Effect of daily and weekly micronutrient supplementation on micronutrient deficiencies and growth in young Vietnamese children[1–3]

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ABSTRACT

Background: Micronutrient deficiencies remain common in preschool children in developing countries. Interventions focus on single micronutrients and often lack effectiveness. Weekly instead of daily supplementation may improve effectiveness.

Objective: The efficacy of weekly and daily supplementation in reducing anemia prevalence and in improving the zinc, vitamin A, and growth status of 6–24-mo-old Vietnamese children was investigated.

Design: In this double-blind, placebo-controlled trial, the daily group (n = 55) received 8 mg elemental Fe (as iron sulfate), 5 mg elemental Zn (as zinc sulfate), 333 μg retinol, and 20 mg vitamin C 5 d/wk for 3 mo. The weekly group (n = 54) received 20 mg Fe, 17 mg Zn, 1700 μg retinol, and 20 mg vitamin C once a week. A third group (n = 54) received a placebo only. Venous blood samples were collected at the start and end of the supplementation period and anthropometric measurements were taken at the start and 3 mo after the end of supplementation.

Results: At baseline, 45.6% of subjects had hemoglobin concentrations < 110 g/L, 36.3% had zinc concentrations < 10.71 μmol/L, and 45.6% had retinol concentrations < 0.70 μmol/L. Hemoglobin, retinol, and zinc concentrations of both the weekly and daily groups increased similarly compared with the placebo group (P < 0.001). There was no significant difference in growth between the supplemented groups and the placebo group. However, the height-for-age of subjects stunted at baseline increased with z scores of 0.48 (P < 0.001) and 0.37 (P < 0.001) for the daily and weekly groups, respectively.

Conclusions: Weekly and daily supplementation improved hemoglobin, zinc, and retinol concentrations similarly. Neither intervention affected growth of the overall population, but growth of children stunted at baseline was improved through both types of supplementation. *Am J Clin Nutr* 1999;69:80–6.

KEY WORDS Iron, zinc, vitamin A, vitamin C, hemoglobin, anemia, supplementation, infants, micronutrient deficiency, growth, Vietnam

INTRODUCTION

Deficiencies of iron and vitamin A are important nutritional problems among preschool children in most of the developing world, including Southeast Asia (1). Although much less epidemiologic information is available on zinc deficiency, because of the nature of the daily diet in that region, zinc deficiency is expected to be about as common as iron deficiency (2). Especially at risk for these micronutrient deficiencies are young children aged 6–24 mo. These children can no longer depend on breast milk alone to supply their requirements, but their complementary food usually contains low amounts of bioavailable vitamin A, iron, and zinc and high amounts of phytate, which inhibits the absorption of iron and zinc (2).

In Vietnam, micronutrient malnutrition among preschoolers is highly prevalent. Although xerophthalmia is no longer found in Vietnam because of the effective vitamin A capsule-distribution program, dietary vitamin A intakes are low and subclinical vitamin A deficiency is common (3). A recent national survey showed that 46.6% of children aged 0.5–5 y were anemic, largely as a result of iron deficiency (4). Because the habitual Vietnamese diet is based mainly on rice, which contains little zinc but a relatively high amount of phytate (5), it can be expected that zinc deficiency is also prevalent.

The consequences of these micronutrient deficiencies during childhood are considerable. Iron deficiency has a negative effect on the motor and mental development of young children (6, 7) and causes anemia. Aside from its adverse effect on vision, vitamin A deficiency increases the risk of mortality (8). Zinc deficiency negatively influences growth (9) and increases the risk of diarrhea and respiratory infections (10). Considering the high prevalence of deficiencies and their negative effects, supplementation of young children with iron, zinc, and vitamin A would be of great benefit, especially because of the practical difficulties in improving the nutritional adequacy of traditional infant feeding patterns.

With large-scale supplementation programs, however, factors such as the cost, availability, and distribution of supplements and

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compliance with prescribed supplement intake often reduce the programs' effectiveness, as experienced with iron supplementation programs for pregnant women (11, 12). Therefore, alternatives to currently used supplementation strategies need to be investigated to raise effectiveness. Supplementation on a weekly basis, instead of daily, is cheaper (13) and may be easier to manage. Program compliance may also be better. Weekly supplementation of iron was shown to be efficacious for the reduction of anemia in children from Indonesia (14, 15), China (16), and Bolivia (17). Weekly supplementation with a combination of iron and vitamin A was effective in improving the iron and vitamin A statuses of adolescent girls (18). However, to date, weekly supplementation has not been investigated in very young children and no information is available on its efficacy.

