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Safety and impact of vitamin A supplementation delivered with oral polio vaccine as part of the immunization campaign in Orissa, India

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Abstract

A study was carried out in Orissa, India, to evaluate the impact on vitamin A status of vitamin A supplementation integrated with an immunization campaign. Data were collected from a representative sample of 1,811 children, aged 12 to 48 months, at baseline and then at 4 and 16 weeks following implementation of vitamin A supplementation. The primary outcome indicator was serum retinol. The coverage of vitamin A supplementation was 97%. There was a significant decline in the prevalence of Bitot's spots from 2.9% to 1.9% at 4 weeks, but the prevalence increased to 3.6% by 16 weeks. Serum retinol concentrations increased between baseline and 4 weeks (from 0.62 ± 0.32 to 0.73 ± 0.23 μmol/L, p *< .001) but then decreased to 0.50 ± 0.19 μmol/l at 16 weeks, which was significantly lower than at baseline (*p *< .001). The greatest increase in serum retinol from baseline to 4-week follow-up was among children with lowest baseline serum retinol and children with Bitot's spots at baseline. This study demonstrates the short-term benefits of vitamin A supplementation to be significant, especially for those whose status is most compromised. At the same time, the benefit of vitamin A supplementation in this population was transient. The impact of the vitamin A could not be sustained for the full 16 weeks in the study population. This finding calls for exploration of other means to improve vitamin A status, perhaps by adjusting the vitamin A supplementation schedule with more aggressive measures to improve intake of foods rich in bioavailable vitamin A, such as small amounts of animal foods or fortified foods. The study demonstrates the feasibility of integrating vitamin A supplementation with immunization campaigns.*

Key words: EPI; immunization campaigns; Orissa, India; serum retinol; vitamin A deficiency; vitamin A supplementation, xerophthalmia

Introduction

The persistence of vitamin A deficiency among preschool children in developing countries has led to the search for strategies to improve vitamin A intake and vitamin A status. Vitamin A deficiency has long been a significant public health problem in India, in part due to the low levels of bioavailable vitamin A in the traditional diet [1]. A national vitamin A deficiency control program was initiated in India in 1970, with one component being the routine provision of vitamin A supplementation to preschool children.

However, coverage of vitamin A supplements through the routine delivery system remains low [2–4]. In 1999, the State of Orissa decided to integrate the distribution of vitamin A supplements with the intensified pulse polio immunization (IPPI) on national immunization days, as has been done in other countries [5–7]. High-dose vitamin A was provided with the first and last rounds of IPPI on October 24, 1999 (for children 12–42 months of age), and March 26, 2000 (for children 12–48 months of age). At the request of the State Government of Orissa, the World Health Organization (WHO) assessed the safety and feasibility of linking vitamin A supplementation with national immunization days and measured the impact of this strategy [8].

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A safety study was carried out on October 25 and 26, 1999, in Orissa following the administration of vitamin A with the first IPPI round. Safety was assessed by evaluating the development of signs and symptoms of illness (fever, diarrhea, vomiting, and anterior fontanelle bulging) among 879 randomly selected preschool children within 48 hours of receiving vitamin A on national immunization days. Of the total sample, 26 children (3.0%; 95% confidence interval, 2.0%–4.2%) displayed at least one sign of illness, and there were no differences in the prevalence of symptoms of illness between those children who received vitamin A (3.0%; 95% confidence interval, 1.9%–4.6%) and those children who did not receive vitamin A (2.8%; 95% confidence interval, 1.1%–5.7%). Further stratification by age did not reveal any differences in the prevalence of side effects that may have been attributable to receipt of vitamin A. Thus, it was concluded that administration of vitamin A on national immunization days is safe, confirming evidence reported from other countries [9–11]. A second study was subsequently conducted to measure the impact of the integrated approach.

The main objectives of the impact study were to assess the extent of vitamin A deficiency in children between 12 and 48 months of age in Orissa at baseline and to measure the impact on vitamin A status of receipt of vitamin A. One of the important questions was whether receipt of a single high dose of vitamin A would lead to a significant and sustainable improvement in vitamin A status as well as a reduction in clinical and subclinical deficiency. The study also examined whether vitamin A supplementation would lead to changes in nutritional status, anemia, and morbidity.

Methods

Data were collected from children at three points in time over a six-month period. The baseline enumeration was implemented between March 1 and 7, 2000, preceding the delivery of high-dose vitamin A supplements (200,000 IU provided as a liquid in a spoon) on a national immunization day (March 26, 2000). The first follow-up enumeration was undertaken 4 weeks after the national immunization day, from April 29 to May 4, 2000. The second follow-up enumeration was conducted 16 weeks after the national immunization day, between August 1 and 8, 2000. The study was an evaluation to assess the impact of the supplementation activity in Orissa under normal operating program conditions. In the original design, a control group was identified in neighboring Andhra Pradesh, but because of differences between the two groups it was decided to present only the data for Orissa independently. There were significant differences between Orissa and Andhra Pradesh in key demographic and health parameters. Perhaps more critical was the fact that children in Andhra had been exposed to vitamin A supplementation as part of the routine health delivery system, and it was not possible to determine the interval between vitamin A receipt and enumeration for this study, thereby making comparisons with Orissa inappropriate.

A sample size of 2,100 was initially estimated to ensure adequate power to detect a reduction in the prevalence of Bitot's spots from 3% to 1% with 95% confidence, with a design effect of 2, and allowing for a 30% dropout rate.

Demographic and socioeconomic data collection and clinical examinations were performed for all children. Anthropometric measurements were performed at baseline and at the second follow-up among two-thirds of the children who were randomly selected. In this subsample of children, information on morbidity was collected, while every fourth child had blood taken for the determination of retinol and hemoglobin (fig. 1).

Six teams were recruited for the study, each including a medical officer, anthropometrist, laboratory technician, and local auxiliary nurse worker. Bitot's spots were assessed by clinical examination, while information on night-blindness was obtained by a questionnaire administered to the respondents of children above 24 months of age. Local terminology for night-blindness was used to facilitate reliable responses. Data for the follow-up rounds distinguished between children whose Bitot's spots had resolved ('healed') from earlier rounds and those whose Bitot's spots remained ("persistent") in subsequent rounds and those who developed Bitot's spots ("new cases"). The distinction between new cases (incidence) and total cases (preva-

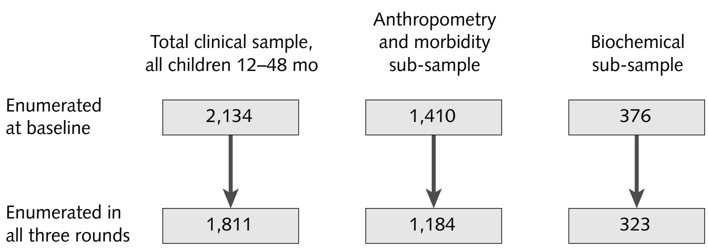

FIG. 1. Flow chart of sample design

lence) at the two follow-up points in time allowed for the differentiation between the benefits of the vitamin A supplements to prevent vitamin A deficiency and the response of preexisting vitamin A deficiency to supplementation.

Socioeconomic status was based on a wealth index derived from a principal-components analysis of data collected on household ownership of assets, including electricity, bicycle, telephone, and radio. Reliable information regarding vitamin A supplementation coverage was verified from records maintained by health workers. For analysis of coverage of the March 1999 vitamin A campaign and the October 1999 national immunization day, only those children who were eligible to receive the vitamin A were included, i.e., those who were old enough at the time of the respective distribution.

Morbidity data based on a two-week recall and clinical examination were also collected by using standard WHO classification criteria [12]. Respiratory illness was indicated by the following parameters: difficulty in breathing, chest indrawing, and rapid respiration. The presence of either or both of the last two symptoms was taken as an indication of acute lower respiratory infection. In addition to a two-week recall of diarrhea (defined as three or more loose stools in a 24-hour period), information on the current presence of acute diarrhea was recorded, and if it was present, its duration was noted.

Weight was measured with hanging Salter scales, and height or length was recorded with a measuring board or height rod, depending on the age of the child. Recumbent length was measured on children up to 24 months of age, and standing height was measured on older children.

Fingerprick blood samples were collected, and hemoglobin was determined in the field with portable HemoCue photometers (HemoCue AB, Angelholm, Sweden)[13]. Dried blood spot samples were prepared on coated filter paper (Schleicher & Schuell No. 903) and transported to Craft Technologies, Wilson, N.C., USA, where they were analyzed for their retinol concentration according to established high-pressure liquid chromatographic (HPLC) methodology [14, 15].

Both dried blood samples and venous blood samples were taken from 51 preschool children to validate the dried blood sample method. The results of this analysis are seen in figure 2, where a significant correlation ($R^2 = 0.86$) was observed between the serum retinol estimates from the two methods of blood collection.

The nutritional status of children was estimated by calculating Z scores for weight-for-age (WFA), height-for-age (HFA), and weight-for-height (WFH) using the WHO reference standards [16]. Children whose values were less than –2 SD from the reference median for each indicator were classified as malnourished according to WHO guidelines.

For analyses of changes over time, only those children who had an ophthalmologic examination at all three enumeration rounds were included (n = 1,811). In order to identify characteristics of children who received vitamin A, student's t-tests and chi-square tests were used for continuous and categorical variables, respectively. Independent-sample t-tests were used to compare mean serum retinol levels of children who took vitamin A and those who did not take vitamin A, whereas paired t-tests were used to compare the impact of vitamin A supplementation between baseline and each of the two follow-up points.

A stepwise logistic-regression model was developed to examine the factors associated with low serum retinol levels (< 0.70 μmol/L). Bivariate analyses of serum retinol and a set of morbidity, anthropometric, and Bitot's spots measures were performed. Differences in mean serum retinol levels from baseline to each follow-up point were compared by paired t-tests. All statistical significance was accepted at the 5% probability level, and 95% confidence intervals were presented where appropriate.

The study objectives and data-collection methods were described to all participants. All mothers provided consent to be included, while those not willing to participate, either at baseline or at any time during the study period, were dropped from the sample.

Results

The total sample size of children covered at baseline in the study was 2,134 (fig. 1). All children underwent clinical examinations, and 1,410 also had anthropometric measurements and morbidity recorded. In addition, 376 children underwent biochemical investigations. Of the total baseline sample, 1,811 (85%) were available and enumerated at both follow-up rounds. There were only minor differences

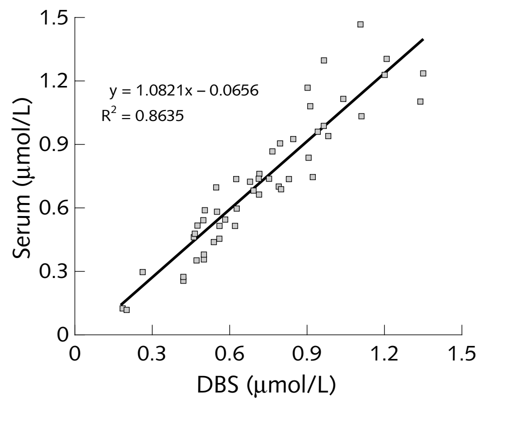

FIG. 2. Correspondence between serum retinol levels estimated from dried blood spot (DBS) samples and venous blood samples: validation study

in the key baseline characteristics between the children who were followed up during all three rounds of data collection and those who were enumerated only at baseline, as seen in table 1. Higher birth order and larger family size were associated with retention in the study. The literacy rate was slightly higher among mothers of children who were not followed up than among mothers of children who were followed up. There were no differences in the other key outcome parameters, including vitamin A status, morbidity, and nutritional status.

Baseline characteristics of anemia, morbidity, growth, and vitamin A deficiency

The prevalence of low serum retinol (< 0.70 μmol/L) was 63.8% (95% confidence interval, 58.4%–69.0%), which is more than three times higher than the cutoff point recommended by WHO to indicate a severe public health problem [17]. The prevalence of severe vitamin A deficiency (serum retinol < 0.35 μmol/L) was 20.4% (95% confidence interval, 16.3%–25.1%), and the mean serum retinol level was 0.62 ± 0.32 μmol/L. The prevalence of Bitot's spots at baseline was 2.9% (95% confidence interval, 2.2%–3.7%) (table 2).

Anemia was highly prevalent at baseline; more than two-thirds of the children had low hemoglobin levels (< 11.0 g/dl), and the mean hemoglobin level was 10.27 ± 1.41 g/dl. The prevalence of current diarrhea at the time of the baseline enumeration was 4.9% (95% confidence interval, 3.8%–6.3%). Acute lower respiratory infection was observed among 1.9% (95% confidence interval, 1.2%–2.8%) of the children at baseline. Just over one-half of the children were underweight (< –2 SD weight-for-age), while stunting (< –2 SD height-for-age) was present in 44.6% of the children and wasting (< –2 SD weight-for-height) in 25.7%.

Coverage rates

Data on the coverage of vitamin A supplementation are presented in table 3. Among those children who were eligible to receive vitamin A at the time of the March 1999 vitamin A distribution (not linked to the national immunization day), 59.8% actually received vitamin A. At the time of the October 1999 distribution (as part of the national immunization day), 95.8% received a dose of vitamin A. Finally, 97% of the children were covered with vitamin A on the March 2000 national immunization day. No other vitamin A was distributed during the course of the study period.

TABLE 1. Demographic and socioeconomic characteristics of baseline sample: cohort vs. noncohort[a]

Characteristic	Noncohort (*n* = 323)	Cohort (*n* = 1,811)	*p* value
Sex			NS
Male	50.2%	53.2%	
Female	49.8%	46.8%	
Age group (mo)			NS
12–24	24.5%	27.4%	
24–48	75.5%	72.6%	
Socioeconomic status			
Birth order ≥ 5	3.7%	7.8%	< .01
Family size ≥ 6	32.5%	41.0%	< .01
Kacha[b] type of house	50.5%	48.9%	NS
Maternal literacy	58.2%	49.6%	< .01
Ownership of at least 1 luxury item[c]	13.9%	13.4%	NS
Mean (SE) wealth index[d]	1.68 (0.084)	1.53 (0.033)	NS
Vitamin A deficiency status			
Night blindness (XN)	0.4%	0.5%	NS
Bitot's spots	2.5%	2.9%	NS
Mean (SD) μmol/L serum retinol	0.59 (0.29)	0.62 (0.32)	NS

a. Cohort members are children measured at all three rounds; noncohort members are children measured at only one or two rounds.

b. A *kacha* house is one that has a mud wall and a thatched or tiled roof.

c. A luxury item is defined as a telephone, automobile, or tractor.

d. The wealth index is calculated by scoring one point each if the household had electricity, a radio, television, and a bicycle, and then adding the points together.

Changes in morbidity, growth, and vitamin A deficiency over the study period

Table 4 outlines changes in Bitot's spots over the course of the study period. The prevalence of Bitot's spots at the time of the baseline examination was 2.9% (95% confidence interval, 2.15%–3.75%); the prevalence declined at the 4-week follow-up to 1.9% (95% confidence interval, 1.35%–2.68%) and then increased to 3.6% (95% confidence interval, 2.78%–4.55%) by the 16-week follow-up. The changes between the 4-week and 16-week follow-up were statistically significant. At the 4-week follow-up, the incidence (new cases) of Bitot's spots was 0.8% (95% confidence interval, 0.46%–1.36%), and the incidence by the time of the 16-week follow-up was 3.0% (95% confidence interval, 2.25%–3.87%). Almost 62% of all cases of Bitot's spots initially seen at baseline had resolved one month after baseline, and 68.5% of the cases seen at the 4-week follow-up (24 of the 35 cases) had healed by the time of the 16-week follow-up.

