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Research article

EFFECTIVENESS OF MULTIPLE MICRONUTRIENT SUPPLEMENTS FOR SUPPORTING ADEQUATE HEMOGLOBIN, FERRITIN, AND ZINC LEVELS AMONG CHILDREN AGED 6–11 MONTHS IN RURAL VIETNAM: A RANDOMIZED CONTROL TRIAL

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Micronutrient deficiencies remain a major public health concern among infants in rural Vietnam. Nutrition during the 6–11-month period, which is characterized by the introduction of complementary feeding, plays a critical role in child development. This study aimed to evaluate effectiveness of a multiple micronutrient supplement, Bibomix, for improving hemoglobin, ferritin, and zinc levels in children aged 6–11 months.

A double-blind, randomized controlled trial was conducted across 10 communes in Quang Xuong District, Thanh Hoa Province, Vietnam. A total of 360 infants were randomly assigned to either an intervention or control group stratified by age and sex. The intervention group received a daily sachet of Bibomix, while the control group received a placebo for 12 months.

After 12 months, the intervention group showed significantly greater improvements than the control group in hemoglobin levels (Mean ± SD: 7.9 ± 7.2 g/L vs. 3.9 ± 1.3 g/L; Difference-in-Differences (DID) = 4.41; p < 0.001), ferritin concentrations (Median [IQR]: 8.5 [1.0–16.6] vs. 5.52 [-7.4–13.4]; DID = 2.97; p = 0.001), and serum zinc levels (Mean ± SD: 1.67 ± 1.33 vs. 1.26 ± 1.47 μmol/L; DID = 0.41; p = 0.008). The intervention also reduced anemia prevalence by 18.4 % (RR = 25.0; 95 % CI: 1.8–333.3) and zinc deficiency by 31.0 % (RR = 7.1; 95 % CI: 3.3–14.3).

The multiple micronutrient supplementation program demonstrated significant efficacy in improving key micronutrient statuses among infants in rural areas. Scaling up this nutritional intervention is recommended for regions with high rates of anemia and micronutrient deficiencies.

Keywords: *Vietnam, rural areas, infants aged 6–11 months, randomized control trial (RCT), double-blind trial, multiple micronutrients.*

Adequate nutrition during the first 1,000 days of life is essential for laying a strong foundation for optimal growth, brain development, and long-term health outcomes throughout the life course [1]. Scientific evidence has demonstrated effectiveness and sustainability of early nutritional interventions in promoting physical and cognitive development in children. Optimal nutritional interventions during this critical "golden window" of 1,000 days can

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play a pivotal role in comprehensively addressing and fundamentally reducing prevalence of undernutrition and micronutrient deficiencies [1–4].

Iron and zinc deficiencies are among the most common micronutrient deficiencies globally, particularly prevalent in pregnant women, infants, and young children due to their increased nutritional demands during periods of rapid growth [5]. According to the World Health Organization (WHO), the global prevalence of anemia among children under five years of age is approximately 40 %, with the highest rates observed in Africa, followed by Asia [6, 7]. A 2021 survey conducted across 32 African countries reported an anemia prevalence of 64.1 % among children under five [8]. In 19 European countries, prevalence of iron deficiency in children aged 6–12 months ranges from 2 to 25 % [9]. In Russia, iron deficiency anemia is a common condition among children, with prevalence rates varying between 6 and 40 % depending on a region [10]. Another study in Russia indicated that 10 to 40 % of children were zinc deficient and zinc supplementation has been shown to enhance physical growth and reduce prevalence of respiratory and gastrointestinal illnesses [11]. In Vietnam, findings from the 2019–2020 National Nutrition Survey on children under five conducted by the National Institute of Nutrition revealed a zinc deficiency rate of 58 % and anemia prevalence of 19.6 %. Notably, the anemia rate among children aged 6–11 months was 25.6 % [12]. High prevalence of anemia and zinc deficiency in children under two years of age is primarily attributed to their increased physiological demands during rapid growth, insufficient intake of iron and zinc due to poor-quality complementary diets, low nutrient absorption, and, in some cases, infections or blood loss[1].

Children aged 6 to 11 months are particularly vulnerable to micronutrient deficiencies and have high incidence of infectious diseases [12]. This may be attributed to complementary feeding practices that fail to meet nutritional requirements of young children. Such inadequacies are more prevalent in impoverished rural areas, where economic and socio-cultural conditions are limited. In these settings, caregivers often face barriers in accessing health education and communication resulting in poor knowledge and suboptimal practices regarding child health care and nutrition [1]. Numerous international studies have demonstrated effectiveness of multiple micronutrient supplementation in improving hemoglobin (Hb), ferritin, and zinc levels in young children [2, 13, 14]. However, in Vietnam, similar studies remain limited, particularly among children aged 6–11 months living in rural communities. Meanwhile, an intervention using *Bibomix* – a fortified dietary supplement containing 15 essential vitamins and minerals, formulated in accordance with recommendations from the Vietnam National Institute of Nutrition[2] and the WHO[3] – combined with nutrition education and communication, has not yet been widely evaluated for its real-world effectiveness at the community level. Therefore, we conducted this study.

