Supplemental Vitamin A Improves Anemia and Growth in Anemic School Children in Tanzania

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ABSTRACT We conducted a randomized controlled trial of the effects of dietary supplements on anemia, weight and height in 136 anemic school children from a low socioeconomic background in Bagamoyo District schools in Tanzania. The aim of the current study was to investigate the impact of dietary supplements on anemia and anthropometric indices of anemic school children. The supplements were vitamin A alone, iron and vitamin A, iron alone or placebo, administered in a double-blinded design for 3 mo. All supplements were provided with local corn meals. Hemoglobin concentration, body weight and height were measured at baseline and at follow-up after supplementation. Vitamin A supplementation increased the mean hemoglobin concentration by 13.5 g/L compared with 3.5 g/L for placebo ($P < 0.0001, 95\%$ confidence interval (CI) 6.19–13.57), the mean body weight by 0.6 kg compared with 0.2 kg for placebo ($P < 0.0001, 95\%$ CI 0.19–0.65) and the mean height by 0.4 cm compared with 0.1 cm for placebo ($P = 0.0009, 95\%$ CI 0.08–0.42). However, the group of children who received combined vitamin A and iron supplementation had the greatest improvements in all indicators compared with placebo (18.5 g/L, $P < 0.0001, 95\%$ CI 14.81–22.23; 0.7 kg, $P < 0.0001, 95\%$ CI 0.43–0.88 and 0.4 cm, $P < 0.0001, 95\%$ CI 0.22–0.56 for hemoglobin, weight and height, respectively). It is likely that vitamin A supplementation may have a useful role in combating the problems of vitamin A deficiency and anemia, as well as in improving children’s growth, in developing countries. J. Nutr. 130: 2691–2696, 2000.

KEY WORDS: • anemia • rural school children • vitamin A • iron • randomized controlled trial • Tanzania

Iron deficiency anemia (IDA), which affects 1.2 billion persons, is the most prevalent nutritional deficiency worldwide. In 1991, >290 million school-aged children were anemic, of whom 150 million attended school (Viteri 1991). World Health Organization (WHO) data suggest that up to 46% of school-aged children in developing countries have IDA (Viteri 1998).

In Tanzania, anemia is a widespread and important problem among school children. Surveys conducted by the Tanzania Partnership for Child Development, known locally as Ushirikiano wa Kumwendeleza Mtoto Tanzania (UKUMTA), revealed that ~80% of school children have hemoglobin concentrations of less than the 120-g/L cutoff point recommended by the WHO (UKUMTA 1996). In some parts of the country, a prevalence rate of 100% has been reported (Berger and Salehe 1986, Kavishe 1991).

Anemia occurs when the tissue stores of iron are depleted, leading to a lowered level of serum iron, a decrease in transferrin saturation and an increase in erythrocyte protoporphyrin. When tissue stores are seriously depleted, hemoglobin levels decline. Thus, low levels of hemoglobin may be taken to indicate IDA (Seshadri and Gopaldas 1989, Viteri 1998).

In many developing countries, iron deficiency arises from inadequate food intake, impaired absorption and/or utilization, excessive losses or a combination of these factors (Viteri 1998). In developing African countries such as Tanzania, staple diets are plant based and hence contain high levels of phytic acid and dietary fibers, which can inhibit the absorption of iron (Gibson 1994). Both the content and bioavailability of iron in Tanzania, especially in rural areas, are likely to be low (Tatala et al. 1998).

Growth retardation is an important public health problem among children living in poverty in developing countries (UNICEF 1995). The extent to which catch-up growth in later childhood reduces deficits incurred in early childhood is not well documented. However, the biological potential for catch-up growth has well been illustrated in studies that evaluated the responses to clinical intervention with supplementary feeding, treatment of illness or hormone therapy (Golden 1994). Tanner (1981) advanced the general hypothesis that when undernourished children are exposed to a better envi-

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enironment and good nutrition, the likelihood of catch up is greater, with the degree of recovery depending on the severity of growth retardation and the timing of exposure. Martorell et al. (1994) suggested that catch up may depend on whether undernutrition is associated with delayed maturation, which in turn could allow for a prolonged adolescent growth spurt with greater time for recovery before skeletal growth is complete.