Table 5 outlines the change in major parameters over the duration of the study. The prevalence of low serum retinol (< 0.70 µmol/L) declined from 63.8% (95% confidence interval, 58.4%–69.0%) at baseline to 46.1% (95% confidence interval, 40.8%–51.4%) at the 4-week follow-up and then increased significantly

TABLE 2. Health and nutritional status of baseline sample (cohort only)

Characteristic	Value
Clinical vitamin A deficiency	
Night blindness [XN] (24–48 mo; *n* = 1,313)	0.5%
Bitot's spots (12–48 mo; *n* = 1,811)	2.9%
Serum retinol (*n* = 318)	
Mean (SD) µmol/L serum retinol	0.62 (0.32)
< 0.35	20.4%
0.35–0.70	43.4%
< 0.70	63.8%
Anemia (*n* = 323)	
Mean g/dl hemoglobin (SE)	10.27 (1.41)
< 7	2.5%
7–10.9	65.0%
< 11	67.5%
Diarrhea (*n* = 1,174)	
Past 2 wk	12.9%
Current (past 24 h)	4.9%
Duration of current diarrhea (days)	
1–7	4.5%
7–14	0.3%
> 14	0.1%
Respiratory infection	
Cough or difficulty breathing (past 2 wk)	19.6%
Cough or difficulty breathing (current)	8.2%
Acute lower respiratory infection (current)	1.9%
Nutritional status[a]	
Wasting (WFH < –2 SD)	25.7%
Stunting (HFA < –2 SD)	44.6%
Underweight (WFA < –2 SD)	57.8%

a. WFH, Weight-for-height; HFA, height-for-age; WFA, weight-for-age.

TABLE 3. Coverage of vitamin A supplements (cohort only)

Month administered	Eligible children[a]	% receiving vitamin A
March 1999	1,272	59.8
October 1999	1,568	95.8
March 2000[b]	1,782	97.0

a. The number of children eligible to receive the dose at each distribution round.
b. Data on vitamin A coverage were not available for a total of 29 children in the March 2000 baseline round.

TABLE 4. Incidence of Bitot's spots (follow-up rounds: cohort only, *n* = 1,811)

Characteristic	*n*	% (95% confidence interval)[a,b,c]	%
Baseline cases	52	2.9% (2.15%–3.75%)	
1st follow-up (4 wk)[a]			
Resolved cases (from baseline)	32		61.5
Total cases	35	1.9% (1.35%–2.68%)[c]	
New cases	15	0.8% (0.46%–1.36%)[c]	
Old cases	20		
2nd follow-up (16 wk)[b]			
Resolved cases (from 1st follow-up at 4 wk)	24		68.5
Total cases	65	3.6% (2.78%–4.55%)	
New cases	54	3.0% (2.25%–3.87%)	
Old cases	11		
Bitot's spots in all 3 rounds[c]	9		17.3

a. Statistically significant difference ($p < .05$) between baseline and 4-week follow-up.
b. Statistically significant difference ($p < .05$) between baseline and 16-week follow-up.
c. Statistically significant difference ($p < .05$) between 4-week follow-up and 16-week follow-up.

to 86.4% (95% confidence interval, 82.4%–89.8%) by the 16-week follow-up. These changes all reached statistical significance. The prevalence of severe vitamin A deficiency (serum retinol < 0.35 μmol/L) was 20.4% (95% confidence interval, 16.3 %–25.1%) at baseline and declined more than fourfold to 5.0% (95% confidence interval, 3.0%–7.7%) by the 4-week follow-up. The prevalence then increased to a level similar to that seen at baseline (22.4%; 95% confidence interval, 18.1%–27.1%) by the 16-week follow-up.

TABLE 5. Trends in major outcome variables over the study period

Variable	Time of measurement	*n*	Prevalence (%)	95% confidence interval	*p* value
Night-blindness (age 24–48 mo)	Baseline	1,313	0.46	0.09%–0.82%	
	1st follow-up (4 wk)		0.08	0.00%–0.23%	
	2nd follow-up (16 wk)		0.30	0.1%–0.60%	
Bitot's spots (age 12–48 mo)	Baseline	1,811	2.9	2.2%–3.7%	
	1st follow-up (4 wk)		1.9	1.4%–2.7%	*c*
	2nd follow-up (16 wk)		3.6	2.8%–4.6%	
Serum retinol < 0.70 μmol/L	Baseline	318	63.8	58.4%–69.0%	*a,b*
	1st follow-up (4 wk)		46.1	40.8%–51.4%	*c*
	2nd follow-up (16 wk)		86.4	82.4%–89.8%	
Serum retinol < 0.35 μmol/L	Baseline	318	20.4	16.3%–25.1%	*a*
	1st follow-up (4 wk)		5.0	3.0%–7.7%	*c*
	2nd follow-up (16 wk)		22.4	18.1%–27.1%	
Anemia (hemoglobin < 11 g/dl)	Baseline	323	67.5	65.2%–72.4%	
	1st follow-up (4 wk)		70.3	65.3%–74.9%	
	2nd follow-up (16 wk)		60.9	55.7%–66.0%	
Current diarrhea	Baseline	1,174	4.9	3.8%–6.3%	
	1st follow-up (4 wk)		4.3	3.2%–5.5%	
	2nd follow-up (16 wk)		4.6	3.5%–6.0%	
Current acute lower respiratory infection	Baseline	1,174	1.9	1.2%–2.8%	*a*
	1st follow-up (4 wk)		0.5	0.2%–1.0%	
	2nd follow-up (16 wk)		0.8	0.4%–1.5%	
Wasting	Baseline	1,153	25.7	23.2%–28.3%	*b*
	2nd follow-up (16 wk)		18.8	16.6%–21.2%	
Stunting	Baseline	1,164	44.6	41.7%–47.5%	*b*
	2nd follow-up (16 wk)		35.4	32.7%–38.3%	
Underweight	Baseline	1,164	57.8	55.0%–60.6%	*b*
	2nd follow-up (16 wk)		48.5	45.6%–51.4%	

a. Statistically significant difference ($p < .05$) between baseline and 4-week follow-up.
b. Statistically significant difference ($p < .05$) between baseline and 16-week follow-up.
c. Statistically significant difference ($p < .05$) between 4-week follow-up and 16-week follow-up.

TABLE 6. Changes in prevalence of Bitot's spots over the study period, stratified according to exposure to October 1999 cyclone (cohort only)

	Prevalence (95% confidence interval)	
Time of measurement	Exposed to cyclone ($n = 878$)	Not exposed to cyclone ($n = 933$)
Baseline	5.1% (3.81%–6.74%)	0.8% (0.33%–1.48%)
1st follow-up (4 wk)	3.1% (2.08%–4.38%)	0.9% (0.40%–1.62%)
2nd follow-up (16 wk)	6.6% (5.05%–8.40%)[a]	0.8% (0.33%–1.48%)

a. Statistically significant difference ($p < .05$) between 4-week follow-up and 16-week follow-up.

There was little change in the prevalence of diarrhea over the course of the study, with levels consistently between 4.3% and 4.9%. On the other hand, there was a significant reduction in the prevalence of acute lower respiratory infections 4 weeks after baseline, from 1.9% to 0.5%, and the prevalence remained at approximately the same level at the 16-week follow-up (0.8%).

Anthropometric measurements were only collected at baseline and at the time of the second follow-up 16 weeks later. The prevalence of wasting declined significantly from 25.7% to 18.8% over the study period. There was also a significant decline in the prevalence of long-term malnutrition (i.e., underweight and stunting) over the study period.

Three districts in Orissa (Khurda, Cuttack, and Jajpur) were affected by a major cyclone 4 months preceding the baseline enumeration. As noted in table 6, the prevalence of Bitot's spots in these districts was significantly higher (5.1%; 95% confidence interval, 3.81%–6.74%) at baseline than in those areas not affected by the cyclone (0.8%; 95% confidence interval, 0.33%–1.48%). In the cyclone-affected areas, a significant decline in the prevalence of Bitot's spots was observed 4 weeks after the national immunization day to 3.1% (95% confidence interval, 2.08%–4.38%), whereas there was no change in the areas unaffected by the cyclone (0.9%, 95% confidence interval, 0.40%–1.62%). However, a significant rise in the prevalence of Bitot's spots to 6.6% (95% confidence interval, 5.05%–8.40%) was seen in the affected areas at the time of the 16-week follow-up, while the prevalence in the nonaffected areas remained stable.

Changes in serum retinol

Table 7 presents data on trends in serum retinol over the course of the study period. The mean serum retinol level for all children at the time of the baseline enumeration was 0.62 ± 0.32 μmol/L; the level showed a significant improvement to 0.73 ± 0.23 μmol/L within 4 weeks, with a subsequent significant decline to 0.50 ± 0.19 μmol/L by the 16-week follow-up. Changes in serum retinol were also assessed with respect to baseline serum retinol levels to evaluate the degree of improvement among those children with severe vitamin A deficiency as compared with those with no vitamin A deficiency.

Children who had vitamin A deficiency at baseline (serum retinol < 0.70 μmol/L) showed a statistically significant improvement in serum retinol levels by the 4-week follow-up measurement (0.42 ± 0.15 μmol/L to 0.70 ± 0.23 μmol/L), which decreased again by the 16-week follow-up (to 0.46 ± 0.17 μmol/L) to levels similar to those at baseline. In contrast, the serum retinol levels among children with adequate vitamin A status at baseline (serum retinol ≥ 0.70 μmol/L) declined by the 4-week follow-up (from 0.97 ± 0.24 to

Table 7. Changes in serum retinol [mean (SD) μmol/L] over the study period

Time of measurement	All children	Low serum retinol (< 0.70 μmol/L)	High serum retinol (≥ 0.70 μmol/L)	Bitot's spots	No Bitot's spots	Exposed to cyclone	Not exposed to cyclone	Vitamin A not received[a]	Vitamin A received
Baseline to 4-wk follow-up	$n = 314$	$n = 202$	$n = 112$	$n = 12$	$n = 302$	$n = 160$	$n = 154$	$n = 10$	$n = 295$
Baseline	0.62 (0.32)	0.42 (0.15)	0.97 (0.24)	0.29 (0.11)	0.62 (0.32)	0.52 (0.29)	0.72 (0.32)	0.49 (0.16)	0.62 (0.33)
4 wk	0.73 (0.23)	0.70 (0.23)	0.78 (0.23)	0.61 (0.20)	0.73 (0.23)	0.67 (0.22)	0.80 (0.23)	0.64 (0.17)	0.73 (0.24)
	$p < .001$	$p < .001$	$p < .001$	$p < .001$	$p < .001$	$p < .001$	$p < .05$	NS	$p < .001$
Baseline to 16-wk follow-up	$n = 311$	$n = 197$	$n = 114$	$n = 12$	$n = 299$	$n = 158$	$n = 153$	$n = 10$	$n = 292$
Baseline	0.62 (0.32)	0.42 (0.15)	0.97 (0.23)	0.29 (0.11)	0.63 (0.32)	0.52 (0.28)	0.72 (0.32)	0.49 (0.16)	0.63 (0.33)
16 wk	0.50 (0.19)	0.46 (0.17)	0.55 (0.20)	0.43 (0.11)	0.50 (0.19)	0.49 (0.19)	0.50 (0.19)	0.37 (0.13)	0.50 (0.19)
	$p < .001$	$p < 0.01$	$p < .001$	$p < .05$	$p < .001$	NS	$p < .001$	NS	$p < .001$

a. Only 10 children in Orissa for whom serum retinol data were available did not receive vitamin A at the time of the national immunization day (March 2000): 1 whose baseline serum retinol was ≥ 0.70 μmol/L and 9 whose baseline serum retinol was < 0.70 μmol/L.

0.78 ± 0.23 μmol/L) and then fell further by the time of the 16-week follow-up (to 0.55 ± 0.20 μmol/L).

Children with Bitot's spots at baseline had extremely low baseline vitamin A status (mean serum retinol, 0.29 ± 0.11 μmol/L), which increased dramatically 4 weeks after supplementation (to 0.61 ± 0.20 μmol/L). By 16 weeks post-supplementation, the serum retinol levels of these children were still higher than baseline levels but had declined somewhat from the initial increase (mean, 0.43 ± 0.11 μmol/L). In contrast, the serum retinol levels of children who did not have Bitot's spots at baseline increased by the 4-week follow-up (from 0.62 ± 0.32 to 0.73 ± 0.23 μmol/L) and then declined to levels that were significantly lower than at baseline (to 0.50 ± 0.19 μmol/L).

Finally, the mean serum retinol level at baseline was significantly lower in the cyclone-affected districts (0.52 ± 0.29 μmol/L) than in the cyclone-unaffected region (0.72 ± 0.32 μmol/L). Both areas showed a significant rise in serum retinol levels by the first follow up, with the cyclone-affected areas increasing more. However, by the time of the 16-week follow-up, the mean serum retinol had decreased in both areas to similar levels (fig. 3).

Vitamin A supplementation

An additional series of analyses was conducted to evaluate the changes in the main outcome parameters between groups of children stratified on the basis of vitamin A receipt. Because of the high coverage of vitamin A in Orissa, such comparisons have limited statistical power, and it is important to control for the possible bias associated with self-selection. Nonetheless, a few notable results were observed, which may have important policy implications. There were no significant differences in the baseline characteristics of preschool-age children receiving and not receiving vitamin A.

Vitamin A supplementation had a positive impact on Bitot's spots by the time of the 4-week follow-up (table 8), with the prevalence of Bitot's spots among those receiving vitamin A (1.8%; 95% confidence interval, 1.2%–2.5%) being less than half that among those not receiving vitamin A (3.7%; 95% confidence interval, 0.6%–11.7%). However, by the 16-week follow-up, the positive impact was no longer evident among the children who received vitamin A, with the prevalence of Bitot's spots virtually the same as at baseline.

There were some interesting observations with respect to morbidity as well. Again, although the numbers were low, children who received vitamin A were significantly less likely to have diarrhea by the time of the 4-week follow-up (3.9%; 95% confidence interval, 2.9%–5.1%) than were children who did not receive vitamin A (18.8%; 95% confidence interval, 8.0%–35.0%).

Conclusions

Vitamin A deficiency is a significant public health problem among preschool children in Orissa, as indicated by the high prevalence of Bitot's spots and the low serum retinol levels at baseline. This was not surprising, given the chronic low intake of bioavailable vitamin A and the high burden of infectious morbidity in this population. These conditions were exacerbated by the lingering effects of a devastating cyclone that took place in Orissa four months before the study began. Further to this, a drought occurred during the later part of the study period, approximately 12 weeks following the administration of vitamin A.

The integration of vitamin A supplement distribution with national immunization days demonstrated high coverage for vitamin A on the national immunization days in October 1999 (95.8%) and March 2000 (97%). No significant differences in gender, age group, morbidity status, socioeconomic status, or clinical or biochemical markers of vitamin A deficiency were evident between those children who received and those who did not receive vitamin A before and during the

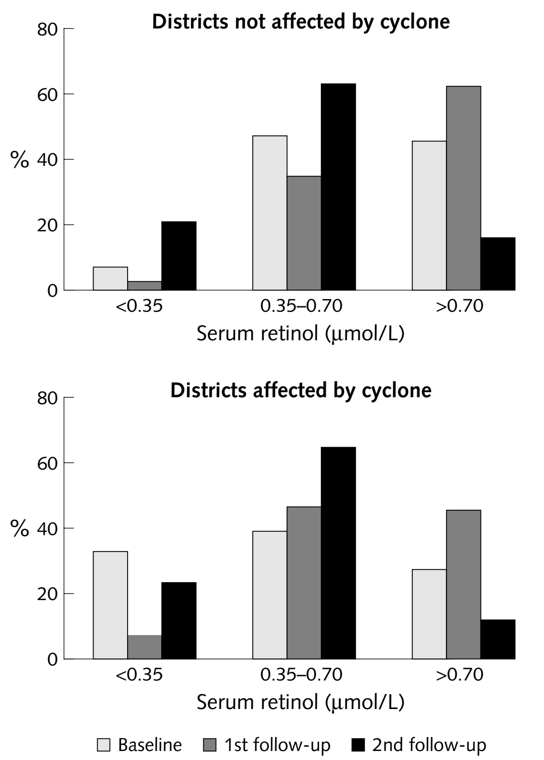

FIG. 3. Trends in serum retinol in districts affected and not affected by cyclones

study period. Such uniformly high coverage rates reflect a distinct advantage of the delivery of vitamin A with national immunization days in this population as compared with routine programs.

