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Provision of Pre- and Postnatal Nutritional Supplements Generally Did Not Increase or Decrease Common Childhood Illnesses in Bangladesh: A Cluster-Randomized Effectiveness Trial

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ABSTRACT

Background: Nutritional interventions may affect child morbidity.

Objective: The aim of this study was to examine whether providing lipid-based nutrient supplements (LNSs) to pregnant and lactating women or LNS or micronutrient powder (MNP) to their infants influences child morbidity.

Methods: In a 4-arm cluster-randomized effectiveness trial, participants enrolled at ≤20 weeks of gestation ($n = 4011$) received: *1*) maternal LNSs until 6 mo postpartum and child LNSs from 6–24 mo of age (LNS-LNS); *2*) iron and folic acid (IFA) until 3 mo postpartum and child LNSs at 6–24 mo (IFA-LNS); *3*) IFA (as above) and child MNP at 6–24 mo (IFA-MNP); or *4*) IFA and no child supplement (IFA-Control). At 6, 12, 18, and 24 mo of age, we collected information on acute lower and upper respiratory infection (ALRI/AURI), diarrhea, and fever in the previous 14 d, and on episodes of illness in the previous 6 mo.

Results: At 6 mo, prevalence of ALRI, fever, or diarrhea in the previous 14 d (17.6%, 18.9% and 6.8%, respectively) did not differ between infants of women who received LNS and infants of women who received IFA, but prevalence of AURI was lower in the LNS-LNS group than in all other groups combined (27.7% compared with 31.7%; OR: 0.83; 95% CI: 0.70, 0.99). At 12, 18, and 24 mo, the 4 arms did not differ in prevalence of fever (~18.3%) or ALRI (≤15%) in the previous 14 d, but prevalence of AURI at 12 mo was lower in IFA-LNS than in IFA-Control infants (27.6% compared with 33.9%, OR: 0.74; 95% CI: 0.56, 0.99). The mean ± SD number of diarrhea episodes in the previous 6 mo was significantly higher among IFA-LNS than among IFA-Control infants at 6–12 (0.46 ± 0.04 compared with 0.33 ± 0.03) and 12–18 (0.45 ± 0.03 compared with 0.33 ± 0.02) mo. No other pairwise group differences were significant.

Conclusion: Providing LNSs to women or LNSs or MNP to children generally did not increase or decrease childhood illnesses. This trial was registered at clinicaltrials.gov as NCT01715038. *J Nutr* 2019;149:1271–1281.

Keywords: child morbidity, acute upper respiratory infection, diarrhea, lipid-based nutrient supplements, micronutrient powder

Introduction

A variety of interventions are being implemented to reduce child undernutrition in low- and middle-income countries like Bangladesh, including education on complementary feeding, provision of food supplements and micronutrient supplements for pregnant women and young children, deworming, hand washing or hygiene, and promotion of breastfeeding (1). Home fortification of food is another approach to prevent undernutrition of vulnerable target groups in situations where diets do not provide adequate amounts of essential nutrients (2). Home fortification involves the use of specialized products such as multiple micronutrient powder (MNP) or food-based products such as small-quantity lipid-based nutrient supplements (LNSs), which are added to food prepared at home to enrich the local diets of pregnant and lactating women and of infants and young children (3).

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Nutritional interventions such as these may affect child morbidity either positively or negatively (4, 5). Some of the nutrients provided via home fortification play a role in immune function, and may thus reduce morbidity risk, including vitamin A (6), vitamins B-6 and B-12 (7), vitamin C (7), vitamin D (6, 8), vitamin E (7), zinc (7, 9, 10), iron (7, 11), selenium (7), copper (7), and fatty acids (12). On the other hand, although MNPs have been shown to reduce anemia (13–15), they have also been linked to increased diarrhea among children in some studies (15–17), which has been linked to the iron provided by MNPs. Trials that included supplementing children with LNSs have so far shown no increase or decrease in gastroenteritis, acute lower respiratory infection (ALRI), fever, or malaria (18–20). However, previous published research on this topic has not included groups receiving both maternal and child nutrient or food supplementation. As prenatal nutritional adequacy may influence infant immune function (21), combined maternal and child supplementation may be more likely to have a beneficial impact on child morbidity than child supplementation alone.

The Rang Din Nutrition Study (RDNS) was a cluster-randomized controlled trial conducted within a community-based program in rural northwest Bangladesh and designed to evaluate the effectiveness of home-fortification approaches in the first 1000 d for preventing maternal and child undernutrition. In the RDNS, pregnant women were provided with LNSs for pregnant and lactating women (LNS-PL) or iron and folic acid (IFA) during pregnancy and early postpartum, and their children were provided with LNSs for children (LNS-C), MNP, or no supplement from 6 to 24 mo. We previously demonstrated that LNS-PL increased birth weight and reduced newborn stunting (22), and that the group receiving both LNS-PL and LNS-C had improved child growth status at 18–24 mo of age compared with the group in which the mothers received IFA and the children received MNP from 6 to 24 mo (23). This article reports the effects of these interventions on childhood illnesses, which are secondary outcomes. In this analysis, we hypothesized that the infants whose mothers received LNS-PL would have less fever, respiratory illness, and diarrhea between birth and 6 mo of age than the infants whose mothers received IFA, and that the children who received LNS-C or MNP would have less fever, respiratory illness, and diarrhea between 6 and 24 mo of age than the children who did not receive LNS-C or MNP.