The present study aimed to investigate the efficacy of weekly and daily multimicronutrient supplementation in increasing hemoglobin, retinol, and zinc concentrations in young Vietnamese children. Furthermore, the effect of supplementation on growth was investigated.

SUBJECTS AND METHODS

The study was carried out from October 1996 to April 1997 in Chi Lang Bac commune, Thanh Mien district, Hai Duong province in Vietnam. Chi Lang Bac is a village with ≈8150 inhabitants situated ≈80 km north of Hanoi. Subjects were children aged 6–24 mo. For subject selection, a list of all village children belonging to the defined age category was obtained from the health center, where information on the birth date and birth weight of the children was also available. A total of 248 children were listed. Of these, 55 were excluded for having an infectious disease at the time of enrollment and an additional 25 were excluded for having a birth weight < 2.5 kg according to the birth record. No further information about age and sex was recorded for the excluded children. Sample size calculations indicated that with ≥50 children per group a between-group difference in treatment effect of 5 g hemoglobin/L, 0.2 μmol retinol/L, and 0.3 for the *z* score for height-for-age could be detected with a power of 0.8 and a *P* value of 0.05.

The study was a double-blind, placebo-controlled trial. The 168 children were randomly divided into 3 groups by using a table with randomly assorted digits. The 3 groups were supplemented according to the schedule shown in **Table 1**. The daily group was supplemented Monday through Friday (5 d/wk). The weekly group was supplemented on Thursdays, and was given a placebo on Monday, Tuesday, Wednesday, and Friday. A control group was given a placebo Monday through Friday that was similar in color and appearance to the supplement. Supplementation lasted 12 wk. Supplements and placebo were provided in the form of a syrup, of which 1 mL/d was given. The syrup was put into the children's mouth by syringe by a research staff member who visited the children daily between 0700 and 1000. The syrup was produced at the Department of Pharmacy, Faculty of Mathematics and Natural Sciences, University of Indonesia and was based on a sucrose solution with benzoic acid added as a preservative and vanilla extract added to improve the taste. The syrup was kept in dark bottles that were stored in a refrigerator at 4–6 °C. Blind supplementation was guaranteed by coding the 3 treatment groups as A, B, and C and by putting the syrups to be used for each group in bottles having a corresponding code. For each treatment group, there were 60 bottles with syrup, numbered from 1 to 60. For every day of the total 60 d of supplementation, 1 bottle was used. For example, bottle A10 was used to supplement children in group A on the 10th day of supplementation. Neither the main researcher and his assistants nor the mothers knew which supplement was represented by which code. Before the start of the study, the acceptability of the syrup was tested in 12 children. Mothers of these children reported good acceptance and no side effects. Acceptability throughout the study remained good, and the children took all of the supplements as intended.

TABLE 1
Micronutrient composition of 1 mL (equal to 1 dose) supplement[1]

Micronutrient	Daily[2]	Weekly	Placebo
Retinol (μg)	333	1700	0
Iron (mg)	8	20	0
Zinc (mg)	5	17	0
Vitamin C (mg)	20	20	0

[1] Retinol was in the form of retinyl acetate, iron was given as ferrous sulfate, and zinc was given as zinc sulfate.

[2] Provided Monday through Friday only.

At the start and end (1 wk after supplementation ended) of the study, 2 mL venous blood was collected in non-heparin-treated tubes between 0730 and 1130. Plastic syringes were used for blood collection. Tubes were covered by plastic stoppers and were rinsed and cleaned to meet requirements for zinc analysis (2). Hemoglobin concentrations were measured in duplicate in 5 μL blood immediately after samples were collected in the field according to the cyanomethemoglobin method (19) by using a portable photometer (Compur Minilab 3; Bayer Diagnostic, Munich, Germany). Estimated variability (SD) based on duplicate samples was 4.1 g/L (19). Serum was obtained by centrifuging the blood in the field at 3600 × *g* for 15 min. The serum was placed on ice and transported to the laboratory (Vietnam-Holland laboratory, Hanoi) within 2 h, where it was stored at −20 °C until analyzed. Retinol was analyzed by HPLC in a darkened room (20). Duplicate analyses of retinol were done on only 10 samples and the estimated variability (SD) based on these 10 measurements was 0.065 μmol/L (19). Zinc was analyzed by flame atomic absorption spectroscopy (21). Duplicate analyses of zinc were done for 20 samples and the estimated variability (SD) was 0.236 μmol/L (19). Because the population was expected to have a high prevalence of anemia, it was decided not to measure ferritin but only hemoglobin because hemoglobin measurement would indicate whether the main problem of anemia could be addressed by supplementation.