The prevalence of Bitot's spots declined from 2.8% to 1.9% in the study population at the 4-week follow-up, and then increased to 3.6% by the time of the 16-week follow-up. At the 4-week follow-up, 61.5% of the cases of Bitot's spots seen at baseline had resolved and an incidence of only 0.8% (the percentage of children with new cases) was observed. Although no change in the recovery rate of Bitot's spots was observed between the first and second follow-up periods (remaining at over 60%), the incidence of new cases increased significantly 16 weeks after the national immunization day to 3.0%. New cases of Bitot's spots are clinically indistinguishable from chronically persistent Bitot's spots that have resisted vitamin A therapy, and the only way to distinguish between the two types is by monitoring clinical changes longitudinally, as was done in the current study. Active lesions normally respond to therapy in two to five days. Past research has concluded

TABLE 8. Trends in major outcome variables over the study period, stratified according to receipt of vitamin A

		Vitamin A not received			Vitamin A received		
Variable	Time of measurement	*n*	Prevalence (%)	95% confidence interval	*n*	Prevalence (%)	95% confidence interval
Night-blindness (age 24–48 mo)	Baseline	31			1,265	0.47	0.2%–1.0%
	1st follow-up (4 wk)					0.08	0.0%–0.4%
	2nd follow-up (16 wk)					0.20	0.1%–0.6%
Bitot's spots (age 12–48 mo)	Baseline	54	1.9	0.1%–8.8%	1,728	2.8	2.1%–3.7%
	1st follow-up (4 wk)		3.7	0.6%–11.7%		1.8	1.2%–2.5%
	2nd follow-up (16 wk)		5.6	1.4%–14.4%		3.4	2.6%–4.4%
Serum retinol < 0.70 µmol/L	Baseline	10	90.0	59.7%–99.5%	299	63.2	57.6%–68.5%
	1st follow-up (4 wk)		58.3	30.2%–82.8%		45.3	39.7%–50.9%
	2nd follow-up (16 wk)		100	100%–100%		85.8	81.6%–89.4%
Serum retinol < 0.35 µmol/L	Baseline	10	10.0	0.5%–40.3%	299	21.4	17.0%–26.3%
	1st follow-up (4 wk)		8.3	0.4%–34.7%		4.7	2.7%–7.4%
	2nd follow-up (16 wk)		50.0	23.4%–76.6%		21.9	17.6%–26.8%
Anemia (hemoglobin < 11 g/dl)	Baseline	10	60.0	29.1%–85.8%	304	67.1	61.7%–72.2%
	1st follow-up (4 wk)		75.0	45.9%–93.2%		70.0	64.9%–74.8%
	2nd follow-up (16 wk)		66.7	37.7%–88.4%		60.6	55.1%–65.8%
Current diarrhea	Baseline	30	10.0	2.6%–24.9%	1,119	4.9	3.8%–6.3%
	1st follow-up (4 wk)		18.8	8.0%–35.0%		3.9	2.9%–5.1%
	2nd follow-up (16 wk)		13.8	4.5%–30.0%		4.2	3.1%–5.5%
Current acute lower respiratory infection	Baseline	30	3.3	0.2%–15.4%	1,119	1.9	1.2%–2.8%
	1st follow-up (4 wk)		3.1	0.2%–14.5%		0.4	0.2%–1.0%
	2nd follow-up (16 wk)		0.7	0.0%–1.8%		0.8	0.4%–1.5%
Wasting	Baseline	35	14.3	5.4%–28.9%	1,095	26.2	23.7%–28.9%
	2nd follow-up (16 wk)		21.2	9.8%–37.5%		18.5	16.2%–20.9%
Stunting	Baseline	35	60.0	43.3%–75.1%	1,105	44.0	41.1%–47.0%
	2nd follow-up (16 wk)		45.5	29.2%–62.5%		34.8	32.0%–37.7%
Underweight	Baseline	35	68.6	52.0%–82.2%	1,105	57.3	54.4%–60.2%
	2nd follow-up (16 wk)		66.7	49.5%–81.1%		47.9	44.9%–50.9%

that Bitot's spots that do not respond to high doses of vitamin A represent sequelae of past deficiency rather than current vitamin A deficiency. The period of time before conjunctival lesions become unresponsive to vitamin A treatment has not yet been determined, and children have been found to wax and wane in and out of a vitamin A deficiency state.

There was a significant improvement in the serum retinol levels between baseline and the 4-week follow-up, which indicated an important short-term improvement in vitamin A status. However, a subsequent decline in serum retinol between the 4-week and 16-week follow-ups revealed problems in sustaining the improvements in vitamin A status over a 16-week period in this population. This finding is consistent with earlier studies in India and Indonesia that noted transient effects of high doses of vitamin A [18, 19].

A foundation of adequate dietary intake of vitamin A is essential for the periodic high-dose vitamin A supplement to build and sustain hepatic vitamin A stores. The present study provides evidence that among children with very low baseline vitamin A status and stores, the high-dose vitamin A supplements, as currently recommended by WHO, were insufficient to maintain serum retinol levels beyond 12 to 16 weeks in children. It has been suggested that dietary intake of as little as 150 RE/day* may lengthen the period of prophylactic protection of high-doses of vitamin A [20].

An assessment of the dietary intake of vitamin A–rich foods in this population would have been useful in explaining the observed results in this study, particularly in light of the unexpected drought occurring during the study period. A significant worsening of vitamin A status prior to the time of the 16-week follow-up occurred before the onset of the monsoon season. Thus, it is likely that a seasonal effect associated with a decline in the availability of green leafy vegetables, which are the primary sources of affordable β-carotene in this population, contributed to a worsening of serum retinol levels and increased the prevalence of Bitot's spots at that point of the study.

The coastal districts of Orissa experienced two devastating cyclones prior to the study during October and November 1999, leaving thousands of people homeless, with deteriorated food availability and an increased risk of infectious diseases. In addition to this, the interior districts of Orissa experienced severe drought during the summer months during the study period. Hence, the results of the present study need to be interpreted with these environmental considerations in mind.

Although several relief measures were launched and food supplements were provided for the victims of the October cyclones in Orissa, the intake of micronutrients, particularly β-carotene, would probably have been low for a prolonged period in these areas. Food supplements are generally prepared from cereal and pulse combinations. Although such foods contribute certain micronutrients, such as B-complex vitamins and iron, the β-carotene content of these foods is typically inadequate.

The results obtained from the cyclone and noncyclone regions were interesting. Cuttack, Khurda, and Jajpur are coastal, cyclone-affected districts, whereas Angul, Kalahandi, and Sundergarh are interior districts that were not affected by the cyclone. The prevalence of vitamin A deficiency was significantly higher in cyclone-affected districts. Nearly one-third of all children in the cyclone-affected area had serum retinol levels < 0.35 μmol/L at baseline, whereas severe vitamin A deficiency (serum retinol < 0.35 μmol/L) was noticed in only 7.2% of the children in those regions not affected by the cyclone. In a district-level survey conducted in Orissa during 1996–97 [22], the prevalence of Bitot's spots reported for one- to five-year-old children in Cuttack, Jajpur, and Khurda was 0%, 2.7%, and 0.8%, respectively. In contrast, in the present study, 5.5% of children had Bitot's spots in Cuttack, whereas the prevalence was 9.8% in Jajpur. In Khurda the prevalence rate was 0.3%, which was lower than the value reported in the preceding three to four years. Although these two reports are not strictly comparable because of the difference in the age groups of the samples (one to five years in the 1996–97 survey and two to five years in the present survey), the huge differences observed in Cuttack and Jajpur districts suggest a definite increase in vitamin A deficiency.

The interior districts presented a different profile of vitamin A deficiency. Angul had no cases of Bitot's spots in either survey, whereas Sundergarh recorded a decline from 4.9% in 1996–97 to 0.6% in the present study. Kalahandi registered a slight increase from 0.5% to 1.7% in the present survey. Children from both the coastal and the interior regions were recipients of 200,000 IU of vitamin A four months prior to the study period (October 1999). However, children in the coastal districts that were affected by the cyclones probably had severe food deprivation over a long period of time, and the high prevalence of deficiency might be attributed to the extremely poor vitamin A intakes by these children over the three- to four-month period preceding the survey. In the interior districts, which

* 1 RE = 1 μg retinol or 3.33 IU vitamin A activity from retinol. Thus, 150 RE per day would translate to 450 IU, or about 75% of the mean recommended level for vitamin A per day [21].

Two units are currently used for quantifying vitamin A activity in foods, as a result of recent research findings. Both refer to 1 μg of all-*trans*-retinol (vitamin A). The retinol equivalent (RE) is defined as equivalent to 6 μg of dietary all-*trans*-β-carotene. The more recently recommended retinol activity equivalent (RAE) is defined as equivalent to 12 μg of dietary all-*trans*-β-carotene. Current food-composition research may still use the 6:1 ratio, since that is what is available in food-composition tables.

did not face any such calamity between the October national immunization day and baseline enumeration, the prevalence of Bitot's spots was < 1%, suggesting the possible positive sustained effect of the previous supplementation. These observations suggest that in populations having at least minimal intakes of dietary vitamin A, supplements may have a more sustained effect on controlling vitamin A deficiency.

During the summer season preceding the second follow-up, the interior (cyclone-unaffected) districts experienced severe drought. Food intake, and particularly vitamin A intake, are generally low in the summer because of the scarcity of green leafy vegetables, which are affordable sources of β-carotene. The low food intake could explain the negative shift in vitamin A status in both regions during the second follow-up. The added stress of drought might have contributed to the precipitation of more severe deficiency in the interior districts as compared with the coastal districts, where life started to settle following the devastation caused by cyclones.

Further analysis of the impact of vitamin A supplementation on serum retinol, taking account of baseline vitamin A status, revealed some important observations. Children with vitamin A deficiency (serum retinol < 0.70 µmol/L) at baseline had a significant improvement in their serum retinol status by the 4-week follow-up. Although their serum retinol levels declined by the second follow-up, they remained above their baseline values, suggesting that there was a more sustained response among this subgroup of children. Improvement of vitamin A status was also evaluated in relation to baseline Bitot's spots status. Children with Bitot's spots at baseline were found to have extremely low serum retinol levels as compared with children without Bitot's spots. At the 4-week follow-up, both groups of children improved their serum retinol and were not statistically different from each other, but the increase among those who had Bitot's spots at baseline was much more dramatic. This finding is consistent with earlier studies in Indonesia, where children with xerophthalmia prior to receiving vitamin A had a significant increase in serum retinol following vitamin A receipt, while children with no ocular signs of xerophthalmia at baseline did not have any change in serum retinol following vitamin A administration. This pattern was seen in Indonesia with both a low dose (100,000 IU) and a high dose (200,000 IU) of vitamin A, although the higher dose led to a higher increase of serum retinol among those children with xerophthalmia at baseline [23].

Vitamin A supplementation also had an impact on the prevalence of morbidity, particularly current diarrhea, in this study. The prevalence of current diarrhea fell from 4.9% to 3.9% between the baseline enumeration and the 4-week follow-up among children receiving vitamin A and was about four times lower than that observed among children who had not received vitamin A. By the time of the 16-week follow-up, the prevalence of diarrhea was still significantly lower among children who received vitamin A than those who did not. These findings are somewhat different from those seen in other studies, in which vitamin A supplements had no impact on the prevalence of diarrhea, but only had an impact on the severity of infection [24, 25].

Respiratory morbidity improved from 1.9% to 0.3% by the 4-week follow-up and remained low at the time of the second follow-up. It is possible that this trend may reflect a seasonal change in morbidity due to acute respiratory infection, which was reduced much more between baseline and the 4-week follow-up among children who received vitamin A (table 8). However, these observations should be treated with caution, since the number of children not receiving vitamin A was very low.

The results of past studies have been conflicting with respect to the effects of vitamin A on morbidity among preschool-age children, although dramatic reductions in mortality have been reported. In 13 intervention studies reviewing the association between vitamin A and morbidity, vitamin A supplementation was found to have no effect on the prevalence or duration of diarrhea or respiratory infections, but only to affect their severity [26]. Six studies found no effects of vitamin A supplementation on morbidity incidence and duration, five studies found some evidence of a reduction in morbidity incidence and severity and two studies actually found an increased morbidity after vitamin A supplementation [27]. The variability in the relationship between vitamin A deficiency and morbidity in past studies may be influenced by environmental factors, including diet, access to health care, and cultural practices [28]. In the current study, the mean serum retinol levels among children with diarrhea, fever, and anemia who received vitamin A significantly increased from baseline to the 4-week follow-up.

Child growth and undernutrition are influenced by multiple factors, including dietary intake, environmental conditions, and socioeconomic status. A substantial long-term effect on physical growth would not be expected from a single micronutrient intervention such as vitamin A supplementation except in populations where vitamin A deficiency is a significant growth-limiting factor.

This study clearly demonstrates that the short-term benefits of vitamin A supplementation are significant in this population, especially for those who are most severely depleted. At the same time, it was also made clear that these benefits were temporary and limited to a period of less than 90 days at most. This finding calls for an exploration of other means of ensuring sustainable improvement in vitamin A status in similar populations, such as more frequent vitamin A supplementation dosing and measures to improve the nutritive value of the general diet, as well as public health measures to improve infection control and sanitation.

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Anthelmintic treatment improves the hemoglobin and serum ferritin concentrations of Tanzanian schoolchildren

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Abstract

To investigate the relationships between helminth infections and iron status among school-aged children, 1,115 Tanzanian children in grades 2 through 5 were randomly assigned to treatment or control groups. The children in the treatment group were screened for infection with Schistosoma haematobium *and hookworm at baseline, 3 months, and 15 months; infected children were given albendazole against hookworm and praziquantel against schistosomiasis. The control group received a placebo and did not undergo parasitological screening until 15 months after the baseline. Hematological variables were compared between the treatment and control groups. The main results were, first, that the hemoglobin concentration significantly improved after treatment for hookworm ($p < .001$) by 9.3 g/L in children treated for hookworm only and by 8.8 g/L in children treated for hookworm and schistosomiasis. The ferritin concentration also improved in children treated for schistosomiasis ($p = .001$) or hookworm ($p = .019$). Second, a longitudinal analysis of the data from the children in the control group showed that hookworm and schistosomiasis loads were negatively associated with hemoglobin and ferritin concentrations. Moreover, ferritin concentrations increased as C-reactive protein levels increased. Overall, the results showed that anthelmintic treatment is a useful tool for reducing anemia in areas with high hookworm and schistosomiasis endemicity. The empirical relationship between ferritin and C-reactive protein indicated that simple procedures for adjusting cutoff points for the use of ferritin as an indicator of low iron stores were unlikely to be useful in this population.*

Key words: Anemia, anthelmintic treatment, ferritin, hemoglobin, iron deficiency, longitudinal data, schistosomiasis, schoolchildren, Tanzania

Introduction

Iron deficiency and iron-deficiency anemia are widely prevalent in low-income countries [1]. Iron-deficiency anemia adversely affects the physical and mental development of children [2–4] and may consequently hamper economic development [5]. In sub-Saharan Africa, helminth infections contribute significantly to the prevalence of anemia [6–8]. School-age children bear the largest burden of these diseases; there is a high prevalence of anemia (hemoglobin < 120 g/L) in schoolchildren across sub-Saharan Africa [9].

Treatment for hookworm can improve hemoglobin concentration and iron stores [10, 11], but there are mixed results regarding the effect of treatment for schistosomiasis on hemoglobin concentration [12–14] and iron stores [13]. However, observational studies [15] have demonstrated a relationship between schistosomiasis and iron stores. For both hookworm and schistosomiasis, it may be necessary to administer iron supplementation in addition to anthelmintic treatment to see an improvement in iron status [13].