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Supplemental Tables 1–3 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/.

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Abbreviations used: ALRI, acute lower respiratory infection; AURI, acute upper respiratory infection; CHDP, Community Health and Development Program; CHW, community health worker; icddr,b, International Centre for Diarrhoeal Disease Research, Bangladesh; IFA, iron and folic acid; LAMB, Lutheran Aid for Medicine in Bangladesh; LNS, lipid-based nutrient supplement; LNS-C, lipid-based nutrient supplement for children; LNS-PL, lipid-based nutrient supplement for pregnant and lactating women; MNP, micronutrient powder; RDNS, Rang-Din Nutrition Study; SDU, safe delivery unit; UCD, University of California, Davis.

Methods

Study setting and design

The study (NCT01715038) was conducted in 11 rural unions of the Badarganj and Chirirbandar subdistricts in northwest Bangladesh, as described previously (22). The study was carried out by 3 partners: Lutheran Aid for Medicine in Bangladesh (LAMB; a nongovernment organization in Dinajpur, Bangladesh); the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b); and the University of California, Davis (UCD), with technical support provided by the Food and Nutrition Technical Assistance (FANTA) project. It was implemented within the Community Health and Development Program (CHDP) operated by a local nongovernment organization (LAMB), which delivered the study interventions. UCD and icddr,b jointly evaluated the interventions. Health services normally provided by the CHDP include maternity services at a safe delivery unit (SDU) in each union; regular home visits for antenatal, postnatal, and child care by village health volunteers and community health workers (CHWs); and monthly educational sessions to promote maternal and child health. The RDNS was designed to be implemented within an existing community program, to examine the impact of providing supplements under real-world circumstances, and thus it was an effectiveness trial. Other studies in several countries had been completed or were underway to evaluate the efficacy of LNSs (2, 24).

The trial was a researcher-blind, longitudinal, cluster-randomized effectiveness trial with 4 equal-sized arms: *1*) comprehensive LNS: women received LNS-PL during pregnancy and the first 6 mo postpartum, and their children received LNS-C from 6 to 24 mo of age (LNS-LNS group); *2*) child-only LNS: women received IFA (1 tablet of 60 mg Fe and 400 μg folic acid) daily during pregnancy and every alternate day during the first 3 mo postpartum, and their children received LNS-C from 6 to 24 mo of age (IFA-LNS group); *3*) child-only MNP: women received IFA (as described above) and their children received MNP containing 15 micronutrients from 6 to 24 mo of age (IFA-MNP group); and *4*) control group: women received IFA (as described above) and their children received no supplements (IFA-Control). A cluster in this study was defined as the working area of a CHW, who was responsible for delivery of study supplements in her cluster. We chose a cluster-randomized design rather than an individual-randomized design because it would have been difficult for a CHW to distribute >1 type of study supplement in her cluster. For the randomization, the study statistician at UCD first stratified all 64 clusters in the 11 unions (the lowest administrative unit of the local government of Bangladesh) by subdistrict and union, and then randomly assigned each cluster to 1 of the 4 arms (each containing 16 clusters) (22). The study statistician replicated this procedure several thousand times and tested each randomization for balance across groups with respect to average cluster population, number of health facilities and health workers per 1000 of population in the cluster, number of health- and nutrition-related nongovernment organizations per cluster, funding source for the CHDP, and SD of cluster population size. Final randomization to the 4 arms was chosen randomly from the acceptable potential randomizations; then the letters A, B, C, and D were assigned to the 4 arms, randomly permuting them by sorting on a randomly generated, uniformly distributed number (using SAS version 9.2 for Windows; SAS Institute Inc.) and assigning them to control, child-only MNP, child-only LNS, and comprehensive LNS, respectively.

The study protocol was approved by the institutional review boards of UCD; icddr,b; and LAMB. We obtained community consent from the union representatives before beginning the study and completed randomization of clusters before seeking informed consent from the participants (22).

Study interventions

Table 1 shows the supplement composition. LNS-PL (one 20-g sachet/d) was modeled on the UNICEF/WHO/United Nations University international multiple micronutrient preparation for pregnant and lactating women and similar products used in Ghana and Malawi (3). LNS-C (two 10-g sachets/d) was similar to the LNS-C used in Ghana and

TABLE 1 Nutrient content of LNSs, MNP, and IFA used in the study[1]

