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SEROCONVERSION RATES AND MEASLES ANTIBODY TITERS INDUCED BY MEASLES VACCINE IN LATIN AMERICAN CHILDREN 6-12 MONTHS OF AGE[1]

Collaborative Study by the Ministries of Health of Brazil, Chile, Costa Rica, Ecuador, and the Pan American Health Organization[2]

To help define the optimal age for measles vaccination in Latin America, a study was conducted of how 2,042 infants responded serologically to measles vaccine in six study areas. The results suggest that local factors affect the seroconversion rate and that 90 per cent success can first be attained by vaccinating at nine to 11 months of age, depending on the area. Postvaccination titers were also found to vary, higher titers generally being observed in groups with higher seroconversion rates.

Introduction

Maternal antibodies against measles, transmitted across the placenta, provide infants with protection against measles in the first several months of life. Over approximately the same age span, these antibodies also interfere with development of measles immunity following vaccination.

Several studies in the United States have revealed that maternal antibodies may persist in infants and may interfere with their response to measles vaccine even beyond the twelfth month of extrauterine life *(1-4)*. Up to 22 per cent of the infants included in these studies failed to develop antibodies against measles when vaccinated at 12 months of age. Children vaccinated at or after 14 months of age had seroconversion rates of at least 93 per cent. Since measles infection during the first year of life is unusual in U.S. children *(5)*, the recommended age for routine administration of measles vaccine in the United States has been set at 15 months *(6)*.

However, in many other countries 30 per cent or more of the children will have already developed measles by 12 months of age *(7-8)*; the highest incidence of death due to measles occurs in the first two years of life; and measles case-fatality rates in excess of 10 per cent have been noted in children under 12 months of age, especially in areas with a high prevalence of malnutrition *(7-12)*. To delay measles vaccination until 15 months of age in these countries would be to allow a substantial percentage of the morbidity and mortality due to measles to continue.

It has recently become clear that in countries where a large proportion of the measles cases occur early in life, the response to early vaccination may be better than in the United States. A study in Kenya revealed that 92 per cent of the study infants beyond seven and a half months of age did not have detectable hemagglutination-inhibition (HI) antibodies to measles, and that over 90 per cent seroconverted after administration of measles vaccine *(13)*. Separate studies in Rhodesia, South Africa, and Taiwan found that maximal postvaccination seroconversion rates were reached at nine months of age *(14-16)*.

In Latin America, the reported incidence of measles and measles-related deaths in young

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[2] A complete list of participants in the investigation appears in Appendix 1.

infants is high, as it is in Africa and South Asia, but these statistics are notoriously unreliable. Furthermore, the age-specific distribution of measles cases is influenced not only by the age at which maternal protection is lost, but also by other factors which affect the rate of virus circulation. Therefore, age-specific attack rates cannot be used by themselves to estimate the optimal age for vaccination.

The level of maternal antibody has been shown to correlate with the level of measles antibody in cord blood, and infants whose mothers have lower levels of measles antibody are more likely to seroconvert to measles immunity at a younger age *(1,13,17)*. Also, infants born prematurely have been shown to seroconvert to measles vaccine at younger ages than term infants, presumably because they receive less maternal antibody before birth *(18)*. Although the initial level of maternal antibody does correlate with the duration of infant protection, it is not known whether other factors influence the rate at which children lose maternal antibody to become susceptible to measles and responsive to measles vaccine. Race, anemia, and underlying nutritional status may be relevant factors.

The purpose of the study reported here was to determine the relationships which may exist between nutritional status, place of residence or geographic area, and that refractoriness to measles vaccine which is a normal effect of passively acquired antibody in young infants. A knowledge of these relationships might make it possible to estimate the best age for administering measles vaccine without carrying out independent studies in every area. Knowing this optimal age is important, because measles vaccine is too expensive for many countries to administer repeatedly, and because once a particular response is obtained it cannot readily be boosted by more vaccine.

Materials and Methods

A single lot of the Moraten strain of further-attenuated measles vaccine was used to perform the study.

