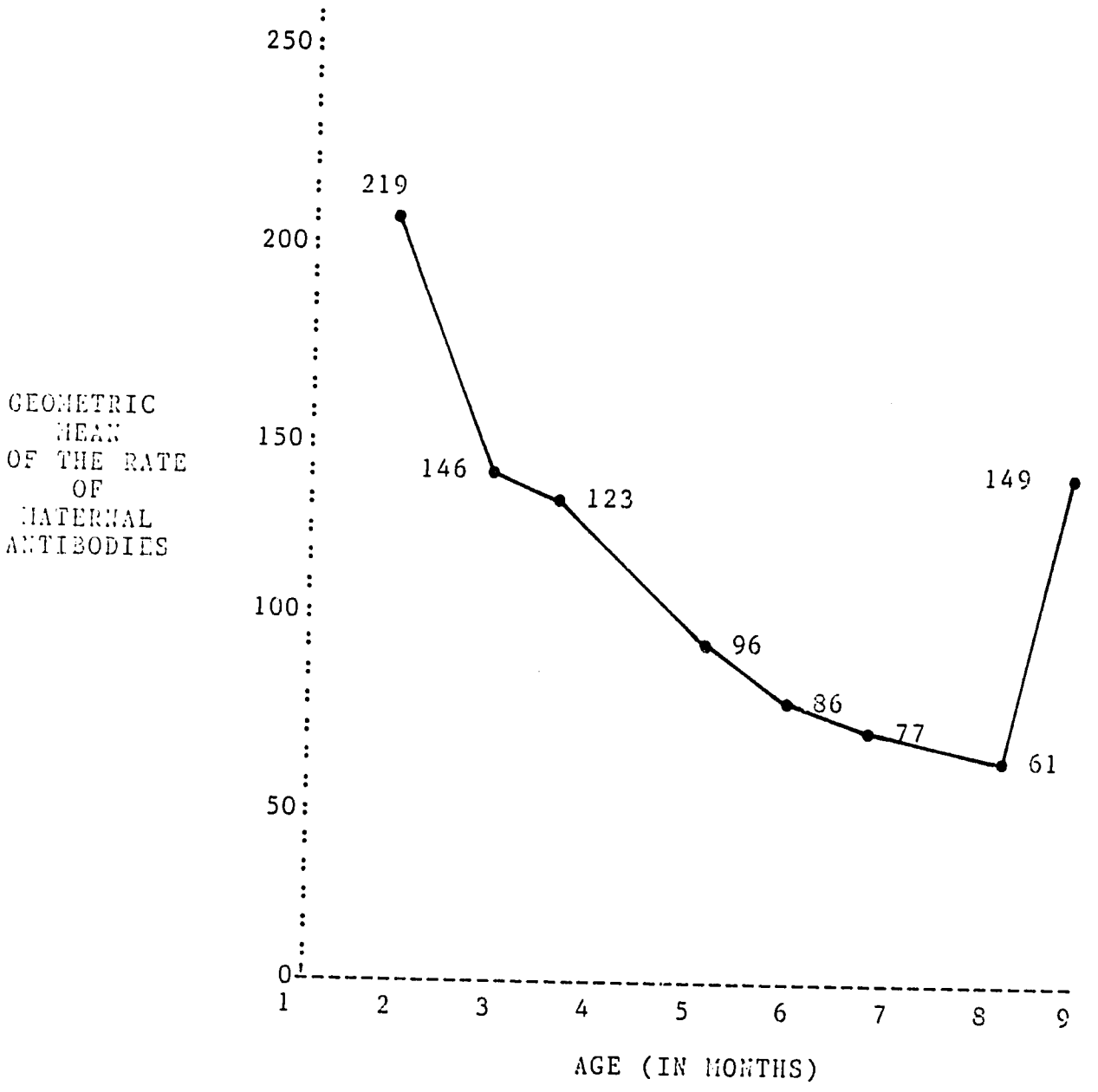


TABLE 10

RELATIONSHIP BETWEEN THE RATE OF MEASLES ANTIBODIES AND AGE
BRAZZAVILLE STUDY
AUGUST - SEPTEMBER, 1986

252 Infants

Corr. Coeff. X : AGE Y : AB3

Count:	Covariance:	Correlation:	R-squared:
252	-183.829	-.469	.22

Simple - Y : AB3 X : AGE

DF:	R-squared:	Std. Err:	Coef. Var.:
251	.22	157.319	205.029

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	Variance:	T-Value:
INTERCEPT	299.746	28.346	803.493	10.575
SLOPE	-37.826	4.504	20.289	-8.398

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION:	1	1745307.436	1745307.436	70.519
RESIDUAL	250	6187322.215	24749.289	$p \leq .0001$
Total	251	7932629.651		