Nutrient (amount per daily dose)	LNS-PL (20 g/d)	IFA tablet (1 tablet/d)	LNS-C (20 g/d)	MNP (1 sachet/d)
Energy, kcal	118	0	118	0
Protein, g	2.6	0	2.6	0
Fat, g	10	0	9.6	0
Linoleic acid (18:2n–6), g	4.59	0	4.46	0
α-Linolenic acid (18:3n–3), g	0.59	0	0.58	0
Vitamin A (retinyl acetate), μg	800	0	400	400
Vitamin C, mg	100	0	30	30
Thiamin, mg	2.8	0	0.5	0.5
Riboflavin, mg	2.8	0	0.5	0.5
Niacin, mg	36	0	6	6
Folic acid, μg	400	400	150	150
Pantothenic acid, mg	7	0	2.0	0
Vitamin B-6, mg	3.8	0	0.5	0.5
Vitamin B-12, μg	5.2	0	0.9	0.9
Vitamin D (cholecalciferol), μg	10	0	5	5
Vitamin E (d,l-α-tocopherol acetate), mg	20	0	6	5
Vitamin K (phylloquinone 5%), μg	45	0	30	0
Iron, mg	20	60	9	10
Zinc, mg	30	0	8	4.1
Copper, mg	4	0	0.34	0.56
Calcium, mg	280	0	280	0
Phosphorus, mg	190	0	190	0
Potassium, mg	200	0	200	0
Magnesium, mg	65	0	40	0
Selenium, μg	130	0	20	17
Iodine, μg	250	0	90	90
Manganese, mg	2.6	0	1.2	0

[1] IFA, iron and folic acid; LNS, lipid-based nutrient supplement; LNS-C, lipid-based nutrient supplement for children; LNS-PL, lipid-based nutrient supplement for pregnant and lactating women; MNP, micronutrient powder.

Malawi (25–27). LNS-PL and LNS-C were produced by Nutriset SA in Malaunay, France. MNP was produced by Renata Ltd. in Bangladesh and had the same nutrient composition as the MNP being scaled-up in Bangladesh by BRAC, an international development organization based in Bangladesh. We chose this option so that the results for the MNP group in the RDNS would be programmatically relevant. The dose of IFA was based on WHO recommendations (28). IFA tablets were produced by Hudson Pharmaceuticals Ltd. in Bangladesh. Nutriset SA tested the content of protein, lipid, and selected micronutrients in each batch of LNS-PL and LNS-C before shipping to the field site. They also conducted stability tests of vitamin content every 3 mo in a stored sample of MNP from the first batch. Every year Renata Ltd. stored samples from 1 batch to conduct stability analysis of all the ingredients every 3 mo, until the date of expiry. For our trial, temperature and humidity were maintained, and monitored twice daily in the supplement storage areas in the main project office and in the field offices as per the manufacturers' instruction. A standard guideline for storage of supplements at home was given to the participants as well.

Supplements were delivered to participants by CHDP staff. The distribution scheme and key educational messages are described elsewhere (22, 29). In the Badarganj subdistrict, the government of Bangladesh began distributing MNP (containing vitamin A, vitamin C, folic acid, iron, and zinc) for 6–24-mo-old children after we started our intervention. For study participants receiving LNS-C or MNP from the RDNS, the study team told caregivers not to feed any other vitamin and mineral tablets, capsules, or MNP sachets.

Enrollment and data collection

The CHWs and village health volunteers identified pregnant women via LAMB's pregnancy surveillance system (22). Women potentially eligible for the RDNS evaluation were contacted at home by evaluation staff, to obtain consent for screening. Eligibility criteria included gestational age ≤20 wk and no plans to move away during pregnancy or the following 3 y. All eligible women were invited to participate in the study. Women who consented were interviewed to collect baseline data and scheduled for anthropometric and clinical data collection at the SDU. Supplement delivery began after each woman's baseline SDU visit.

Data collection was performed by 2 separate teams: the "SDU visit team," which collected clinical and anthropometric data at the SDU; and the "home visit team," which enrolled mothers and collected baseline and follow-up data at participants' homes, including child illness data.

Baseline data were collected on socioeconomic status; diet; food security; and knowledge, attitudes, and practices relevant to nutrition from the women who consented to take part in the study. For household socioeconomic status a set of 19 yes/no questions were asked about whether or not a household owned a particular item. These items included televisions, irrigation pumps, tables, bicycles, sewing machines, and other goods (22, 29). We collected data on household food security using the questionnaire in the Household Food Insecurity Access Scale for measurement of household food access (30). A set of 5 questions about cooking place, cooking fuel, and smoking was asked to collect data on indoor air pollution. Trained data collectors gathered information on type of toilet used and garbage disposal system by observation.

Follow-up during pregnancy and just after childbirth is described elsewhere (22). At 6, 12, 18, and 24 mo postpartum, mothers were asked if their children had had specific symptoms or illnesses *1*) in the previous 2 wk and *2*) in the previous 6 mo. Interviewers used standard procedures to help the mother understand the period of recall and probed for each symptom or illness. For the 2-wk recall, the symptom list included fever (any fever; high fever, defined as very hot to the touch), cough, nasal discharge, fast breathing (faster than usual), difficulty in breathing, wheezing or grunting or whistling (any abnormal

