

# International Research on Infant Supplementation: Randomized Controlled Trials of Micronutrient Supplementation During Infancy

## Multiple Micronutrient Supplementation Improves Anemia, Micronutrient Nutrient Status, and Growth of Vietnamese Infants: Double-Blind, Randomized, Placebo-Controlled Trial<sup>1,2</sup>

Le Thi Hop<sup>3</sup> and Jacques Berger\*

National Institute of Nutrition, Hanoi, Vietnam, and \*The Institute of Research for Development, Research Unit "Nutrition, Food, Societies," Montpellier, France

**ABSTRACT** A randomized, double-blind, placebo-controlled trial was performed to assess the efficacy of different micronutrient supplementation regimes for improving micronutrient status, preventing anemia, and growth faltering of Vietnamese infants. A population-based sample of 306 infants aged 6–12 mo, split in 4 treatment groups, received daily multiple micronutrient (DMM), daily placebo (P), weekly multiple micronutrient (WMM), or daily iron (DI) supplements for 6 mo, 7 d/wk, under supervision. Weight and length were measured monthly, and anemia and plasma levels of ferritin, zinc, riboflavin, retinol, tocopherol, and homocysteine were determined before and after the supplementation. Z-scores for length-for-age and weight-for-age worsened significantly in all groups, but the length-for-age Z-score decreased significantly less in the DMM group ( $-0.32 \pm 0.05$ ) than in the P and WMM groups ( $-0.49 \pm 0.05$  and  $-0.51 \pm 0.05$ , respectively,  $P = 0.001$ ). Hemoglobin levels increased significantly more in the DMM group [mean (95%CI): 16.4 g/L (12.4–20.4)] than in the P group [8.6 g/L (5.0–12.2),  $P = 0.04$ ], with intermediate nonsignificant increases in the WMM [15.0 g/L (11.5–18.5)] and the DI [12.9 g/L (8.4–17.3)] groups. Ferritin changes were significantly greater in DMM (12.1  $\mu\text{g/L}$ ) and DI (9.5  $\mu\text{g/L}$ ) than in P ( $-14.7 \mu\text{g/L}$ ) and WMM groups ( $-9.7 \mu\text{g/L}$ ). Of the other micronutrients, only tocopherol showed a significantly greater level in the DMM group compared with P. Anemia still affected a quarter and zinc deficiency affected a third of infants although there was no iron deficiency after 6 mo of supplementation with DMM, suggesting that multiple factors are causing anemia and that the dose of zinc is too small. J. Nutr. 135: 660S–665S, 2005.

**KEY WORDS:** • multiple micronutrient • supplementation • anemia • Vietnam • infant growth

Undernutrition and micronutrient deficiencies, such as vitamin A, iron, and iodine, are important nutritional problems among preschool children in Vietnam (1), and a more serious problem than in many other developing countries. Although rates have improved in the last 2 decades, the prevalence of stunting remains high and was 60%, 49%, and 36% in 1985, 1990, and 2000, respectively (2–4). Early introduction of poor quality and inadequate amounts of complementary foods, a low rate of exclusive breast-feeding and the high frequency of diseases during early infancy may be the reasons for growth retardation (5–7). In rural areas of Vietnam, multiple micronutrient deficiencies are common throughout the life span and

particularly in small children, such that 45% of children < 5-y old suffered from anemia in 1995 and 34% in 2000 (8,9). A major achievement in recent years has been the effective implementation of the high-dose vitamin A capsule supplementation program, which has substantially reduced the magnitude of vitamin A deficiency in the country. Nutritional blindness, which previously threatened 5000 to 7000 children a year, has been eradicated. The incidence of active xerophthalmia has fallen from 7 times above to below the WHO cutoff point that indicates a significant public health problem (10). The prevalence of subclinical vitamin A deficiency (defined as serum retinol < 0.7  $\mu\text{mol/L}$ ) among children aged < 5 y was reduced from 14% in 1995 to 10% in 2000 (10,11).