Recently, it was suggested that there may be a synergistic relationship between vitamin A and iron. Garcia-Casal et al. (1998), Garcia-Casal and Layrisse (1998) and Layrisse et al. (1997) showed in isotopic studies that relatively low doses of vitamin A or \( \beta \)-carotene can double the absorption of endogenous nonheme iron from cereal (staple) meals in anemic adults in Venezuela. More interactions between vitamin A and other essential micronutrients, which are largely deficient in diets in developing countries, have been reported in several studies. For example, Christian and West (1998) showed that zinc in retinol binding protein (RBP) increases lymphatic absorption of iron both its intercellular and intracellular transport, whereas vitamin A affects the synthesis of a zinc-dependent binding protein and therefore the absorption and lymphatic transport of zinc. The interaction of these two essential nutrients when ingested by persons who are deficient in both was shown by Udomkesmalee et al. (1992). They observed the synergistic activities of these two nutrients on eye parameters and RBP.

These findings suggest that vitamin A supplementation may have a crucial role in the control of IDA, which is highly prevalent in many developing countries. However, supplementation has most often been viewed as a short-term measure to combat micronutrient deficiencies, because there is little evidence from field trials in developing countries regarding its efficacy (Darnton-Hill 1998). In the current study, we investigated the impact of dietary supplements administered with local foods on anemia and anthropometric indices in anemic children in Tanzania, where anemia and growth retardation are public health problems.

SUBJECTS AND METHODS

Subject selection. The study was conducted in three primary schools in the Bagamoyo District in Tanzania. Bagamoyo is a rural district in the coastal region ~120 km from Dar es Salaam, the capital city of Tanzania. The people in these communities of low socioeconomic status depend on subsistence farming as the main source of income. The diets are predominately high in unrefined staple foods with low levels of animal proteins. Corn is the main staple and is associated with high levels of tannins and phytates, which inhibit the absorption of iron from staple foods. Although vegetables are consumed on a relatively regular basis, fruits are eaten mainly when in season. Vegetables with the potential to provide vitamin A, such as carrots, are expensive and scarce.

The subjects were selected according to the following criteria: 1) children of either sex aged 9–12 y (only nonmenstruating girls were invited to participate in the study), 2) children who had attended school for ≥2 y, 3) children who were not ingesting any supplements and 4) children of parents or guardians from whom informed consent (written or verbal) to participate in the study was received. All of the children were of rural families and had a similar low socioeconomic status. Children with obvious chronic illnesses, such as chronic otitis media, or physical impairments, such as limb deformities, were excluded before randomization because these would impair performances on tests of cognitive, motor function and educational achievement, which were also administered as part of the study. The subjects were dewormed for helminthiasis 2 wk before the baseline measurements were taken.

After all of the selection criteria were met, 208 children were selected for the initial hemoglobin screening. Of these children, 197 were willing to participate in the study. Fingerprick blood samples were screened for hemoglobin using a portable battery-operated hemoglobinometer (Hemocue, Sheffield, U.K.) that was calibrated daily using reference blood samples before and after the survey. Selection of the final study subjects was based on a hemoglobin concentration of <120 g/L (WHO 1968).

One hundred thirty-eight children (70%) had hemoglobin concentrations of <120 g/L and so were regarded as anemic. Two children were found to have severe anemia (hemoglobin concentration <80 g/L); these children were excluded from the study, and their parents were notified and referred to the local health facility for further investigation. The final study population consisted of 136 children who were enrolled for the study. At the end of the study, data from 135 children were available for analysis; 1 child was lost to follow-up measurements because her parents had moved to a location far from the study area.

Study design. A randomized, double-blind, placebo-controlled trial was used to determine the effect of the provision of vitamin A and iron supplements on anemia and the nutritional status of anemic school children. The supplements were packed in tablet form by the Department of Pharmacy, Women and Children's Hospital, in Adelaide. The study was designed in such a manner that neither the study subjects, the teachers, the research team members nor the investigator had knowledge of the group assignments.