Vaccination trials were initiated in seven geographic areas: Costa Rica; Ecuador; Metropolitan Santiago, Chile; Rio Grande do Sul, Brazil; Metropolitan São Paulo, Brazil; Pernambuco, Brazil; and several towns in the state of Pará, Brazil. These areas are shown in Figure 1. The plan was to select children six through 12 months old for vaccination in such a way that each of seven one-month age groups in each area would contain 70 subjects. This would have meant vaccinating 490 children in each area and would have brought the total sample size to 3,430 subjects. It was agreed that these studies would be undertaken in the off-season in those areas where measles is seasonal, and that if a major epidemic broke out, the program would be suspended. An epidemic did break out in Costa Rica, and it proved impractical to resume the program. The data obtained from that country were therefore inadequate for analysis.

It was considered desirable that the children in each geographic area be evenly distributed between urban and rural populations, and participating clinics were chosen with this aim in mind. All the children coming to these clinics were invited to participate if they (1) were in the appropriate age group, (2) had not been previously vaccinated and had no history of prior measles, (3) did not have fever at the time of presentation, and (4) had a weight that was at least 60 per cent of the norm for their age *(19,20)*. In Rio Grande do Sul, São Paulo, and Santiago intensive vaccination programs had already reduced the number of unvaccinated children 10 months of age or more, so that these groups were not proportionately represented in the initial sample. Vaccination records from the participating clinics in these areas were searched, and unvaccinated children in the upper age groups were actively sought out. Despite these efforts, the desired numbers of vaccinees were not attained in São Paulo or Santiago. The numbers of vaccinated children in Ecuador likewise failed to reach the desired levels because of repeated

Figure 1. Location of measles vaccination trials.

administrative changes of a political nature.

As already noted, any child with a history of measles or measles vaccination was excluded from the study. In addition, serologic studies showed that prevaccination specimens from 74 children yielded HI titers of 1:20 or more. It is improbable that passive antibody would frequently persist at this titer in children more than six months old. These titers were therefore considered indicative of unrecognized prior measles infection, and the children providing these specimens were excluded from further analyses. Fifteen children were excluded because they did not meet the age-for-weight standard, and others were excluded because of incomplete data (Table 1). The final sample was distributed as shown in Table 2.

The definition of rural versus urban locales proved to differ in the different study areas. The Pará sample resided entirely in small cities or large towns and surrounding farming areas. About half the Ecuadorian sample came from one of the two largest cities (Quito and Guayaquil), while the other half came from small cities, towns, and farms. Most of the study children in Pernambuco came from the city of Recife while those with ostensibly "rural" residences lived in compact towns located in an agricultural area. In Santiago, Rio Grande do Sul, and São Paulo, the "rural" residence places were periurban. This situation made invalid any comparison of the total urban population with the total rural population.

Aside from excluding those subjects who

Table 1. Numbers of forms received and numbers progressively excluded, by area.

		Area						
	Total	Chile	Costa Rica	Ecuador	Pará	Pernambuco	Rio Grande do Sul	São Paulo
Total received	*2,553*	*241*	*62*	*492*	*515*	*540*	*478*	*225*
Reason for exclusion:								
Age	107	6	–	46	21	23	11	–
History of infection or vaccination	25	–	–	5	17	1	–	2
Third-degree malnutrition	15	–	–	5	5	2	2	1
Missing prevaccination titer	198	–	–	173	15	1	–	9
Prevaccination titer of 1:20 or more	74	16	–	9	23	9	12	5
Missing postvaccination titer	1	–	–	–	1	–	–	–
Unknown nutritional status	29	–	–	1	6	–	18	4
Total excluded	511	22	62	239	88	36	43	21
(% of total received)	(20.0)	(9.1)	(100.0)	(48.6)	(17.1)	(6.7)	(9.0)	(9.3)
Total analyzed	2,042	219	0	253	427	504	435	204

Table 2. Numbers of children receiving measles vaccine in each area and percentages seroconverting, by age and weight-for-age.