Although the consequences of these micronutrient deficiencies during early childhood are considerable, in Vietnam, programs to resolve them are still dispersed and incomplete. Iron deficiency causes anemia and has negative effects on the motor and the mental development of young children (12). Aside from its effect on vision, vitamin A deficiency increases the risk of morbidity and mortality (13). Zinc deficiency negatively influences growth of children (14,15) and increases the

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<sup>3</sup> To whom correspondence should be addressed.  
E-mail: Hopnin@hn.vnn.vn.

risk of diarrhea and respiratory infections (16), but, as yet, there is no program aimed at controlling it. Child populations in Vietnam typically suffer simultaneously from these different micronutrient deficiencies, and yet supplementation programs for different single micronutrients are implemented in parallel, so that efforts and resources are duplicated and cost-effectiveness is reduced. Alternatives to the current single-nutrient supplementation strategies thus need to be investigated to increase effectiveness, and multiple micronutrient supplementation has been suggested as one such alternative. Several studies have been conducted to test the efficacy of multiple micronutrient supplementation in schoolchildren and adolescents. However, little is known about the efficacy of multiple micronutrient supplementation in infants, the age group mainly affected by these deficiencies. The main objective of the study was to evaluate the efficacy of multiple micronutrient supplementation for improving nutrition status of infants from micronutrient deficient populations in rural Vietnam.

## MATERIALS AND METHODS

### Study design and randomization

This study was part of the international multicenter trial carried out in 4 countries (Peru, South Africa, Indonesia, and Vietnam) and implemented according to a master protocol written with the contributions from all principal investigators in the country sites. The study began in March 2000 with a preparation phase from March to May 2000 and an intervention phase from June 2000 to January 2001. The study was conducted in 4 communes (Phu Minh, Duc Hoa, Xuan Thu, and Phu Lo) in the rural district of Socson, Hanoi City. The Scientific Committee of the National Institute of Nutrition approved the study in accordance with the guidelines of the Council for International Organizations of Medical Sciences (17). Infants aged from 6 to 12 mo were identified by a house-to-house search, and the mothers and/or caretakers were invited to participate in the study. The mothers were informed about the purpose of the study, and only infants of mothers who agreed with the informed consent were included. Additional exclusion criteria were severe wasting (weight-for-height Z-score  $< -3$  Z), fever ( $>39^{\circ}\text{C}$ ), premature birth ( $<37$  wk) or low birth weight ( $<2500$  g), and severe anemia [hemoglobin (Hb)  $<80$  g/L]. In this randomized, double-blind, placebo-control study, subjects were randomly assigned to 4 treatment groups: daily multiple micronutrients (DMM)<sup>4</sup>; weekly multiple micronutrients (WMM); daily iron supplements (DI), and daily placebo (P). A random number selection process was used to assign children to treatment groups, with each child having a specific number that matched the numbered packages of supplements.

### Intervention

The micronutrient supplement and placebo treatments, packed in identical-looking blister packs containing 7 foodlets, one for each day of the week, were developed and produced centrally as has been described previously (18). The DMM supplement contained the daily adequate intake (AI) of 15 micronutrients for young children. The WMM supplements had twice the daily AI amount of the same micronutrients. The DI supplement contained the daily AI for iron. Supplements and placebo were given 7 d/wk, with the WMM supplement given one day, followed by placebo supplements on the other 6 d. The parents of infants were requested to take their infant every day to the house of the health collaborators selected in each village/hamlet participating in the study. Treatments were numbered and were put in a plastic bag for each child and were given by the

collaborators to infants each day, with one collaborator responsible for 5 to 10 infants. The commune health center workers supervised the quality of the work of the field collaborators weekly, and the National Institute of Nutrition (NIN) investigators visited the selected households twice per month.