sound during breathing in or out), chest indrawing (not asked at 6-mo interview), diarrhea (passage of abnormally loose or watery stool >3 times in a 24-h period), convulsion (shaking of hands, legs, or body when ill), and lethargy/drowsiness (too weak to speak, move, or play normally). If the mother reported "yes" for any of the symptoms, she was then asked for how many days in the last 2 wk the child had had that symptom. If the mother mentioned ≥2 symptoms in the last 2 wk, she was also asked which of those symptoms were present at the same time. For the 6-mo recall, the mother was asked how many episodes of 3 common illnesses or sets of symptoms her child experienced: *1*) cough or nasal discharge, *2*) cough or nasal discharge accompanied by rapid or difficult breathing (subset of previous question), and *3*) diarrhea. We collected data on adherence to LNS-LNS and IFA at 6 wk postpartum by asking the women how often they consumed the nutrient supplements (22), and to LNS-C and MNP at 12, 18, and 24 mo of age by asking caregivers how often the child had consumed the nutrient supplements during the previous 6 mo [not at all; sometimes (1–3 d/wk); almost every day (4–6 d/wk); or regularly (every day)] and how many sachets had been consumed during the previous week (23).

To the extent possible, data collectors were kept blind to group assignment, although those conducting home visits might have seen supplements in the home. Quality-control procedures (22) included having supervisors and quality-control team members re-interview ≥10% of randomly selected participants. When there was a discrepancy of ≥25% between the original and re-interview data, a third and final interview was conducted by the supervisor of the data collector.

Sample size calculation and statistical analyses

When designing the study, we calculated a minimum required sample size of 788 per group (total of 3152), based on detecting an effect size of ≥0.2 (difference between groups, divided by pooled SD) for the primary outcome (length-for-age *z* score) with 1-sided hypotheses, power = 0.8, and $\alpha = 0.05$, assuming an intracluster correlation = 0.01, and allowing for 20% attrition by the time all children reached 24 mo (23). Because we exceeded the target sample size during enrollment (22), we subsequently decided to conduct our analyses by using a more conservative 2-sided hypothesis approach, to be consistent with other recent trials.

Taking into account several socioeconomic status variables, we used principal components analysis to calculate a household socioeconomic status index from the set of 19 yes/no questions about whether or not a household owned a particular item, in which higher values represented higher socioeconomic status. Participants were categorized into 4 levels of household food insecurity: severe, moderate, mild, and none. Season at birth was categorized into 7 intervals (22). We created an indoor air quality variable from principal components analysis on 5 questions about cooking method and smoking (type of cooking facility, place of cooking, type of fuel used for cooking, hours per day spent for cooking, and number of household members who smoked), and then categorized the score into 5 categories. Toilet facility was categorized into best (sanitary and water seal latrines), intermediate (pit latrine with slab and water seal), and worst (pit latrine without water seal, hanging/open latrine, or no latrine). Garbage disposal system was categorized into better (burned or dumped in a designated place) and worse (no specific place to dump, dumped in open space, or dumped in pond/river/canal).

Primary outcomes were the number of days of reported high fever, nasal discharge, cough, or diarrhea in the 2 wk before 6, 12, 18, and 24 mo. Secondary morbidity outcomes were *1*) occurrences of high fever, diarrhea, acute upper respiratory illness (AURI), and ALRI in the 2 wk before 6, 12, 18, and 24 mo; and *2*) number of episodes of cough or nasal discharge, cough or nasal discharge accompanied by rapid or difficult breathing, and diarrhea in the 6 mo before 6, 12, 18, and 24 mo. AURI was defined as caregiver report of cough and nasal discharge on the same days but no difficult breathing, rapid breathing, wheezing/grunting/whistling, chest indrawing, convulsion, or lethargy during those days. ALRI was defined as caregiver report of cough together with ≥1 of the following symptoms on the same days: difficult breathing, rapid breathing, wheezing/grunting/whistling, or chest indrawing. We also examined neonatal and post-neonatal child mortality as additional secondary outcomes, defined as deaths between 0–28 d and between 28 d and 24 mo of age, respectively.

We developed a detailed data analysis plan before starting the analysis. Statistical analysis code was developed and finalized before unblinding treatment arms. Primary analysis was performed using R version 3.5.1 (R Foundation) with a complete-case intention-to-treat framework and 2-sided testing. Because our continuous measures were whole number sums of days/events with generally low totals, we treated them as counts as opposed to imposing a normality assumption. Thus, we analyzed effects of the intervention using negative binomial regression for the count outcomes and logistic regression for dichotomous outcomes. The analysis used mixed models to account for the cluster randomization, so all models included a random effect of cluster nested within treatment group, and a random effect of union nested within subdistrict. In the case of convergence problems, union nested within subdistrict was treated as a fixed effect. We first evaluated the unadjusted effect of intervention group and then repeated the analysis with adjustments for prespecified covariates (maternal BMI, age, education, and parity; number of children aged <5 y in the household, type of toilet, garbage disposal system, indoor air quality, household socioeconomic status, and food insecurity; time period in study; and child sex) if they were associated with the outcome ($P < 0.10$) in bivariate analysis. For all analyses, when the global null hypothesis was rejected at the 0.05 level, we performed post hoc pairwise comparisons using the Tukey–Kramer adjustment for multiple hypothesis testing. Mortality outcomes were rare events and so analysis results were further confirmed using both exact logistic regression and Fisher's exact test. We used Benjamini–Hochberg corrections for multiple hypothesis testing within each category of outcomes (number of days within the past 2 wk; occurrence within the past 2 wk; episodes within the past 6 mo) at each time point.