Area	Weight-for-age (N or D)	Age in months															
		6		7		8		9		10		11		12		Total	
		No. vaccinated	% seroconverting	No. vaccinated	% seroconverting	No. vaccinated	% seroconverting	No. vaccinated	% seroconverting	No. vaccinated	% seroconverting	No. vaccinated	% seroconverting	No. vaccinated	% seroconverting	No. vaccinated	% seroconverting
Chile	N	56	64.3	43	74.4	61	83.6	22	81.8	6	83.3	1	100.0	2	100.0	191	75.9
	D	1	100.0	7	85.7	15	100.0	4	100.0	1	100.0	–	–	–	–	28	96.4
Ecuador	N	31	64.5	30	76.7	33	90.9	32	90.6	24	91.7	21	85.7	23	100.0	194	85.1
	D	5	80.0	8	100.0	8	100.0	6	100.0	12	91.7	11	81.8	9	88.9	59	91.5
Pará	N	53	54.7	50	70.0	52	84.6	40	90.0	41	95.1	32	93.8	34	97.1	302	81.5
	D	4	75.0	13	76.9	19	79.0	19	94.7	25	88.0	20	95.0	25	88.0	125	87.2
Pernambuco	N	58	72.4	58	82.8	63	87.3	74	90.5	48	95.8	43	97.7	31	100.0	375	88.3
	D	17	82.4	21	95.2	19	100.0	11	100.0	24	95.8	23	100.0	14	92.9	129	95.4
Rio Grande do Sul	N	79	51.9	71	52.1	59	72.9	49	83.7	37	91.9	49	93.9	41	92.7	385	72.7
	D	3	66.7	2	100.0	2	50.0	7	71.4	14	78.6	8	100.0	14	71.4	50	78.0
São Paulo	N	42	47.6	57	68.4	44	86.4	16	75.0	11	90.9	8	100.0	8	100.0	186	72.6
	D	1	100.0	5	100.0	4	100.0	2	100.0	1	100.0	4	100.0	1	100.0	18	100.0
Total	N	319	58.9	309	69.3	312	83.7	233	87.1	167	93.4	154	94.2	139	97.1	1,633	79.7
	D	31	80.7	56	91.1	67	92.5	49	93.9	77	89.6	66	95.5	63	85.7	409	90.5

were markedly underweight, the study did not select subjects on the basis of nutritional status. A subject's actual weight relative to the expected weight at that age was used to screen rapidly for malnutrition. Any child whose weight was between 60 and 85 per cent of the median weight for its age on a U.S. standard curve *(20)* was designated as belonging to an underweight ("D") group. Others were designated as belonging to a normal ("N") group.

Each child was weighed, and a blood sample was collected before vaccination. The blood was taken by finger-prick and capillary tube in Ecuador and by venipuncture and syringe elsewhere. The infant's birth date was recorded. Twenty-eight to 35 days later, the subject returned to the clinic and a second blood sample was collected. Serum was separated in the country of origin. This was to have been done promptly after the blood had clotted, but because of the large number of clinics involved no real control could be maintained. In general, the amount of hemolysis was small except in the Ecuadorian samples, where the finger-prick procedure was associated with substantial cell lysis. Sera were frozen at − 20°C and stored in the country of origin until the whole collection could be taken by courier to the Instituto Evandro Chagas in Belém, Brazil, for testing. A single lot of measles antigen (from Microbiological Associates of Bethesda, Maryland, U.S.A.) was used to measure serum HI titers according to a standard procedure *(21),* starting with a dilution of 1:5.

Children who demonstrated a fourfold or greater increase in titer and whose second specimen yielded a titer of at least 1:10 were considered to have seroconverted.

Geometric mean titers were calculated by including titers of 1:5 but not titers below that level. In our analyses, a titer of 1:10 or greater was taken as an indication of sufficient response to provide lasting protection. A titer of 1:5, when accompanied by a negative test on an earlier serum specimen, was taken as indicative of some reaction and hence was included in computing mean titers. We consider it probable, however, that the normal decline in titer that occurs more than one month after vaccination would leave these children without protective antibody levels. (Only 54 children, 2.6 per cent of the study population, had postvaccination titers of 1:5.)