### Measurements, data, and blood sample collection

Trained NIN anthropometrists measured children's weight and length monthly. Weight was recorded to the nearest 0.1 kg, while children were minimally clothed, with an electronic weighing scale (SECA). Length was recorded to the nearest 0.1 cm using the WHO-recommended length-measuring board for infants (Ahrtag). Venous blood was drawn from the vein in the morning between 700 and 1100 at the commune health center and was transported to the micronutrient laboratory of NIN. Blood samples were taken at baseline and at the end of the intervention.

### Biochemical analysis

Hb concentration was determined in the Micronutrient Laboratory of NIN using the cyanomethemoglobin method. Blood was then centrifuged at  $3000 \times g$  for 10 min at  $4^{\circ}\text{C}$  and aliquots of plasma were placed in Eppendorf tubes. Plasma was stored at  $-20^{\circ}\text{C}$  and was sent to Germany for biochemical analysis for ferritin, retinol, zinc, tocopherol, EGRAC, homocysteine, and C-reactive protein at the University of Hohenheim, in accordance with methods indicated in the master protocol and reported elsewhere (19).

### Statistical analysis

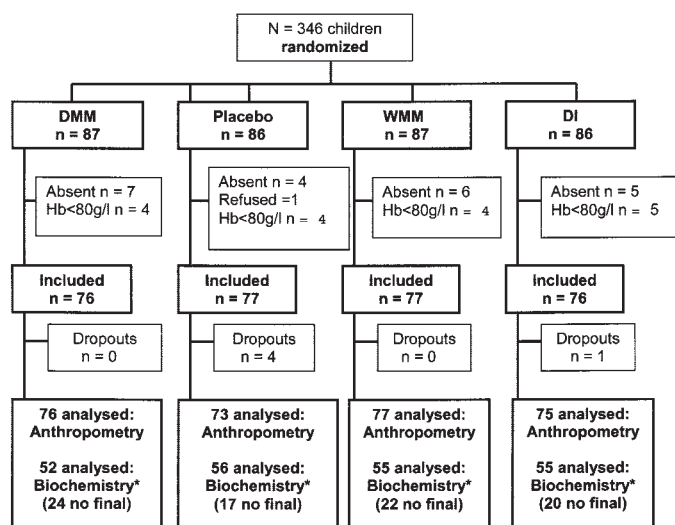
Statistical analysis of data were carried out using SAS software release 8.2 for Windows. All statistical analysis on anthropometrical and biochemical data were done after adjustment for gender and age at baseline. Means of anthropometrical indices are presented as adjusted means  $\pm$  SE. Other biochemical continuous variables are presented as means (SD) except for ferritin and homocysteine, which are presented as geometric mean and 95% CI. To take into account the repeated measurement structure of the data, for each response variable a repeated measures ANOVA model was used. The compound symmetry covariance structure was chosen to model the structure of dependence of the error terms, which is equivalent to including a subject random effect in the model (multilevel model) (20). Models featuring visit, treatment group, and interaction group  $\times$  visit as fixed effects were fitted using maximum likelihood estimation. Effect of treatment on the evolution of the response variables was assessed by the test of group  $\times$  visit interaction term (null hypothesis of no differential evolution between the 4 groups). When relevant (i.e., "significant" *F*-test for visit  $\times$  group effect at the chosen type I error risk level of 0.05) specific contrasts were computed to assess differential evolution between specific groups. Bonferroni's correction was applied by dividing the cutoff of significance of 0.05 by the number of comparisons between groups, i.e., 6 comparisons or  $0.05/6 = P < 0.0083$ . All the models also included gender and age at entry as covariates. The models were fitted with Proc Mixed (21) in the SAS release 8.2 for Windows. For biochemical variables that were not normally distributed (ferritin and homocysteine), statistical analysis was carried out after log transformation of data.