Residual Information Table

SS [e(i)-e(i-1)]²	e ≥ 0:	e < 0:	DW test:
9899401.108	101	151	1.6

FIGURE 3

RELATIONSHIP BETWEEN THE RATE OF MEASLES ANTIBODIES AND AGE
BRAZZAVILLE STUDY
AUGUST TO SEPTEMBER, 1986

252 NURSING INFANTS

y=37.826x + 299.746 R-squared: .22

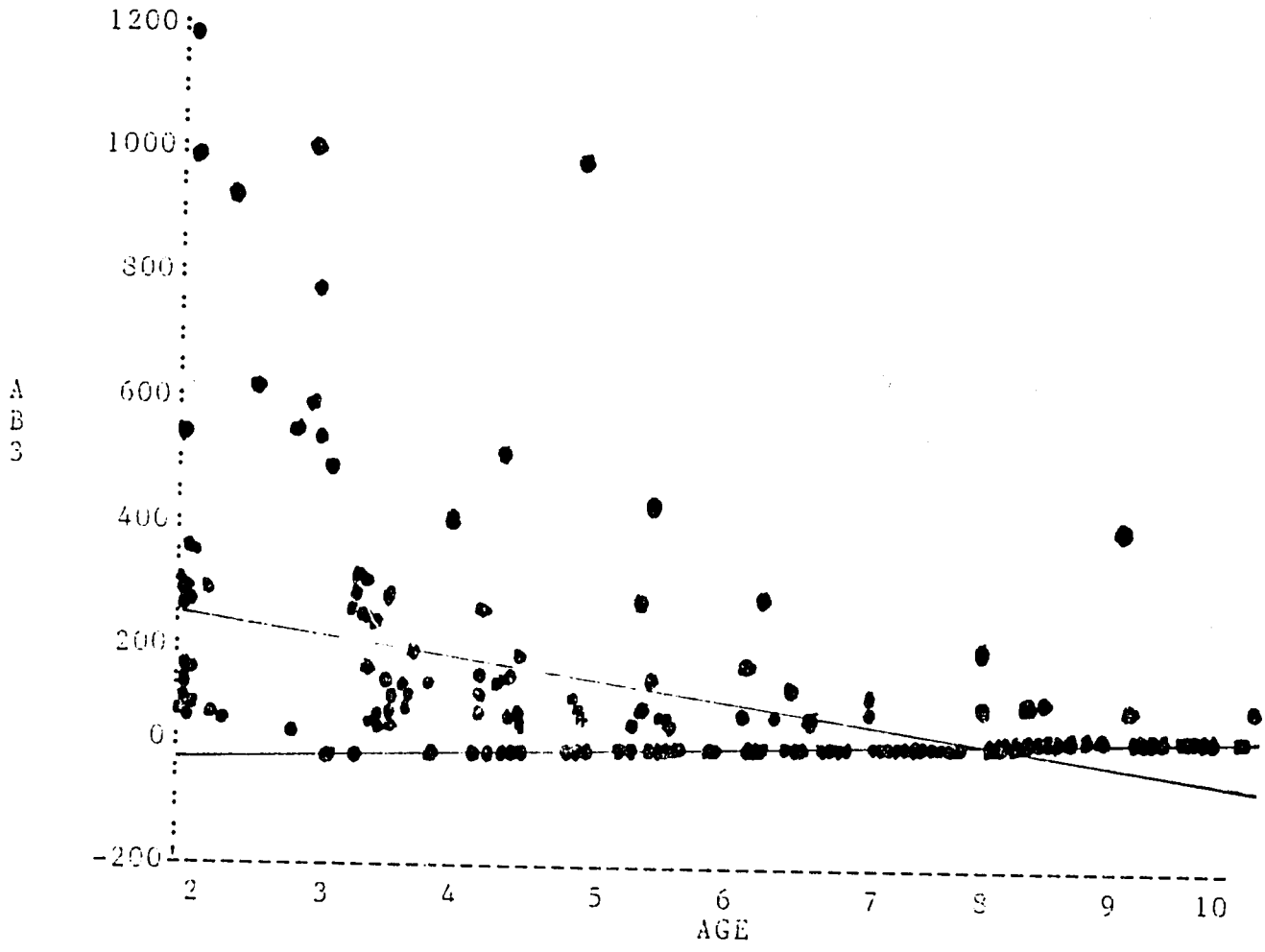


TABLE 11

RELATIONSHIP BETWEEN THE MEASLES ANTIBODY RATE AND FIVE DEPENDENT VARIABLES (MULTIPLE REGRESSION)
BRAZZAVILLE STUDY
AUGUST - SEPTEMBER, 1986

252 Infants

Multiple - Y :AB3 Five X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
240	.23	160.705	204.218

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square :	F-test:
REGRESSION:	5	1817948.566	363589.713	14.078
RESIDUAL	235	6069128.712	25826.08	$p \leq .0001$
TOTAL	240	7887077.278		

Note: 11 cases deleted with missing values

Beta Coefficient Table

Parameter:	Value:	Std.Err.:	T-Value:	Partial F:
INTERCEPT	193.387	104.235	1.855	
AGE	-37.874	4.908	-7.717	59.557
SEX	-23.578	20.951	-1.125	1.267
BIRTH WT.	7.595	23.086	.329	.108
W/AZ	.622	.941	.661	.437
AGEM	1.577	1.926	.819	.671

TABLE 12

DROP IN MEASLES ANTIBODIES AS A FUNCTION OF AGE
BRAZZAVILLE STUDY
AUGUST - SEPTEMBER, 1986

N=252

Simple - Y : % SERONEGATIVES X : MEDIAN AGE (IN WEEKS)

DF:	R-squared:	Std. Err.:	Coef. Var.:
7	.847	15.236	24.319

Beta Coefficient Table

Parameter:	Value:	Std.Err.:	Variance:	T-Value:
INTERCEPT	-13.447	14.241	202.809	-.944
SLOPE	3.277	.568	.322	5.772

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	1	7735.311	7735.311	33.321
RESIDUAL	6	1392.853	232.142	$.0001 < p \leq .005$
TOTAL	7	9128.164		

Residual Information Table

SS [e(i)-e(i-1)]	e ≥ 0:	e < 0:	DW test:
1372.011	4	4	.985

Corr. Coeff. X : MEDIAN AGE (IN WEEKS) Y : % SERONEGATIVES

Count:	Covariance:	Correlation:	R-squared:
8	337.256	.921	.847

TABLE 12 (CONTINUED)