A modified linear logistic model was used to relate the variables studied to the percentages of children seroconverting (see Appendix 2). This model caused the relationship between percentage seroconversion and age to be expressed as a straight line. (The probability of seroconversion was assumed constant within each age group.)

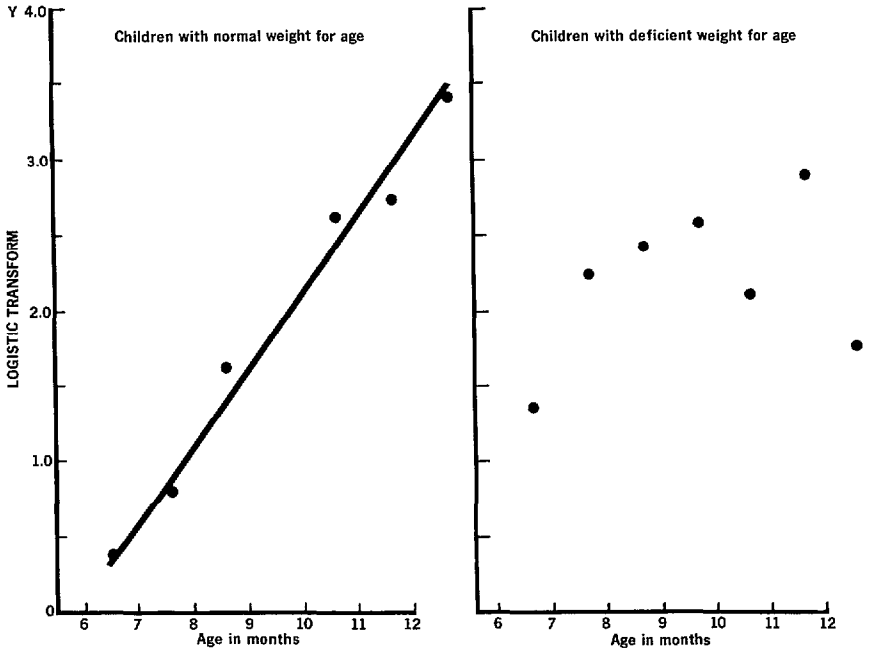
Results

A preliminary analysis showed that urban versus rural residence was not significantly correlated with seroconversion in any area except Santiago. The number of rural children in the Santiago area was small, and this was especially true in the upper age groups. For these reasons, this variable was omitted from further consideration, leaving age, weight-for-age, and geographic study area as the variables subjected to further analysis.

As a second step, data for the two nutritional groups were compared (Figure 2). The overall proportion of underweight children increased with age, suggesting progressive nutritional deterioration within the study populations.

The N-group data fit a straight line closely and showed a strong relationship between the proportion seroconverting and age. Although there were 409 children in the D group, the number that failed to seroconvert was relatively small in all age groups; a linear relationship between seroconversion and age could not be detected. Inspection of the data shows, however, that for most age groups the proportion of underweight children who seroconverted

Figure 2. Regression of seroconversion on age for all areas.