The aim of the current study was to investigate further the effects of anthelmintic treatment on the iron status of school-age children; the methodology for assessing iron status was also important for the investigation. Thus far, there is no general agreement

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on the interpretation of indicators of iron stores or on the choice of indicators to define iron deficiency in populations where subclinical parasitic infections are endemic. For example, the disease environment can complicate the interpretation of ferritin as a measure of iron stores [16–18]. Some researchers have suggested that the cutoff points for ferritin should be increased in populations where C-reactive protein levels are elevated [18]. Such adjustments may be misleading in situations where, for example, ferritin increases unabatedly with increases in C-reactive protein levels. The current study aimed to investigate the relationships among children's hemoglobin, ferritin, and C-reactive protein status by assessing the impact of treatment for hookworm and schistosomiasis on these indicators over a period of 15 months and by analyzing these relationships in children in the control group during the observation period.

Methods

Participants

The data were collected in Tanzania as part of a larger study to investigate the effects of anthelmintic treatment on schoolchildren's cognitive function and educational achievement [19]. The study was conducted in 10 schools in the coastal area of Bagamoyo and Kibaha districts, and measurements were taken at baseline, 3 months, and 15 months. A school was eligible if more than 100 children were enrolled in grades 2 through 5, if it was accessible by road during the rainy season, and if it had a relatively high (> 20%) prevalence of *Schistosoma haematobium*, as estimated by self-report questionnaires. Children were eligible to participate in the study if they were 9 to 15 years old and were enrolled in grades 2 through 5. Children were excluded if the parent or guardian refused consent, or if the child had severe clinical symptoms of infections, physical or mental handicaps, or other chronic diseases. The study design was explained to the children and parents in Kiswahili, and the children and the parents signed a written consent form before participation. The ethics committees of the Institute of Child Health, London, the Tanzania Ministry of Health, and the Tanzania Ministry of Education and Culture approved the study design. The surveys started in May 1997, and each round lasted approximately three months. Survey round 2 commenced in September 1997 and was completed by December 1997. Survey round 3 started in October 1998 and was completed by December 1998.

A total of 2,004 children in grades 2 through 5 were eligible for participation in the study. Of these, 1,650 children returned the signed consent form and were included in the longitudinal study (fig. 1). The children were then divided into two equal groups; one group was screened for their parasitological status at the beginning of the study (treatment group), and the other was not screened until the end of the study (control group). Children were randomized to these groups after stratification according to sex and the four grade levels in the 10 schools. Following the baseline parasitology survey, children in the treatment group were selected to take further part in the study if they were either "uninfected" (< 50 eggs per gram of stool for hookworms and < 5 eggs per 10 ml of urine for schistosomiasis) or "heavily infected" (> 400 eggs per gram of stool for hookworm and/or > 50 eggs per 10 ml of urine for schistosomiasis). Children with "moderate infections" (> 50 and < 400 eggs per gram of stool for hookworm, > 5 and < 50 eggs per 10 ml of urine for schistosomiasis) took no further part in the study, partly because the broader objective of the study was to assess the impact of anthelmintic treatment on cognitive function. Hereafter, "infected" refers to "heavily infected," as defined above. Children infected with hookworm were given 400 mg of albendazole (SmithKline Beecham, Brentford, UK) for three consecutive days. A single dose of praziquantel (40 mg/kg of body weight; E. Merck Pharmaceutical Division, Darmstadt, Germany) was given against schistosomiasis. The chemotherapy was repeated at survey round 2 for children in the treatment group who had become infected since survey round 1.

In survey round 3, children in the control group were also tested for hookworm, schistosomiasis, and other parasitic infections; all infected children in the control and treatment groups were treated at the end of the study. All children received three vitamin B tablets containing mixtures of 1 mg of thiamine, 1 mg of riboflavin, and 10 mg of nicotinamide in the three survey rounds; the nurses who treated the children were blinded to the nature of the tablets administered. Overall, 1,115 children entered the trial, 270 with heavy infections, 116 with no or very light infections, and 729 in the control group, whose infection status was unknown at baseline (fig. 1).

Demographic and socioeconomic variables

The child's date of birth was recorded from the school register. Children for whom only the year of birth was known were assigned a birth date of June 15. Detailed background information was collected for the households, including the construction materials of the roof, walls, and floor. The source of drinking water, availability of toilet facilities, and number of key household possessions (bicycle, radio, refrigerator) and livestock were recorded. The information was collected through interviews with children and validated for a subsample by observation in the home and interviews with parents. An overall index of economic wealth was created by summing the scores across selected variables. The investigators designed and carried out the surveys.

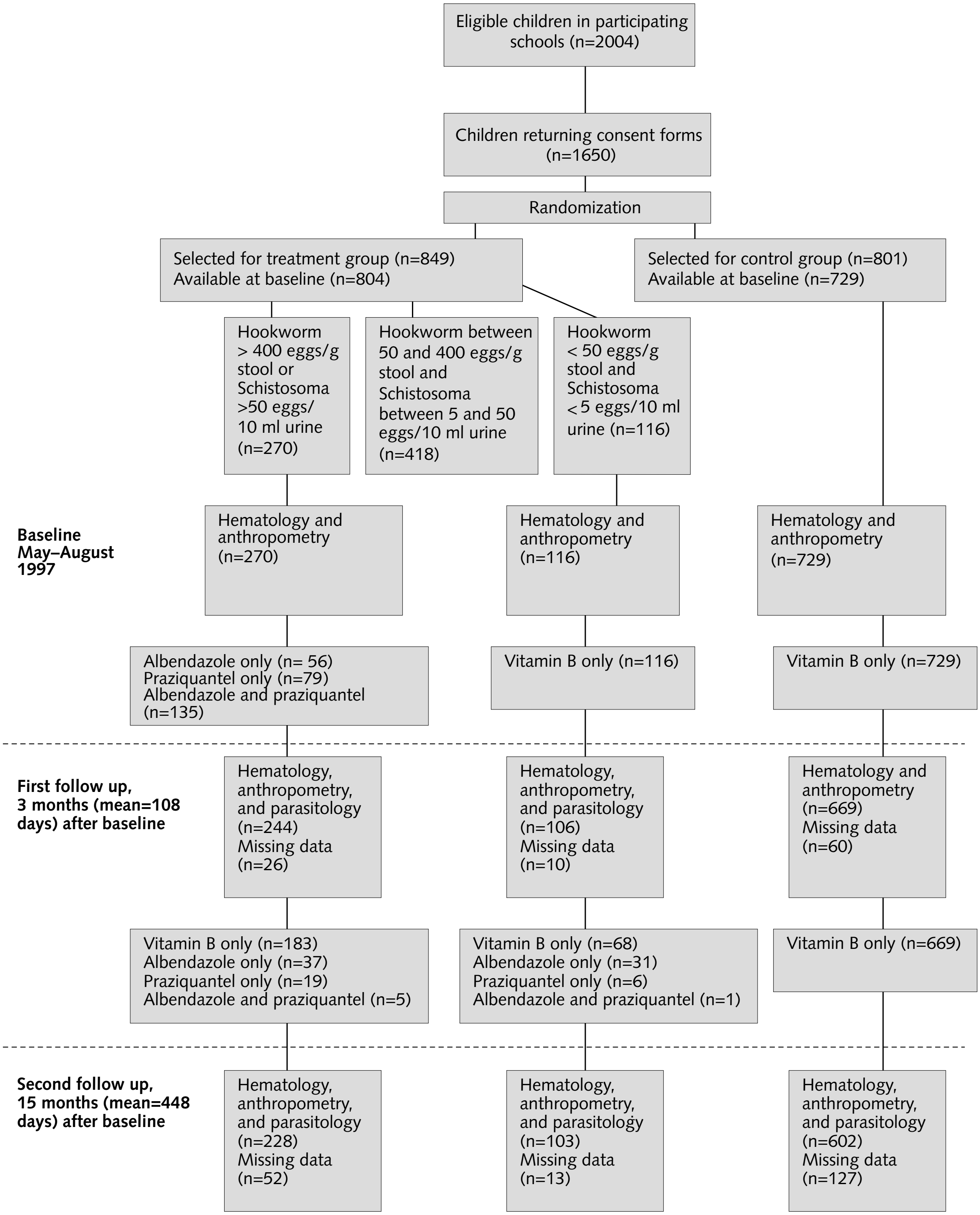

FIG. 1. Randomization of children to treatment and control groups and retention in trial

Anthropometry and hematology

The children's weight, height, mid-upper-arm circumference, and skinfold thickness were measured in each survey round by trained observers. Electronic scales (Soehnle, Germany) were used to measure weight to the nearest 0.1 kg; the scales were intermittently checked for accuracy. The children were weighed barefoot in school uniforms. Height was measured twice with a portable stadiometer (CMS Weighing Equipment, London) with the child standing upright. If the observations differed by more than 2 mm, a third measurement was taken. The correlation between the two measurements was very high (> 0.98). Left mid-upper-arm circumference was measured to a precision of 2 mm with a waxed paper insertion tape (TALC, St. Albans, UK). Duplicate measurements of triceps skinfold thickness were taken with Holtain calipers (CMS Weighing Equipment, London).

In each survey round, the nurses drew 2 ml of blood with sterilized syringes and transferred the blood to a prelabeled tube that had a drop of EDTA to prevent clotting. A cuvette was filled immediately with blood for analysis with a portable photometer (HemoCue, Sheffield, UK). If the hemoglobin was < 80 g/L, the child's blood was retested on the next day, and if the second value was also < 80 g/L, the child was referred to a physician. The nurses prepared a malaria thick smear, and the dried slides were placed in a box with ice packs along with the tubes containing blood. The boxes were immediately transferred to the local storage area, and the tubes containing the blood samples were centrifuged at 3,000 revolutions/min. Aliquots of 250 µl of plasma were pipetted into three separate tubes; the samples were stored in a freezer at –20°C.

The slides for malaria diagnosis were processed within three days of collection and were stained with 3% Giemsa stain, which was prepared in the laboratory by diluting 1.5 ml of Giemsa stock with 150 ml of buffered water. The slides were immersed for 45 minutes, washed and dried, and then read under an oil-immersion objective. The results were recorded as the number of parasites per 200 white blood cells. Ten fields were examined. Ferritin and C-reactive protein were measured by sandwich enzyme-linked immunosorbent assay (ELISA) using capture and horseradish peroxidase-conjugated antibodies to ferritin and C-reactive protein (Dako, Cambridge, UK). The C-reactive protein and ferritin standards were supplied by Behring Diagnostic (Milton Keynes, UK) and Dako, respectively. The substrate used was 3, 3´, 5, 5´-tetramethylbenzidine dihydrochloride (Sigma, Poole, Dorset, UK). Samples and quality controls were diluted in phosphate-buffered saline containing 0.05% Tween 20 and were run in duplicate.

Parasitology

Three urine samples were taken at each survey round from children in the treatment group on three consecutive days during school hours; the children brought stool samples to the school in a prelabeled container. For children in the control group, urine and stool analyses were performed in the third survey round. Approximately 20 ml of the urine sample was transferred to a universal tube with a pinch of Borax to stop bacterial growth without distorting the eggs. The urine and stool samples were placed in plastic bags and transported to the local laboratory for examination of parasite eggs. For *S. haematobium,* a 10-ml sample was filtered through a 12-mm-diameter polycarbonate membrane with a 12-µm pore size (Costar, UK). The slides were read under a microscope at low power. The number of eggs counted was expressed per 10 ml of filtered urine as an indicator of infection intensity. Two sets of observations were made, and the results were averaged to produce a more reliable estimate of egg count. A random sample of 10% of the urine samples was analyzed for accuracy by the chief technician at the laboratory.

The stool samples were examined for hookworm and other infections, such as *Ascaris lumbricoides* and *Trichuris trichiura*. For hookworm, duplicate slides containing approximately 25 mg of stool were prepared using the Kato-Katz technique [20]. A cellophane piece that had been soaked overnight in glycerol/malachite solution was placed on top of the sample. The slide was left for 7 to 10 minutes at room temperature before it was read under a microscope. Hookworm eggs were counted and expressed as eggs per gram of stool. Similarly, the number of eggs per gram of stool was estimated for other parasite species. The duplicate observations on hookworm egg counts were averaged for the data analysis.

Statistical analyses

Two lines of analysis are presented here. First, the effects of anthelmintic treatment on hemoglobin and ferritin were assessed by analyses of data from three survey rounds, performed separately for the treatment and control groups. Data from the treatment group were analyzed according to baseline infection status. Because the control group's baseline infection status was not known, these children could not be included in one of the analyses for the treatment group. Second, a longitudinal analysis of children in the control group at the three time points was performed to estimate the relationship of schistosomiasis and hookworm egg counts to hemoglobin, ferritin, and C-reactive protein, taking into account the interrelationships among these three variables.

The first line of analysis used three-way praziquantel treatment × albendazole treatment × survey round repeated-measures analysis of variance (ANOVA) to test the null hypotheses that treatment had no effect on hemoglobin, ferritin, and C-reactive protein. A statistical software package [21] was used to compute the descriptive statistics and perform the ANOVAs. The longitudinal analysis of hemoglobin, ferritin, and C-reactive protein status for 602 children in the control group was conducted by using random-effects models [22]. Econometric methods [23] were used to estimate three models, assuming a random-effects error structure that allowed for between-children differences. The advantage of using econometric techniques was that they permitted child-specific random effects to be correlated with some of the explanatory variables in the model. For example, poor diet quality due to low income may affect children's hemoglobin status; low income can also affect C-reactive protein levels by its effects on hygiene and sanitation. Thus, C-reactive protein was potentially correlated with the errors on the model for hemoglobin status. Standard statistical techniques do not allow such correlations and would result in inconsistent parameter estimation.

The dependent variables in the three models were hemoglobin, ferritin, and C-reactive protein concentrations. For all three models, explanatory variables included household possessions and socioeconomic status, age, height, malarial parasite count, and hookworm and schistosoma egg counts. The interdependence of hemoglobin, ferritin, and C-reactive protein status was incorporated according to the following two *a priori* considerations:

First, ferritin is known to increase with C-reactive protein levels [16], although the rate of increase may vary with C-reactive protein levels. The model for ferritin included both the C-reactive protein level (CRP) and the square of the C-reactive protein level (CRP^2) as explanatory variables to investigate whether ferritin increased with C-reactive protein at a decreasing or an increasing rate.

Second, hemoglobin status can be an important indicator of the ability to resist infection [24, 25]. Thus, the model for C-reactive protein included hemoglobin status as an explanatory variable.

C-reactive protein was also included as an explanatory variable in the model for hemoglobin to test for possible effects of infection on hemoglobin levels.

Results

Descriptive statistics

The sample means of selected variables for 602 children in the control group and 331 children in the treatment group with complete observations in all three survey rounds are presented in table 1. The sample means for the two groups in the first survey round were very close. The differences in the means between the two groups were statistically significant only for the number of possessions ($p = .03$), which was slightly higher in the treatment group.