Weight and length were measured at the start and end of the supplementation period and 3 mo after supplementation had ended. Weight was recorded to the nearest 0.1 kg, while children were minimally clothed, with a pediatric scale for infants (SECA beam balance, Hamburg, Germany). Length was recorded to the nearest 0.1 cm, with the children lying down, by using a World Health Organization model length-measuring board for infants (22). *z* Scores of the indicators weight-for-age, length-for-age, and weight-for-length were calculated with EPI-INFO 6 (Centers for Disease Control and Prevention, Atlanta) by using the National Center for Health Statistics data (23) as a reference.

All parents gave their written, informed consent for their children's participation, and at the end of the study children from the placebo group received supplementation. The research proposal

conformed with the *International Guidelines for Ethical Review of Epidemiological Studies* (24) and was approved by the Research and Ethical Review Board of the Regional SEAMEO-TROPMED Center for Community Nutrition.

Statistical analysis

A one-sample Kolmogorov-Smirnov test was used to investigate whether the concentrations of hemoglobin, retinol, and zinc and the anthropometric indicators were normally distributed. Retinol concentrations were not normally distributed but became so after normal logarithmic transformation. Differences between groups in concentrations of biochemical indicators at the start of the study were tested by analysis of variance and post hoc multiple-comparison tests (Student-Neuman-Keuls). Differences in treatment effects among the 3 groups and between the daily and weekly groups were tested by using the multivariate analysis of variance (MANOVA) repeated-measures design of SPSS for WINDOWS (SPSS Inc, Chicago) (25) with supplement type as a between-subject factor (3 groups) and treatment effect (baseline compared with 12 wk) as a within-subject factor. A significant P value for the within-subject factor treatment effect indicated a change over time in the combined values of the 3 groups and was further investigated by using a paired t test for each individual group. Between-group differences in treatment effect were indicated by significant interactions between treatment effect and supplement type. Baseline values for hemoglobin (in 2 classifications: <110 and ≥110 g/L), retinol (in 2 classifications: <0.70 and ≥ 0.70 μmol/L), and zinc (in 2 classifications: <10.71 and ≥10.71 μmol/L) were also included in the analysis as between-subject factors to correct for their possible confounding influence on the changes in hemoglobin, retinol, and zinc. None of the 3-way interactions (treatment effect × supplement type × baseline value) were significant. Differences in prevalence were tested with a chi-square test.

A procedure similar to that used for the biochemical indicators was followed to investigate changes in the anthropometric indicators. Between-group differences in treatment effect on anthropometric z scores were also analyzed with MANOVA repeated-measures analysis including age as a covariant and the baseline values as between-subject factors (divided into 3 classes: z score < -2 (<2 SDs below the National Center for Health Statistics mean), z score between -2 and -1, and z score ≥ -1).

RESULTS

Of the 168 children enrolled at baseline, complete data sets were available for 163 children for anthropometric data and for 160 children for biochemical data. Reasons for attrition included families' moving to other places (n = 3), mothers' refusing further participation because of time limitations (n = 2), and fear of blood collection (n = 3). Anthropometric and biochemical values of dropouts at baseline were similar to those of the remaining children. Most of the subjects (70.6%) were still being breast-fed at the start of the study (**Table 2**); those who were not breast-fed anymore had been breast-fed for ≥9 mo. Prevalences of single micronutrient deficiencies as indicated by low concentrations of hemoglobin, retinol, and zinc are presented in Table 2. Hemoglobin concentrations <100 g/L were measured in 18.8% of the children, whereas none of the children had a retinol concentration <0.35 μmol/L. A combination of low hemoglobin (<110 g/L) and low retinol (<0.70 μmol/L) occurred in 24.3% of the subjects, 16.9% had low hemoglobin and low zinc concentrations (<10.71 μmol/L), 21.2% had low zinc and low retinol concentrations, and 11.2% had low concentrations of all 3 indicators.