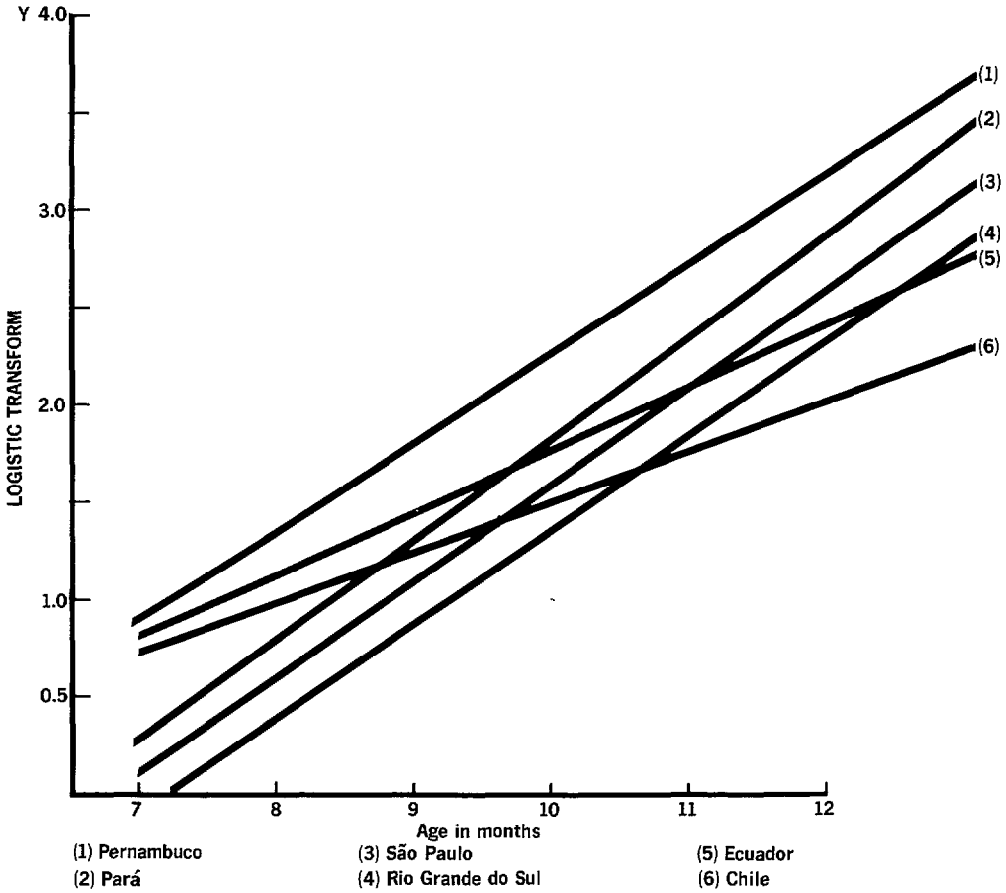
was at least equal to the proportion of N-group children who did so.

Inter-Area Comparisons

Comparison of seroconversion rates between different areas was confined to the 1,633 children in the N group. The slopes of the regression lines for individual areas (Figure 3) are very similar in all areas except Ecuador and Chile. Since the slopes did not differ from one another ($P > .05$), it was concluded that the data may be represented by a model in which the areas have parallel lines—that is, lines with a common slope but with different intercepts. Ecuador, Chile, and Pará have almost identical intercepts, while Pernambuco has the highest elevation and Rio Grande do Sul the lowest. At the .05 significance level, Pernambuco was found to be different from all other areas; Ecuador, Chile, Pará, and São Paulo were not different from each other; and Rio Grande do Sul was not different from São Paulo but was significantly different from all other areas.

Therefore, it was concluded that the data are best represented by a model using three lines with the same slope but different intercepts for Pernambuco, Rio Grande do Sul, and the pooled data from Chile, Ecuador, Pará, and São Paulo, respectively. It should be noted that this model explains 95.2 per cent

Figure 3. Regression of seroconversion on age for children with normal weight-for-age.



of the variation in the weighted transformed logistic values of the proportions seroconverting.

Seroconversion Rates by Age

In accordance with the preceding conclusions, the resulting estimates for the proportions seroconverting are shown in Figure 4. The curve for Pernambuco lies above the curve for the four pooled areas—Chile, Ecuador, Pará, and São Paulo—and the curve for Rio Grande do Sul lies below.

These curves provide a basis for estimating the average age at which vaccination is expected to result in a prespecified proportion of seroconversions, under conditions similar to those prevailing for the children studied. The resulting estimates are shown in Table 3. These indicate that the children should be 8.5 months old to attain a seroconversion rate of 80 per cent, and that they should be vaccinated one-and-a-half months later to attain a rate of 90 per cent.