DROP IN MEASLES ANTIBODIES AS A FUNCTION OF AGE
BRAZZAVILLE STUDY
AUGUST - SEPTEMBER, 1986

N=252

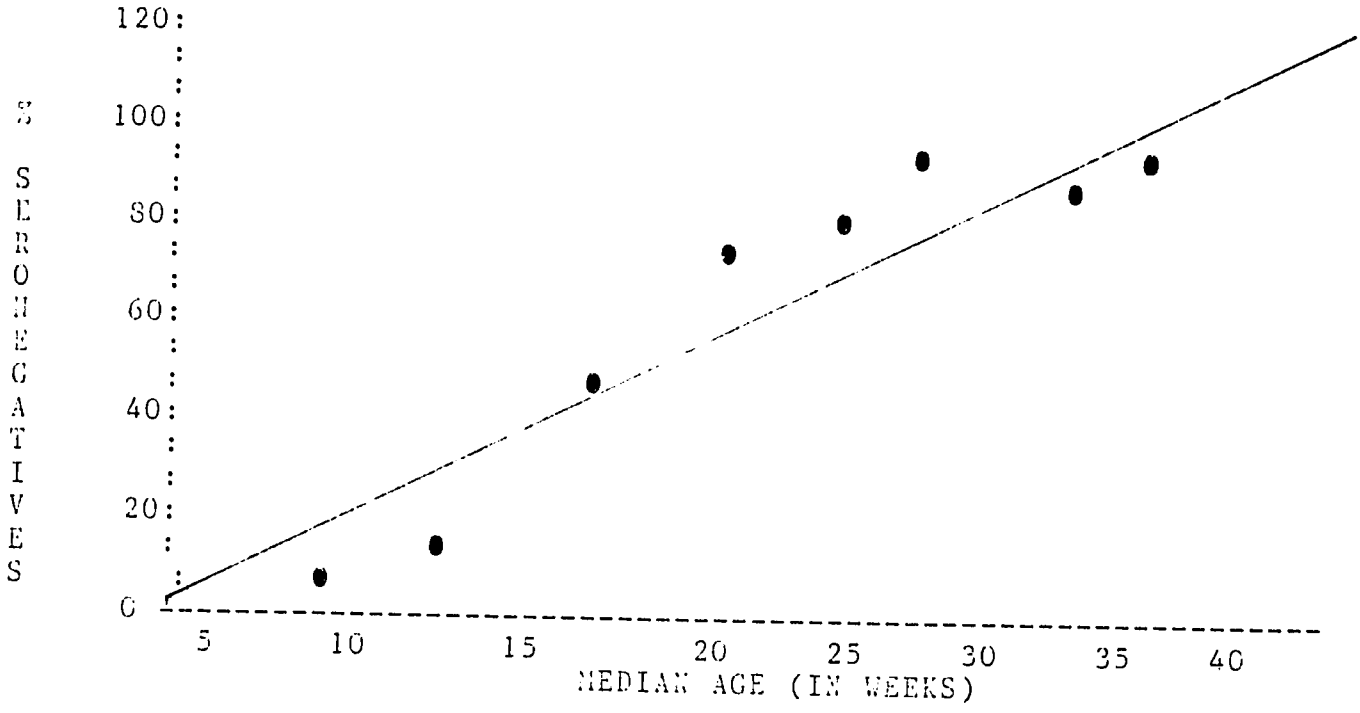
Age Group	Median Age	Cases
8-11 Weeks	8.4	n=24
12-15 Weeks	12.6	n=31
16-19 Weeks	17.2	n=33
20-23 Weeks	21.2	n=38
24-27 Weeks	25.9	n=42
28-31 Weeks	29.8	n=29
32-35 Weeks	34.0	n=32
36-39 Weeks	36.7	n=23

FIGURE 4

DROP IN MEASLES ANTIBODIES AS A FUNCTION OF AGE
BRAZZAVILLE STUDY
AUGUST TO SEPTEMBER, 1986

N = 252

y = 3.277x + -13.477 R-squared: .847



y = 0% seronegatives; x = 1.0 months
y = 50% seronegatives; x = 4.5 months
y = 90% seronegatives; x = 7.3 months
y = 100% seronegatives; x = 8.0 months

APPENDIX 1

PROPOSAL FOR MEASLES ANTIBODY STUDIES
COMBATTING CHILDHOOD COMMUNICABLE DISEASES PROGRAM
07/24/86

ANNEXE 1

PROPOSAL FOR MEASLES ANTIBODY STUDIES
COMBATTING CHILDHOOD COMMUNICABLE DISEASES PROGRAM
07/24/86

OBJECTIVE:

To identify the optimum age for providing measles vaccine to children in selected African countries, by assessing the level of maternal antibodies against measles during the first year of life and documenting its relationship to child and maternal factors.

BACKGROUND:

Measles is a major killer of children in Africa and is particularly severe before their first birthday (1). Currently available vaccines produce seroconversion rates of 90% or greater only in children older than eight months of age (2). In younger children, most vaccine failures are due to the fact that passively acquired maternal antibodies neutralize the attenuated vaccine virus. In several regions of Africa where immunization programmes have promoted vaccination at nine months and where vaccination coverage levels of 50% or higher have been reached, at least 20% of all reported measles cases are in children less than nine months of age (3,4).

In an unpublished study from Tanzania, researchers from the London School of Hygiene and Tropical Medicine found a linear relationship between the loss of maternal antibodies and the age of the child, with a decrease of about 5% per week beginning at the 13th week of life (5). The technique used in that study was a plaque neutralization assay, which some experts recommend for the measurement of maternal antibodies because of its high sensitivity and its ability to produce quantitative results.