It is government policy in Vietnam that all children older than 6 mo receive a vitamin A capsule through a nationwide vitamin A supplementation program twice per year (3). Vitamin A capsules had been distributed ≈4 mo before the start of the study, and 96.8% of the children who were older than 6 mo at the time of vitamin A distribution had received a capsule. None of the children received any further large dose of vitamin A nor any iron or zinc supplement during the study besides the supplements provided by the research team. So as to not confound the effect of supplementation on retinol concentrations, the children received the second vitamin A capsule from the government program only after the end of the supplementation, ≈4 wk later than was originally scheduled by the health center.

Hemoglobin concentrations at baseline were not correlated (Spearman correlation coefficient) with retinol (r = 0.136, $P > 0.10$) or zinc (r = 0.038, $P > 0.10$) concentrations. Baseline concentrations of zinc and retinol showed a similar lack of correlation (r = 0.10, $P > 0.10$). At baseline, there were no significant differences in hemoglobin or zinc concentrations between the 3 groups (**Table 3**); the retinol concentration of the daily supplemented group, however, was lower than that of the other 2 groups (P = 0.02).

After 12 wk of supplementation there were significant within-group increases in hemoglobin, retinol, and zinc in the weekly and daily supplemented groups ($P < 0.001$), whereas no significant changes occurred in the placebo group. The changes in hemoglobin, retinol, and zinc were correlated with the baseline values of these respective variables: $r = -0.57$, $P < 0.001$ for hemoglobin; $r = -0.31$, $P < 0.001$ for retinol; and $r = -0.49$, $P < 0.001$ for zinc. Therefore, to evaluate the between-group difference in treatment effect, the initial concentrations of hemoglobin, retinol, and zinc were included as between-subject factors in the analysis of variance to correct for possible confounding influence. The increases in hemoglobin, retinol, and zinc concentrations in each of the supplemented groups were larger than the changes in the placebo group (P = 0.001 for interaction between supplement type and treatment effect), as shown in Table 3. There was no significant difference in treatment effect between the daily and weekly supplemented groups for any of the biochemical indicators, although the increase in zinc concentration tended to be higher in the weekly than in the daily supplemented group (P = 0.055 for the interaction between supplement type and treat-

TABLE 2
Characteristics of the study children at baseline according to age

Characteristic	<12 mo (n = 66)	12–17.9 mo (n = 50)	≥18 mo (n = 47)
		%	
Male sex	43.9	48.0	46.8
Breast-fed at baseline	93.9	84.0	23.4
Received colostrum at birth	92.4	82.0	76.6
Height-for-age z score < −2	15.2	36.0	66.0
Weight-for-height z score < −2	4.5	2.0	4.3
Weight-for-age z score < −2	19.7	22.0	57.4
Hemoglobin <110 g/L	46.9	48.0	41.3
Serum retinol <0.70 μmol/L	48.4	44.0	43.5
Serum zinc <10.71 μmol/L	34.4	34.0	32.6

TABLE 3
Concentrations of hemoglobin, retinol, and zinc at the start and finish of the supplementation study[1]

	Start	Finish	Difference
Hemoglobin (g/L)			
Daily (n = 53)	108.8 ± 11.6	124.3 ± 9.3[2]	15.5 ± 13.4
Weekly (n = 54)	110.3 ± 11.2	123.5 ± 10.3[2]	13.2 ± 12.1
Placebo (n = 53)	111.9 ± 10.9	111.4 ± 10.6	−0.5 ± 8.8[3]
Retinol (μmol/L)			
Daily (n = 53)	0.67 ± 0.17[4]	0.92 ± 0.19[2]	0.25 ± 0.18
Weekly (n = 54)	0.75 ± 0.18	0.99 ± 0.20[2]	0.24 ± 0.16
Placebo (n = 53)	0.73 ± 0.14	0.72 ± 0.14	−0.01 ± 0.13[3]
Zinc (μmol/L)			
Daily (n = 53)	12.66 ± 3.73	16.05 ± 3.96[2]	3.42 ± 3.69
Weekly (n = 54)	12.89 ± 3.58	16.97 ± 2.97[2]	4.07 ± 3.47
Placebo (n = 53)	12.93 ± 3.50	12.84 ± 3.07	−0.09 ± 3.29[3]

[1] $\bar{x}$ ± SD.
[2] Significantly different from at the start, $P < 0.001$.
[3] Significantly different the daily and weekly supplemented groups, $P < 0.001$ for both groups.
[4] Significantly different from the weekly and placebo groups, $P < 0.05$.