One hundred thirty-six children were randomly assigned to one of four treatment groups within each of six sex/school strata to help ensure sex and geographical balance of treatment allocations. The RAND function of Excel (Microsoft, Redmond WA) was used to implement randomization. The four treatments were administered 3 d/wk for 12 wk as follows:

- Treatment group 1 was assigned to receive 5000 IU vitamin A (1.5 mg retinyl acetate) and placebo for iron (magnesium stearate, dextrose monohydrate and hydrogenated vegetable oil).
- Treatment group 2 was assigned to receive both vitamin A and iron in tablet form: 1.5 mg retinyl acetate (5000 IU) and 200 mg ferrous sulfate were administered to each child.
- Treatment group 3 was assigned to receive iron (200 mg ferrous sulfate) and placebo for vitamin A (magnesium stearate and dextrose monohydrate).
- Treatment group 4 was assigned to receive both the placebo for vitamin A and the placebo for ferrous sulfate.

Procedure. Each subject underwent a physical examination by the field investigator (L.M.) that involved the following: 1) examination of the eyes for pallor of conjunctiva and of the tongue, both of which are signs of anemia, and 2) examination of the eyes for signs of xerophthalmia (dry eye due to a deficiency of vitamin A), Bitot's spots (milky white spots on the eye) and corneal scars, all of which are signs of vitamin A deficiency (Kavish 1991).

The children were weighed in clothing and without shoes using a Soehnle electronic weighing scale (CMS Weighing Equipment, London, U.K.). Each child's body weight was recorded to a precision of 0.1 kg. Height was measured to a precision of 0.1 cm using a portable fixed-base stadiometer (CMS Weighing Equipment). All measurements were made first at baseline and then at follow-up, 3 mo after treatment, by the same persons.

Provision of supplements. After the baseline measurements had been completed, all treatments, including placebo, were administered with a corn preparation in gruel for 3 d/wk for 3 mo; this duration has been shown to increase hemoglobin concentration (Pollitt et al. 1989, Soemantri 1989). Supplements were provided during the mid-morning break in school by either the head teacher or the health education teacher. This appeared to be convenient to both teachers and children because it did not involve teaching time. After 3 mo, the intervention was terminated, and follow-up measurements were taken. In addition, children who had received placebo only were treated for anemia.

Special forms were designed to record each child's supplement use for the duration of the study; this allowed monitoring for compliance during the entire study period. All except one child (99.3%) completed the supplementation according to protocol.

The study protocol was approved by the University of Adelaide Humans Ethics Committee in Australia and the Ministries of Health, Education and Culture in Tanzania. The protocol was also revised.
and approved by the Ethical and Research Committee of the Tanzania Food and Nutrition Center in Tanzania.

Data analysis. For each of the three outcome variables, hemoglobin, weight and height, we present i) mean changes within treatment groups during the 3-mo follow-up period and ii) comparisons of mean changes between pairs of treatments. Each within-treatment change and between-treatment comparison was specified a priori, but we used the Bonferroni method to control for type 1 error such that within each group of comparisons, the overall type 1 error is limited to 0.05 and the joint coverage of the confidence intervals (CI) is 95%.

Both the changes within treatments and the differences in change between treatments were estimated from an ANCOVA model, with one model for hemoglobin, for weight and for height. Models were adjusted for baseline measurements. For hemoglobin, the model underlying analyses was

\[
\Delta Hb_t = \beta_0 + (\beta_1 \times \text{VitA}_t) + (\beta_2 \times \text{Fe}_t) + (\beta_3 \times \text{VitA + Fe}_t) \\
+ \beta_4 \times (\text{Hb}_0 - \text{mean Hb}_0) + \beta_5 \\
\times (\text{Wt}_0 - \text{mean Wt}_0) \\
+ \beta_6 \times (\text{Ht}_0 - \text{mean Ht}_0) + \epsilon
\]