G. Mann proposed that by determining the rate of decline of materna antibodies in a given population and by selecting a desired seroconversion rate, one could easily determine the optimal age of vaccination in this population for a given vaccine without necessaril having to repeat vaccine seroconversion trials done elsewhere (5). I addition, the demonstration of a sharp and rapid decline of maternal antibodies before nine months of age could lead to the use of the currently available vaccine in children less than nine months of age.

Clinical trials of measles vaccine carried out in infants less than nine months of age in several African countries have suggested that levels of maternal antibodies at a given age might be different in children from different places (5).

STUDY POPULATION:

Children three to ten months of age will be enrolled in the study. Ideally, the study will be repeated in a rural and an urban zone in a least three countries.

SAMPLE SIZE:

The study will include a minimum of 30 to 50 children in each month age group, or a total of 240 to 400 children three to ten months of a at each study site.

STUDY SITE:

The study will be carried out in the busiest Maternal and Child Health Clinics of the study area. The well-baby clinics will be the primary location for enrollment. The study will start on days when immunization sessions for BCG, DTP-Polio, and measles vaccinations ar

scheduled, i.e., when mothers usually bring their infants to the clinic. In addition, children brought in for consultation on the same day in the curative section of the clinic could also be enrolled. If more children are needed, the study could be extended to include children from the houses closest to the clinic.

PROTECTION OF HUMAN SUBJECTS:

Written permission for carrying out the study will be obtained from the national and local authorities before the study is started.

The consent of each mother will be obtained orally, as is the usual practice in Africa, by reading the following statement in the local language(s): "Measles is a major health problem in African children, especially in this country. According to the current immunization policy in your country, the best time to vaccinate your child against measles is at nine months of age. To understand if there is a better age for vaccinating children against measles, we would like to get a small sample of your child's blood, similar to what is collected for a malaria smear, to perform some laboratory tests. This procedure will not harm your child. Should you not want to participate, you will still be eligible to receive all the services available at this clinic."

Granting of oral permission will be documented on a line listing

All previously unvaccinated children 9-11 months of age will be vaccinated with measles vaccine at the time of the study. Caretakers children less than nine months of age will be informed of the appropriate time to return for measles vaccination. All children in need of other vaccines recommended by the national Expanded Program on Immunization will be offered these vaccinations at the time of the study.

PARAMETERS STUDIED:

For each child enrolled in the study, a blood sample of no more than 100 microliters will be collected using the finger stick method. A second sample will be collected from one child every 25 children in order to look at internal consistency of the laboratory technique. A new sterile, disposable lancet will be used for each child, after the finger has been cleaned with alcohol. Specimens will be centrifuged within 24 hours, the sera separated and kept in a refrigerator. Specimens will be encoded by the investigator.

Data will be recorded by study number.

The following child variables will be recorded

- date when the specimen was taken
- specimen number
- date of birth (one will specify whether or not there was written proof of the date of birth; if there is no document, the age will be defined as the total number of complete months lived according to the mother)
- sex
- weight and height, using a salter-spring balance scale and a measuring board
- breast-feeding status (not breast-fed, partially or fully breast-fed)
- birth weight, if documented
- vaccination status (non-vaccinated, written proof of measles vaccination, mother's history of measles vaccination)
- history of measles illness

The following maternal variables will be recorded:

- age
- parity

ANALYSIS:

Blood samples will be either hand-carried on wet ice by the investigator at the end of the field phase of the study or air-freight to London where plaque neutralization assays will be performed (Department of Microbiology, London School of Hygiene and Tropical Medicine). The laboratory will only be provided code numbers at the time of the analysis. The validity of the results will be assessed by randomly including confirmed positive and negative sera in the lot of specimens provided to the laboratory. All children with antibody level of 55 milli-international reference units/ml or less will be defined as seronegative. Geometric mean titers will be calculated only for children with detectable antibody levels and for each age group, i.e., by month. Correlations between the antibody levels and the various child and mother variables will be explored using Student's t-test, Chi square tests, and multivariate analyses when appropriate.

LOGISTICS AND BUDGET:

At each site, two to four weeks of field work will be necessary depending on the use of health services by the study population. The Technical Officer or the Field Epidemiologist from the CCCD Program or a consultant will supervise field activities involving one physician with knowledge and training in immunization and epidemiologic surveys.

Support staff such as a driver and a secretary will be provided by the national CCCD Program and will be paid according to the local scale. Transportation costs will be supported by the CCCD Program.

Equipment: 500 non-heparinized collection tubes, 400 disposable lancets, measuring boards, and salter spring-balance scales (2).

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(1) Walsh JA. Selective primary health care: strategies for contr of diseases in the developing world. IV Measles. Rev Infect Dis 1983 5(2):330-40.

(2) Collaborative Study Group of the Pan American Health Organization. Seroconversion rates and measles antibody titers indud by measles vaccine in Latin American children 6-12 months of age. Bu Pan Am Health Organ 1982; 16(3): 272-85.

(3) Taylor W, et al. Importance of measles under nine months in children in urban Africa (in preparation).

(4) Dabis F, et al. The epidemiology of measles in a partially vaccinated African city: implications for immunization programmes (submitted for publication).

(5) Markowitz L (Rapporteur). Workshop on the use of measles vacci in infants under nine months of age. Centers for Disease Control, Atlanta, GA (USA). November 21-22, 1985.

LABORATORY ANALYSIS:

Laboratory analyses will be performed in the Department of Microbiology of the London School of Hygiene and Tropical Medicine and will cost 546 British pounds ($835) for a batch of 150 tubes. The tot laboratory cost for one study site will be about $2,500 for the children's blood.