Materials and methods. This study was a community-based, randomized, double-blind, placebo-controlled trial designed to test the hypothesis that using the Bibomix dietary supplement, combined with direct nutrition and health education (NHE) for caregivers, would improve anemia, iron deficiency, and zinc deficiency among children aged 6–11 months after 12 months of intervention.

The intervention period lasted 12 months, from February 2019 to April 2020. Study loca-

[1] Nutritional anaemias: tools for effective prevention and control. Geneva, WHO, 2017; WHO guideline on use of ferritin concentrations to assess iron status in populations. Geneva, WHO, 2020.

[2] Recommended Nutrient Intake for Vietnamese People. *National Institute of Nutrition*. Hanoi, Medical Publ. House, 2016 (in Vietnamese).

[3] World Health Statistics 2011. Geneva, WHO, 2011; Programmatic Guidance Brief on Use of Micronutrient Powders (MNP) for Home Fortification. *HF-TAG*. Available at: https://hftag.org/content/user_files/2023/06/HF-TAG-Micronutrient-Powder-Program-Guidance-Brief1.pdf (June 25, 2023).

tion: Quang Xuong District, Thanh Hoa Province, Vietnam.

The study protocol was approved by the Institutional Ethics Review Board for Biomedical Research of the National Institute of Nutrition under Decision No. 259/VDD-QLKH, dated June 15, 2018.

Randomization. ***Selection of communes.*** Ten rural communes were selected based on similar socioeconomic conditions, absence of prior nutrition intervention programs, and a population density of over 5,000 residents per commune.

Selection of study participants. A complete list of all infants in the selected communes was compiled including information on date of birth and sex. Birth dates were obtained from the children's birth certificates.

Group allocation. Following baseline assessment of 436 children across the 10 communes, participants were randomly allocated into two groups – the intervention group and the control group – with an equal number of children in each. Children in the intervention group were selected first according to predefined eligibility criteria. Subsequently, children in the control group were selected to ensure comparability between the two groups in terms of sex and age distribution. The study scheme is shown in Figure 1.

Nutrition and Child Care Communication Intervention for Both Groups. Communication materials were developed based on resources from the Vietnam National Institute of Nutrition, including materials from the Pediatric Malnutrition Prevention Program (PEM), and best practices in infant and young child feeding (IYCF) as recommended by the World Health Organization [15, 16]. The communication also incorporated guidelines on optimal practices for clean water, personal hygiene, and environmental sanitation (WASH).