TABLE 1. Selected variables in three survey rounds of Tanzanian schoolchildren in the treatment and control groups[a]

	Control group ($N = 602$)[b]			Treatment group ($N = 331$)[b]		
Variable	Round 1	Round 2	Round 3	Round 1	Round 2	Round 3
Age (mo)	146.1 ± 14.6			146.9 ± 15.5		
Household possessions[c]	1.36 ± 0.78			1.47 ± 0.76		
Socioeconomic status index[d]	59.98 ± 11.9			61.07 ± 11.8		
Malaria (prevalence)	33%	51%	38%	38%	49%	43%
Malaria (merozoites/200 white blood cells)	28.3 ± 80.0			29.6 ± 47.0		
Hookworm (eggs/g stool)	—	—	845 ± 1500	423 ± 929	79 ± 297	165 ± 566
Schistosomiasis (eggs/10 ml urine)	—	—	204.6 ± 509	192.0 ± 375	5.48 ± 39	107.8 ± 370
Hemoglobin (g/L)	114.7 ± 12.6	112.8 ± 11.9	116.1 ± 14.0	115.0 ± 13.6	115.8 ± 11.9	121.0 ± 12.5
C-reactive protein (mg/L)	23.9 ± 38.2	20.9 ± 35.0	20.6 ± 30.7	21.0 ± 29.7	20.9 ± 33.1	20.7 ± 33.8
Ferritin (µg/L)	30.8 ± 25.4	27.3 ± 19.8	30.2 ± 21.9	30.0 ± 24.8	28.0 ± 20.6	31.6 ± 20.7
Height (m)	1.37 ± 0.90	1.39 ± 0.90	1.43 ± 0.90	1.37 ± 0.83	1.39 ± 0.81	1.43 ± 0.85
Weight (kg)	31.1 ± 6.4	31.9 ± 8.5	35.4 ± 7.6	31.0 ± 5.6	32.0 ± 5.9	35.4 ± 6.7

a. Plus-minus values are means ± SD.
b. Complete data were available in all three survey rounds from these children.
c. One point each was given for ownership of a bicycle, radio, or refrigerator.
d. The socioeconomic status index was based on the quality of materials used for construction of walls, roof, and floor; the source of drinking water; and the type of fuel used.

Impact of anthelmintic treatment on hemoglobin, ferritin, and C-reactive protein

The means for the three hematological variables, hemoglobin, ferritin, and C-reactive protein, in survey rounds 1, 2, and 3 are presented in tables 2 and 3 for the treatment and control groups, respectively. In table 2, children in the treatment group were classified according to the type of treatment received. For comparison, children in the control group in table 3 were classified according to infection status in the same way as the treatment group. However, children in the control group were classified according to their infection status in survey round 3; because of ethical considerations, these were the only parasitological data taken from these children.

Table 2 shows that the baseline hemoglobin concentration was lower in infected children than in uninfected children by approximately 4 g/L for those infected only with schistosoma and by approximately 7 g/L for those infected either with hookworm alone or with both species of helminth. After treatment, the hemoglobin concentrations were at approximately the same levels in all groups. The results of ANOVA showed a significant improvement in hemoglobin after albendazole treatment (albendazole × survey round interaction: $F(1, 326) = 15.1, p < .001$). Mean Hb levels in children treated for hookworm increased by 9.3 g/L ($P < 0.001$) over the course of the study compared with an increase of only 2.7 g/L for the uninfected group. The effect of praziquantel treatment ($F(1, 326) = 1.0, p = .36$) and the interaction between albendazole treatment and praziquantel treatment ($F(1, 326) = 0.81, p = .44$) were not significant.

Anthelmintic treatment also had a significant impact on the number of children suffering from anemia (hemoglobin < 120 g/L). Before treatment, 67% (189/284) of infected children were anemic; after treatment, only 44% (118/266) were anemic. The proportions of children with more severe anemia were also reduced. The prevalence of children with hemoglobin < 110 g/L fell from 36% (102/284) to 14% (37/266); the prevalence of children with hemoglobin < 100 g/L fell from 11% (31/284) to 3% (8/284). The full distribution of hemoglobin levels in infected children before and after treatment is illustrated in figure 2.

Ferritin levels also improved after the treatment. There was a significant increase (table 2) in ferritin levels following treatment for hookworm (albendazole × survey time interaction: $F(1, 326) = 4.0, p = .019$) and for schistosomiasis (praziquantel × survey time interaction: $F(1,326) = 6.7, p = .001$). There was no significant interaction between the two treatments (albendazole × praziquantel × survey time interaction: $F(1, 326) = 1.0, p > .36$). The analysis of C-reactive protein levels found these to be unrelated to levels of infection with hookworm or schistosoma in the treatment group ($F(1, 326) < 0.02, p > .8$ in both cases); there was no effect of either albendazole or praziquantel treatment on C-reactive protein levels ($F(1, 326) < 7.9, p > .39$ in both cases).

By contrast, the levels of the three hematological

TABLE 2. Sample means and standard deviations of hemoglobin, C-reactive protein (CRP), and ferritin concentrations in the treatment group, classified according to baseline infection status[a]

Variable	Infection status and treatment			
	Uninfected ($N = 116$)	Hookworm only; albendazole only ($N = 56$)	*Schistosoma haematobium* only; praziquantel only ($N = 79$)	Hookworm and *S. haematobium*; albendazole and praziquantel ($N = 135$)
Hemoglobin (g/L)				
Baseline	119.0 ± 11.7	111.2 ± 16.4	114.4 ± 13.6	112.1 ± 15.2
3 mo	116.4 ± 10.2	113.6 ± 12.6	114.7 ± 14.5	115.6 ± 13.0
15 mo	121.7 ± 12.7	120.5 ± 12.6	119.0 ± 13.7	120.9 ± 11.4
Ferritin (μg/L)				
Baseline	43.2 ± 40.4	26.3 ± 28.1	30.5 ± 31.0	24.4 ± 17.2
3 mo	33.3 ± 24.3	23.7 ± 14.9	26.8 ± 18.6	27.4 ± 23.5
15 mo	32.0 ± 21.6	32.5 ± 22.2	31.1 ± 25.6	32.2 ± 20.6
CRP (mg/L)				
Baseline	2.73 ± 3.12	2.04 ± 3.29	1.92 ± 2.26	2.08 ± 3.13
3 mo	2.24 ± 3.07	1.67 ± 2.54	1.91 ± 2.81	2.25 ± 3.94
15 mo	2.22 ± 3.57	1.74 ± 2.40	1.61 ± 1.97	2.53 ± 3.91

a. "Infected" means "heavily infected" as defined in the text: > 400 eggs per gram of stool for hookworm and > 50 eggs per 10 ml of urine for schistosoma.

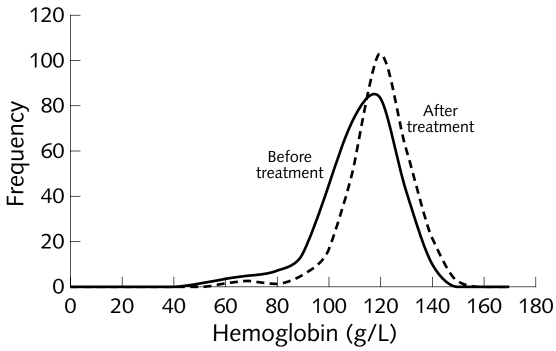

FIG. 2. The distribution of Hb levels in children infected with intestinal helminths before and 15 months after anthelmintic treatment (Hb < 120 g/L is the definition of anemia for this age group)

variables in infected, untreated children (control group; table 3) did not change over time relative to those in uninfected children. Those who were infected in survey round 3 had lower levels of hemoglobin than the uninfected children throughout the study (main effect of hookworm infection: $F(1, 448) = 13.9, p < .001$; main effect of schistosoma infection: $F(1, 448) = 4.4, p = .036$; interaction between the two infections: $F(1, 448) = 4.3, p = .039$). There was a significant improvement in hemoglobin concentration over time (main effect of survey round: $F(1, 448) = 4.12, p = .045$), but this improvement was similar in all four groups (all survey round × infection status interactions were not significant: $F(1, 448) < 1.9, p > .15$ in all cases).

The ferritin concentration in the control group, like the hemoglobin concentration, was lower in children infected with hookworm throughout the study (main effect of hookworm infection: $F(1,448) = 32.0, p < .001$). Unlike hemoglobin, the level of ferritin did not improve in untreated children over time (main effect of survey round: $F(1, 448) = 1.64, p = .20$). Similarly, children infected with hookworm had significantly lower levels of C-reactive protein than other children ($F(1, 448) = 5.3, p = .021$); infection with schistosoma had no effect on C-reactive protein levels ($F(1, 448) = 0.14, p = .71$). C-reactive protein levels decreased over time in the control group ($F(2, 448) = 3.14, p = .044$), but this decline did not vary according to infection status (all infection × time interactions: $F(2, 448) < 1.5, p > .23$).

The effect of treatment was most apparent when the pattern over time of the hematological variables in the control and treatment groups was compared. However, it was not immediately apparent that these two groups were comparable, because parasitological classifications were made at different time points and the baseline infection status of the control group was unknown. Nevertheless, the comparison was somewhat justified by the consistency in hemoglobin, ferritin, and C-reactive protein levels of infected children across the two groups. For example, the mean hemoglobin levels of infected children were similar in the two groups at baseline (approximately 113 g/L), as were the hemoglobin levels of uninfected children in the two groups (approximately 119 g/L), suggesting that these groups had similar levels of infection. Furthermore, the relationship between infection status and hemoglobin in the control group was relatively stable over time, sug-

TABLE 3. Sample means and standard deviations of hemoglobin, C-reactive protein (CRP), and ferritin concentrations in the control group, classified according to baseline infection status[a]

	Infection status			
Variable	Uninfected (N = 70)	Hookworm only (N = 115)	*Schistosoma haematobium* only (N = 48)	Hookworm and *S. haematobium* (N = 220)
Hemoglobin (g/L)				
Baseline	119.0 ± 11.1	112.9 ± 12.1	114.8 ± 11.3	112.7 ± 13.0
3 mo	117.7 ± 12.2	110.3 ± 11.7	112.6 ± 10.0	110.8 ± 11.9
15 mo	120.8 ± 11.8	114.1 ± 14.5	115.9 ± 9.9	113.0 ± 14.5
Ferritin (µg/L)				
Baseline	40.8 ± 34.3	26.2 ± 22.6	38.8 ± 33.3	26.8 ± 19.1
3 mo	32.2 ± 23.7	24.3 ± 18.9	33.3 ± 19.3	24.2 ± 17.1
15 mo	37.6 ± 28.4	27.2 ± 25.1	34.1 ± 20.4	25.4 ± 15.4
CRP (mg/L)				
Baseline	3.20 ± 5.88	2.21 ± 3.88	3.25 ± 5.36	2.10 ± 2.87
3 mo	2.83 ± 5.61	1.82 ± 2.83	2.32 ± 4.00	1.88 ± 2.47
15 mo	2.60 ± 4.94	2.27 ± 3.43	2.32 ± 2.88	1.97 ± 2.72

a. "Infected" means "heavily infected" as defined in the text: >400 eggs per gram of stool for hookworm and >50 eggs per 10 ml of urine for schistosoma.

gesting that the infection levels were stable.

Since *prima facie* evidence for the comparability of the two groups has been established, the results of the comparison will be examined. Treatment against hookworm improved levels of hemoglobin and ferritin in infected children; treatment against schistosomiasis improved levels of ferritin. Similarly, hemoglobin and ferritin levels in infected but untreated children did not improve over the same time period. Thus, anthelmintic treatment had a specific and beneficial effect on children's iron status.

Results for the longitudinal random-effects models for hemoglobin, ferritin, and C-reactive protein status of children in the control group

Table 4 presents the results from estimating random-effects models using the data on hemoglobin, C-reactive protein, and ferritin status of 602 children in the control group. The independent and dependent variables were transformed into natural logarithms to reduce heteroscedasticity [26]. This procedure leads to estimated coefficients that are "elasticities" (percentage change in the dependent variable resulting from a 1% change in an explanatory variable). Certain hypotheses were tested using chi-square statistics.

The aim of these analyses was to investigate the relationships among hookworm, schistosomiasis, and the outcome variables (hemoglobin, C-reactive protein, and ferritin concentrations), taking into account the interdependence in the outcome variables. For the analysis of hemoglobin concentration, the elasticities of hookworm eggs per gram of stool and schistosoma eggs per 10 ml of urine were –0.006 and –0.004, respectively; both coefficients were statistically significant ($p < .05$). Calculations based on these coefficients imply that reducing the hookworm load by 50%, for example, would predict an increase of 1.2% in hemoglobin concentration. The negative coefficient of C-reactive protein was statistically significant.

The results for C-reactive protein levels showed that the numbers of hookworm eggs per gram of stool and schistosoma eggs per 10 ml of urine were not significantly associated with C-reactive protein status. By contrast, high levels of malaria parasites were associated with high C-reactive protein levels ($p < .001$). Hemoglobin status was a significant predictor of C-reactive protein with a negative coefficient, indicating that children with higher hemoglobin levels had lower C-reactive protein levels.

The model for ferritin concentration included the same explanatory variables as the models for hemoglobin and C-reactive protein but assumed a quadratic relationship between ferritin and C-reactive protein.

TABLE 4. Longitudinal random effects model for the hemoglobin and ferritin concentration and C-reactive protein (CRP) of 602 Tanzanian schoolchildren in the control group in three survey rounds explained by socioeconomic and anthropometric variables and helminth infections,[a] malaria, and age

	Dependent variable					
	Hemoglobin (g/L)		Ferritin (μg/L)		CRP (mg/L)	
Independent variable	Coefficient	SE	Coefficient	SE	Coefficient	SE
Constant	3.962*	0.288	3.610*	1.429	13.060*	3.329
Age (mo)	–0.078*	0.046	–0.363	0.224	–0.782	0.432
Household possessions[b]	0.008	0.006	0.043	0.028	–0.053	0.054
Socioeconomic status index[c]	0.0006*	0.0003	0.001	0.002	0.001	0.004
Malaria (merozoites/ 200 white blood cells)	0.001	0.003	–0.005	0.012	0.117*	0.023
Height (m)	0.232*	0.058	0.293	0.304	–0.338	0.624
Hookworm (eggs/g stool)	–0.006*	0.001	–0.049*	0.007	–0.022	0.013
Schistosomiasis (eggs/10 ml urine)	–0.004*	0.002	–0.005	0.007	0.009	0.014
Hemoglobin (g/L)	—	—	—	—	–1.631*	0.447
CRP (mg/L)	–0.006*	0.002	0.158*	0.010	—	—
CRP^2 (mg^2/L^2)	—	—	0.023*	0.006	—	—
Ferritin (μg/L)	—	—	—	—	—	—
χ^2, df = 3[d]	1.25		4.72		7.88*	

a. Values are slope coefficients and standard errors. The dependent and independent variables are in natural logarithms.
b. One point each was given for ownership of a bicycle, radio, or refrigerator.
c. The socioeconomic status index was based on the quality of materials used for construction of walls, roof, and floor; the source of drinking water; and the type of fuel used.
d. Chi-square test for the exogeneity of the time means of C-reactive protein in the models for hemoglobin and ferritin concentrations, and for exogeneity of time means of hemoglobin concentration in the model for C-reactive protein.
* $p < .05$.

The results indicated that children with higher hookworm egg counts had lower levels of ferritin. Both CRP and CRP^2 were estimated with positive coefficients that were statistically significant. These associations suggested that children's ferritin concentration increased at an increasing rate with C-reactive protein levels in this population; the implications of this finding are discussed below.

Discussion

This paper presents an analysis of the data from a randomized school-based intervention in coastal regions of Tanzania, where hookworm and schistosomiasis infections were widely prevalent. The results showed the effectiveness of anthelmintic treatment on children's hemoglobin and ferritin status. There were clear and independent effects of praziquantel treatment and albendazole treatment on ferritin concentration and of albendazole treatment on hemoglobin levels. This extends the results of previous studies in showing that praziquantel treatment can improve the iron status of infected schoolchildren. Further, for the design of control programs, the results indicated that children's iron status can be increased to the level of that of uninfected controls after just two rounds of anthelmintic treatment over a course of 15 months. Given that children's iron status is also compromised by malaria [27], and that their diets are likely to be iron deficient [28], one might expect that removal of intestinal parasites would not be sufficient for hemoglobin levels to recover without iron supplementation [13]. That hemoglobin levels recovered to the levels of those in uninfected children after two rounds of anthelmintic treatment has encouraging implications for reducing anemia in areas of high helminth endemicity. Such treatments are inexpensive and can be delivered in school health programs [29]. Of course, improving diet quality should be the long-term objective of food and nutrition policies.