A final report will be prepared within two months after laboratory results have been received.

APPENDIX II

MEASLES ANTIBODY STUDY
BRAZZAVILLE - AUGUST,1986

1. Date DATE ___ ___ . ___ ___ . ___ ___
Day Month Year

2. Code Number IDSN ___ . ___ ___ ___

3. Weight (in kgs) WEIG ___ ___ . ___ ___

4. Height (in cms) HEIG ___ ___ ___

5. Specimen Number (1) SCS 1 ___ ___ ___

6. Specimen Number (2) SCS 2 ___ ___ ___

7. Child's Date of Birth DATN ___ ___ . ___ ___ . ___ ___
Day Month Year

7a) If the date of birth is unknown, number of months that have gone by. MNBC ___ ___

8. Sex of the child: 1=male; 2=female SEXC ___

9. Has this child had measles? If yes, when? MMOM ___ ___ . ___ ___
Month Year

99.99=Previous history of measles without precise information
88.88=No previous history of measles

10. Measles vaccination: MVAC ___

1=Vaccination noted in the carnet; 2=Not vaccinated; 3=Vaccination reported by the mother

10a) Date of the measles as noted in the carnet DOMV --- --- . --- --- . --- ---

11. Is this infant breast-fed? BRFE ___

1=Maternal breast-feeding only; 2=Composite feeding modalities; 3=Weaned: 4=Infant never breast-fed

12. Birth weight (in kgs): BIWE ___ . ___ ___ ___

8.888=Not available

13. Mother's age: 1=Less than 20 years; 2=20-29 years; 3=30-39 years; 4=40 years and older; 9=Age unknown AGEM ___

14. Ask the mother the following question: PREG --- ---

Including with this child, how many times have you been pregnant?

99=Do not know; 88=Person asked is not the mother

APPENDIX III

PRELIMINARY REPORT
MEASLES ANTIBODY STUDY - CONGO

Francois Dabis, M.D.

PRELIMINARY REPORT

MEASLES ANTIBODY STUDY - CONGO

A Report Prepared By PRITECH Consultant:
FRANCOIS DABIS, M.D.

During The Period:
AUGUST 22 - SEPTEMBER 6, 1986

TECHNOLOGIES FOR PRIMARY HEALTH CARE (PRITECH) PROJECT
Supported By The:
U.S. Agency for International Development
AID/DPE-5927-C-00-3083-00

AUTHORIZATION:
AID/S&T/HEA:
ASSGN. NO: SS 156

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Date: September 19, 1986

From: François Dabis, M. D.,
Pritech & Combatting Childhood Communicable Diseases (CCCD)

Subject: Trip report - Congo

To: Director, Pritech
Director, Evaluation and Research Division, IHPO, CDC

1. Dates and places visited:

August 22 - September 6, 1986	Brazzaville
September 6 - 9	London

2. Purpose:

Brazzaville:
1) To conduct a serological investigation into the prevalence of maternal antibodies against measles in children aged 2-9 months.
2) To review the status of oral rehydration therapy (ORT) activities at Makelekele Hospital.
London:
To deliver the specimens collected in Brazzaville to the Virology Laboratory of the London School of Hygiene and Tropical Medicine and to discuss the scheme for data analysis.

3. Persons contacted:

Brazzaville:
Dr. Madzou, CCCD Coordinator and Director of Preventive Medicine, Ministry of Health (MOH)
Mr. Obe Andzouoko, Director of the Diarrheal Diseases Control (CDD) Program, Direction of Preventive Medicine (DMP), MOH
Mr. Ognangue, Laboratory Technician, Service de l'Epidémiologie et des Grandes Endémies, DMP
Mrs. Nkoue, Expanded Program on Immunization, DMP
Dr. Moka, Director of Maternal and Child Health Services for Brazzaville, MOH
Dr. Ondzoto, Director of MCH clinic, Makelekele Hospital
Dr. Mavoungou, Pediatrics Department, Makelekele Hospital
Mr. Fitzgibbon, CCCD Technical Officer, DMP
Mr. Wilson, Deputy Chief of Mission, American Embassy

London:
Dr. Mann, Department of Medical Microbiology, London School of Hygiene and Tropical Medicine

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4. Summary of accomplishments:

4.1 Measles antibody study:

a) Background:

Measles remains a major public health problem in Brazzaville, despite the increasing levels of vaccination coverage achieved in the past five years through the Expanded Program on Immunization (Figure 1). Transmission is still endemic, peaking during the rainy season. During the first semester of 1986, 2,107 children were hospitalized for measles in Brazzaville, of which 84 (4.0%) died. The overall number of reported cases through the sentinel surveillance system was 2,207 for the same six-month period, slightly less than during the same period of 1985 when 2,516 cases had been reported. Although a trend is noticeable in terms of reduction of the morbidity (Figure 2), the disease burden is still high, and 20% of the cases are unpreventable with the current vaccination policy at nine months of age (Figure 3).

b) Study design:

The study protocol presented in Annex 1 was used. All provisions were made to guarantee the protection of human subjects as proposed in the protocol.

c) Field work:

The consultant, with the assistance of a laboratory technician (Mr. Ognangue) and a nurse (Mrs. Nkoue) from the Expanded Program on Immunization spent ten days selecting the sample and gathering the necessary information. All children were selected from the well-baby clinics of eight Maternal and Child Health Units (SMI). For each child, a questionnaire was filled out and a blood specimen taken, as described in the protocol. In each month age group, two specimens were collected from three children, to look at the internal consistency of the results. In addition, six specimens were obtained from young adults, to be used as controls known to have measles antibodies. Six specimens were also obtained from rabbits, to be used as antibody-free controls. Processing the specimens and entering the data on a micro-computer were done daily.

