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INFLUENCE OF MODERATE MALNUTRITION ON MORBIDITY AND ANTIBODY RESPONSE FOLLOWING VACCINATION WITH LIVE, ATTENUATED MEASLES VIRUS VACCINE[1]

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Following vaccination against measles, a group of moderately malnourished Colombian children produced as much antibody and had the same degree of post-vaccination morbidity as did their well-nourished cohorts. It appears on the basis of these findings that live, attenuated measles vaccine is both safe and effective in moderately malnourished populations.

Introduction

The influence of malnutrition upon susceptibility to infection has been well-documented in man (*1, 2*). Hence increased morbidity and mortality observed in malnourished populations can be explained, at least in part, by the detrimental effects of malnutrition on various aspects of the humoral (*3, 4*), cell-mediated (*5, 6*), and secretory (*7, 8*) immune responses. These effects have been most clearly demonstrated in children suffering from the more severe forms of protein and energy malnutrition, although recent studies indicate that subclinical malnutrition may also significantly impair a child's ability to respond immunologically to infectious agents (*9, 10*). The latter findings have far-reaching implications for vaccination and other disease management programs in developing parts of the world, since more than half the children in these areas are suffering from some degree of moderate malnutrition (*11*).

Measles infection is known to cause severe disease and death in badly malnourished populations (*12*). Yet it has been shown repeatedly that vaccination with live, attenuated measles virus stimulates antibodies in malnourished populations (*13, 14*), and there is experimental evidence suggesting that post-vaccination morbidity in such populations is no more severe than in normal populations (*14, 15*). Due to the severity of the natural infection in malnourished children, however, physicians in many parts of the world are reluctant to vaccinate with the live, attenuated virus for fear of causing severe illness in vaccinees.

Many early vaccine studies failed to adequately document the vaccinee's nutritional status, and lack of long-term follow-up left some uncertainty about the ability of malnourished children to maintain an adequate anti-measles antibody titer during a time when their nutritional status may be deteriorating.

In an attempt to clarify these points, humoral antibody response and post-vaccination morbidity were studied in groups of normal and moderately malnourished Colombian children subsequent to adminis-

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tration of live, attenuated measles virus vaccine. The children were followed for more than a year to determine the influence of chronic malnutrition upon antibody titers.

Test Subjects and Methods

A total of 74 children from a poor urban population in Cali, Colombia, were included in this study. All came from a homogeneous cultural and socioeconomic background, and all lived in the same part of the city. Thirty-nine children were classified as normal and 35 as suffering from some degree of malnutrition (26 from grade I, 7 from grade II, and 2 from grade III) on the basis of failure to gain weight appropriately for their age (*16*). All the children were 10 months of age when vaccinated. None had suffered a clinical measles infection prior to vaccination and none was seriously ill at the time.

Each child received a single dose of live, attentuated measles virus vaccine (Attenuvax, Merck, Sharp and Dohme) intramuscularly in the midlateral muscles of the thigh. Blood samples were taken immediately before vaccination and 2, 8, and 14 months afterwards. Sera were assayed for measles antibody using a micro-modification of the hemagglutination-inhibition (HI) technique (*17*). Commercial reagents (Flow Laboratories, Inc., Maryland) were employed. A close approximation has been demonstrated between virus neutralization titers and HI titers in human and animal sera containing moderate to high levels of antibody (*18, 19*).

For 21 consecutive days following vaccine administration the children were visited at home by a nurse who noted the presence of conjunctivitis, diarrhea, skin eruptions, or fever. Symptoms appearing before 5 days post-vaccination were not considered related to the vaccination. Children showing these early symptoms were excluded from the morbidity analysis.

For purposes of statistical analysis, children with grade II and grade III malnutrition were grouped together. The analysis of variance was used to test for a significant influence of nutritional status on either antibody response or post-vaccination morbidity.

Results

Before vaccination approximately 17 per cent of the children had detectable levels of anti-measles antibodies yielding titers of at least 1:8. The existence of this pre-vaccination antibody was not related to the nutritional status of the children, nor did it significantly alter their subsequent response to the vaccine.

As the figures in Table 1 indicate, children's nutritional status did not influence

Table 1. Measles antibody titers yielded by sera of vaccinated normal and malnourished children.