## RESULTS

### Sample

A total of 346 infants were included in the study and were randomly assigned to the 4 groups (Fig. 1). Of these infants, 22 did not arrive for the baseline visit, and one refused blood sampling. Blood samples were obtained from 323 infants. Seventeen of these infants (5.3%) had an initial Hb concentration lower than 80 g/L [mean (SD),  $69.2 \pm 10.4$  g/L]. They were excluded from the study and were referred to the commune health center for treatment. Five infants did not return for the final evaluation (6 mo after baseline) and were ex-

<sup>4</sup> Abbreviations used: AGP,  $\alpha$ -1-acid glycoprotein; AI, adequate intake; DI, daily iron supplement; DMM, daily micronutrient supplement; EGRAC, erythrocyte glutathione reductase activity coefficient; Hb, hemoglobin; IRIS, International Research on Infant Supplementation; NIN, National Institute of Nutrition; P, placebo; WMM, weekly multiple micronutrient supplement.



**FIGURE 1** Trial profile: Participation of infants in a micronutrient supplementation trial in Vietnam. \* Based on Hb analysis.

cluded from data analysis. Data analysis thus was conducted on 301 infants. All infants received >80% of the maximum dose of supplements, except for one infant in the DMM treatment group who received 77% of the maximum dose.

### Baseline values

Neither gender distribution nor mean age, anthropometrical indices, or Hb concentration were statistically different among groups at baseline (Table 1). The mean length-for-age and weight-for-age Z-scores of the infants approached -1.0 compared with the National Child Health Survey (NCHS) population, and >80% of infants were anemic.

### Effects of the intervention

The anthropometric values obtained during the study period are presented in Table 2. All anthropometric indices worsened significantly from baseline to posttreatment in all 4 groups, with a significant group by month of visit interaction only for length-for-age ( $P = 0.001$ ). During the study period,

length-for-age growth faltering was significantly less in the DMM group than in the P or WMM groups but not significantly less than in the DI group. The prevalence of stunting was not significantly different among treatment groups at baseline or at the end of the study.

The mean values for a variety of biochemical indicators of nutrient status during the course of the trial are presented in Table 3. Mean Hb concentrations increased significantly in all the groups during the 6-mo study. However, the increase was significantly greater in DMM than in the P group and intermediate but not significantly greater than placebo in both WMM and DI groups. Over the study period, plasma ferritin concentration increased significantly in the DMM and DI groups, whereas it decreased significantly in the WMM and P groups. The mean tocopherol level increased significantly more in the DMM group compared with the 3 other groups. The mean homocysteine concentration fell significantly over time in all groups, and there was no difference among groups in the change over time. There were no significant interactions between time and treatment for mean serum retinol, zinc, or riboflavin status, or differences among treatments in the change over time.

The prevalence of deficiency during the course of the trial, based on biochemical indicators of nutrient status is present in Table 4. The prevalence of anemia, which was very high at baseline, fell in all groups during the course of the trial. Anemia prevalence in the DMM group was reduced by 75% in the 6 mo compared with 39% in the P group ( $P = 0.0087$ ), with the other groups in between these values. The final prevalence of anemia was significantly less in the DMM group than in the P group, with the other groups again intermediate. At the end of the intervention period, no infant had a low ferritin concentration in the groups that received daily iron, either alone or in combination with other micronutrients (DMM or DI). The prevalence of low ferritin concentrations increased in the other groups, doubling in the WMM group and increasing over 4-fold in the P group. In contrast, the prevalence of low serum retinol concentrations fell across time in all groups and was equally low in all groups at the end of the study. The prevalence of zinc deficiency, based on low serum zinc, was high at baseline and tended to increase in all groups during the 6 mo, except in the DMM group, although these differences were not statistically significant.