d) Descriptive statistics:

A sample of 264 children aged 2-9 months was enrolled. The male to female ratio was 1.28, and each month age group was evenly represented (Table 1). Chronic malnutrition, defined as less than 80% of the median weight for age, was present in 7.2% of the sample, with marked differences according to the age group (Table 2). The percentage of children who were breast-fed was 98% (94% were fully breast-fed). Four children (1.5%) had a clinical history of measles, confirmed by the medical record in two instances. No child had been vaccinated against

measles before enrolment into the study. Birth weight was recorded for 263 children (Table 3). Summary figures for maternal variables are presented in Table 4.

e) Laboratory work and data analysis:

All 300 specimens were coded after centrifugation and extraction of the serum. They were kept refrigerated until their delivery in London. It was agreed with Dr. Mann that the coding system would be broken after the laboratory results had been produced. Discussions with Dr. Mann included a review of the technique of the plaque inhibition test and of the findings of the Tanzania study. It was decided that the results, especially the rate of decay of maternal antibodies, would be looked at first by monthly intervals, using an arithmetic scale.

f) Prospects for future studies:

During the discussions with the Congolese authorities, it was decided that any decision regarding changes in measles vaccination policy would have to be postponed until the data from this investigation had been fully analyzed. Dr. Madzou suggested that a similar study be carried out in a rural area of the Congo, the Plateaux area, to get a complete data base for the country before policy changes were discussed. All the equipment (laboratory equipment, measuring boards, and scales) was left to the CCCD Technical Officer to set up this study before the end of the year. During the discussion with Dr. Mann, the importance of gathering blood samples from the mothers themselves was stressed. It was agreed that this procedure could be added to the protocol in future studies, in order to correlate the rate of decay of maternal antibodies in children with the level of antibodies in the mothers' blood. .

4.2 Evaluation of ORT activities:

Makelekele Hospital was the first medical facility in Brazzaville to be offered standard ORT services by the national CDD Program and CCCD Congo eighteen months ago. Currently, three units are in operation in this hospital, one in the Infectious Diseases ward, one in the Pediatrics ward and the last one in the MCH clinic. All units send monthly reports to the CDD Program, which is in charge of feed-back, supervision,and supplies.

The present evaluation focused on the activities performed in the MCH clinic and in the Pediatrics ward. It combined field visits with a review of all statistics available for these ORT units.

Oral rehydration therapy (ORT) is now a major activity in the MCH clinic: during the past year, the demand has rapidly reached a plateau, with about 300 cases treated every month (Figure 4), and 1,500 ORS packets used quarterly. Between July 1985 and June 1986, 4,124 diarrhea cases have been treated with ORT in this clinic. Fifty four (54) percent of them were under one year of age, and 87% under two. The statistics show that dehydrated children are almost never seen in the clinic: a few cases of Plan B at the most every month and virtually no Plan C. From the discussions with the personnel, the following observations were made: 1) although an ORT corner functions adequately from 7am to 2 pm, ORT is not usually provided on-site during the rest of the day. 2) The unit is well equiped and at least six health workers have been trained in ORT. 3) The knowledge of the personnel of the signs of dehydration is good; the monthly statistics are unlikely to be biased by the misdiagnosis of dehydrated children. 4) The policy of giving an ORS packet for maintenance therapy at home after on-site treatment has been changed to the promotion of a salt and sugar solution for home treatment, using the recipe developed by CCCD Congo. 5) The prescription of antidiarrheal drugs, almost systematic before the inception of the program, is now the exception, and 6) The interest of the health workers and the mothers for ORT is very high. Although the overall impression on this ORT unit is very positive, this ORT unit does not entirely play the role of triage that an outpatient department should have in a large hospital. Its use as a demonstration unit by the national CDD program is questionnable, unless trainees have other opportunities to manage dehydration cases.

The Pediatrics ward has reported having treated 260 cases of diarrhea during the first semester of 1986, of which 34% were admitted in Plan B and 26% in Plan C. From the field visit, the following observations can be made: 1) The ORT corner has not been delimited in the ward. 2) Supervision of ORT activities is not assigned to a specific health worker in the shifts. 3) Physicians are not directly involved in ORT activities, performed "independently" by the nurses. 4) The assessment of the level of dehydration is not standardized and the recording system very poor. 5) There is no established system to closely monitor inputs and outputs for the dehydrated patients. Those patients are in general evaluated clinically twice a day and weighed once a day, and 6) Although no data was available, the personnel claimed that the use of IV fluids had been markedly reduced since ORS packets were available. With the recent arrival of a head nurse and a pediatrician who both expressed a strong interest for ORT during our visit, the conditions are favorable to strenghthen this ORT unit.

Recommendations:

1) The national CDD Program and CCCD Congo should provide assistance to the Pediatrics Department of Makelekele Hospital to properly organize an ORT unit. This should essentially be on-the-job training in case management for one to two weeks. A physician, Dr. Coddy (DMP) or a consultant, should conduct this training. If this experience is successful, Makelekele Hospital will be a good model of a combination of outpatient and inpatient ORT services for Brazzaville and for the rest of the Congo.

2) The national CDD Program should collaborate more closely with Nuted. This health education program financed by Care Congo has developed material of good quality, including flyers, posters,and songs promoting various aspects of ORT (SSS, breast-feeding, early feeding). All these messages are in agreement with the current CDD policy in the Congo. More coordination is needed to ensure that health education efforts and ORT services reach the population at the same time, especially outside of Brazzaville.