Time post-vaccination	Log_2 HI titers (mean ± SEM[a])			F-ratio	P
	Normal (n = 39)	Grade I malnutrition (n = 26)	Grades II and III malnutrition (n = 9)		
0 (pre-vaccination)	0.49 ± 0.12	0.58 ± 0.15	0.67 ± 0.29	.103	N.S.[b]
2 months	6.54 ± 0.10	6.87 ± 0.30	6.67 ± 0.31	.076	N.S.
8 months	6.21 ± 0.19	6.39 ± 0.22	6.00 ± 0.45	.422	N.S.
14 months	6.05 ± 0.15	6.00 ± 0.21	5.71 ± 0.22	.563	N.S.

[a]SEM = Standard error of the mean.
[b]N.S. = Not significant ($p > 0.1$).

their antibody response to the vaccination. Children in all three groups responded very well to the attenuated measles virus, and their serum titers showed only a very gradual reduction over the subsequent 14 months.

The nutritional grouping of children at the 0, 2, 8, and 14-month intervals shown in Table 1 is based upon each child's nutritional status at the time of vaccination. During the 14-month period 20 children became more malnourished; specifically, 13 children normal at vaccination later fell into grade I, 5 grade I children descended into grade II, and two grade II children entered grade III. Nevertheless, grouping the children according to their actual nutritional status at each post-vaccination interval did not change the results significantly, and no consistent reduction in antibody titers was observed for those children who became progressively more malnourished.

It was found that about 20 per cent of the children exhibited one or more clinical signs during the first 4 days post-vaccination. For the remainder of the children, the incidence of these sequelae was not influenced significantly by nutritional status. Table 2 shows the proportion of daily visits to children in each nutritional group that detected the indicated sign. In general, the incidence of post-vaccination morbidity was quite low. When present, fever never exceeded 40°C (104°F) in any child. The mean of the highest temperatures for chil-

Table 2. Incidence of post-vaccination sequelae in normal and malnourished children vaccinated against measles.

Sign	Average percentage of days with sign for children in each group (mean ± SEM[a])			F-ratio	P
	Normal (n = 30)	Grade I malnutrition (n = 23)	Grades II and III malnutrition (n = 6)		
Conjunctivitis	13.9 ± 3.8	8.1 ± 2.3	10.2 ± 5.2	0.716	N.S.[b]
Diarrhea	14.4 ± 3.2	12.6 ± 4.3	0	—	—
Skin eruption	7.7 ± 2.7	13.6 ± 3.2	6.4 ± 3.5	1.226	N.S.
Fever	13.9 ± 3.2	13.4 ± 4.2	16.7 ± 5.8	0.115	N.S.

[a]SEM = Standard error of the mean.
[b]N.S. = Not significant (p > 0.1).

Table 3. First appearance of sequelae following measles vaccination of normal and malnourished children.

Sign	First day of sign (mean ± SEM[a])			F-ratio	P
	Normal (n = 30)	Grade I malnutrition (n = 23)	Grades II and III malnutrition (n = 6)		
Conjunctivitis	14.9 ± 1.3	17.5 ± 1.4	14.0 ± 3.3	1.110	N.S.[b]
Diarrhea	13.3 ± 1.3	16.2 ± 1.5	—	—	—
Skin eruption	18.7 ± 1.0	15.6 ± 1.3	15.4 ± 3.9	1.840	N.S.
Fever	11.0 ± 1.6	15.2 ± 1.8	8.8 ± 0.4	2.810	N.S.

[a]SEM = Standard error of the mean.
[b]N.S. = Not significant (p > 0.1).

dren with fever in each nutritional group was as follows: normal, 37.9°C; grade I, 37.9°C; grades II and III, 38.0°C.

The rate of onset of clinical sequelae in the three groups of children was also examined. The results, summarized in Table 3, indicate that nutritional status did not significantly influence the interval between vaccination and first appearance of the signs. Fever appeared somewhat earlier in grade II and III children, but the differences involved were not statistically significant.