**TABLE 1**

Characteristics of treatment groups at baseline in a randomized, double-blind, placebo-controlled, micronutrient supplementation trial in Vietnamese infants

Characteristic	Treatment groups <sup>1</sup>				P
	P (n = 73)	DI (n = 75)	DMM (n = 76)	WMM (n = 77)	
Gender, % male	56.2	62.7	43.4	54.6	0.122
Age, mo	8.0 ± 2.2	7.8 ± 2.1	7.7 ± 1.9	8.0 ± 2.0	0.953
Length-for-age Z-score <sup>4</sup>	-0.87 ± 0.09	-0.96 ± 0.09	-0.97 ± 0.09	-0.90 ± 0.09	0.825 <sup>5</sup>
Weight-for-age Z-score <sup>4</sup>	-0.93 ± 0.10	-0.88 ± 0.10	-0.95 ± 0.10	-0.91 ± 0.10	0.955
Weight-for-length Z-score <sup>4</sup>	-0.33 ± 0.09	-0.19 ± 0.09	-0.28 ± 0.09	-0.27 ± 0.09	0.735 <sup>5</sup>
Hb, <sup>4</sup> g/L	99.5 ± 0.99	99.2 ± 0.98	99.2 ± 0.97	98.7 ± 0.96	0.965

<sup>1</sup> There were no significant differences among treatment groups in any variable.

<sup>2</sup> Chi-square test.

<sup>3</sup> Median test.

<sup>4</sup> Means adjusted for age and gender (SD).

<sup>5</sup> ANOVA.

TABLE 2

Initial, final, and changes in anthropometric indices by treatment group in a randomized, double-blind, placebo-controlled, micronutrient supplementation trial in Vietnamese infants<sup>1</sup>

Anthropometric indices	Timing	Treatment groups <sup>2</sup>				P <sup>3</sup>
		P	DI	DMM	WMM	
Length-for-age Z-score	Pre	-0.88 ± 0.09	-0.97 ± 0.09	-0.96 ± 0.09	-0.90 ± 0.09	10.001
	Post	-1.37 ± 0.09	-1.39 ± 0.09	-1.28 ± 0.09	-1.41 ± 0.09	
	Pre-post change	-0.49 ± 0.05 <sup>b</sup>	-0.43 ± 0.05	-0.32 ± 0.05 <sup>a</sup>	-0.51 ± 0.05 <sup>b</sup>	
Weight-for-age Z-score	Pre	-0.94 ± 0.10	-0.87 ± 0.10	-0.94 ± 0.10	-0.92 ± 0.10	0.33
	Post	-1.60 ± 0.10	-1.51 ± 0.10	-1.52 ± 0.10	-1.56 ± 0.10	
	Pre-post change	-0.66 ± 0.05	-0.64 ± 0.05	-0.58 ± 0.05	-0.64 ± 0.05	
Weight-for-length Z-score	Pre	-0.34 ± 0.09	-0.19 ± 0.09	-0.27 ± 0.09	-0.28 ± 0.09	0.11
	Post	-0.97 ± 0.09	-0.82 ± 0.09	-0.94 ± 0.09	-0.87 ± 0.09	
	Pre-post change	-0.63 ± 0.06	-0.63 ± 0.06	-0.66 ± 0.06	-0.59 ± 0.06	

<sup>1</sup> Means (adjusted for initial age and gender) ±SE of adjusted means.

<sup>2</sup> Post hoc comparisons (difference among groups) were tested only when the group × visit interaction was significant ( $P < 0.05$ ): differences between groups are significant when letters are different.

<sup>3</sup> Group × visit interaction.