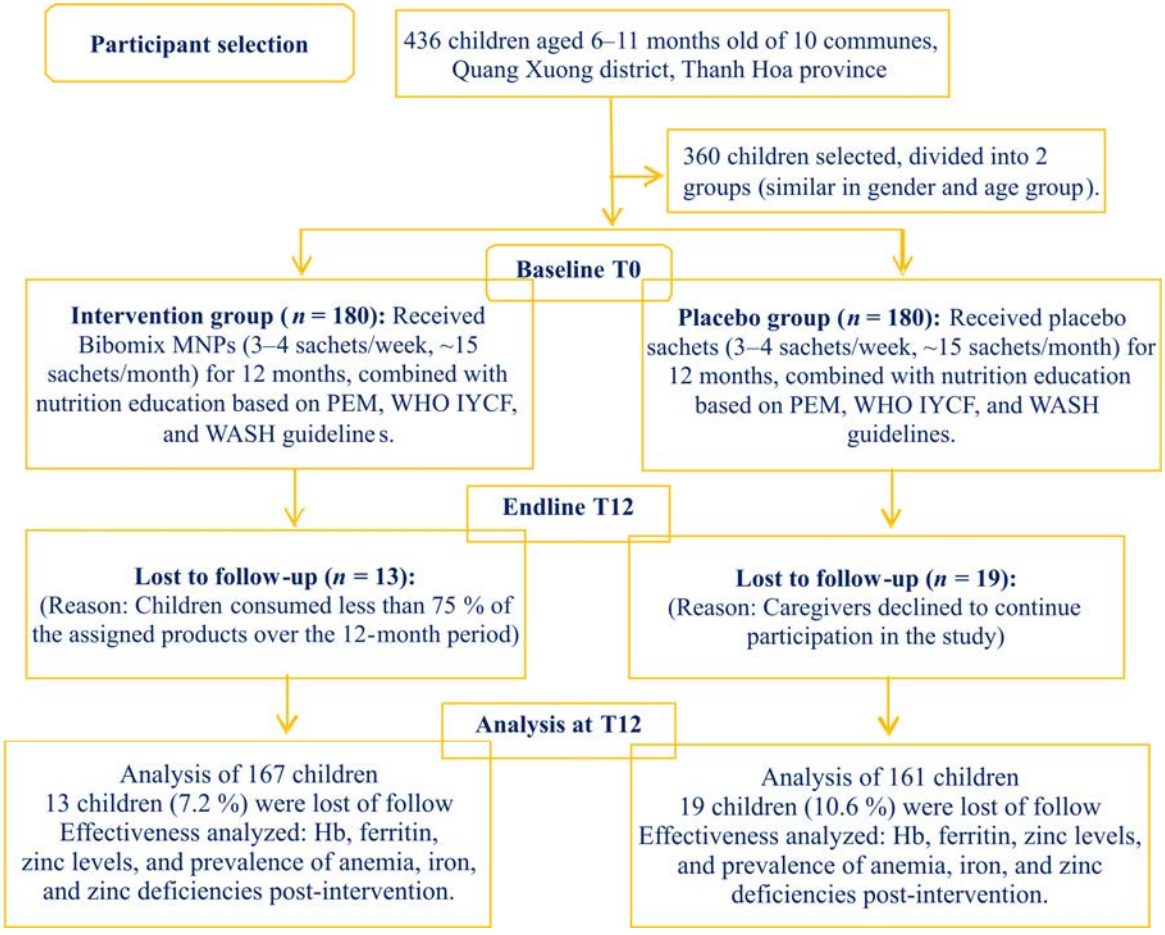

Figure 1. The study scheme

These activities were delivered by staff from the National Institute of Nutrition, district health officers, and community health workers.

Inclusion and Exclusion Criteria. A list of all children aged 6–11 months residing in the 10 selected communes of Quang Xuong District, Thanh Hoa Province was compiled including data on date of birth and sex. Participants were screened for eligibility based on the following criteria:

Inclusion criteria: Children aged 6–11 months residing in the study area whose parents or legal guardians voluntarily consented to participate by signing an informed consent form and agreed to comply with all study procedures.

Exclusion criteria: Children with severe malnutrition (weight-for-height Z-score < -3), severe anemia (Hb < 70 g/L), serious infectious diseases, or those currently participating in or previously enrolled in another nutrition intervention trial. Additionally, children who consumed less than 75 % of the assigned products by the end of the study were also excluded from final analysis.

Nutritional intervention. The intervention group received Bibomix multiple micronutrient powder (MNPs), while the control group received placebo sachets. Both products were identical in appearance to minimize bias during community-based implementation. Packaging was labeled with the month and year of production (March 2021 for the intervention group and September 2021 for the placebo group). Community health workers visited households weekly to monitor adherence and distribute the products according to group assignment. Both groups were instructed to consume one sachet per serving, 3–4 sachets per week, totaling 15 sachets per month for 12 months, mixed into porridge. Neither the participants, nor caregivers, or data collectors could distinguish between the Bibomix and placebo sachets ensuring double-blind conditions throughout the study in accordance with the protocol[4] and the 2016 WHO guidelines on micronutrient supplementation[5].

The placebo product contained 1 gram of rice powder. Both the Bibomix MNP and placebo sachets were manufactured by the Center for Nutrition and Food Science and Technology Services under the National Institute of Nutrition. The products met microbiological safety standards according to Decision No. 46/2007/QĐ-BYT and heavy metal content limits according to QCVN 8-2:2011/BYT, issued by the Ministry of Health of Vietnam.

Table 1

Composition of Bibomix multiple micronutrient powder per 1 gram sachet

Micronutrient	Amount	Micronutrient	Amount
Vitamin A	400.0 µg	Vitamin B12	0.9 µg
Vitamin D	5.0 µg	Folic Acid	150.0 µg
Vitamin E	5.0 mg	Iron	10.0 mg
Vitamin C	20.0 mg	Zinc	4.1 mg
Vitamin B1	0.5 mg	Copper	0.56 mg
Vitamin B2	0.5 mg	Selen	17.0 µg
Vitamin B3 (Niacin)	6.0 mg	Iodine	90.0 µg
Vitamin B6	0.5 mg		
Excipients: Modified starch, magnesium stearate			

[4] Recommended Nutrient Intake for Vietnamese People. *National Institute of Nutrition.* Hanoi, Medical Publ. House, 2016 (in Vietnamese).

[5] World Health Statistics 2011. Geneva, WHO, 2011; Programmatic Guidance Brief on Use of Micronutrient Powders (MNP) for Home Fortification. *HF-TAG*. Available at: https://hftag.org/content/user_files/2023/06/HF-TAG-Micronutrient-Powder-Program-Guidance-Brief1.pdf (June 25, 2023).

Nutritional status assessment. Venous blood samples (2.5 mL) were collected from each participant in the morning between 8:00 and 11:00 AM using sterile syringes. Whole blood was transferred into plain tubes without anticoagulants and 20 μL was used immediately for hemoglobin (Hb) measurement. The remaining blood was stored in coolers and centrifuged within 4 hours at 3,000 rpm for 10 minutes. Serum was separated into Eppendorf tubes and stored at -20 °C at the Provincial Center for Preventive Medicine. After fieldwork completion, serum samples were shipped via express delivery to the laboratory at the National Institute of Nutrition, where they were stored at -80 °C until analysis. All procedures related to blood collection, centrifugation, and sample storage strictly followed protocols to prevent zinc contamination.

Hb concentration. Hemoglobin (Hb) concentration was measured using the Cyanmethemoglobin method at the National Institute of Nutrition. Children with Hb levels below 110 g/L were classified as anemic, while those with Hb levels below 70 g/L were classified as having severe anemia[6].

Serum ferritin. Serum ferritin was measured using the ELISA method with a commercial ferritin kit (Ramco Laboratories, Inc., Stafford, Texas, USA) at the National Institute of Nutrition. Accuracy was verified according to international WHO standards. Iron depletion was defined as ferritin concentration < 12 μg/L when C-reactive protein (CRP) ≤ 5 mg/L, or ferritin > 30 μg/L when CRP > 5 mg/L. Iron deficiency anemia was defined as Hb < 110 g/L in combination with ferritin < 12 μg/L[7].