We also conducted a sensitivity analysis in which children in the subdistrict that received MNP as part of the government program were excluded. As in the previous analyses, all models in this analysis also included a random effect of cluster nested within treatment group and a random effect of union nested within subdistrict.

Results

A total of 4410 women were screened for eligibility between 15 October, 2011 and 31 August, 2012; of these, 4011 were enrolled. As described elsewhere (22), we exceeded the target sample size during enrollment because recruitment was more rapid than expected. After enrollment, 332 (8.3%) women had loss of pregnancy/stillbirth and there was 1 maternal/fetal death (in the IFA-Control arm); another 14 (0.35%) women were lost to follow-up during pregnancy. A total of 3664 live births occurred between 15 January, 2012 and 5 May, 2013 and 24-mo data collection was completed in May, 2015. One twin from 30 twin deliveries (including stillbirth) was randomly selected for analysis. The numbers of children remaining at each time point after birth are shown in **Figure 1**; at 24 mo of age, >90% remained in the study.

The percentage of women who reported regular consumption of the maternal supplement (every day or almost every day) during pregnancy was 64% for LNS-PL and 92% for IFA. Reported adherence to LNS-C or MNP, based on consumption during the previous 6 mo, was high: 94–97% at 6–12 mo and 97–99% at 12–24 mo, as reported elsewhere (23). Based on consumption during the previous week, reported adherence increased from 77–80% at 12 mo to 90–92% at 24 mo and did not differ between intervention groups.

At baseline, sociodemographic, sanitation, anthropometric, and food security characteristics of the mothers of the children