TABLE 3

Initial and final biochemical indices by treatment group in a randomized, double-blind, placebo-controlled, micronutrient supplementation trial in Vietnamese infants

Biochemical indicator		Treatment groups <sup>1</sup>				P <sup>2</sup>
		Placebo	DI	DMM	WMM	
Hb, g/L	N	56	55	52	55	0.04
	Pre <sup>3</sup>	99.8 ± 9.6	99.9 ± 9.4	98.9 ± 7.5	97.5 ± 7.8	
	Post <sup>3</sup>	108.4 ± 14.3	112.8 ± 14.6	115.3 ± 12.7	112.5 ± 12.4	
	Change <sup>5</sup>	8.6 <sup>b</sup>	12.9	16.4 <sup>a</sup>	15.0	
	95% CI	5.0–12.2	8.4–17.3	12.4–20.4	11.5–18.5	
Plasma ferritin, µg/L	N	44	49	45	44	<0.0001
	Pre <sup>4</sup>	28.7 (22.0; 37.4)	38.7 (30.3; 49.6)	34.6 (26.6; 45.0)	30.5 (23.5; 39.5)	
	Post <sup>4</sup>	14.0 (10.9; 17.9)	48.2 (38.3; 60.7)	46.7 (36.5; 59.6)	20.8 (16.3; 26.6)	
	Change <sup>5</sup>	-14.7 <sup>b</sup>	9.5 <sup>a</sup>	12.1 <sup>a</sup>	-9.7 <sup>b</sup>	
	log 95% CI	-1.02 to -0.42	-0.10–0.41	-0.01–0.61	-0.69 to -0.06	
Plasma zinc, µmol/L	N	42	49	44	43	0.26
	Pre <sup>3</sup>	12.8 ± 4.5	12.4 ± 2.4	12.3 ± 3.6	13.1 ± 2.7	
	Post <sup>3</sup>	11.8 ± 2.3	11.8 ± 2.4	12.3 ± 2.0	11.6 ± 1.9	
	Change <sup>5</sup>	-1.0	-0.6	0.0	-1.5	
	95% CI	-2.3–0.2	-1.5–0.2	-1.3–1.3	-2.5 to -0.5	
Plasma retinol, µmol/L	N	44	49	45	45	0.09
	Pre <sup>3</sup>	0.97 ± 0.46	0.89 ± 0.27	0.85 ± 0.22	0.90 ± 0.25	
	Post <sup>3</sup>	1.12 ± 0.36	1.17 ± 0.36	1.17 ± 0.50	1.04 ± 0.21	
	Change <sup>5</sup>	0.15	0.28	0.33	0.14	
	95% CI	0.03–0.26	0.16–0.39	0.18–0.48	0.05–0.23	
Plasma tocopherol, µmol/L	N	44	51	45	46	0.004
	Pre <sup>3</sup>	18.1 ± 4.9	16.6 ± 6.3	16.7 ± 5.6	17.8 ± 5.2	
	Post <sup>3</sup>	20.4 ± 6.6	19.0 ± 5.4	23.0 ± 7.2	20.3 ± 6.1	
	Change <sup>5</sup>	2.3 <sup>b</sup>	2.4 <sup>b</sup>	6.3 <sup>a</sup>	2.5 <sup>b</sup>	
	95% CI	0.7–4.0	0.6–4.1	4.4–8.2	0.6–4.4	
Red blood cell riboflavin (EGRAC)	N	44	51	47	47	0.50
	Pre <sup>3</sup>	1.25 ± 0.14	1.28 ± 0.19	1.27 ± 0.16	1.26 ± 0.14	
	Post <sup>3</sup>	1.23 ± 0.17	1.26 ± 0.13	1.22 ± 0.18	1.28 ± 0.19	
	Change <sup>5</sup>	-0.01	-0.02	-0.05	0.01	
	95% CI	-0.07–0.04	-0.07–0.03	-0.11–0.01	-0.05–0.07	
Plasma homocysteine, µmol/L	N	43	51	45	45	0.04
	Pre <sup>4</sup>	10.7 9.7; 11.8	11.9 10.9; 13.1	12.2 11.1; 13.4	11.4 10.4; 12.6	
	Post <sup>4</sup>	8.5 7.7; 9.3	9.6 8.8; 10.4	8.4 7.6; 9.2	8.4 7.7; 9.2	
	Change <sup>5</sup>	-2.2	-2.3	-3.8	-3.0	
	log 95% CI	-0.31 to -0.15	-0.31 to -0.14	-0.46 to -0.29	-0.40 to -0.22	

<sup>1</sup> Different letters indicate that the change is statistically different between the groups ( $P < 0.0083 = 0.05/6$ ).