TABLE 4
Concentrations of hemoglobin, retinol, and zinc at the start and finish of the supplementation study of children aged <12 mo at baseline[1]

	Start	Finish	Difference
Hemoglobin (g/L)			
Daily (n = 25)	111.7 ± 9.7	124.6 ± 9.4[2]	12.9 ± 12.8
Weekly (n = 18)	109.2 ± 9.8	123.2 ± 10.4[2]	14.0 ± 11.6
Placebo (n = 21)	109.3 ± 11.8	108.9 ± 12.2	−0.4 ± 9.2[3]
Retinol (μmol/L)			
Daily (n = 25)	0.67 ± 0.16	0.93 ± 0.16[2]	0.26 ± 0.15
Weekly (n = 18)	0.78 ± 0.20	0.99 ± 0.22[2]	0.22 ± 0.20
Placebo (n = 21)	0.73 ± 0.14	0.71 ± 0.15	−0.01 ± 0.13[3]
Zinc (μmol/L)			
Daily (n = 25)	12.46 ± 3.67	17.20 ± 4.23[2]	4.75 ± 3.75
Weekly (n = 18)	13.21 ± 3.31	17.49 ± 2.60[2]	4.28 ± 3.60
Placebo (n = 21)	13.30 ± 2.90	12.31 ± 1.93	−1.00 ± 2.23[3]

[1] $\bar{x}$ ± SD.
[2] Significantly different from at the start, $P < 0.001$.
[3] Significantly different from the daily and weekly supplemented groups, $P < 0.001$ for both groups.

ment effect on zinc, excluding the placebo group).

When data for the 2 supplemented groups were combined (n = 107), the change in retinol concentration was correlated with the change in zinc concentration (r = 0.20, P = 0.04), but not with the change in hemoglobin concentration (r = −0.05, P = 0.60). Additionally, the change in zinc concentration was not correlated with the change in hemoglobin concentration (r = −0.05, P = 0.61).

Because daily iron requirements are especially high in children younger than 12 mo of age, it was of interest to compare the treatment effect in this subgroup. Results were similar to those in the whole group. At baseline, no significant differences in concentrations of hemoglobin, retinol, or zinc existed between the different treatment groups (**Table 4**). A significant increase in hemoglobin, retinol, and zinc concentrations occurred in the supplemented groups, which was higher than the changes that occurred in the placebo group ($P < 0.001$ for the interaction between supplement type and treatment effect). There was no significant difference in treatment effect between the daily and weekly supplemented subgroups.

Prevalences of low concentrations of hemoglobin, retinol, and zinc for each group at baseline and at 12 wk are presented in **Figure 1**. Whereas the prevalences in the placebo group did not change significantly, a decrease in all indicators occurred in the supplemented groups. The prevalence of low concentrations at 12 wk was not significantly different in the 2 supplemented groups.

Subjects' heights and weights were measured at baseline and 3 mo after the end of supplementation (6 mo after baseline). Data on the measurements at the end of the supplementation (3 mo after baseline) are not presented in tables because the changes in weight and height over the 3-mo supplementation period were relatively small and the changes occurring over 6 mo provided a clearer picture. Despite the randomized allocation of children to treatment groups, there was a significant difference between groups in initial height-for-age at baseline ($P < 0.05$). The children in the weekly supplemented group tended to have a lower weight-for-age than the other 2 groups, but this difference was not significant (P = 0.062). Immediately after the end of supplementation, height and weight in the daily, weekly, and placebo groups had increased on average by, respectively, 2.9, 3.1, and 2.7 cm ($P < 0.01$ for all groups) and by 0.9, 0.7, and 0.7 kg ($P < 0.01$ for all groups). Average changes in height-for-age z score immediately after supplementation were −0.08, 0.09, and −0.10 for the daily, weekly, and placebo groups. Three months after the end of supplementation, height and weight in all 3 groups had increased significantly by >5 cm and >1 kg, respectively ($P < 0.001$). There were no significant between-group differences in the increases in height and weight (**Table 5**). Changes in the z scores of height-for-age, weight-for-age, and weight-for-height were positively correlated with the age of the subjects ($P < 0.001$) and negatively correlated with their respective values at baseline ($P < 0.001$). Although the change in height-for-age tended to be larger in the weekly supplemented group, there was no significant between-group difference in treatment effect for any of the anthropometric indicators after the confounding influence of age and the respective baseline values were corrected for (no significant interaction between treatment effect and supplement type). Therefore, in the whole group of subjects, supplementation did not influence height-for-age, weight-for-age, or