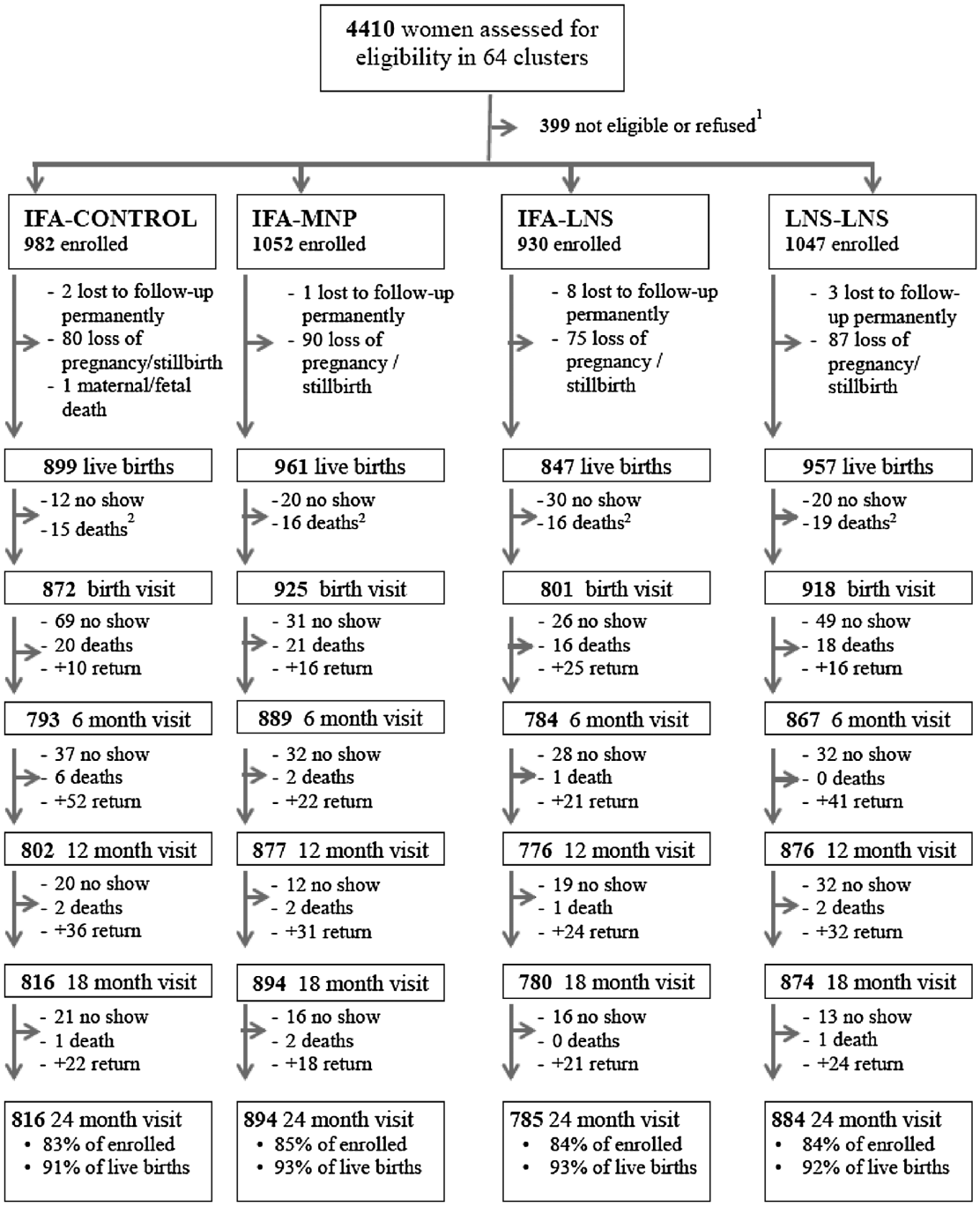

FIGURE 1 Study flowchart. [1]Not eligible or refused: 366 gestational age >140 d; 22 planned to leave the study site; 8 refused to consent; and 3 husbands refused to consent. [2]Most of these deaths occurred at <14 d postpartum: 14 IFA-Control, 15 IFA-MNP, 15 IFA-LNS, and 17 LNS-LNS. IFA-Control, women received iron and folic acid supplements during pregnancy and the first 3 mo postpartum and children did not receive supplements; IFA-LNS, women received iron and folic acid supplements during pregnancy and the first 3 mo postpartum and children received lipid-based nutrient supplements from 6 to 24 mo of age; IFA-MNP, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received micronutrient powder from 6 to 24 mo of age; LNS-LNS, women and children received lipid-based nutrient supplements.

were similar across the study arms (Table 2), except for a small but significant difference in maternal education. Mean age of the women was ~22 y, family size ~4.6, and gestational age at enrollment 92 d. About 40% of the women were nulliparas. Less than 15% of households had a flush or water seal toilet, whereas ~75% had a garbage disposal system categorized as "better." At baseline 9.1%, 29.0%, 14.5%, and 47.4% of households were categorized as having severe, moderate, mild, and no food insecurity, respectively. Socioeconomic characteristics of the mother–infant dyads who were lost to follow-up differed from those of the dyads who were included in this analysis in several ways (**Supplemental Table 1**): in the former, mothers were older, shorter, had less education, a shorter duration of gestation, and lived in households that were more likely to be nuclear families, with lower household assets and greater food insecurity. Infants lost to follow-up were more likely

TABLE 2 Baseline characteristics of mothers of the children[1]

Variable	LNS-LNS	IFA-LNS	IFA-MNP	IFA-Control	*P* value
n	918	820	926	866	
Age, y	21.8 ± 4.9	21.8 ± 4.8	22.0 ± 4.9	22.0 ± 5.2	0.84
Gestational age at enrollment, d	92.0 ± 26.3	92.2 ± 27.5	92.0 ± 26.9	92.0 ± 26.8	0.99
Primipara	41.7	41.9	37.9	38.0	0.17
Height, cm	150.8 ± 5.3	150.5 ± 5.4	150.5 ± 5.4	150.7 ± 5.5	0.74
BMI, kg/m^2	20.0 ± 2.7	20.1 ± 2.6	20.0 ± 2.6	20.0 ± 2.8	0.70
Education, y	6.5 ± 3.1	6.3 ± 3.4	6.1 ± 3.2	6.1 ± 3.2	0.032
Household socioeconomic index	0.1 ± 2.2	0.1 ± 2.4	−0.1 ± 2.2	0.1 ± 2.2	0.36
Number of persons in the household	4.5 ± 2.0	4.7 ± 2.3	4.5 ± 2.3	4.7 ± 2.2	0.39
Children aged <5 y in the household	0.4 ± 0.6	0.4 ± 0.6	0.4 ± 0.6	0.5 ± 0.6	0.44
Toilet facility					0.70
1 (best)	11.2	13.4	14.8	13.0	
2 (intermediate)	28.5	22.6	25.2	25.9	
3 (worst)	60.3	64.0	60.0	61.1	
Better garbage disposal	75.3	72.2	76.2	74.9	0.95
Household food insecurity score	2.7 ± 3.9	3.0 ± 4.0	3.1 ± 4.1	3.2 ± 4.0	0.36
Indoor air quality index	10.9 ± 1.2	10.8 ± 1.1	10.8 ± 1.1	10.8 ± 1.1	0.44

[1]Values are means ± SDs or percentages unless otherwise indicated. *P* values of chi-square tests and ANCOVAs of mean values have been shown in the "*P* value" column. IFA, iron and folic acid; LNS, lipid-based nutrient supplement; MNP, micronutrient powder.

to be born preterm, had a lower birth weight, and were more likely to be stunted at birth than those not lost to follow-up.

Figure 2 illustrates the overall prevalence of fever, AURI, ALRI, and diarrhea during the 2 wk before the interviews at 6, 12, 18, and 24 mo. High fever was reported to have occurred in 17–20% of the children at each time point. AURI was the most common illness, with a prevalence of ~30% at all 4 time points. Prevalence of ALRI declined with age, from 17.6% at 6 mo to 8.8% at 24 mo. Diarrhea was the least commonly reported illness, with a prevalence of ~7–8% at 6–18 mo and 3.4% at 24 mo.