3) The national CDD Program should address the problem of recurrent cost as soon as possible. The introduction of ORS packets in almost all the MCH clinics of Brazzaville has been very well received by the health personnel and the population. The sale of the packets is now likely to be accepted by the mothers, already accustomed to purchasing the drugs. This last step will be the key to the long-term sustainability of the Congolese CDD Program.

4) CCCD Congo should assist the national CDD Program in improving their supervision activities and information system. For the latter, a global review of the existent health information systems in the Direction of Preventive Medicine is urgently needed.

All of the above recommendations were discussed in Brazzaville with the CCCD authorities before the departure of the consultant.

* *
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TABLE 1: Age distribution of the children enrolled in the study
Brazzaville - August-September 1986 - N=264

Age category	n (%)	Specimens
2 months	24 (9.1%)	27
3 months	33 (12.5%)	36
4 months	33 (12.5%)	36
5 months	33 (12.5%)	36
6 months	33 (12.5%)	36
7 months	38 (14.4%)	41
8 months	37 (14.0%)	40
9 months	33 (12.5%)	36
Total	264 (100%)	288

Table 2: Nutritional status of 263[1] children
Measles antibody study - Brazzaville - August-September 1986

Age group	Weight/Age < 80% of Median	
	n	%
2-3 months	2	3.5%
4-5 months	2	3.0%
6-7 months	5	7.0%
8-9 months	10	14.3%
Total	19	7.2%

[1] Weight unavailable for one child.

Table 3: Birth weight of 263[1] children
Measles antibody study - Brazzaville - August-September 1986

Birth weight	n	%
1.5-1.99 kg	6	2.3%
2.0-2.49 kgs	20	7.6%
2.5-2.99 kgs	99	37.6%
3.0-3.49 kgs	94	35.7%
3.5-3.99 kgs	38	14.5%
4.0-4.49 kgs	6	2.3%
Total	263	100%

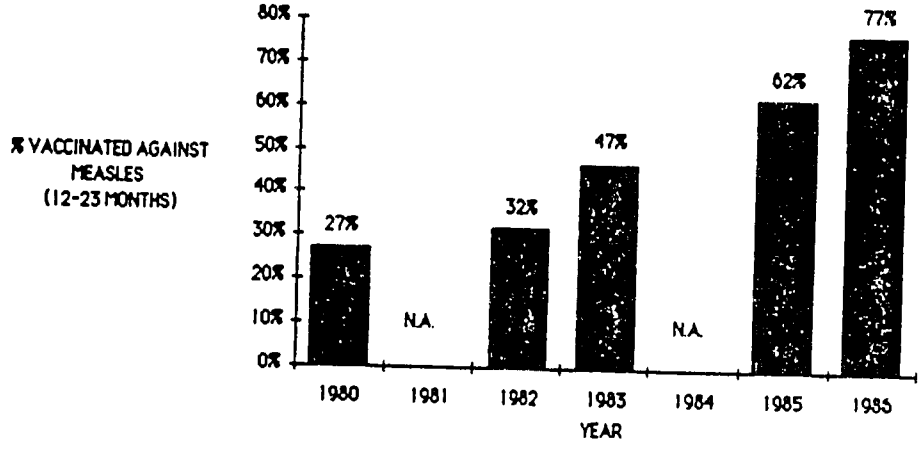
[1] Birth weight unavailable for one child.

Table 4: Maternal characteristics of 262[1] mothers
Measles antibody study - Brazzaville - August-September 1986

Total number of pregnancies	Age (in years) <20	20-29	30-39	40-49	Unknown	Total
1	56	36	0	0	0	92 **(35.1%)**
2-3	10	80	3	0	4	97 **(37.0%)**
4-5	0	33	16	0	1	50 **(19.1%)**
≥6	0	1	17	3	3	23 **(8.8%)**
Total	66 **(25.2%)**	150 **(57.2%)**	35 **(13.4%)**	3 **(1.1%)**	8 **(3.1%)**	262 **(100%)**

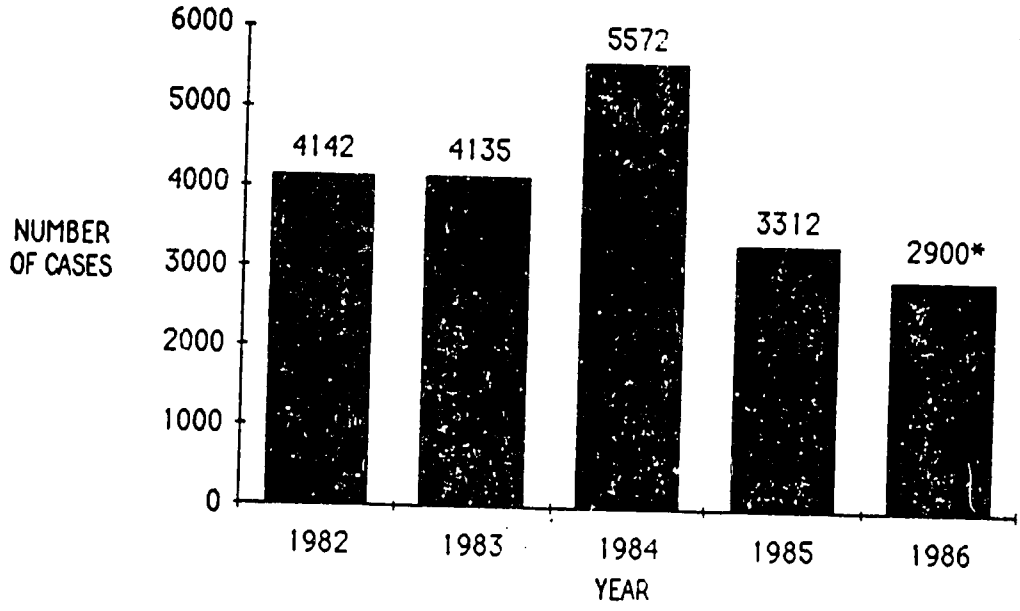
[1] Two mothers had twins.