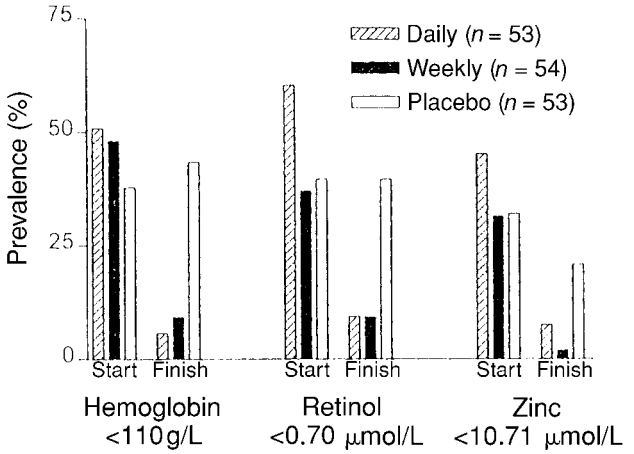

FIGURE 1. The prevalence of low hemoglobin, retinol, and zinc concentrations at the start and finish of 12 wk of daily or weekly supplementation or placebo in children aged 6–24 mo.

TABLE 5
Anthropometric indicators at the start of the study and 6 mo later (3 mo after the end of supplementation)[1]

	Start	6 mo later	Difference
Height (cm)			
Daily (n = 55)	71.5 ± 4.4	76.9 ± 4.0[2]	5.4 ± 1.3
Weekly (n = 54)	72.3 ± 5.3	78.0 ± 5.0[2]	5.7 ± 1.5
Placebo (n = 54)	71.9 ± 4.6	77.0 ± 4.1[2]	5.1 ± 1.6
Weight (kg)			
Daily (n = 55)	8.3 ± 0.9	9.6 ± 1.2[2]	1.4 ± 0.7
Weekly (n = 54)	8.3 ± 1.2	9.6 ± 1.2[2]	1.2 ± 0.5
Placebo (n = 54)	8.3 ± 1.1	9.5 ± 1.1[2]	1.2 ± 0.5
HAZ			
Daily (n = 55)	−1.58 ± 0.81	−1.70 ± 0.63	−0.12 ± 0.63
Weekly (n = 54)	−2.01 ± 0.89[3]	−1.81 ± 0.84	0.20 ± 0.60
Placebo (n = 54)	−1.67 ± 0.64	−1.82 ± 0.70	−0.15 ± 0.53
WAZ			
Daily (n = 55)	−1.48 ± 0.81	−1.42 ± 0.79	0.06 ± 0.74
Weekly (n = 54)	−1.84 ± 0.78	−1.77 ± 0.78	0.06 ± 0.52
Placebo (n = 54)	−1.60 ± 0.81	−1.64 ± 0.67	−0.04 ± 0.54
WHZ			
Daily (n = 55)	−0.63 ± 0.85	−0.54 ± 0.72	0.09 ± 0.90
Weekly (n = 54)	−0.77 ± 0.84	−0.88 ± 0.73	−0.11 ± 0.63
Placebo (n = 54)	−0.70 ± 0.81	−0.73 ± 0.72	−0.01 ± 0.72

[1] $\bar{x}$ ± SD. Average age (in mo) at baseline was 13.4 ± 5.1 for the daily group, 15.4 ± 5.5 for the weekly group, and 13.8 ± 5.0 for the placebo group. HAZ, height-for-age z score; WAZ, weight-for-age z score; WHZ, weight-for-height z score.
[2] Significantly different from at the start, $P < 0.001$.
[3] Significantly different from the daily and placebo groups, $P < 0.05$.

weight-for-height in a statistically significant way.