Figure 4. Average predicted percentages seroconverting among children with normal weight-for-age, by age and area.

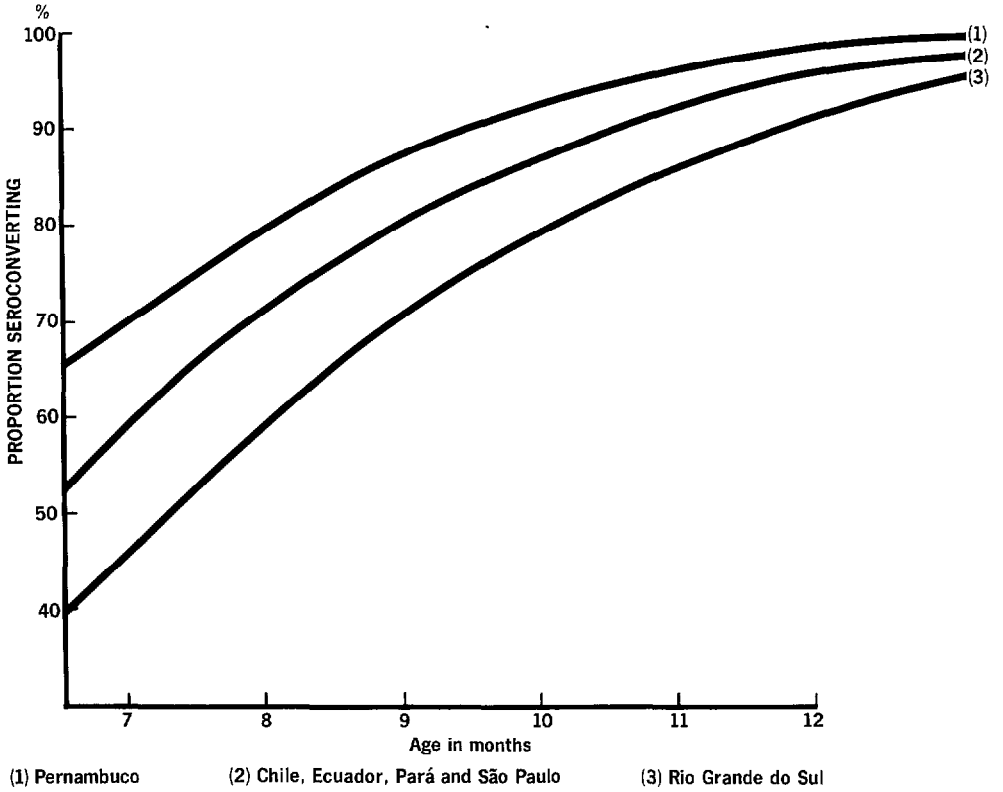


Table 3. Estimated mean vaccination ages needed to attain seroconversion rates of 80 and 90 per cent, by area.