The second question addressed by our study was the relationship between ferritin and C-reactive protein. The results showed that ferritin increased at an increasing rate with C-reactive protein. The implication of this result is that using ferritin alone as an indicator of iron status may provide useful information in children with low C-reactive protein concentrations but overestimate iron status in those with higher C-reactive protein concentrations. Thus, if we classify children with ferritin levels < 30 μg/L as having low iron stores [18], then of the 602 children in the control group at baseline, 217 had ferritin > 30 μg/L and would seem to have adequate iron stores. However, 108 (18%) of these children were anemic (hemoglobin < 120 g/L). By contrast, if we restricted the analysis of ferritin to the 400 children with (nonelevated) C-reactive protein < 2.2 mg/L [30], then only 7 children (1%) were anemic.

The presence of malaria parasites appeared to be a reason for the elevated C-reactive protein levels, and our study supports the conclusions of others [31] that cutoff points should be used with caution in defining iron deficiency in areas of endemic malaria infection. However, ferritin can be used more accurately as an indicator of iron status if C-reactive protein levels are taken into account. Another possibility is to disaggregate ferritin into types H and L subcomponents [32], because infections are known to differentially affect these components [33].

A final issue arising from our results concerned the methods used to investigate the relationship between iron status and helminth infections. We analyzed both longitudinal observational data and data from an intervention study. In the latter, anthelmintic treatment led to an average increase of 8.3 g/L in hemoglobin, an increase of approximately 7.3% from baseline. However, according to calculations made on the basis of estimated parameters from the longitudinal observational model, we would expect an approximately 3% increase in hemoglobin to result from this reduction in worm load. This underprediction by the longitudinal model for hemoglobin may be a result of improvements in nutrient absorption due to the reduction in parasitic loads in treated children. This emphasizes the fact that intervention studies not only investigate the relationship between variables but also can change the relationship; there is a need to use alternative methodological approaches to fully understand the interrelationships. It also suggests that cross-sectional analyses may underestimate the potential benefits of removing helminth infections.

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Household trials with very small samples predict responses to nutrition counseling intervention

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Abstract

Household trials were conducted to test the acceptability and feasibility of the recommendations to be delivered to the mothers in the context of a randomized intervention implemented in Pelotas, Brazil. A first home visit was paid to assess child health and feeding problems. In a second visit, the mother was encouraged to select one or two recommendations to try out over five days. The last visit was used to assess the mothers' experiences in attempting to implement the recommendations. Nonexclusive breastfeeding, use of the bottle, monotonous diet, and low energy density of foods were the most common problems. The most frequently selected recommendations were those aiming to increase the energy density of foods. Mothers generally reported positive responses to the recommendations. The household trials highlighted the acceptability and feasibility of the planned recommendations and correctly predicted the changes that were successfully implemented by the mothers in the large intervention study.

Key words: Child feeding, dietary behavior change, dietary intervention, household trials (HHT), nutrition counseling, trials of improved practices (TIPs)

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Introduction

An efficacy trial was conducted in Pelotas, Brazil, to test the nutrition component of the WHO/UNICEF strategy for Integrated Management of Childhood Illness (IMCI) [1, 2]. All 28 public health centers in the city were pair-matched according to the socioeconomic status and anthropometric indicators of their catchment area populations, and they were then randomly assigned to intervention or control groups. The medical staff in the intervention group received nutrition counseling training with an IMCI-derived training course, after which samples of children who were brought by their caregivers for medical consultations were recruited in both intervention and control clinics. The trial had several purposes, including assessing the efficacy of the nutrition recommendations to improve child growth; evaluating the effectiveness of the training module to provide health workers with nutrition counseling skills; examining the feasibility of delivering the recommendations to caregivers when they bring sick children for care; and determining caregiver responses to the nutrition advice they received. The results describing the impact of the counseling intervention were previously reported [3]. It was found that children in the intervention group grew better than children who were seen by health workers who had not received the IMCI nutrition training. Although the intervention did not completely prevent the growth faltering that is ubiquitous in developing countries among children 6 to 24 months of age, the magnitude was significantly reduced among children whose caregivers received nutrition counseling in the intervention-group health centers.

The health service–based counseling intervention has several features that may contribute to its effectiveness: the quality of the nutrition advice that is given to families; the level of communication skills with which the health workers give the advice; the credibility of the health worker as a source of advice; the appropriateness of the time and place of the medical consultation for the reception of nutrition advice (i.e., this is a "teachable moment"); and the enhanced capacity of families to act on the advice because the recommendations are culturally and economically feasible in the local context. This paper is concerned with the last feature. Specifically, this paper describes the process that was used to adapt IMCI nutrition guidelines to local conditions in Pelotas, southern Brazil, in order to enhance their feasibility for families.

Background

The WHO/UNICEF IMCI strategy was developed, in part, as a means of moving away from a vertical program approach to primary health care for infants and young children. It provided an opportunity to include nutrition advice and other preventive health-care counseling within the context of care for sick children. As with the clinical components of the strategy, the content of the nutrition recommendations was derived from inputs from multiple sources of expertise in nutrition and public health. A consistent theme in expert advice, for the nutrition component as well as the other clinical components, was the need for local adaptation of the generic recommendations. Thus, the approach for establishing IMCI in health services includes an adaptation guide and extensive materials to support the adaptation process.

In the past two to three decades, the importance of local cultural, economic, and social conditions in affecting how families can respond to nutrition recommendations has become widely recognized. A major challenge for putting this recognition into practice was the lack of practical tools and techniques that would permit programs to obtain the necessary information in a timely and feasible manner. In response to that challenge, several approaches have been proposed, and some specific nutrition or nutrition-related tools have been developed [4–7].

The concept of household trials was introduced to nutrition a number of years ago by Marcia Griffiths and others in the Manoff Group [5] and has since been developed as part of a detailed qualitative approach to using formative research to test nutritional messages about complementary feeding [4]. The household trials methodology, also known as Trials of Improved Practices (TIPs), assesses the acceptability and feasibility of nutrition recommendations by consulting with mothers (or other caregivers) about their willingness to try, and their reaction to, the proposed new practices [4]. It has been used to test recommendations for programs promoting breastfeeding, complementary feeding, and increased intake of micronutrients [4, 6, 8, 9]. A version of the household trials, which was used in the current study, was developed as part of the protocol for local adaptation of the IMCI nutrition materials.

Prior to the household trials, the first part of the local adaptation study for nutrition recommendations was completed in Pelotas. This activity involved several steps, including a review of previous studies in the community, interviews with local nutrition professionals, visits to markets to determine the price of various food products, identification of feeding problems according to the child's age (breastfeeding rates for age, and common reasons for stopping breastfeeding or for not breastfeeding exclusively) and reasons for these problems, foods commonly given, frequency of feedings, and typical amounts fed. Based on these multiple sources of input, a number of potential interventions to test in the household trials were identified. These included introduction of chicken liver, whole beans (not just broth), green leafy vegetables, and chicken and cow meat to the child's diet; addition of oil, margarine, or butter to the child's plate; increase in the variety of foods; and use of a cup and spoon to feed the child. Thus, the purpose of the trials was to test the feasibility and acceptability of specific foods, recipes, and food preparations, as well as generic recommendations, such as exclusive breastfeeding, increasing feeding frequency, and feeding with a cup and spoon rather than a baby bottle.

Materials and methods

The household trials study was conducted in a neighborhood of Pelotas that was not part of the main study. The health facility from which the sample was recruited serves a population of about 8,000, is staffed by a multiprofessional team (medical doctors, nurse, and nutritionist) who provide outpatient and maternal and child health services, and is managed by the Federal University of Pelotas. The population covered by this health facility is very similar in terms of socioeconomic and nutritional status to the population served by health services managed by the city government where the main trial was to be implemented. To find households for participation in the trial, we first reviewed the medical records of the facility to identify four children in each of the age groups under 4, 4 to 5, 6 to 11, and 12 to 17 months who had attended a consultation in the previous week.

The household trials were conducted by a team of three fieldworkers, two nutritionists, and a psychology student. The fieldworkers were trained by four of the authors: a medical doctor (I.S.), a nutritionist (D.P.G.), an epidemiologist (N.J.V.), and an anthropologist (H.G.). Their training consisted of detailed discussion of the content of the data-collection instrument and role-playing for situations that might arise in the course of the study.

Following the guidelines on the household trial study, three household visits were planned for each of the selected children. At the initial visit, the fieldworker first obtained informed consent from the mother and then administered a short questionnaire of eight open-ended questions, asking about her child's general health, current breastfeeding, and other feeding practices. Dietary intake data were then collected using a 24-hour dietary recall and a weekly food-frequency checklist. No counseling was given to the mother at that time, but the fieldworker made an appointment to meet with her the following day.

On the same day, at the study headquarters, a case conference was held in which the data from the interview were reviewed with the investigators (I.S., D.P.G., H.G., and N.J.V.). For each case, specific feeding problems were identified, based on the World Health Organization (WHO) guidelines.

Taking into account the socioeconomic and cultural reality of the family, as well as the availability of food in the household, the study team (fieldworker and investigator) formulated anywhere between two and nine specific recommendations for presentation to the mother. Only recommendations presumed to be relevant and feasible were made. The types of recommendations included the following: increase the frequency of breastfeeding, breastfeed exclusively, diversify the child's diet, give meat and chicken liver, add one teaspoonful of oil or margarine to the child's plate, give mashed bean grain instead of just the broth, increase the energy density of the food, and use a cup and spoon to feed the child.

The counseling visit was made 24 hours after the first visit. At the beginning of the visit, the fieldworker reviewed with the mother a brief summary of her current child-feeding practices. Good maternal practices were highlighted and the mother was praised. The fieldworker than tried to elicit from the mother her own perceptions about possible problems in her current practices, and if these were forthcoming she discussed potential solutions. She then went on to discuss some improvements that could be introduced to the child's diet, based on the recommendations for the mother that had been decided at the case conference.

From the set of identified problems, the mother was asked to select which ones she would like to modify. Typically the mother wanted to try out more than one modification, although she was encouraged to focus on only one or two for the coming five-day period, after which the fieldworker would return. As a recall aid, a written reminder with the chosen recommendations was left with the mother. An appointment was made for the third visit.

The follow-up visit, which took place four to five days later, was devoted to exploring the mother's experience in attempting to implement the recommendations she had agreed to try. In addition to discussing her experiences and perceptions, the mother was asked to give a second 24-hour recall.

Results

A total of 16 children who attended consultation at the primary health care facility were enrolled in the study. Only one child was lost between the second and the third visit, a girl 10 months old. For that child it was not possible to check compliance with and acceptability of the two recommendations made. Table 1 shows the distribution of the children according to sex, age, and current breastfeeding status. Six children were still being breastfed, and most of them were under six months of age.

Table 2 presents the feeding problems detected during the initial visit through the 24-hour dietary

TABLE 1. Age groups, sex, and breastfeeding status of children in the household trials

Age (mo)	Boys	Girls	No. breastfed
< 4	2	2	3
4–5	3	1	2
6–11	1	3	1
12–17	0	4	0
Total	6	10	6

TABLE 2. Distribution of the nutritional problems identified in the first household visit

Age (mo)	Problem	Frequency
< 4 ($n = 4$)	Nonexclusive breastfeeding	3
	Use of bottle	3
	Premature weaning	1
4–5 ($n = 4$)	Use of bottle to give water, tea, or cow's milk	3
	Nonbreastfeeding[a]	2
	Low variety (monotonous diet)	3
	Nonexclusive breastfeeding	2
	Low energy density	2
	Insufficient quantity of food offered	1
6–11 ($n = 4$)	Low variety (monotonous diet)	4
	Use of bottle to give water, tea, or cow's milk	3
	Low energy density	3
	Low meal frequency	1
12–17 ($n = 4$)	Use of bottle to give water, tea, or cow's milk	4
	Low variety (monotonous diet)	3
	Low energy density	2
	Insufficient quantity of food offered	1
	Low meal frequency	1

a. Nonbreastfeeding means that the child had been completely weaned.

recall. Nonexclusive breastfeeding was a problem for three of the four children under four months of age. In one household the mother had returned to work, and the child was fully weaned off the breast and was receiving cow's milk. The use of baby bottles to give water, tea, or cow´s milk was reported by three of the four mothers. Only two of the four children aged four to five months were still receiving maternal milk. For both of them, however, breastfeeding followed a nonexclusive pattern.

Most of the children over three months of age were given milk or liquids (fruit juices, water, or tea) by bottle. Across all age groups, the diets tended to be low in variety, consisting nearly exclusively of bean broth, rice, potatoes, pumpkin, and, eventually, only one type of meat (beef). Another problem detected in the majority of the children was the low energy density of the foods they consumed, especially as a result of the practice of giving diluted soup and only the broth when beans were cooked. Problems in the amount of food offered and low frequency of meals were also detected.

Table 3 shows the nutritional recommendations delivered at the counseling visit, according to the child's age. Each mother received as many suggestions as necessary to alert her to problems with her feeding practices. Mothers of infants under four months of age were given advice related to breastfeeding. As expected, most of the recommendations (nearly 85%) were directed to mothers of children four months of age or older. Mothers of children under four months of age received an average of three recommendations. Mothers of older children (4 to 17 months) received an average of five recommendations.

Among mothers of the youngest children, recommendations aimed at promoting exclusive breastfeeding included advice to increase the number of breastfeedings; feeding from both breasts; stop giving tea, water, or any other milk or food; and advice on relactation. For children four or five months of age who were already receiving other foods, the recommendations consisted of beginning the intake of fruits, vegetables, and different types of animal products (chicken meat and liver, egg yolk, and dairy foods). For children six months of age and above, the recommendations were focused especially on increasing dietary diversity (changing the monotonous diet) and increasing the consumption of high-energy-density foods. Replacement of the bottle by the cup and spoon and advice to offer fruits and vegetables were the two specific recommendations most frequently delivered.

The mothers' selections of recommendations they would try to practice for the trial are also shown in table 3. Approximately one-third of the messages delivered were selected. Recommendations that were intended to increase the energy density of foods were the most frequently chosen (11 of 25). The second most frequently chosen group of recommendations consisted of those that were intended to change feeding methods (5 of 16). Practices aiming at breaking the monotony of the children's diets were selected less frequently (8 of 27).

Table 3 also shows the mothers' experiences in following up on the recommendations. At the third visit, the mothers generally reported positive reactions to the fieldworkers. Moreover, their follow-up, as assessed from both their verbal comments to the fieldworkers and the 24-hour-recall, was high. Among the mothers of children 12 months of age and older, all of the selected recommendations were followed. Among the mothers of children less than 12 months old, there were three cases in which the mother did not follow through with the recommendation after she had indicated to the fieldworker that she would be willing to give it a try. The first case was the recommendation on relactation. According to the fieldnotes of the interviewer, the mother, who had resumed full-time work outside the household, said that she had "tried to take the child with her to work, but even so the child refused to breastfeed." The second was a recommendation to increase energy density, but the mother reported, "I read the food box and it said that type of food should not be given to small children." In the third case, it was suggested and the mother initially agreed to try to modify her preparation of milk formula. However, at the third visit, that mother said, "I did not stop adding flour because I thought it was the best for him."

Discussion and conclusions

To successfully address problems in child-feeding practices through nutrition counseling delivered to families at health facilities, a number of prerequisites must be met. One of these prerequisites is that the recommendations that are made by the health-care providers need to be feasible and culturally acceptable. Together with other procedures that are contained in the IMCI guidelines on adapting nutrition recommendations, household trials are an important tool for assessing acceptability and feasibility.