where \(\Delta Hb\) is the change in hemoglobin (follow-up value minus baseline value); \(\text{Hb}_t, \text{Wt}_t, \text{Ht}_t\) are the hemoglobin, weight and height measurements at baseline, respectively, and, for convenience in the model, they are centered at their overall means; \(\text{VitA}_t\) and \(\text{Fe}_t\) are dummy variables that indicate treatment with vitamin A, iron or both, respectively (the reference group is therefore placebo); \(\beta\) through \(\beta_6\) are coefficients to be estimated; \(\epsilon\) is the error term, with the assumption \(iid \sim N(0, \sigma^2)\) and \(i\) indicates that the model holds for each of the 135 subjects.

The ANCOVA models showed no evidence of interaction between baseline covariates and treatment groups. Regression diagnostics showed no important violations of the assumptions of the linear model. Tests of contrasts of interest are based on the usual Wald statistics formed from appropriate linear combinations of estimated coefficients and standard errors derived from elements of the full variance–covariance matrix of the model.

The Stata statistical package (Stata Corporation, College Station, TX) was used for all analyses.

RESULTS

Baseline characteristics. Of 136 anemic children between 9 and 12 y old who were recruited in this study, 70 (51.5%) were girls and 66 (48.5%) were boys. None of the children who were examined showed clinical signs of vitamin A deficiency, although most of the children had clinical signs of anemia such as pale conjunctiva, tongue and gums. Differences among groups in demographic and nutritional characteristics at the beginning of the study, although not statistically significant, showed the need for adjusted comparisons (Table 1).

Effects of supplements on hemoglobin. At the 3-mo follow-up, 135 subjects were reexamined. With adjustments for baseline, hemoglobin levels in each group revealed significant increases over time. The most substantial increase was seen in the combined vitamin A and iron group (adjusted change 22.1 g/L, 95% CI 19.64–24.62; Table 2); the group also showed the greatest change in hemoglobin relative to that in the placebo group (adjusted differences in change 18.5 g/L, 95% CI 14.81–22.23; Table 3). The combined group also showed significant improvements relative to each of the vitamin A–alone and iron-alone groups.

To further explore the data, we calculated the proportion of children who recovered from anemia after 3 mo of treatment. Most (88%) of the children who received both vitamin A and iron were not anemic (hemoglobin ≥120 g/L) after 3 mo of supplementation compared with only 3% of the placebo group. Most (79%) of the children who received iron alone recovered from anemia, whereas only 50% of children who received vitamin A alone were not anemic at the end of the study. These results indicate that there was a 9% advantage of correcting anemia when children were supplemented with both vitamin A and iron compared with treatment with iron alone. A test for a linear trend in proportions across treatment groups was significant (\(\chi^2 = 15.2\) on 1 df, \(P = 0.0001\)).

Effects of supplementation on weight. Mean changes in weight for each group, with adjustment for baseline, after 3 mo

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Vitamin A</th>
<th>Iron</th>
<th>Vitamin A + iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>10.9 ± 1.1</td>
<td>11.0 ± 1.1</td>
<td>11.1 ± 1.0</td>
<td>10.0 ± 0.8</td>
</tr>
<tr>
<td>Sex, M, F</td>
<td>16.18</td>
<td>17.17</td>
<td>16.18</td>
<td>17.17</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>103.9 ± 10.5</td>
<td>104.3 ± 0.8</td>
<td>106.1 ± 0.8</td>
<td>106.5 ± 10.5</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>26.0 ± 3.7</td>
<td>26.7 ± 2.2</td>
<td>27.2 ± 3.9</td>
<td>26.6 ± 4.4</td>
</tr>
<tr>
<td>Height, cm</td>
<td>130.1 ± 6.3</td>
<td>129.5 ± 6.8</td>
<td>133.0 ± 8.2</td>
<td>139.0 ± 6.7</td>
</tr>
</tbody>
</table>

1 Values are means ± se, n = 34, for 136 children enrolled in the study and randomly assigned to one of four treatment groups.