Serum zinc. Serum zinc was analyzed using flame atomic absorption spectrometry (Australia) at the Micronutrient Department of the National Institute of Nutrition employing procedures designed to prevent metal cross-contamination. Zinc concentrations were validated against quality control and hydrochloric acid reference samples. Zinc deficiency in children was defined as serum zinc concentration < 9.9 μmol/L for morning, non-fasting blood samples[8].

C-reactive protein (CRP). CRP was measured by ELISA using a commercial kit (Diagnostic Systems Laboratories Inc., Webster, TX, USA) at the Micronutrient Department, National Institute of Nutrition. A plasma CRP concentration > 5 mg/L was used as the threshold for acute phase response [17].

General Information collection. Data were collected through structured questionnaires administered by trained field investigators from the research team. The questionnaire included information on such child-related factors as age (quantitative), sex (binary variable: female/male), birth weight (binary variable: ≥ 2500 g / < 2500 g), and exclusive breastfeeding during the first six months (binary variable: < 6 months / ≥ 6 months). Morbidity status in the past two weeks was also recorded including symptoms of acute respiratory infections, diarrhea, and fever (binary variable: yes / no)[9]. Maternal variables included age (binary variable: ≤ 30 years / > 30 years), education level (binary variable: ≤ high school, mothers who completed grade 12 or below or > high school, mothers who completed more than grade 12), and occupation (binary variable: formal employment including government workers and small business owners / other occupations including farmers, factory workers, housewives, and freelance workers). Use of multiple micronutrient supplements during pregnancy was recorded as a binary variable (yes/no). Household variables included total monthly family income (binary variable: > 5 million VND / ≤ 5 million VND)

[6] Nutritional anaemias: tools for effective prevention and control. Geneva, WHO, 2017.

[7] WHO guideline on use of ferritin concentrations to assess iron status in populations. Geneva, WHO, 2020.

[8] International Zinc Nutrition Consultative Group. Assessing population zinc status with serum zinc concentration: IZiNCG Technical Brief, no. 2. Davis, CA, University of California, 2016.

[9] Guidelines for managing diarrhea in children; issued under Decision No. 4121/QĐ-BYT, October 28, 2009. *Ministry of Health* (in Vietnamese); Bach V.C., Pham V.Q. Handbook of Pediatric Treatment. Ho Chi Minh City, Pham Ngoc Thach University of Medicine, 2017 (in Vietnamese).

and number of children in the household (binary variable: > 2 children / ≤ 2 children).

Sample size calculation and statistical analysis. The sample size was calculated using the standard formula for intervention trials[10]:

$$n = \frac{2\delta^2 (Z_{1-\alpha/2} + Z_{1-\beta/2})^2}{(\mu_0 - \mu_a)^2},$$

where n is a required sample size per one group;

α is likelihood of type I error, set at 5 % ($Z_{1-\alpha/2} = 1.96$);

β is likelihood of type II error, set at 10 %, corresponding to a statistical power of 90 % ($Z_{1-\beta/2} = 1.28$);

δ is standard deviation;

$\mu_0 - \mu_a$ is expected difference in mean intergroup values.

The sample size was calculated to detect a difference in mean hemoglobin (Hb) concentrations between groups. With an expected effect size of $\mu_0 - \mu_a = 3.07$ and a standard deviation (δ) of 6.5 [18] the calculated sample size for assessing the effect of the intervention on hemoglobin concentration was $n = 59$ per group. For serum zinc concentration, the estimated difference between means was $\mu_0 - \mu_a = 0.83$ with a standard deviation $\delta = 2.28$ [18] resulting in a required sample size of $n = 101$ per group. Based on these calculations, the minimum required sample size was 101 children per group. In this study, we enrolled 180 children in each group resulting in a total sample size of 360 participants for the intervention trial.

Statistical analysis. Data were entered, verified, and analyzed using EpiData 3.1 and SPSS version 26.0. Prior to statistical testing, all variables were assessed for normality of distribution. Categorical variables were presented as frequencies and percentages. Quantitative variables with normal distribution were expressed as mean ($\bar{X}$) ± standard deviation (SD), while non-normally distributed variables were presented as median and interquartile range (IQR).

To evaluate the intervention's effectiveness, the absolute risk reduction (ARR) was used. ARR represents the difference in risk between the two groups, expressed as a percentage along with the 95 % confidence interval (95 % CI)[11]. A positive ARR (> 0) at the end of the intervention indicates lower prevalence of adverse outcomes in the intervention group compared to the placebo group.

Generalized linear models (GLM) were used to analyze the intervention's effects after adjusting for potential confounding factors. Quantitative covariates included child's age in months at baseline (T_0), hemoglobin concentration at T_{12}, ferritin concentration at T_{12}, CRP concentration at T_{12}, and zinc concentration at T_{12}. Categorical covariates included child's sex at T_0; birth weight at T_0; exclusive breastfeeding during the first six months at T_0; morbidity during the two weeks prior to the T_{12} assessment, including acute respiratory infection, diarrhea, and fever; maternal age at T_0; maternal education level at T_0; maternal occupation at T_0; use of multiple micronutrient supplements during pregnancy at T_0; total household income per month at T_0; and number of children in the household at T_0. Multicollinearity among independent variables was assessed using variance inflation factors (VIF). All VIF values were below 2.0, indicating no significant multicollinearity.