Because their objective is to provide feedback for program development, it is important to carry out household trials with families who are representative of the population the program is intended to serve. The household trials reported here were conducted with families who attended a primary health-care facility in a poor area of Pelotas and who displayed the types of feeding practices that have been previously shown to be typical of the population that the nutrition-counseling intervention was designed to reach. The common problems detected by other studies in Pelotas included nonexclusive breastfeeding of children less than six

TABLE 3. Nutrition counseling recommendations and responses of mothers in the household trials

Age (mo)	Type of recommendation	Suggested	Selected	Followed
< 4	Promote breastfeeding			
	Begin to breastfeed again	1	1	0
	Breastfeed more frequently	4	2	2
	Stop giving tea (breastfeed exclusively)	3	2	2
	Offer both breasts	1	1	1
	Subtotal	11	6	5
4–5	Promote breastfeeding			
	Stop giving other foods	1	0	0
	Offer both breasts	1	0	0
	Break monotonous diet			
	Give fruits or vegetables	3	1	1
	Give meat or liver	3	2	2
	Give egg yolk	2	0	0
	Give dairy foods	1	1	0
	Increase energy density			
	Increase the density of "papa"[a]	3	2	2
	Add 1 teaspoonful of oil or margarine	2	0	0
	Give porridge	1	1	0
	Change the method of feeding			
	Use cup and spoon	3	1	1
	Prepare fruit juice appropriately	2	1	1
	Increase the quantity of milk	1	0	0
	Subtotal	23	9	7
6–11	Break monotonous diet			
	Give fruits or vegetables	4	2	1[b]
	Give egg yolk	3	0	0
	Give meat or liver	2	1	1
	Increase energy density			
	Give mashed bean grain	5	2	2
	Give porridge	3	1	1
	Increase the density of "papa"	1	1	0
	Do not give coffee	1	0	0
	Change the method of feeding			
	Use cup and spoon	5	0	0
	Prepare milk appropriately	1	1	0
	Subtotal	25	8	5
12–17	Break monotonous diet			
	Give fruits or vegetables	4	1	1
	Give meat or liver	3	0	0
	Give egg yolk	2	0	0
	Increase energy density			
	Give porridge	3	2	2
	Give mashed bean grain	3	1	1
	Give the family's food	2	1	1
	Add 1 teaspoonful of oil or margarine	1	0	0
	Change the method of feeding			
	Use cup and spoon	4	2	2
	Subtotal	22	7	7
	Total	81[c]	30[d]	24

a. A thick mixture of cooked and mashed vegetables with or without meat or chicken liver.
b. Lost follow-up in one child, in the third visit.
c. Number of recommendations per mother varied from 2 to 9.
d. Two mothers selected only one recommendation.

months of age and feeding diets that are low in energy density and variety [10–17].

Compared with an intervention in which mothers are counseled in the context of a medical consultation, the home-visiting approach used in the household trials could be considered a gold standard for assessing the feasibility of recommendations. Although the sample was very small, the indications of acceptability that emerged from the trials were borne out in the intervention study. For example, the recommendations for practices aimed at increasing the energy density of foods, which showed a high level of acceptance and follow-through in household trials, had a high level of maternal recall in the large study.

At the same time, if maternal acceptance and follow-through were low in home visits in household trials, an even lower rate of adherence would be expected during the intervention. In fact, the low acceptance of use of the cup and spoon observed during the intervention study could be foreseen from the experiences in the household trials. In the household trials, a recommendation to use the cup and spoon instead of the bottle was given a total of 14 times, but only 3 mothers agreed to try this feeding mode. This reluctance adumbrated the responses in the large trial, in which the suggestion was made to 12 mothers out of the 37 observed consultations, but only 3 mothers remembered having received this recommendation when they were interviewed at home, eight days after the consultation. The reasons the mothers in the household trials gave for not selecting this recommendation were that feeding with the cup and spoon was too time-consuming and that it would also waste food. The message to replace bottles with cups and spoons was kept as an intervention message in the large study because of its unequivocal relevance for preventing diarrheal diseases [18].

In the main intervention study, 57% of the recommendations given by trained doctors were focused on measures aimed at breaking the monotony of child diets. In the household trials, 27 specific recommendations were made, but only 8 were selected by mothers as something they would be willing to try. With respect to other suggestions, mothers noted the importance of giving different types of food to their children but said that because of financial constraints, they would not be able to try it, at least in the short time interval of the household trial.

The household trials showed that most of the recommendations that were included in the training materials for the health workers were acceptable to the mothers. Their initial reactions were positive, and most of the women were able to follow through with implementing the recommendations they had agreed to try. Thus, the trials were an efficient method of acquiring fundamental information to assist the researchers in planning and conducting the major community trial. Where the household trials showed that maternal choices were similar for every kind of message delivered, it could be concluded that the acceptability of the recommendations was comparable and that any constraints to the main intervention would be expected.

Apart from predicting with high precision the maternal responses to the nutritional recommendations, the results of the household trials, functioning as a pilot test of the main intervention, reassured the investigators regarding the acceptability and feasibility of the messages to be delivered. It would be desirable if all large, complex, and expensive nutritional interventions could be supported by a process that examined the feasibility and acceptability of recommendations. Together with other sources of information about the local context, household trials are an important tool in the process of designing effective nutrition interventions.

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Acceptability of community-based growth monitoring in a rural village in South Africa

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Editorial commentary

A qualitative investigation of mothers' perceptions of community-based growth monitoring activities is indeed welcome. Attitudes to and acceptability of growth monitoring are obviously key to programmatic success.

The results of this study contrast with concerns raised in the wider literature on the efficacy and cost-effectiveness of clinic-based growth monitoring (low coverage, poor attendance, favoring the younger child, poor understanding, and lack of follow-up action). In particular, three World Bank-funded nutrition projects based on growth promotion activities have come under criticism in recent months [1]. These criticisms include the inadequate attention given to the analysis of causes of malnutrition in each country, which meant that "blueprint approaches remained unchallenged."

In contrast, the current study includes a detailed situation analysis prior to the intervention, and the aim of "creating a platform for nutrition activities" that goes beyond the usual health-related actions to include agricultural activities that directly address limited access to micronutrient-rich foods.

To make comparisons between small-scale pilot projects and large-scale operational programs may not be fair or valid, but nevertheless the current study highlights some key factors that contribute to increased acceptability. These include the detailed situation analysis, the expansion from public health actions to include the food and care-related determinants of malnutrition, and the importance of nutrition champions in the local community. In this case, the local headmaster exerted powerful influence to promote the project activities.

The report by SC UK (Save the Children UK) calls for a halt to scaling up the specific World Bank projects under review until objective reviews are complete, and an independent review of the evidence base underlying growth monitoring and promotion as well as nutrition education and supplementary feeding.

The insights gained in this study from participants remaining in the program and from those who dropped out are indeed useful. However, this work could have been usefully extended to include the views of those who had not registered in the first place. In the context of southern Africa, which includes a relatively high proportion of people living with HIV/AIDS, and where demographic profiles and family composition are changing, one wonders how the program would have specifically addressed the needs of households headed by children and older people. Studies of new approaches as described in this report are indeed welcome as a contribution to better understanding of approaches that integrate food security and health determinants of malnutrition.

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Abstract

In rural areas, a lack of infrastructure often limits the promotion and implementation of community-based nutrition activities. Growth monitoring can potentially provide a platform for the promotion and implementation of community-based nutrition activities, provided that the growth-monitoring program has a high coverage. The aim of this study was to determine the acceptability of a community-based growth-monitoring project in terms of child attendance and maternal attitude. The study was done in a mountainous rural village that lacks health facilities in KwaZulu-Natal, South Africa. Attendance registers from 1996 to 2000 were used to determine the attendance ratio, coverage, adequacy of growth monitoring, and frequency distribution of the age of participating children. In 2001, focus group discussions were used for the qualitative assessment of maternal attitudes. The community-based growth-monitoring project had an estimated coverage of 90%, at least 60% of these children were covered adequately, and attendance was equally distributed over one-year-interval age categories for children aged five years and younger. Community-based growth monitoring can therefore provide a suitable platform for the promotion and implementation of community-based nutrition activities.

Introduction

Malnutrition can be addressed through participatory, community-based nutrition programs. For these programs to be successful, an awareness of the nature, causes, and consequences of malnutrition must be created. This can be achieved by using growth monitoring as an entry point [1].

Growth monitoring is defined as the regular measuring, plotting, and interpretation of a child's growth in order to counsel or take action when abnormal growth is detected, with the aim of improving the child's health [2]. The role of growth monitoring can be divided into at least four broad strategies: as a screening tool, for education and promotional purposes, for nutrition surveillance, and as an integrating strategy [3].

Several countries [4–8] have moved towards a participatory approach, with the role of growth monitoring changing from a clinic-based service provided to individuals to a community-based participatory activity. The value of community-based growth monitoring lies in its ability to build confidence and instigate improvements in household practices, motivate community action, integrate and target health and nutrition services, and raise awareness of health and nutrition problems for policy advocacy [9]. Growth monitoring is an important component of several community-based nutrition and health programs, and its role varies from targeting malnourished children for nutrition rehabilitation [10] to promoting health through education [11], increasing community participation in primary health care activities [6], and mobilizing communities [7].

In South Africa, growth monitoring is included in the proposed core package of Primary Health Care (PHC) services [12], and it is a focus area of the Integrated Nutrition Programme (INP) [13] that was introduced by the Department of Health. The aim is to establish and strengthen sustainable growth-monitoring practices, first at health facilities, and second in communities.

Questions have been raised concerning the efficacy and cost-effectiveness of clinic-based growth monitoring in various countries [14–17]. Poor weighing methods, inaccurate equipment, insufficient use of growth charts, poor understanding of normal patterns of weight gain, and ignorance regarding nutritional influences affect the credibility of growth-monitoring programs [14, 17, 18]. Furthermore, a common shortcoming is that growth-monitoring information is not used for family, community, or government action [19].

A major concern regarding clinic-based growth monitoring is the selectiveness and erratic attendance of clinic participants [20]. In South Africa, studies have shown that the nutritional status of clinic attendees is not representative of the population and that clinics do not reach those in greatest need [21, 22]. Furthermore, clinic data favor the younger child [21, 23]. For example, in the Alexander Clinic, children aged 2 years and older were seldom weighed, and 68% of the child visits were by children 12 months of age or younger [21]. The high dropout rate at clinic-based growth-monitoring programs is not unique to South Africa [24]. Low coverage is not uncommon in community-based programs, either. For example, in Bangladesh, the low coverage of a growth-monitoring program carried out by the Bangladesh Rural Advancement Committee (BRAC) was seen as a major failure [25].

Maternal satisfaction with project activities is a good indicator to be used in program evaluations [2]. The benefits of growth monitoring, as perceived by mothers, include the opportunity for mothers to discuss questions about child care [17] and be reassured about the health of their children [2]. Some communities view growth monitoring as a reflection of their pride in their future generations [26]. These perceived benefits are not easily measured, but they may be evaluated by examining maternal satisfaction with the services.

The aims of this study were to measure the acceptability of a community-based growth-monitoring project in terms of attendance with regard to coverage, attendance ratio, age distribution of children attending the growth-monitoring sessions, and adequacy of growth monitoring in terms of the INP Strategy for South Africa [13]; and to determine maternal attitude with regard to the mothers' opinions on what they had learned, aspects either liked or disliked, the way in which the project was run, perceived health benefits, and whether they thought the project was sustainable.

Methods

Study population

The study population resided in Ndunakazi, a mountainous rural village in KwaZulu-Natal Province, South Africa. The village is approximately 11 km long and 1 km wide, with an estimated population of 1,500 people (200 households) and an estimated population density of 141/km^2.

In 1994, the Ndunakazi community requested the Medical Research Council (MRC) of South Africa to assist them in addressing the nutritional needs of the children in the area. The Ndunakazi Primary Health Care Committee (NPHCC) was established to facilitate communication between the MRC and the community. A situation analysis conducted by the MRC showed that the prevalence of stunting doubled from the first to the second year of life (from 10.6% to 19.8%), and that a third of the mothers had lost a child before the age of five years, mostly during infancy [27]. It could be argued that some of these infant deaths could have been prevented if the child had been growth-monitored regularly from an early age, since weight is a sensitive indicator of small changes in nutritional and health status [28]. However, only 3% of infants were taken to the clinic specifically for growth monitoring. Most children were growth-monitored on immunization dates only, a service provided by mobile clinics that were scheduled to service the area once a month. This service was, however, irregular, and many mothers had to walk long distances to reach the service point. Attending the nearest clinic, which was 18 km away, was difficult because of the poor condition of the road and the poor transport system.

During a project-planning workshop, community representatives expressed a need for the regular weighing of children "to see whether the children were healthy" and for nutrition-related activities, such as nutrition education [29]. As a result, a community-based growth-monitoring project that targeted all children from birth to the age of five years was established to supplement the services provided by the mobile clinic and nearby health facilities. The aim of the project was twofold: to create an opportunity for the mothers to have their children growth-monitored monthly, and to create a platform for nutrition activities, such as nutrition education, as well as agricultural activities.

Community-based growth-monitoring project

Growth-monitoring sessions were hosted at households that were identified by the community, taking into consideration geographical location, accessibility, the number of preschool children in the vicinity of the household, the availability of space, and the willingness of the mother of the household to participate. These home-based growth-monitoring points were called *Isizinda*. It was agreed that an *Isizinda* should serve at least 8 to 10 children in order to make it worthwhile for the nutrition monitors. Taking the size of the dwellings into consideration, the mothers suggested a maximum of 20 to 25 children per *Isizinda*. The *Isizinda* operated according to a fixed schedule, and each mother was provided with a roster. In addition, the mothers of the households hosting the *Isizinda* took responsibility for reminding the mothers of the next growth-monitoring date. They also took responsibility for the storage of the equipment used during the growth-monitoring sessions.

Zulu-speaking nutrition monitors were recruited by the NPHCC and employed by the MRC to perform the growth-monitoring activities. It was essential that they be able to read and write. They had to be fluent in English to enable them to communicate with the MRC project team. They were trained according to the guidelines of the World Health Organization for training health workers [30].

During the monthly growth-monitoring sessions, each child was weighed; the weight was plotted on the growth chart (which was based on a revised Road-to-Health card that was introduced in the country [31]); the growth curve was discussed with the mother; counseling was given; and if the child showed growth faltering, the child was referred to the nearest clinic (box 1). The nutrition monitors visited the children who were referred to the clinic at home to make sure that any treatment or advice given by the clinic was followed as prescribed.

Morbidity data were collected monthly from participating children during the growth-monitoring sessions. This helped the nutrition monitors to identify children with problems, and it was useful in targeting information given to the individual mothers (box 2).

The growth-monitoring sessions were used as a platform for nutrition education. The results of a situation analysis [27] were used to identify key messages. New topics were dictated by the needs of the mothers. Nutrition messages were adapted as circumstances changed. For example, when the project started, the river was the main source of drinking water, and a key message was to boil the water before drinking it. Currently, many households have access to tap water, and the relevance of this key message has decreased. Group discussions with the nutrition monitors helped to define the messages within the cultural and socioeconomic context of

BOX 1. Guidelines used by the nutrition monitors to interpret the growth curve and counsel mothers during the growth-monitoring sessions

Growth curve	Interpretation	Counseling
Growth curve parallel to reference curve	Normal growth	Reassure the mother
Growth curve flattened or decreased for the first time	Early growth faltering	Increase the frequency of breastfeeding (if applicable) Increase food portion size Add some fat, peanut butter, or vegetables to porridge Feed more regularly
Growth curve decreased or flattened for 3 consecutive months	Growth faltering	Refer to clinic
Growth curve rises sharply	Gaining too much weight	Ensure formula milk is mixed correctly (if applicable) Reduce portion size Use fat and sugar sparingly

BOX 2. Guidelines used by the nutrition monitors for the use of morbidity data to counsel mothers

Illness	Counseling advice
Diarrhea—present	Oral rehydration therapy Continue to breastfeed (if applicable) Increase fluid intake
Diarrhea—previous episode together with weight loss	Increase food intake
Diarrhea—persistent	Refer to clinic
Loss of appetite	Small, regular feedings
Sores on the body	Keep body clean
Worms	Refer to clinic for deworming

the area. Simple, inexpensive educational material that was attractive and acceptable to both the mothers and the nutrition monitors was developed through discussions with the nutrition monitors, observation, and feedback from the mothers and the nutrition monitors. Nutrition and health messages were given in a group situation, as well as to mothers individually, when needed. In the group situation, active participation of the mothers was encouraged, aiming at group discussions, rather than a classroom atmosphere. The mothers were encouraged to discuss individual constraints to better nutrition and to learn from the experience of others. If a mother attended for the first time, a volunteer from the mothers who had been coming for quite some time would, under the supervision of the nutrition monitor and the other mothers present, explain the growth chart to the newcomer. Measurements taken at the *Isizinda* were explained and demonstrated to the newcomer.