<table>
<thead>
<tr>
<th>Randomized group</th>
<th>Hemoglobin</th>
<th>95% Confidence interval</th>
<th>(p^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3.6 ± 1.0</td>
<td>1.15–6.07</td>
<td>0.001</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>13.5 ± 1.0</td>
<td>11.00–16.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Iron</td>
<td>17.5 ± 1.0</td>
<td>15.00–20.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vitamin A and iron</td>
<td>22.1 ± 1.0</td>
<td>19.64–24.62</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

1 Mean changes ± se (follow-up minus baseline); values are adjusted for baseline hemoglobin, weight and height, with each centered at their respective mean.

2 95% confidence intervals and two-tailed \(P\) values are corrected for multiple comparisons with the Bonferroni method.
are shown in Table 4. There were significant increases in weight over time in each group, with the most substantial increase seen in the combined vitamin A and iron group (0.9 kg, 95% CI 0.73–1.04).

Table 5 shows comparisons of change in mean weight over time between treatment groups. There were significant increases in mean weight in each actively treated group compared with the placebo group. The combined treatment was better than either vitamin A or iron alone. Although the combined treatment with vitamin A and iron compared with vitamin A alone produced a significant weight increment (0.2 kg, 95% CI 0.01–0.46), there was no significant difference in mean weight increment between the group who was treated with combined vitamin A and iron and the group who were treated with iron alone (95% CI −0.04–0.42).

Effect of supplements on height. There were slight increases in mean height over time in each group, with the least increase seen in the placebo group (Table 6). As with the changes in hemoglobin and weight, height increased most in the group of children who received both vitamin A and iron (0.5 cm, \( P < 0.0001, 95\% \text{ CI } 0.42–0.65 \)).

The change in height for each of the three actively treated groups was significantly greater than that in the placebo group (Table 7). However, there was no significant difference in the change between combined supplementation and iron alone.

**TABLE 3**

<table>
<thead>
<tr>
<th>Comparison group</th>
<th>Difference in mean change in hemoglobin(^1)</th>
<th>95% Confidence interval(^2)</th>
<th>(P)(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A versus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>placebo</td>
<td>9.9 ± 1.4</td>
<td>6.19–13.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Iron versus placebo</td>
<td>13.9 ± 1.4</td>
<td>10.14–17.59</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vitamin A + iron versus placebo</td>
<td>18.5 ± 1.4</td>
<td>14.81–22.23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Iron versus vitamin A</td>
<td>4.0 ± 1.4</td>
<td>0.19–7.77</td>
<td>0.0337</td>
</tr>
<tr>
<td>Vitamin A + iron versus vitamin A</td>
<td>8.6 ± 1.4</td>
<td>5.00–12.38</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vitamin A + iron versus iron</td>
<td>4.7 ± 1.4</td>
<td>0.94–8.37</td>
<td>0.006</td>
</tr>
</tbody>
</table>

\(^1\) Differences in mean changes ± SEM; values are adjusted for baseline hemoglobin, weight and height, with each centered at their respective mean.

\(^2\) 95% Confidence intervals and two-tailed \(P\) values are corrected for multiple comparisons with the Bonferroni method.

**TABLE 4**

<table>
<thead>
<tr>
<th>Randomized group</th>
<th>Mean change in weight from baseline at 3 mo(^1)</th>
<th>95% Confidence interval(^2)</th>
<th>(P)(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.2 ± 0.1</td>
<td>0.08–0.38</td>
<td>0.0008</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>0.6 ± 0.1</td>
<td>0.50–0.80</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Iron</td>
<td>0.7 ± 0.1</td>
<td>0.54–0.85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vitamin A and iron</td>
<td>0.9 ± 0.1</td>
<td>0.73–1.04</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(^1\) Mean changes ± SEM (follow-up minus baseline); values are adjusted for baseline hemoglobin, weight and height, with each centered at their respective mean.

\(^2\) 95% Confidence intervals and two-tailed \(P\) values are corrected for multiple comparisons with the Bonferroni method.