Results and discussion. Baseline characteristics were assessed to ensure comparability between groups prior to analyzing intervention outcomes. Table 2 summarizes participant characteristics at baseline (T_0).

Table 2 shows the baseline comparison between the two groups with a high level of homogeneity, with all p-values > 0.05. This supports the comparability and reliability of subsequent analyses evaluating effectiveness of the intervention.

[10] Chow S.-C., Shao J., Wang H., Lokhnygina Y. Sample Size Calculations in Clinical Research, 2nd ed. Boca Raton, Chapman and Hall/CRC Biostatistics Series, 2017.

[11] Nguyen Van Tuan. Data Analysis with R. Ho Chi Minh City, General Publishing House, 2014 (in Vietnamese).

Table 2

Characteristics of study participants

Baseline characteristics	Intervention group $n = 167$	Control group $n = 161$	p
Sex, *n* (%)			
Girls	83 (49.7 %)	89 (55.3 %)	0.312
Boys	84 (50.3 %)	72 (44.7 %)	
Average age (months)			
Mean ± SD (min. – max.)	7.7 ± 1.4 (6.0–11.8)	7.9 ± 1.6 (6.0–11.9)	0.360
Birthweight, *n* (%)			
≥ 2500 g	155 (92.8 %)	147 (91.3 %)	0.613
< 2500 g	12 (7.2 %)	14 (8.7 %)	
Exclusive breastfeeding in 6 months			
< 6 months	105 (62.9 %)	100 (62.1 %)	0.887
≥ 6 months	62 (37.1 %)	61 (37.9 %)	
Mother's age group, *n* (%)			
≤ 30 years	46 (27.5 %)	39 (24.2 %)	0.493
> 30 years	121 (72.5 %)	122 (75.8 %)	
Mother's education, *n* (%)			
≤ high school	122 (73.1 %)	112 (69.6 %)	0.485
> high school	45 (26.9 %)	49 (30.4 %)	
Mother's occupation, *n* (%)			
Government staff	42 (25.1 %)	33 (20.5 %)	0.316
Other*	125 (74.9 %)	128 (79.5 %)	
Total monthly household income, *n* (%)			
> 5 million/month	140 (83.8 %)	141 (87.6 %)	0.333
≤ 5 million/month	27 (16.2 %)	20 (12.4 %)	
Total number of children in the household, *n* (%)			
> 2 children	32 (19.2 %)	29 (18.0 %)	0.789
≤ 2 children	135 (80.8 %)	132 (82.0 %)	

Note: p values were derived from t-tests for comparisons of means or χ^2 tests for comparisons of proportions between the two groups at the same time point. (*) Farmers, factory workers, housewives, and freelancers.

Table 3 indicates that there were no statistically significant differences between the intervention and control groups.

These findings (Table 2, 3) suggest an epidemiologically balanced distribution between the two groups at baseline thus ensuring objectivity and reliability in the subsequent evaluation of intervention effects.

Table 4 presents the comparison of plasma micronutrient status, including Hb, ferritin, zinc, and CRP concentrations.

The difference-in-differences (DID) analysis showed a post-intervention increase in hemoglobin concentration of DID = 4.41 g/L ($p < 0.001$) and an increase in serum ferritin concentration of DID = 2.97 μg/L ($p = 0.001$). The change in serum CRP concentration was DID = –0.11 mg/L ($p = 0.114$). Serum zinc concentration increased by DID = 0.41 μmol/L ($p = 0.008$). These results indicate a significant positive effect of the intervention on children's hemoglobin, ferritin, and zinc status, while its effect on inflammation (as measured by CRP) was not statistically significant.

Figure 2 demonstrates the significant effectiveness of the intervention in improving anemia, iron deficiency, and zinc deficiency among children.

Anemia prevalence was only 3.0 % in the intervention group, significantly lower than 12.4 % in the placebo group ($p = 0.039$). Iron deficiency prevalence was 1.2 % in the intervention group, markedly lower than 10.6 % in the placebo group ($p = 0.004$). Zinc deficiency also showed a substantial reduction, with 13.8 % in the intervention group compared to

Table 3

Baseline levels of micronutrients, hemoglobin concentration, serum ferritin and zinc