Morbidity at 0–6 mo

Table 3 illustrates that there were no significant differences between the maternal LNS and IFA groups in the average reported number of days with high fever, nasal discharge, cough, or diarrhea during the 2 wk prior to 6 mo, or in the percentage with any occurrence of high fever, ALRI, or diarrhea during those 2 wk, but a lower percentage of infants in the maternal LNS group were reported to have AURI than in the IFA group (27.7% compared with 31.7%, $P = 0.040$). There were no significant differences between groups in the reported number of episodes between birth and 6 mo of cough or nasal discharge; cough or nasal discharge accompanied by rapid or difficult breathing; or diarrhea. Adjustment for prespecified covariates did not alter the findings.

Morbidity at 6–12 mo

As shown in Table 4, there were no significant differences between the 4 intervention groups in the average reported number of days with reported high fever, nasal discharge, cough, or diarrhea during the 2 wk prior to 12 mo or in the percentage with any occurrence of high fever, ALRI, or diarrhea during those 2 wk, but a lower percentage of children in the IFA-LNS group were reported to have AURI, compared with the IFA-Control group (27.6 compared with 33.9%, $P = 0.042$). There were no significant differences between groups in the reported number of episodes between 6 and 12 mo of cough or nasal discharge, or cough or nasal discharge accompanied by rapid or difficult breathing. The number of episodes of diarrhea reported was low (overall mean 0.44 episodes per 6 mo), but was significantly higher (by 0.13 episodes per 6 mo, $P = 0.032$) in the IFA-LNS group than in the IFA-Control group.

Morbidity at 12–18 mo

Table 4 shows that there were no significant differences between the 4 intervention groups in the average reported number of days with high fever, nasal discharge, or cough during the 2 wk prior to 18 mo. There was a significant main effect of intervention group with regard to number of days with diarrhea, but none of the pairwise group comparisons was statistically significant. There were no significant differences in the percentage of children with any occurrence of high fever, AURI, ALRI, or diarrhea during those 2 wk or reported number of episodes between 12 and 18 mo of cough or nasal discharge, or cough or nasal discharge accompanied by rapid or difficult breathing. The number of episodes of diarrhea reported was again low (overall mean 0.40 episodes per 6 mo), but was significantly higher (by 0.12 episodes per 6 mo, $P = 0.007$) in the IFA-LNS group than in the IFA-Control group.

Morbidity at 18–24 mo

As Table 4 illustrates, there were no significant differences between the 4 intervention groups in the average reported number of days with high fever, nasal discharge, cough, or diarrhea during the 2 wk prior to 24 mo or in the percentage with any occurrence of high fever, AURI, ALRI, or diarrhea during those 2 wk, nor in the reported number of episodes between 18 and 24 mo of cough or nasal discharge; cough or nasal discharge accompanied by rapid or difficult breathing; or diarrhea.

Mortality

A total of 161 children died before 24 mo of age; 92 were neonatal deaths and 69 were post-neonatal deaths. Neonatal mortality did not differ by treatment group: LNS-LNS, $n = 25$, 26.1/1000 live births; IFA-LNS, $n = 28$, 33.1/1000 live

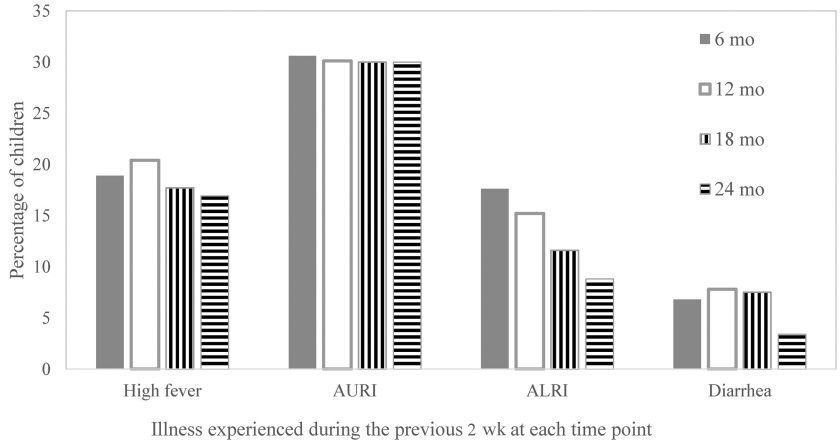

FIGURE 2 Percentages of children who experienced high fever, AURI, ALRI, or diarrhea in the 2 wk before 6, 12, 18, and 24 mo of age. ALRI, acute lower respiratory infection; AURI, acute upper respiratory infection.

births; IFA-MNP, $n = 28$, 29.1/1000 live births; and IFA-Control, $n = 21$, 23.4/1000 live births. Post-neonatal deaths differed by treatment group ($P = 0.043$): LNS-LNS, $n = 15$, 15.7/1000 live births; IFA-LNS, $n = 6$, 7.1/1000 live births; IFA-MNP, $n = 15$, 15.6/1000 live births; and IFA-Control, $n = 23$, 25.6/1000 live births. Pairwise tests indicated that post-neonatal mortality was significantly lower in the IFA-LNS group than in the IFA-Control group (IRR: 0.27; 95% CI: 0.08, 0.92).