Discussion

We have demonstrated that moderately malnourished children do not suffer increased morbidity and do respond as successfully as their normal cohort in producing antibody following vaccination with live, attenuated measles virus vaccine. Previous investigators have examined the response to measles vaccination of populations known to suffer from malnutrition, but few specific data on the nutritional status of the vaccinees were reported (*13, 14*). Hence little information is available comparing the post-vaccination morbidity and antibody responses of normal and malnourished children from a homogeneous population.

Our results support the earlier observations, which suggest that the antibody response to live, attenuated measles virus is normal in malnourished children (*20*). The apparent lack of nutritional status influence on post-vaccination morbidity that we observed in our Colombian children should encourage the use of live, attenuated measles vaccine in other moderately malnourished populations—populations that include over half of all the children in many developing countries (*11*).

It has been postulated that increased morbidity and mortality following natural infection with measles in malnourished populations may be related to deficiencies in cell-mediated immune mechanisms rather than deficient antibody production (*21*). Reduced cellular immunity has been demonstrated in marginally malnourished children (*9*), and we have observed both reduced skin test responsiveness and *in vitro* lymphocyte transformation in our children with grade II and III malnutrition (unpublished results). However, these circumstances did not seem to exacerbate the infection produced by the vaccine strain.

The low levels of antibody detected in some of the children before vaccination were probably the result of exposure to natural infection at an earlier age. Some of this antibody could have been residual IgG of maternal origin, although this is usually metabolized by the child within the first 6 months of life. The presence or absence of pre-vaccination antibody did not influence the subsequent response to vaccination.

The maintenance of high III titers during the 14 months following vaccination is similar to the patterns obtained in studies of normal children (*22, 23*). The literature reports no longitudinal study of measles titers in normal and malnourished vaccinees.

The observation that even a progressive decline in nutritional status (observed in 20 of the study children) failed to adversely affect their antibody levels illustrates the efficacy of measles vaccination in such a population. It should be noted, however, that the continued high titers in our population could be related to the booster effect of exposure to wild-type virus in the environment, as well as to residual antibody produced against the vaccine strain.

Antibody titers have been shown to wane somewhat more quickly in institutionalized, and presumably isolated, populations (*23*). It has also been demonstrated that a decline in the post-vaccination titer to very low levels does not necessarily mean loss of protection, since a rapid anamnestic response in such individuals may adequately cope with a natural infection (*22*).

Chandra (*8*) has recently demonstrated that severely malnourished children have significantly less IgA and specific anti-measles antibody in nasopharyngeal secretions following vaccination with the live, attenuated vaccine. We found reduced levels of IgA in the tears and saliva of our moderately malnourished children (*10*), although we did not measure specific anti-measles activity in these secretions. The apparent sensitivity of the secretory immune system to even moderate malnutrition may be a very significant factor in the response to vaccination and the susceptibility to natural infection with measles, since secretory IgA represents the first line of defense against inhaled virus landing on mucosal surfaces.

There is a well-documented synergism between infection and nutritional status. Even the mild infections produced by vaccination with living agents such as polio, BCG, cowpox, and measles can precipitate a series of metabolic events resulting in negative nitrogen balance and anorexia (*24, 25*). Kielmann has demonstrated significant reductions in weight-for-age in vaccinees less than 6 months of age (*26*). Although we were unable to demonstrate increased morbidity in the malnourished children who received live measles vaccine, it is possible that the deteriorating nutritional status noted in 20 of the children during the subsequent months was related, at least in part, to the subclinical measles virus infection. However, given the high risk of natural exposure in this population and the excellent antibody response in both normal and malnourished children, vaccination with measles vaccine as early as 10 months of age is warranted.

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SUMMARY

Seventy-four Colombian children from a poor urban population were given one dose of a live, attenuated measles virus vaccine at the age of 10 months. Nearly half of these children (35) were suffering from some degree of moderate malnutrition, as indicated by lack of the weight expected for their age.

In terms of the incidence and onset dates of fever, conjunctivitis, diarrhea, and skin eruptions in this population, the children's nutritional status had no influence on post-vaccination morbidity. In addition, all the children responded serologically to the same degree, regardless of nutritional status, mean hemagglutination-inhibition titers being only slightly reduced in all nutritional groups 14 months after vaccination. On the basis of these findings, the use of live, attenuated measles vaccine in moderately malnourished children appears to be safe and effective.

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