Baseline characteristics	Intervention group $n = 167$	Control group $n = 161$	p
Prevalence of anemia, *n* (%)	49 (29.3 %)	42 (26.1 %)	0.510
Prevalence of iron deficiency, *n* (%)	22 (13.2 %)	30 (18.6 %)	0.176
Prevalence of iron deficiency – CRP**, *n* (%)	23 (13.8 %)	32 (19.9 %)	0.139
Prevalence of iron deficiency anemia, *n* (%)	15 (9.0 %)	22 (13.7 %)	0.180
Prevalence of zinc deficiency, *n* (%)	124 (74.3 %)	113 (70.2 %)	0.411
Hemoglobin concentration (г/л)			
Mean ± SD (min. – max.)	113.8 ± 8.3 (88.9–137.2)	115.2 ± 8.9 (89.5–137.4)	0.145
Serum ferritin concentration (μg/L)			
Mean ± SD (min. – max.)	27.7 ± 17.5 (1.9–101.6)	26.5 ± 18.4 (1.0–85.1)	0.564
CRP (mg/L)			
Mean ± SD (min. – max.)	1.33 ± 1.21 (0.15–8.69)	1.17 ± 0.99 (0.04–8.43)	0.221
Serum zinc concentration (μmol/L)			
Mean ± SD (min. – max.)	8.95 ± 1.62 (4.28–13.64)	9.00 ± 1.51 (4.32–13.38)	0.752

Note: p values were derived from t-tests for comparisons of means or χ^2 tests for comparisons of proportions between the two groups at the same time point. Iron deficiency was defined as ferritin < 12 μg/L with CRP ≤ 5 mg/L or ferritin > 30 μg/L with CRP > 5 mg/L. SD is standard deviation.

Table 4

Comparison of plasma micronutrient status, hemoglobin, ferritin, and zinc

Characteristics	Intervention group Baseline ($n = 167$)	Intervention group Endline ($n = 167$)	Mean difference	p	Control Baseline ($n = 161$)	Control Endline ($n = 161$)	Mean difference	p	DID	p
Hemoglobin (g/L)										
Mean ± SD	113.8 ± 8.3	121.8 ± 8.4	7.9 ± 7.2	< 0.001[b]	115.2 ± 8.9	119.4 ± 8.7	3.9 ± 1.3	< 0.001	4.41	<0.001[a]
CRP (mg/L)										
median (p25; p75)	1.12 (0.7; 1.5)	0.74 (0.16; 1.51)	0.00 (-0.4; 0.4)	0.022[d]	1.05 (0.7; 1.4)	1.1 (0.8; 1.5)	0.11 (-0.2; 0.5)	0.885[d]	-0.11	0.114[c]
Serum ferritin (μg/L)										
median (p25; p75)	24.2 (17.3; 32.9)	34.0 (23.6; 50.6)	8.5 (1.0; 16.6)	< 0.001[d]	21.9 (14.8; 33.5)	26.4 (19.4; 35.5)	5.52 (-7.4; 13.4)	0.002[d]	2.97	0.001[c]
Serum zinc (μmol/L)										
mean ± SD	8.95 ± 1.62	10.62 ± 0.97	1.67 ± 1.33	< 0.001[b]	9.01 ± 1.51	10.26 ± 1.31	1.26 ± 1.47	< 0.001	0.41	0.008[a]

Note: DID is difference in differences; SD is standard deviation; p^a is independent t-test comparing means between intervention and control groups at the same time point (for normally distributed variables); p^b is paired t-test comparing means within the same group before and after the intervention (for normally distributed variables); p^c is Mann – Whitney U-test comparing the intervention and placebo groups at the same time point (for non-normally distributed variables); p^d is Wilcoxon signed-rank test comparing medians within the same group before and after the intervention (for non-normally distributed variables).

40.4 % in the placebo group ($p < 0.001$). These findings indicate a strong and statistically significant impact of the intervention.

Table 5 shows that the intervention led to an absolute reduction in anemia prevalence of 18.4 % (95 % CI: 2.3–34.5), with an adjusted relative risk (RR) of 25.0 (95 % CI: 1.8–333.3; $p = 0.025$). The reduction in iron deficiency prevalence was 13.2 % (95 % CI: -5.2–31.6) with an adjusted RR of 12.5 (95 % CI: 0.7–250.0; $p = 0.092$). For zinc deficiency, the intervention resulted in a 31.0 % reduction (95 % CI: 19.5–42.3) with an adjusted RR of 7.1 (95 % CI: 3.3–14.3; $p < 0.001$). After adjusting for confounding factors, the intervention had a clearly significant effect on reducing anemia and zinc deficiency among children who had these deficiencies at baseline

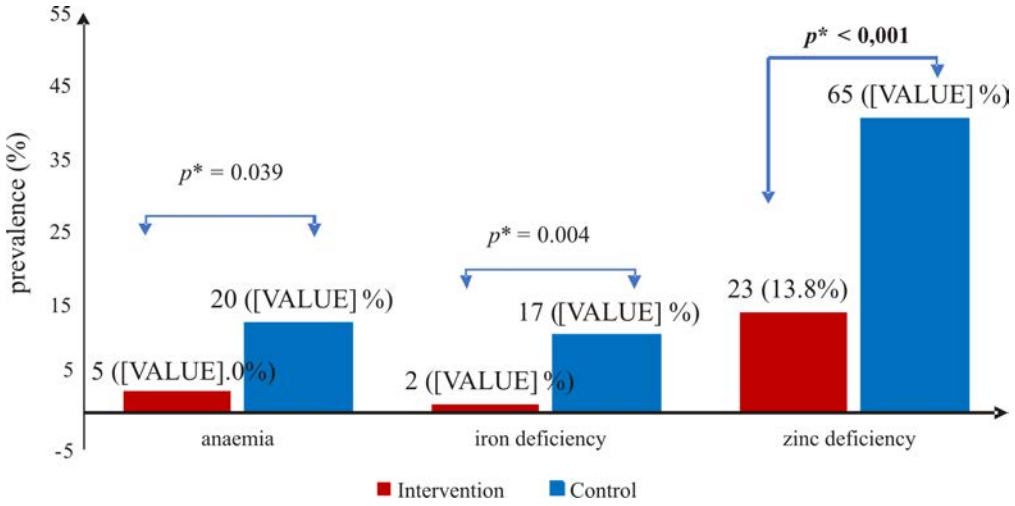

Figure 2. Post-intervention changes in prevalence of anemia, iron deficiency, and zinc deficiency among children