FIGURE 1: VACCINATION COVERAGE SURVEYS: BRAZZAVILLE, 1980-1986



N.A. No survey was carried out

FIGURE 2: MEASLES SURVEILLANCE BY YEAR
BRAZZAVILLE - 5 SENTINEL POSTS



*1986: ESTIMATE

FIGURE 3: AGE DISTRIBUTION OF 2,207 MEASLES CASES
BRAZZAVILLE, 5 SENTINEL POSTS - JANUARY-JUNE 1986

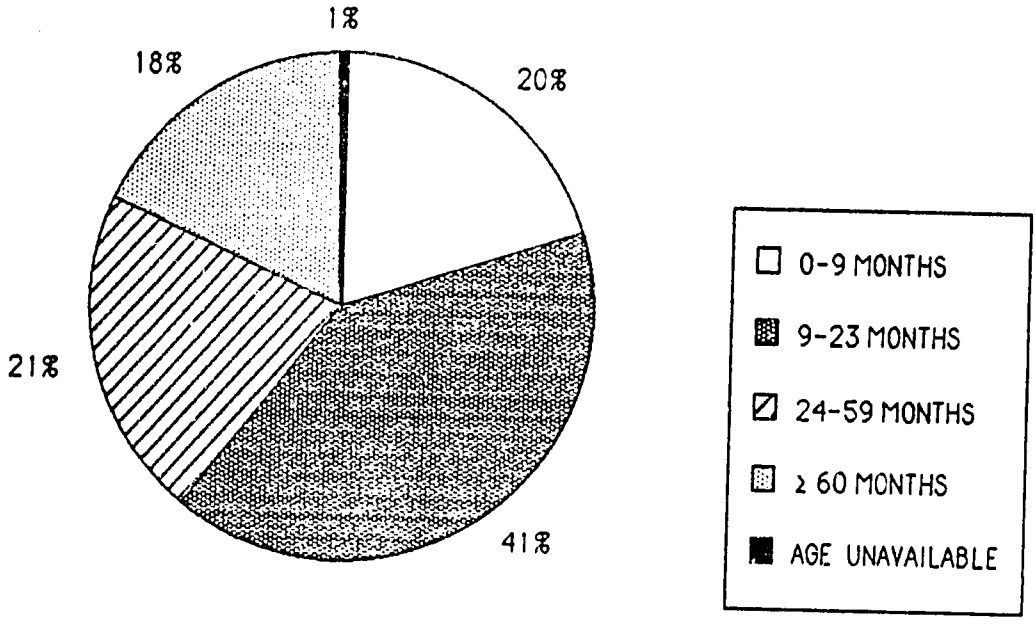
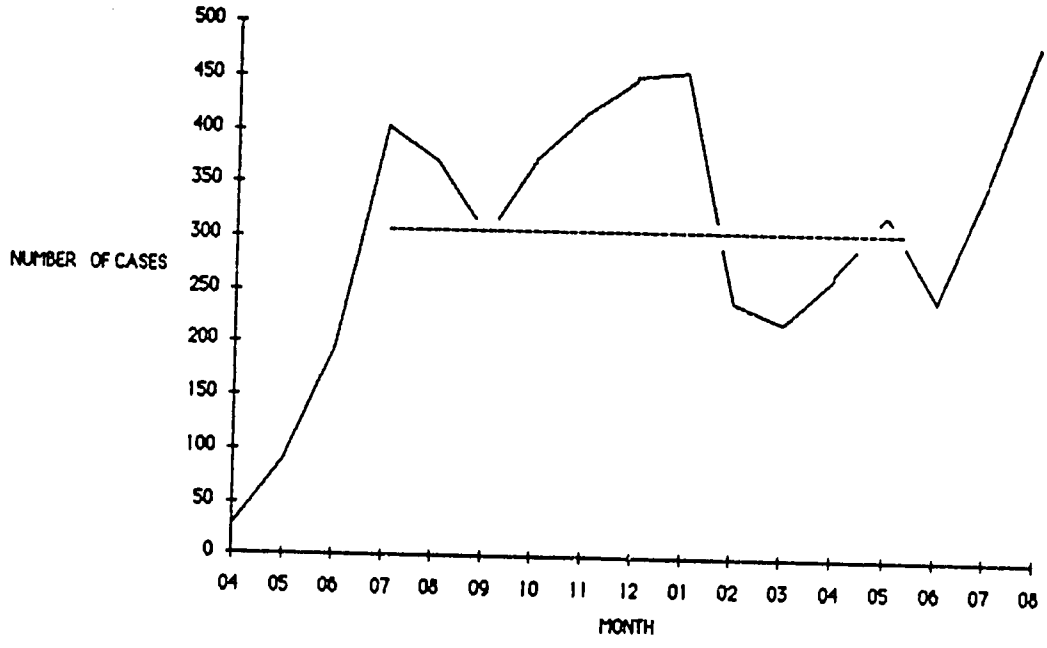



FIGURE 4: MONTHLY NUMBER OF DIARRHEA CASES RECEIVING ORT
SMI MAKELEKELE - APRIL 1985-AUGUST 1986