When data from the subgroup of children who had an initial height-for-age z score < −2 (stunted) were analyzed, there was a significant treatment effect on height-for-age of both supplemented groups ($P < 0.001$), whereas the values for the placebo group did not change significantly (**Table 6**). The micronutrient status of the stunted children did not differ much from that of the overall group. Prevalences of low values of hemoglobin, retinol, and zinc at baseline in this subgroup of stunted children were, respectively, 50.0%, 45.0%, and 33.3%, which was similar to the corresponding prevalences in the whole group of children (as shown in Table 2).

DISCUSSION

Micronutrient deficiencies were common in the population studied. Almost half of the subjects had low hemoglobin or retinol concentrations and up to 24% had low concentrations of ≥2 indicators of micronutrient status. Such a high prevalence of micronutrient malnutrition is not exceptional in Vietnam. A 1995 nationwide survey estimated that ≈31% of Vietnamese children aged 0.5–1.9 y had hemoglobin concentrations <100 g/L (4). In the present study, ≈19% of children had hemoglobin concentrations <100 g/L, less than the estimated national prevalence. These data stress the potential benefit of multisupplementation and the need to investigate the optimal composition of supplements and frequency of delivery.

The composition of the daily supplement was based on the daily recommended allowances of the Food and Agriculture Organization (26) and the World Health Organization (27). Vitamin C was added to enhance the bioavailability of iron. The

TABLE 6
Height and height-for-age z score (HAZ) at the start of the study and 6 mo later (3 mo after the end of supplementation) of children who were stunted (HAZ < −2) at baseline[1]

	Start	6 mo later	Difference
Height (cm)			
Daily (n = 16)	73.8 ± 2.7	79.2 ± 2.7[2]	5.4 ± 0.8
Weekly (n = 27)	71.8 ± 5.7	77.3 ± 5.0[2]	5.5 ± 1.5
Placebo (n = 17)	72.5 ± 4.5	77.0 ± 4.3[2]	4.6 ± 1.0[3,4]
HAZ			
Daily (n = 16)	−2.63 ± 0.41	−2.15 ± 0.47[2]	0.48 ± 0.40
Weekly (n = 27)	−2.76 ± 0.44	−2.39 ± 0.57[2]	0.37 ± 0.59
Placebo (n = 17)	−2.38 ± 0.38[5]	−2.40 ± 0.47	−0.02 ± 0.56[3,6]

[1] $\bar{x}$ ± SD. Average age (in mo) at baseline was 18.4 ± 3.6 for the daily group, 17.0 ± 5.9 for the weekly group, and 16.5 ± 5.0 for the placebo group.
[2] Significantly different from at the start, $P < 0.001$.
[3] Significantly different from the daily group, $P < 0.02$.
[4–6] Significantly different from the weekly group: [4] $P < 0.03$, [5] $P < 0.05$, [6] $P < 0.01$.

composition of the weekly supplement was based on rough estimates because no previous data existed for multisupplementation on a weekly basis. In a previous study, a weekly supplement of 30 mg Fe resulted in a significant increase in hemoglobin among 2–5-y-old children (15). The subjects in the present study were younger so we decided to give <30 mg Fe. The combined amount of iron and zinc was not made too high to avoid gastrointestinal side effects, and the ratio of iron (mg) to zinc (mg) was kept close to 1 to avoid possible difficulties with bioavailability. The daily supplement provided 40 mg Fe, 25 mg Zn, and 1665 μg retinol when calculated on a weekly basis, whereas the weekly supplement provided less iron (20 mg) and zinc (17 mg) but a similar amount of retinol (1700 μg).

The supplementation was effective in reducing the prevalence of anemia; in the daily and weekly supplemented groups, the prevalence of anemia was reduced from ≈50% to <10%, whereas in the placebo group it increased from 38% to 43%. The average increases in hemoglobin concentrations in the daily and weekly supplemented groups relative to the placebo group were 16.0 and 13.7 g/L, respectively. This result agrees with previously reported findings with weekly iron supplementation of older children from Bolivia (17), China (16), and Indonesia (14, 15).