Table 5

Effectiveness of the intervention in reducing anemia, iron deficiency, and zinc deficiency among children after the intervention

Characteristics	Intervention *n* (%)	Control *n* (%)	ARR % (95 % CI)	RR (95 % CI)	*p*	RR* (95 % CI)	*p**
Effect on anemia status							
Anemia	5 (10.2 %)	12 (28.6 %)	18.4 (2.3–34.5)	2.8 (1.1–7.1)	**0.025**	25.0 (1.8–333.3)	**0.015**
No anemia	44 (89.8 %)	30 (71.4 %)					
Effect on iron deficiency status							
Iron deficiency	2 (8.7 %)	7 (21.9 %)	13.2 (-5.2–31.6)	2.5 (0.6–11.1)	0.193	12.5 (0.7–250.0)	0.092
No iron deficiency	21 (91.3 %)	25 (78.1 %)					
Effect on zinc deficiency status							
Zinc deficiency	22 (17.7 %)	55 (48.7 %)	31.0 (19.5 – 42.3)	2.8 (1.8 – 4.2)	**< 0.001**	7.1 (3.3–14.3)	**< 0.001**
No zinc deficiency	102 (82.3 %)	58 (51.3 %)					

Note: *p** is comparison of adjusted risk between the groups based on generalized multivariate regression analysis. Anemia was established as hemoglobin level < 110 g/L; iron deficiency, as ferritin < 12 µg/L; zinc deficiency, as serum zinc level < 9.9 µmol/L; ARR is absolute risk reduction after 12 months of intervention; RR (95 % CI) – crude relative risk, unadjusted for confounders; RR* (95 % CI) is adjusted relative risk after controlling for confounders; *p*-value (from χ^2 test) is comparison of changes in proportions between the groups.

($p < 0.001$). However, the effect on iron deficiency was not statistically significant ($p > 0.05$).

The study results showed that after 12 months of intervention, the mean hemoglobin (Hb) concentration increased by 4.41 g/L in the intervention group compared to the control group (DID = 4.41; $p < 0.001$). The intervention also significantly reduced anemia prevalence with an adjusted relative risk (RR) of 4.1 (95 % CI: 1.6–10.8; $p < 0.001$) and an absolute risk reduction (ARR) of 18.4 % (95 % CI: 2.3–34.5). Serum ferritin levels and overall prevalence of iron deficiency also improved significantly ($p < 0.001$). These findings indicate that the intervention improved hemoglobin and ferritin concentrations and reduced anemia prevalence and iron deficiency prevalence more effectively than in a previous study by Susan L. Jack et al. (2012) conducted in Cambodia among children aged 6–11 months [14]. In comparison, a study by Ali Albelbeisi

et al. (2019) conducted in the Gaza Strip, Palestine, among children aged 6–24 months found that hemoglobin concentrations decreased in both the intervention and control groups after 12 months of multiple micronutrient powder (MNP) supplementation [2]. Both authors suggested that the lack of improvement in anemia and iron deficiency following the intervention may have been due to the iron content in the supplements being lower than the children's physiological requirements or due to generally inadequate dietary intake.

Compared to similar intervention studies conducted in Vietnam, the effectiveness observed in our study is markedly higher. For example, in the study by Huynh Van Dung, nutritional education interventions promoting use of locally available micronutrient-rich foods for children aged 6–23 months resulted in an increase in hemoglobin concentration of 6.23 ± 2.61 g/L in the intervention group after six months, compared to 2.94 ± 2.51 g/L in the control group. Anemia prevalence decreased by 21.05 % in the intervention group, while the control group saw a reduction of only 11.27 % [13]. In the study conducted by Nguyen Van Dung on children aged 6–23 months following treatment for acute respiratory infections, supplementation with Bibomix multi-micronutrient powder over a six-month period resulted in a decrease in hemoglobin concentration of 0.3 ± 13.7 g/L in the intervention group, with the prevalence of anemia decreasing from 38.3 to 33.3 %. In contrast, the placebo group experienced a greater reduction in hemoglobin concentration (2.4 ± 15.3 g/L), and the prevalence of anemia increased from 40.7 to 55.9 %[12].

Our findings indicated a statistically significant reduction in CRP levels within the intervention group ($p < 0.05$); however, no significant difference was observed between the two groups after the intervention ($p > 0.05$). As CRP responds rapidly to minor or even asymptomatic infections [19], it may be influenced by environmental factors beyond the control of the study. Consequently, the intrinsic fluctuations of CRP may have diluted the between-group effect, despite a trend toward improvement in the intervention group thereby resulting in a lack of statistically significant difference.