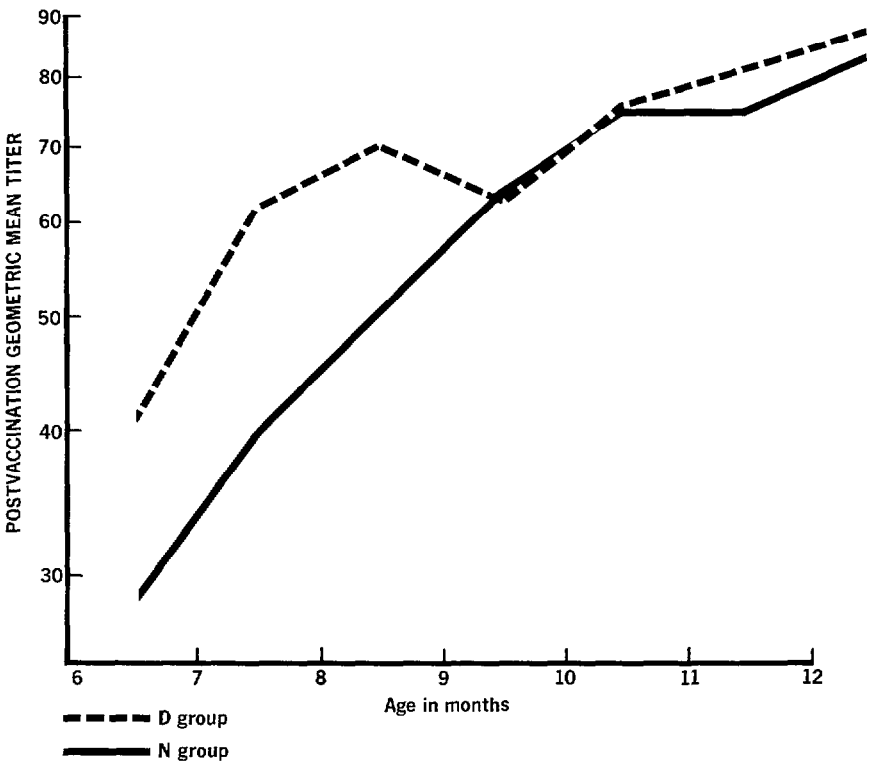
Area	Average age in months[a]	
	80% seroconversion	90% seroconversion
Pernambuco	7.4 months	9.0 months
Rio Grande do Sul	9.4 months	11.0 months
All other areas	8.4 months	10.0 months

[a]Analysis using upper one-sided 95 per cent confidence intervals indicates a seroconversion rate as high as the one stated may be achievable at ages 10 to 15 days lower than the averages shown

Serologic Titers

Not only did the proportion of study children responding to the vaccine increase with increasing age, but the geometric mean titers (GMT) obtained four weeks after vaccination also increased with age (Figure 5). For example, the GMT for the average six-month-old N-group child was 29, while for the average twelve-month-old child it was 83. The titers for D-group children were generally higher than for N-group children of the same age.

Figure 5. Postvaccination geometric mean titers (GMT),* by age, for N and D groups in all the study areas combined.



*Excludes 276 "normal" weight-for-age and 29 "deficient" weight-for-age children with non-detectable postvaccination titer.

There were also differences in the mean titers obtained from subjects in different areas. Table 4 presents the mean of the GMTs for the six, seven, eight, and nine-month age groups in six areas. The older age groups were not included for lack of adequate numbers of subjects in some areas. The rank order of the areas determined by these GMTs is very similar to that determined by the rate of seroconversion for the same age groups ($P = 0.01$ for Spearman's rank correlation test).

Table 4. Geometric mean titers (GMT) and percentages seroconverting in the 6-9 month age groups four weeks after vaccination, by area.

Area	GMT	% seroconversion
São Paulo	28.4	71.3
Rio Grande do Sul	30.9	65.0
Chile	39.6	78.1
Pará	60.3	75.5
Ecuador	61.8	83.3
Pernambuco	64.5	85.7

Discussion and Conclusions

Except in Pernambuco, the South American seroconversion rates observed were intermediate between those observed in Africa *(13-15)* and North America *(1-4,18)*. The Pernambuco results were not significantly different from the results obtained in Kenya *(13)* and Taiwan *(16)*. It remains difficult, however, to discover a basis on which these results might be generalized so as to make predictions regarding untested areas. It may be that the factor or factors that determine the response rate are influenced by economic development of the area, but we have no specific comparison data for the Brazilian states.

The observed seroconversion rates were not attributable to nutritional deficits, such as those recognized by the division between the D and N groups, because on the average the underweight children did not respond less frequently than the normal-weight ones. The empirical observation of higher seroconversion rates in the D group is consistent with the higher titers observed in these children. It may seem implausible that poorly nourished children would not be impaired in their immune responses, but in this case the capability for seroconversion reflects the absence of passive protection.

In view of the observed differences between seroconversion rates in different areas, it was surprising that urban-rural differences were not demonstrable within individual areas. Not only did the Ecuadorian response rates in cities fail to differ from those in small towns, but the Pará response rates in small towns did not differ from those in the surrounding farm areas.