**TABLE 5**

<table>
<thead>
<tr>
<th>Comparison group</th>
<th>Difference in mean change in weight(^1)</th>
<th>95% Confidence interval(^2)</th>
<th>(P)(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A versus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>placebo</td>
<td>0.4 ± 0.1</td>
<td>0.19–0.65</td>
<td>0.0000</td>
</tr>
<tr>
<td>Iron versus placebo</td>
<td>0.5 ± 0.1</td>
<td>0.24–0.69</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vitamin A + iron versus placebo</td>
<td>0.7 ± 0.1</td>
<td>0.43–0.88</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Iron versus vitamin A</td>
<td>0.0 ± 0.1</td>
<td>−0.18–0.27</td>
<td>1.0000</td>
</tr>
<tr>
<td>Vitamin A + iron versus vitamin A</td>
<td>0.2 ± 0.1</td>
<td>0.01–0.46</td>
<td>0.0386</td>
</tr>
<tr>
<td>Vitamin A + iron versus iron</td>
<td>0.2 ± 0.1</td>
<td>−0.04–0.42</td>
<td>0.1707</td>
</tr>
</tbody>
</table>

\(^1\) Differences in mean changes ± SEM; values are adjusted for baseline hemoglobin, weight and height, with each centered at their respective mean.

\(^2\) 95% Confidence intervals and two-tailed \(P\) values are corrected for multiple comparisons with the Bonferroni method.

**TABLE 6**

<table>
<thead>
<tr>
<th>Randomized group</th>
<th>Mean change in height from baseline at 3 mo(^1)</th>
<th>95% Confidence interval(^2)</th>
<th>(P)(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.1 ± 0.0</td>
<td>0.03–0.26</td>
<td>0.0063</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>0.4 ± 0.0</td>
<td>0.28–0.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Iron</td>
<td>0.4 ± 0.0</td>
<td>0.29–0.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vitamin A and iron</td>
<td>0.5 ± 0.0</td>
<td>0.42–0.65</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(^1\) Mean changes ± SD (follow-up minus baseline); values are adjusted for baseline hemoglobin, weight and height, with each centered at their respective mean.

\(^2\) 95% Confidence intervals and two-tailed \(P\) values are corrected for multiple comparisons with the Bonferroni method.

**DISCUSSION**

We believe that this study is the first of its kind to investigate the effect of vitamin A supplementation administered with local foods in rural anemic school children of a low socioeconomic background in a developing country. The study was conducted under field conditions according to strict ex-
creased (probably subclinical) infections, increased erythro-
receptor synthesis, decreased sequestration resulting from de-
mobilization of iron from the tissue stores through increased
established in this study. Possible mechanisms include im-
ment in the health of children.

to long-term changes in the food supply, supplementation may
implemented to combat vitamin A deficiency.

dietary modification. Similar but separate programs have been
reduce IDA, including iron supplementation, fortification and
countries and may coexist (Bloem et al. 1989, Mejia and
vitamin A deficiencies are widespread in many developing
met the requirements of the body (Viteri 1998). Iron and
received placebo.

tamin A either singly or in combination had a significant
effects on the anemic status and growth of these children.

end of the study. The findings can be treated with confidence
because possible confounding factors were controlled for in the
statistical analysis.

The results of our study reveal that supplementation with
iron or vitamin A either singly or in combination had major
effects on the anemic status and growth of these children.
After the combined treatment, only 12% of the subjects re-
mained anemic compared with 97% of the children who
received placebo. Similarly, supplementation with iron or vi-
tamin A either singly or in combination had a significant
effect on weight and height compared with the children who
received placebo.

Iron deficiency occurs when insufficient iron is absorbed to
meet the requirements of the body (Viteri 1998). Iron and
vitamin A deficiencies are widespread in many developing
countries and may coexist (Bloem et al. 1989, Mejia and
Arroyave 1982). Many programs have been implemented to
reduce IDA, including iron supplementation, fortification and
dietary modification. Similar but separate programs have been
implemented to combat vitamin A deficiency.

The relative simplicity and low cost of the current inter-
vention strongly suggest that vitamin A and iron supplemen-
tation has a place in the prevention of IDA and growth
retardation. Rather than being seen as an exclusive alternative
to long-term changes in the food supply, supplementation may
be used to enhance normal diets and to effect major improve-
ment in the health of children.