<sup>2</sup> Group × visit interaction.

<sup>3</sup> Mean (SD).

<sup>4</sup> Geometric mean and 95% CI.

<sup>5</sup> Mean and 95% CI.

TABLE 4

Initial and final prevalence (%) of anemia, iron deficiency, vitamin A deficiency, and zinc deficiency by treatment group in a randomized, double-blind, placebo-controlled, micronutrient supplementation trial in Vietnamese infants

Clinical biochemical indicator	Time	Treatment groups <sup>1</sup>				P <sup>2</sup>
		P	DI	DMM	WMM	
Anemia (<110 g/L)	Pre	84.9	90.7	93.4	93.5	0.0087
	Post	51.8 <sup>b</sup>	36.4	23.1 <sup>a</sup>	38.2	
Low ferritin (<12 µg/L)	Pre	9.1	5.9	6.7	15.2	<0.0001
	Post	50.0 <sup>b</sup>	0 <sup>a</sup>	0 <sup>a</sup>	28.9	
Low retinol (<0.70 µmol/L)	Pre	15.9	17.6	26.7	21.7	0.41
	Post	6.8	7.8	4.4	2.2	
Low zinc (<10.7 µmol/L)	Pre	26.2	15.7	29.5	17.8	0.18
	Post	31.8	25.7	17.8	26.7	

<sup>1</sup> The post hoc comparisons (differences among groups) were tested when the group × visit interaction was significant ( $P < 0.05$ ). Post hoc were significant when  $P < 0.0083$  (0.05/6) after Bonferroni's correction. Different letters indicate that the change and final prevalence were different between the groups.

<sup>2</sup> Group × visit interaction.

## DISCUSSION

DMM supplementation had a positive effect on length growth in infancy. All anthropometric indices worsened significantly between baseline and the final evaluation at the end of the first year of life in all treatment and placebo groups. Although there were no differences in weight-growth faltering rates, length-growth faltering was significantly less in the DMM group than in the P group. Furthermore, stunting rates only increased 74% in the DMM group (from 11% to 19%) compared with a 327% increase in the P group (from 5.5% to 23.3%), with the other treatment groups showing intermediate increases. Although these differences were not significantly different across the groups, if the period of supplementation had been continued beyond the first year of age, the impact of the DMM supplement on stunting rates at 2 y of age, when length-growth faltering ceases, would likely be significant.

These results confirm those of the many other micronutrient supplementation trials that have shown a positive effect on growth of Vietnamese infants. For example, Ninh et al. (14) showed that daily zinc supplementation for 6 mo improved the growth of children who were already stunted. Thu et al. (22) showed that the growth of children already stunted was improved by both weekly and daily multiple micronutrient supplementation, with a multiple micronutrient supplement that only contained iron, zinc, retinol, and vitamin C. That micronutrient supplements show such an effect on growth is surprising, considering that well implemented growth promotion activities have found it difficult to improve growth of young preschool children in Vietnam, including improving complementary feeding practices (23,24).

The DMM supplement was the best treatment for improving both anemia and iron status during infancy. Those infants who received DMM had a significant increase in mean Hb level and a lower prevalence of anemia at the end of the intervention compared with the P group. The mean Hb concentration and the anemia prevalence of the other treatments (WMM and DI) were intermediate compared with DMM and P treatments but not significantly different from the placebo children. Iron stores as reflected by plasma ferritin were significantly improved in the DMM and DI groups but fell in the P and WMM groups. Although anemia rates were very high, at about 90% at the beginning of the study period when the infants averaged 8 mo of age, low iron stores were less preva-