With respect to zinc, to our knowledge, no other studies using once-weekly zinc supplementation have been published previously. In the Vietnamese children, weekly and daily supplementation resulted in similar, significant decreases in prevalence of low serum zinc concentrations. Serum zinc concentrations increased 3–4 μmol/L in both supplemented groups, similar to increases measured in supplementation trials among Mexican (28) and Guatemalan children (29). Although serum zinc concentrations are not a reliable indicator of zinc status at the individual level, the average changes in concentration in the supplemented groups compared with the placebo group do suggest that the supplementation improved zinc status and that weekly and daily supplementation had about the same effect.

Daily and weekly supplementation of retinol also gave similar results in terms of increases in serum concentrations and reductions in the prevalence of low retinol concentrations. Although the use of the serum retinol concentration as an indicator of vit-

amin A status has its limitations, concentrations < 0.70 μmol/L are likely to indicate a low status in preschool children (30). Therefore, the likely low vitamin A status at baseline, despite the capsule distribution program, stresses the possible benefit of regular supplementation as well as the need to strive for improved dietary intake of vitamin A.

In summary, the initially high prevalence of anemia and of low zinc and vitamin A statuses improved similarly and significantly with both weekly and daily supplementation during a 3-mo period. No significant difference in efficacy in improving hemoglobin, retinol, or zinc concentrations was detected between daily and weekly supplementation. With the sample size used and the variation obtained it would have been possible to detect a difference in treatment effect between the daily and weekly supplemented groups of 6.8 g hemoglobin/L, 1.97 μmol zinc/L, and 0.09 μmol retinol/L with a power of 0.8 and α of 0.05.

Although the children were young (aged < 24 mo), 37% were already stunted. This high prevalence was similar to the prevalence found among children from the same age group in a 1994 national survey (3). Some studies have reported positive effects of iron (31, 32) and vitamin A (33) on child growth, but the evidence for the growth-enhancing effect of zinc is thought to be more conclusive (9, 34). Although serum zinc concentrations improved in the supplemented groups, no significant treatment effect on height-for-age occurred after confounding influences of between-group differences in initial height-for-age and age were corrected for. This result is not controversial but similar to that of other studies carried out among more-or-less representative groups of preschool children from developing countries. Zinc supplementation of preschool children from Chile (35), Mexico (28), and Gambia (36) also did not result in increased linear growth. Positive effects of zinc supplementation on growth have been reported for specifically selected subgroups of children, however. Zinc improved the recovery of children suffering from severe malnutrition (37–39). A supplementation study in 4–36-mo-old Vietnamese children also resulted in an improvement of height-for-age, but the average initial height-for-age *z* score of these children was already low at < -2.66 (10). The growth of 6–9-mo-old Guatemalan children who were stunted improved more than that of nonstunted peers after zinc supplementation (40).

It appears, therefore, that zinc supplementation influences the growth of children only when they have lower-than-average values for anthropometric indicators and are zinc deficient. This effect was observed in the present study. In the subgroup of children who had an initial height-for-age *z* score < -2, there was a significant treatment effect on the height-for-age of both supplemented groups, whereas the values for the placebo group did not change significantly. Weekly and daily supplementation had similar effects on height-for-age. It can be concluded that the linear growth of the most growth-retarded part of the population was positively affected by zinc supplementation, but that the average value of the whole population was not significantly affected. The results of the present and previous studies indicate that the enhancing effect of zinc supplementation on the average growth of a whole population of children aged < 5 y from developing countries is probably small. A larger effect at the population level may be reached if supplementation is started at an earlier age. It was shown that 3 mo of zinc supplementation prevented growth retardation of 4–9-mo-old breast-fed infants from immigrant families of a low economic class living in France (41).

Supplementing such young infants with iron would also be beneficial because it would prevent anemia, as well as the possibly resulting retardation in mental and motor development. Supplementation with vitamin A would reduce morbidity and mortality. Such a combined iron-zinc–vitamin A supplementation would probably have to be started at 4–6 mo of age, or even earlier when mothers are malnourished (42, 43). The results of our study suggest that supplementation would not need to be done daily but that a once-weekly supplement would be sufficient for reducing anemia and improving zinc and vitamin A status. However, because these results were obtained from a small, carefully supervised efficacy trial, the effectiveness of infant supplementation on a weekly basis at the community level needs to be investigated further.

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