The mechanism by which combined vitamin A and iron
led to improvements in hemoglobin concentration was not
established in this study. Possible mechanisms include im-
proved iron absorption from the corn-based food, increased
mobilization of iron from the tissue stores through increased
receptor synthesis, decreased sequestration resulting from de-
creased (probably subclinical) infections, increased erythro-

poiesis or formation of a complex between vitamin A and
nonheme iron, keeping it soluble in the intestinal lumen and
preventing the inhibitory effects of inhibitors of iron absorp-
tion.

In developing countries, growth retardation arises primarily
as a result of malnutrition and infection. Rapid rates of catch-
up growth have been described in extremely severe and pro-
longed cases of growth retardation from children recovering
from severe malnutrition, provided epiphyseal fusion has not
occurred (Ashworth and Millward 1986, Martorall et al. 1994).
Furthermore, these authors reviewed many instances in
which catch-up growth occurred. For example, they cite the
case of a 3-3y-old child who had had severe anorexia for more
that half of her life yet achieved full catch up in height, weight
and skeletal maturation by 5 y of age. In other settings,
researchers have observed prolonged growth spurts that
resulted in a reduction in adult height deficits (Cameron and
Kgamphe 1993), which were hypothesized to be the result of
delayed pubertal age. In a noninterventional longitudinal study
of 2- to 12-y-old Filipino children, Adair (1999) de-
scribed the potential for catch-up growth in children into
preadolescent years. These observations suggest a considerable
degree of possible catch-up growth at different age groups in
childhood when there is the removal of growth-retarding
factors. The findings of our study suggest that dietary supple-
mentation has some potential to effect catch-up growth in
later childhood in undernourished children.

In addition, our findings provide the strongest evidence
that vitamin A may have a useful role in combating vitamin A
deficiency, IDA and growth retardation. The consistency in
improvements in anemia and growth among the treatment
groups suggests that supplementation programs are likely to
bring about major reductions in the numbers of anemic and
malnourished children. The role of vitamin A in combating
micronutrient deficiencies, which remain a serious global and
public health scourge, requires further investigation.

In the long term, the substitution of high iron plus vitamin
A staples (e.g., corn, which is now available) for the current
lower-yield varieties would also help prevent IDA and
growth retardation when combined with other preventive measures,
such as anthelmintic programs.

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LITERATURE CITED

Adair, L. S. (1999) Filipino children exhibit catch-up growth from age 2 to 12
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metabolism and vitamin A deficiency in children in the northwest Thailand.

TABLE 7

<table>
<thead>
<tr>
<th>Comparison group</th>
<th>Difference in mean change in height1</th>
<th>95% Confidence interval2</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A versus placebo</td>
<td>0.2 ± 0.1</td>
<td>0.08–0.42</td>
<td>0.0009</td>
</tr>
<tr>
<td>Iron versus placebo</td>
<td>0.3 ± 0.1</td>
<td>0.08–0.43</td>
<td>0.0007</td>
</tr>
<tr>
<td>Vitamin A + iron versus placebo</td>
<td>0.4 ± 0.1</td>
<td>0.22–0.56</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Iron versus vitamin A</td>
<td>0.0 ± 0.1</td>
<td>−0.17–0.18</td>
<td>1.0000</td>
</tr>
<tr>
<td>Vitamin A + iron versus vitamin A</td>
<td>0.1 ± 0.1</td>
<td>−0.03–0.31</td>
<td>0.1837</td>
</tr>
<tr>
<td>Vitamin A + iron versus iron</td>
<td>0.1 ± 0.1</td>
<td>−0.04–0.3072</td>
<td>0.2454</td>
</tr>
</tbody>
</table>

1 Differences in mean changes ± SEM; values are adjusted for base-
line hemoglobin, weight and height, with each centered at their respec-
tive mean.

2 95% Confidence intervals and two-tailed P values are corrected for multiple comparisons with the Bonferroni method.