lent, with <20% low ferritin values. At the end of the intervention period, no infant had low ferritin concentrations in the groups receiving daily iron, either alone (DI) or in combination with other micronutrients (DMM), whereas the prevalence of low ferritin values increased to 50% and 30% in the P and WMM groups, respectively. Other studies in children (25–27), both in Vietnam and elsewhere, have shown that weekly iron supplementation, either alone or with multiple micronutrients, can be as effective as daily iron supplementation for improving iron status or reducing anemia. The WMM supplementation in this study showed an improvement in Hb concentration compared with the P group but was not able to prevent the depletion of iron stores during the second semester of life. Indeed, even in DMM, the most successful treatment group, a quarter of the children were still anemic after 6 mo of supplementation. Because the DMM supplementation was more effective than daily iron for reducing anemia in these Vietnamese infants, this suggests that the anemia is not due to iron deficiency alone but also to deficiencies of micronutrients that are contained in the multiple micronutrient supplement.

There was no difference among the different micronutrient supplements in their effect on other plasma micronutrient concentrations, except for tocopherol. All groups showed an increase in plasma tocopherol levels during the 6-mo trial period, but the increase in the DMM group was significantly greater than in the other groups. Whether these higher plasma tocopherol levels confer any benefit is unclear, but it suggests that the antioxidant status of the DMM group is better than that of the others. All groups showed improvement in mean vitamin A concentrations during the course of the intervention, and there was no significant interaction between time and treatment for plasma retinol levels. That the prevalence of low retinol values improved during the course of the trial in all supplement groups, including those without vitamin A, suggests that the Vietnamese vitamin A capsule program was effective in reaching most of the infants in the second semester of life in the area of the trial. About 20% of these infants had deficient plasma retinol concentrations at the beginning of the study period, which probably reflects the fact that the coverage of high-dose vitamin A capsules to mothers at or near birth is not very high and that exclusive breast-feeding during the first 6 mo is not extensively practiced. The lack of an impact of the DMM on either riboflavin or homocysteine values suggests

that the folate, the B-12, and the riboflavin status of these infants were adequate or that the amount in the supplement was too low. However, the lack of impact of the DMM on plasma zinc does not mean that their zinc status is adequate, because between a third and a quarter of infants had deficient plasma zinc values at the end of the trial, with little difference across groups. This strongly suggests that the level of zinc used in the DMM supplement is not enough to treat and/or to prevent zinc deficiency in these Vietnamese infants.

The results of this trial are of relevance beyond the study area in the Red River Delta, because the nutritional status of infants included in the trial is similar to that of infants in Vietnam as a whole. At the end of the trial, when the average age of the trial children was 14 mo, the underweight rate was 32%, which compares well with the underweight rates of 35% of preschool children for Vietnam overall (4). Iron-deficiency anemia was more common in the study population than nationally, because 90% of the studied infants were affected compared with the national estimated prevalence of 34% in preschool children (9). Anemia rates are highest in infancy and then tend to decrease, and similar levels were found in another study conducted in Bac Ninh Province, where the prevalence of anemia in infants was >60% (25).

In conclusion, the DMM supplementation had the best overall performance of the micronutrient supplements tested. Only the DMM supplement reduced the rate of length-growth faltering. Weight-growth faltering was not influenced by any of the treatments tested. The DMM supplements also had the best hematinic effect. Only groups that received daily iron supplements, alone or in combination with other micronutrients, improved their iron stores, and, by the end of intervention, none of these infants had low iron stores, whereas in the other 2 groups, iron status worsened. The impact on the status of other micronutrient was less consistent, with just plasma tocopherol showing a significantly greater concentration in the DMM group compared with placebo. Zinc status was deficient in a third of infants and was not improved even in the DMM group, suggesting that the zinc dose in the DMM supplement is too small. These results are very encouraging overall and suggest that further larger scale effectiveness trials should be carried out over a longer period of intervention, looking at supplements with a greater dose of zinc.

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