Since 1999, the *Isizinda* have also served as training centers and provided the infrastructure that was needed for the promotion of the agricultural activities of a home-garden project [32] that was established to address the vitamin A deficiency prevalent in the area [27]. During the growth-monitoring sessions, the local production and daily consumption of β-carotene–rich vegetables and fruits were promoted through education regarding vitamin A nutrition, cooking of locally produced vegetables, and demonstrations of the planting process in a demonstration garden. Most of the mothers were not familiar with the β-carotene–rich crops, and the cooked vegetables were used to introduce the mothers and children to these vegetables on growth-monitoring days, teach the mothers various ways of preparation, and give the mothers the opportunity to observe their children eating and enjoying the vegetables. The latter served as motivation for the mothers to plant these vegetables at the household level and to prepare them at home.

The project was coordinated by the headmaster of the local school, assisted by the NPHCC. The nutrition monitors gave feedback on the progress of the project and discussed problems, if any, during monthly staff meetings with the project coordinator. Community meetings were held twice a year, or more often when needed. During these meetings, the community had the opportunity to raise questions and concerns regarding the project, which were then discussed and acted on according to popular vote.

The performance of the nutrition monitors and the quality of the service provided were continuously monitored by the project leader, who attended at least one growth-monitoring session every month. The project leader met monthly with the nutrition monitors to discuss the progress of the project and problems they encountered in carrying out their tasks, and to review the information collected.

Acceptability of the community-based growth-monitoring project

Attendance

Children were registered at the *Isizinda* when attending a growth-monitoring session for the first time, and they remained registered in the project until they started school, moved out of the area, or died. Data were obtained from the *Isizinda* registers from 1996 until 2000.

Attendance ratio. For each month, the numbers of children who were registered in the project and attended the growth-monitoring sessions were recorded. The attendance ratio was calculated as

$$\frac{\text{number of children who attended}}{\text{number of children registered}} \times 100\%$$

The average attendance ratio for each calendar year was calculated.

Coverage. The coverage ratio is an estimate of the number of age-eligible children who were registered in the project. In 1998, all preschool children in the village were counted during a house-to-house survey. The information was used to calculate the coverage as

$$\frac{\text{number of children who were registered}}{\text{number of children in the village}} \times 100\%$$

Age distribution of children attending the growth-monitoring sessions. For each calendar year, the proportion of child visits to the *Isizinda* per age category, in one-year intervals, was summarized.

Adequacy of growth monitoring. According to the guidelines defined by the INP Strategy, children should be growth-monitored at least five times during the first year of life, four times during the second year of life, and three times per year thereafter until the age of five years [13]. The number of times that each child who was registered in the project from the beginning until the end of the study was growth-monitored per one-year interval was compared with the INP guidelines.

Maternal attitude

In 2001, a qualitative assessment of maternal attitudes of participants and nonparticipants was performed by an independent organization (Child Development Programme of the University of Natal) using focus group discussions. It was reasoned that the mothers might find it embarrassing to voice criticisms to the project staff but be willing to speak more freely to an independent organization. Before each session, it was stressed to the mothers that the independent organization was not related in any way to the *Isizinda* project. It was explained to them that the purpose of the discussions was to improve the quality of the project, and they were asked to give their honest opinions about the project. Focus group discussions were conducted with four groups of participating mothers, recruited through the nine *Isizinda* (eight mothers per focus group), and two groups of mothers who had not been attending the growth-monitoring sessions regularly during the past year. The participants within a group were all more or less of the same age; people known to be in conflict with each other were not included in the same group; and dominating or passive people were excluded. Each focus group discussion lasted approximately one hour and was conducted by two Zulu-speaking facilitators. While one facilitator chaired the discussion, the other recorded the session and took notes. The information was later transcribed and translated.

Results

Coverage and attendance

From the establishment of the *Isizinda* project in August 1995 until December 2000, a total of 329 children aged five years and younger participated in the *Isizinda* project. Since the launch of the project (in August 1995), when 38 children attended the first growth-monitoring session, the number of children registered increased steadily, and it reached a plateau of 110 to 120 during 1997. Data collected during 1998 showed an estimated coverage of 90%.

The average monthly attendance ratio for the duration of the study was 71±10% (table 1). The frequency of child visits to the *Isizinda* was equally distributed over one-year-interval age categories for children younger than five years (fig. 1). Nearly two-thirds of infants and at least 70% of children one year of age and older who were registered at the *Isizinda* met the minimum requirements defined in the INP strategy [13] (table 2).

Maternal attitude

Mothers attending the Isizinda

The results of the focus group discussions with mothers who attended the *Isizinda* are summarized in box 3.

TABLE 1. Mean ± SD percentage of the total number of children registered at the *Isizinda* who attended the growth session each month

Year	% attending
1996	79 ± 8
1997	63 ± 7
1998	69 ± 7
1999	69 ± 7
2000	77 ± 8

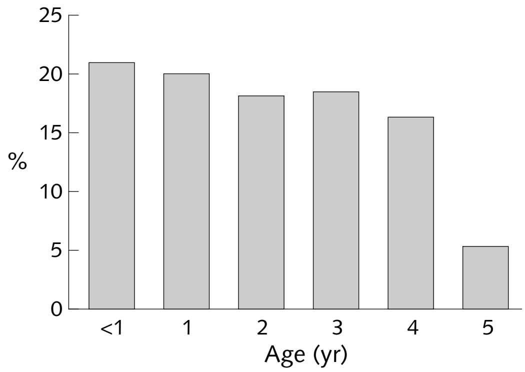

FIG. 1. The distribution of child visits to the *Isizinda* over one-year interval age categories, for all children who attended the *Isizinda* from the start until the end of the study (2000)

The respondents were enthusiastic about the project and were keen to have their children's weight checked regularly at the *Isizinda*. They were pleased that they understood the link between appropriate weight gain, nutrition, and their children's health. An important outcome was a sense of empowerment gained through a better understanding of what made their children healthy, how to check this, and skills to produce food to achieve this. The latter was accomplished by integrating the growth-monitoring activities with

TABLE 2. Adequacy of growth monitoring of children in different age categories according to the guidelines of the Integrated Nutrition Programme for South Africa[a]

Age (yr)	*N*	% monitored adequately
0–< 1	166	64
1–< 2	154	70
2–< 3	149	76
3–< 4	146	81
4–< 5	127	82

a. Guidelines for minimum growth monitoring: age 0–12 months, at least five times per year; age 1–2 years, at least four times per year; age 2–5 years, at least 3 times per year [13].

BOX 3. Maternal attitude towards the project, as determined by focus group discussions with mothers who attended the *Isizinda*

Opinions about the project

What was learned

» That poor growth was a cause of concern
» That the child's weight should be checked regularly and correctly
» How to monitor weight changes
» The link between weight change, the child's health, and good nutrition

What was liked about the project

» That they were taught how to care for their children better
» That they were taught how to check height and weight
» The improved health of the children
» Information on whether their children were ill
» The close proximity to their homes was convenient and saved transport costs

What was disliked about the project

» They would have liked more assistance with basic health care
» They wanted basic health care and medical supplies at the *Isizinda*

How did they feel about the way the project was run

» The nutrition monitors were trying hard to make the project work
» The project was well run
» The good communication style of project team and nutrition monitors was valued

Feelings about the weighing project

» They were pleased that they understood the link between weight gain and their children's health
» Before the project they were not motivated to take their children for regular growth monitoring because the rationale had not been explained to them
» They felt encouraged when they learned their children were growing well

Perceived health improvement

» Knowledge gained at the *Isizinda* has helped to treat diarrhea
» The education changed the caregivers' attitudes about the importance of appropriate weight gain

Sustainability of the project

» There was a strong desire for the project to continue
» The project should continue with local nutrition monitors, but they would need assistance from the project team from time to time
» The extension to other areas was supported

agricultural activities that promoted the local production and daily consumption of β-carotene–rich fruits and vegetables.

Overall, they were satisfied with the way in which the project was run. On the other hand, they were unhappy with the government's mobile clinic and perceived the clinic staff as hostile and unhelpful. Prior to the *Isizinda* project, the mothers were not motivated to take their children to the clinic for regular growth monitoring because the rationale was never explained to them. Their experience with the staff of the mobile clinic was that the children were treated but parents were not given any information as to the nature of the problem. At the *Isizinda*, however, they found the nutrition monitors helpful and informative.

Some of the respondents felt that basic health care should be available at the *Isizinda*. Nonetheless, a reduction in mortality, better child health, and more energetic children were cited as perceived health benefits.

The mothers were keen for the *Isizinda* project to continue and unanimously agreed that the project should be extended to other areas. There was a desire for some kind of follow-up support, even if it was intermittent. Some mothers feared that the gains made in the community thanks to the *Isizinda* project would be lost if the project team left.

Mothers not attending the Isizinda

The respondents who either did not attend or did not attend regularly all agreed that the project had been beneficial, but for some the benefits no longer outweighed the disadvantages. Nonparticipants complained that they were too busy to attend the *Isizinda.* The lack of medicines at the *Isizinda* was seen as a disadvantage. Disputes with the owner of the household hosting the *Isizinda* prevented some from attending the growth-monitoring sessions.

Discussion

Studies in South Africa have shown that the coverage of health facility–based growth monitoring is low and biased towards the younger child [21, 23]. Clinics are often not accessible to those in greatest need [21], and clinic attendees are generally not representative of the population as a whole [21, 22]. In contrast, the *Isizinda* project had a high coverage and attendance ratio, and the visits to the growth-monitoring sessions were distributed almost equally over one-year-interval age categories. A benefit of the high coverage and attendance ratio is that a large number of mothers had access to the nutrition-education and agricultural training activities that were given during the growth-monitoring sessions.

The growth curve was incorporated in all education messages, thereby reinforcing the importance of regular growth monitoring. For example, when diarrhea was discussed, a deleterious effect of diarrhea was explained as a sudden weight loss, as seen on the growth curve. Since the establishment of the *Isizinda* project, the mothers showed a more positive attitude toward growth monitoring, probably because of a better understanding of the benefits of weighing children regularly. They appreciated the close proximity of the *Isizinda* to their homes, since this was convenient and saved transport costs. The *Isizinda* operated in households, and disputes with the owner of the household prevented some mothers from attending the growth-monitoring sessions. Should this become a major problem, venues such as neighborhood halls [33], church buildings, schools, and crèches [23] could be used.

The time available in clinics is often restricted [34], and clinic staff often do not have time to complete the growth chart [35], let alone give nutrition counseling. Nutrition education was an integral part of the activities at the *Isizinda*. The number of children attending the growth-monitoring sessions was relatively small (8–20 children), and sufficient time was available for nutrition education. The mothers appreciated these lessons and valued the knowledge that they gained. Most mothers could interpret the growth curve [29], and therefore they could visualize the child's growth pattern and, as a result, appreciate the benefits of regular growth monitoring.

The nutrition monitors were seen as helpful and informative. The clinic staff had tertiary education and often westernized lifestyles, resulting in a wide gap between them and the community [36]. The nutrition monitors had some level of secondary school education and were of similar socioeconomic background as the participants. Griffiths et al. recommended that the people responsible for community-based growth monitoring should be from the community [9]. In Ndunakazi (and neighboring areas), the performance of nutrition monitors from the area was easily affected by conflict within the community, and they were not as highly respected as nutrition monitors who did not live in the area. On the other hand, nutrition monitors not living in the area were dependent on public transport, which was costly and, at times, unreliable.

Because of the small numbers, the *Isizinda* were not overcrowded; the mothers did not have to wait long and they could interact. This created a relaxed and sociable atmosphere. This was strengthened by the preparation of locally produced vegetables during the latter half of the study. Furthermore, the nutrition monitors reassured mothers when their children's growth curves were normal, thereby creating a positive and encouraging atmosphere. Growth monitoring in clinics is often linked to immunization, and mothers often do not appreciate the value of growth monitoring and discontinue it once the immunization schedule is completed [1, 23]. Children were not immunized at the *Isizinda,* but the nutrition monitors continuously checked the immunization status of the children from the children's clinic cards.

The *Isizinda* project was not in competition with the services delivered at nearby health facilities. The referral and follow-up system between the *Isizinda* and the nearest clinic was well accepted by the clinic staff. The staff of the mobile clinic servicing the area expressed their appreciation to the project coordinator. Studies have shown that mothers often wait until their children are very ill before taking them to a clinic [23, 37]. The purpose of the referral system was to make sure that children were taken to the clinic during the early stages of illness or growth faltering. The nutrition monitors visited the children who were referred to the clinic at home and made sure that the treatment or advice given by the clinic was followed as prescribed. This strengthened the curative services of the clinic and reassured the mothers of the nutrition monitors' interest in their children. It also allowed the mothers to discuss nutritional issues with the nutrition monitors in the privacy of their homes.

For nutrition programs, effective, dynamic leadership is frequently cited as an element of success [1]. The role of the project coordinator, who was also the headmaster of the local school, was invaluable, and his strong, dedicated, and enthusiastic leadership strengthened the community's acceptance of the project. Decisions were taken *with* the community and not *for* the community, and as a result there was little resistance to project activities.

The impact of community-based growth monitoring *per se* on nutritional status was not measured because of the lack of a suitable control group. The small scope of the project made it difficult to measure its impact. However, behavioral changes were observed. For example, the average age of introduction of solid foods in 1995 was 2.8 ± 0.8 months [38], versus 3.6 ± 0.8 months during 1997 [39]. This could be the result of the nutrition education that addressed, among other things, infant-feeding practices. Nutrition education at the *Isizinda* also addressed issues regarding the causes, consequences, prevention, and treatment of diarrhea. The number of children for whom diarrhea was reported during the growth-monitoring sessions decreased steadily from 8.0% in 1996 to 2.2% in 2000 [29]. This can probably be ascribed, to some extent, to the education lessons given at the *Isizinda*. The installation of taps in 1999 and the improved vitamin A status resulting from the home-garden project [32] could have contributed to the decline in the prevalence of diarrhea during the last two years of the study.

The situation analysis that was done in Ndunakazi showed that 44.9% of preschool children were marginally deficient in vitamin A (serum retinol concentrations below 20 μg/dl) [27]. The regular consumption of animal products was not within their financial reach, and β-carotene–rich vegetables were not widely available within the area (personal observation). The high coverage and attendance ratio made the growth-monitoring activities an ideal platform for the promotion of the local production and daily consumption of β-carotene–rich vegetables. For a consistent supply of these vegetables, it was essential that staggered planting and cyclic production be promoted continuously. This would have been very difficult to accomplish without the platform that the growth-monitoring activities provided. The mothers attending the *Isizinda* had access to agricultural training and nutrition education with regard to vitamin A nutrition as part of the home-garden project. Maternal knowledge with regard to vitamin A nutrition improved significantly. Within 20 months, more than 70% of mothers could name at least three vitamin A–rich foods, they associated vitamin A–rich vegetables with the colors orange-yellow and dark green, and they could name at least one symptom related to vitamin A deficiency [32]. Dietary intake of β-carotene–rich vegetables increased, resulting in an improvement in the vitamin A intake [40] and ultimately in the vitamin A status [41] of two- to five-year-old children, with the prevalence of marginal vitamin A deficiency decreasing from 58% to 34% ($p = .001$). A contributing factor to the success of the home-garden project was the mothers' understanding of the underlying factors of poor growth and health of their children, which was obtained through monthly growth monitoring and nutrition education.

In conclusion, community-based growth monitoring at home-based centers was acceptable to the mothers, and a high coverage and attendance ratio were achieved. Growth monitoring was therefore an ideal platform for the promotion of the agricultural activities of a home-garden project, which resulted in a significant improvement in child malnutrition.

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