The fact that the postvaccination titer varies with the subjects' age at vaccination is a new observation relevant to choosing the age at which measles vaccine should be administered. This study chose to take a titer of 1:10 at four weeks postvaccination as the lower limit of a positive response, because it was felt that after the twofold to fourfold titer decline that normally occurs in the year after vaccination, this is the lowest titer that would correlate with solid immunity. Conversely, it was believed that any titer of 1:10 or higher would correlate with immunity, and that titer differences in this range would have little effect on the child.

After the first year, however, measles antibody titers remain remarkably stable for the rest of a person's life. Titers above 1:2 are not usually boosted by reexposure to measles virus—because these levels prevent virus replication and because the amount of antigen in an infecting dose, or in a dose of vaccine, is inadequate by itself to stimulate the immune system. Children with such levels will therefore maintain only low levels throughout their lives.

This means that female children with low titers who grow to become mothers will have very little anti-measles IgG to pass on to their offspring, and so the children of these vaccinees will be susceptible to measles infection at a very early age, when the risk of death is particularly high. Such antibody titer suppression is more pronounced in areas where the seroconversion rate is low than in areas where good early response rates are obtained. This fact serves to underscore the importance of using the locally appropriate age for vaccination.

To determine the optimal age for vaccination in any given area, it is necessary to couple these data on seroconversion rates and titers with the following information:

(a) Local age-specific measles morbidity and mortality rates, so as to determine how much harm would be done by measles in children below the age chosen for vaccination.

(b) The prospects for having a sufficiently comprehensive and consistent program to reduce the amount of virus in circulation. Reduction of virus circulation reduces the number of children infected at an early age. This is an important short-term consideration in determining when the vaccine should be given, because it will affect the age-specific attack

rates. It will also have importance for the next generation, when susceptibility in the youngest age groups will be determined by the age at which vaccine is given now.

(c) The attitude of the local population towards vaccine failure. The earlier the vaccine is given, the more failures must be expected. If these failures are sufficiently common to damage the credibility of the program, participation will wane and the program may fail for lack of public confidence.

SUMMARY

Studies in the United States have shown that maternal antibodies against measles may persist in infants and may interfere with their response to measles vaccine even beyond the twelfth month of extrauterine life. Since measles infection during the first year of life is unusual in the U.S., the recommended age for vaccination against measles in that country has been set at 15 months.

On the other hand, infants in a number of African countries have been found to contract measles earlier, and so delaying vaccination until 15 months would allow a substantial amount of measles morbidity and mortality to continue. For this reason, the generally recommended age for measles vaccination in Africa is seven-and-a-half months.

To help define the situation in Latin America, a study was conducted of how 2,042 infants six to 12 months old responded to measles vaccine. The results showed that seroconversion rates in Latin American children were generally intermediate between the previously reported rates for Africa and those for the United States. Infants whose weights were 60 to 85 per cent of normal for their ages seem to have good seroconversion rates relative to children closer to the weight-for-age norm.

In general, postvaccination antibody titers were lower for younger than for older infants. There is no evidence that these lower titers will impair immunity in these infants, but when the female infants grow up and have children, their lower antibody levels could cause them to pass lower levels of maternal antibodies to their children and so could permit measles infection at an earlier age in the next generation.

The choice of an optimal age for vaccination at any given place in South America should take local factors into account, but in general the best age should be less than the 15 months recommended in the U.S. and more than the seven-and-a-half months recommended in Africa.

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APPENDIX 2: STATISTICAL NOTE

A modified linear logistic model *(22)* was used; the logistic transform being defined as

$$Y_i = 1n\ [(P_i + 1/2n_i) / (1 - P_i + 1/2n_i)],$$

where P_i denotes the proportion of children who seroconverted among a total of n_i vaccinated children in the i^{th} age group.

For the weighted least squares analysis, weights were assigned to the i^{th} age group by the multiplier

$$W_i = n_i \left[\frac{(P_i + 1/2n_i) + (1 - P_i + 1/2n_i)}{n_i + 1} \right]^{1/2}$$