In evaluating effectiveness of the intervention, serum zinc levels demonstrated the most notable improvement, both in terms of concentration and in reducing the overall prevalence of zinc deficiency in both the intervention and control groups. After 12 months, the mean zinc concentrations improved in both groups, with the zinc deficiency treatment effectiveness reaching 31.0 % ($p < 0.05$). This result is superior to that reported in the study by Huynh Van Dung, in which, after six months, the mean serum zinc concentration in the intervention group increased by 1.38 ± 2.3 μmol/L, compared to an increase of 0.66 ± 2.86 μmol/L in the control group yielding an intervention effectiveness of 25.7 % [13]. In the study by Nguyen Van Dung, after six months of intervention, the mean serum zinc concentration in the intervention group increased by 1.90 ± 3.17 μmol/L, with a 28.3 % reduction in zinc deficiency. In comparison, the placebo group showed only a slight increase of 0.03 ± 3.26 μmol/L and a 10.1 % reduction in zinc deficiency[12]. Another study by Susan L. Jack, conducted among children aged 6 to 11 months in Cambodia, reported a between-group difference in serum zinc concentration of 2.88 μmol/L after 12 months of intervention ($p < 0.05$), with an intervention effectiveness in reducing zinc deficiency of 5.2 % [14].

There is an increasing shift toward use of multiple micronutrient supplementation (MMS) for high-risk populations replacing the previous approach of supplementing individual nutrients. MMS, when provided in accordance with recommended dietary requirements through various delivery methods, has been

[12] Nguyen Van Dung [Effects of Bibomix multiple micronutrient powder on nutritional status of children aged 6–23 months after acute respiratory infection treatment]: PhD Dissertation. Hanoi, National Institute of Nutrition, 2022 (in Vietnamese).

emphasized as a practical strategy to address the widespread issue of micronutrient deficiencies. This is especially relevant in young children, who are often deficient in multiple micronutrients simultaneously rather than in isolated nutrients. Furthermore, MMS has shown greater effectiveness in preventing and treating conditions such as stunting, anemia, iron deficiency, and zinc deficiency, due to the synergistic interactions among the combined micronutrients. These nutrients work together to enhance therapeutic outcomes. For instance, vitamins A, B12, folic acid, vitamin C, and B-complex vitamins (B1, B2, B3) play critical roles in enhancing iron absorption, iron metabolism, and red blood cell formation thereby improving hemoglobin concentration, serum ferritin, and serum zinc levels. These mechanisms contribute significantly to preventing anemia, iron and zinc deficiencies, and other micronutrient-related disorders. Based on our study's methodology and findings, we provide additional evidence supporting implementation of early MMS intervention ideally beginning in children aged 6–11 months and sustained over a 12-month period to achieve optimal nutritional and clinical outcomes.

Strengths and limitations of the study. The intervention involving multiple micronutrient powder (MNPs) Bibomix – containing 15 essential vitamins and minerals as recommended by WHO and the National Institute of Nutrition – is among the few studies in Vietnam that combine health education communication (GDSK) with micronutrient supplementation. This intervention model offers an optimal solution for regions with moderate to high prevalence of micronutrient deficiencies serving both preventive and supportive treatment roles for anemia, iron deficiency, and zinc deficiency in young children. Bibomix MNPs have several advantages including ease of use, convenient transportation, child-friendly taste, affordable cost, and proven effectiveness in improving anthropometric indicators and micronutrient status. Therefore, this intervention approach has strong potential for large-scale implementation to help reduce undernutrition and micronutrient deficiencies in this vulnerable age group in the near future.

However, some limitations remain. Notably, the study did not observe a significant treatment effect on iron deficiency after 12 months of intervention. Sustainability of the intervention was also not assessed following discontinuation of supplementation, which would be necessary to evaluate the long-term impact of combining Bibomix MNPs with direct GDSK communication. Additionally, in the generalized linear regression analysis, it was challenging to control for all confounding variables, particularly behavioral changes in mothers influenced by exposure to various health communication methods.

Conclusion. After the intervention, the mean differences between the two groups were 4.41 g/L for hemoglobin concentration, 2.97 μg/L for serum ferritin, and 0.41 μmol/L for serum zinc, all with $p < 0.05$. The intervention effectiveness on anemia status was 3.4 (95 % CI: 1.1–10.7; $p = 0.039$); on iron deficiency, 12.2 (95 % CI: 2.2–67.8; $p = 0.004$); and on zinc deficiency, 4.2 (95 % CI: 2.3–7.4; $p < 0.001$). Regarding therapeutic support effectiveness, the impact on anemia was 25.0 (95 % CI: 1.8–333.3; $p = 0.015$); on iron deficiency, 12.5 (95 % CI: 0.7–250.0; $p = 0.092$); and on zinc deficiency, 7.1 (95 % CI: 3.3–14.3; $p < 0.001$). These findings demonstrate a significant improvement across multiple nutritional indicators. Therefore, it is recommended to administer Bibomix MNPs at a dosage of 3–4 sachets per week (15 sachets/month) for a duration of 12 months or longer, particularly for children aged 6–11 months living in areas with similar socioeconomic and geographic conditions as the study site to reduce risks of impairements in some blood indicators in this age group.

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