Sensitivity analysis

We conducted a sensitivity analysis to examine the effect of LNS and MNP in the subdistrict in which the Bangladesh government did not provide any MNP. The results were generally similar, but some differences in respiratory illness became significant (number of days with cough at 6 and 24 mo) and some of the differences in diarrhea became nonsignificant (number of episodes between 6 and 12 mo and between 12 and 18 mo) (**Supplemental Tables 2** and **3**).

Discussion

This study aimed to examine the effect of providing LNS-PL to pregnant and lactating women or providing LNS-C or MNP to their children from 6 to 24 mo on common childhood illnesses measured at 6, 12, 18, and 24 mo of age. Overall, we found few differences between the 4 intervention groups in reported prevalence or number of episodes of fever, respiratory illness, or diarrhea, except for *1*) a lower percentage of infants with AURI in the LNS group than in the IFA group at 6 mo; *2*) a lower percentage of infants with AURI in the IFA-LNS group than

TABLE 3 Infant morbidity between birth and 6 mo, by maternal intervention group[1]

Illness	LNS mother ($n = 907$)	IFA mother ($n = 2575$)	IRR or OR (95% CI)	*P* value
Days of illness[2]				
High fever	0.54 ± 0.06	0.60 ± 0.04	0.90 (0.70, 1.16)[3]	0.43
Nasal discharge	5.09 ± 0.21	5.23 ± 0.13	0.97 (0.88, 1.07)[3]	0.56
Cough	3.39 ± 0.20	3.76 ± 0.13	0.90 (0.78, 1.03)[3]	0.13
Diarrhea	0.36 ± 0.07	0.23 ± 0.03	1.61 (0.99, 2.60)[3]	0.05
Occurrence[4]				
High fever	18.9	18.9	1.02 (0.83, 1.24)[5]	0.87
AURI	27.7	31.7	0.83 (0.70, 0.99)[5]	0.040
ALRI	16.8	17.8	0.97 (0.77, 1.22)[5]	0.78
Diarrhea	8.8	6.1	1.35 (1.00, 1.82)[5]	0.05
Number of episodes[6]				
Cough and nasal discharge	4.66 ± 0.11	4.53 ± 0.06	1.03 (0.98, 1.09)[3]	0.29
Rapid or difficult breathing plus cough and nasal discharge	0.78 ± 0.05	0.70 ± 0.02	1.11 (0.97, 1.27)[3]	0.13
Diarrhea	0.31 ± 0.03	0.29 ± 0.01	1.08 (0.89, 1.31)[3]	0.41

[1] ALRI, acute lower respiratory infection; AURI, acute upper respiratory infection; IFA, iron and folic acid supplement; IRR, incidence rate ratio; LNS, lipid-based nutrient supplement.
[2] Number of days of illness (mean ± SD) reported in the last 2 wk.
[3] IRR (95% CI).
[4] Occurrence (%) of illness reported in the last 2 wk.
[5] OR (95% CI).
[6] Number of reported episodes of illness during the 6-mo period (mean ± SD).

TABLE 4 Child morbidity between 6 and 24 mo by intervention group[1]

Illness	LNS–LNS ($n = 908$)	IFA-LNS ($n = 810$)	IFA-MNP ($n = 907$)	IFA-Control ($n = 838$)	*P* value
6–12 mo					
Days of illness[2]					
High fever	0.56 ± 0.06	0.56 ± 0.06	0.70 ± 0.07	0.55 ± 0.06	0.32
Nasal discharge	4.70 ± 0.20	4.47 ± 0.20	4.63 ± 0.20	4.82 ± 0.21	0.69
Cough	2.83 ± 0.17	2.70 ± 0.17	2.93 ± 0.17	2.93 ± 0.18	0.75
Diarrhea	0.21 ± 0.04	0.24 ± 0.05	0.26 ± 0.05	0.22 ± 0.04	0.82
Occurrence[3]					
High fever	19.2	19.9	23.5	18.9	0.09
AURI[4]	28.6[a,b]	27.6[a]	30.3[a,b]	33.9[b]	0.042
ALRI	15.0	13.9	16.3	15.5	0.61
Diarrhea	7.1	8.5	8.7	6.8	0.47
Number of episodes[5]					
Cough and nasal discharge	3.64 ± 0.09	3.55 ± 0.10	3.49 ± 0.09	3.50 ± 0.09	0.63
Rapid or difficult breathing plus cough and nasal discharge	0.47 ± 0.04	0.44 ± 0.04	0.43 ± 0.04	0.40 ± 0.03	0.64
Diarrhea[6]	0.41 ± 0.03[a,b]	0.46 ± 0.04[a]	0.45 ± 0.03[a,b]	0.33 ± 0.03[b]	0.032
12–18 mo					
Days of illness[2]					
High fever	0.45 ± 0.05	0.53 ± 0.06	0.49 ± 0.05	0.48 ± 0.05	0.75
Nasal discharge	4.25 ± 0.20	4.37 ± 0.22	4.36 ± 0.21	4.38 ± 0.21	0.97
Cough	2.29 ± 0.15	2.43 ± 0.17	2.19 ± 0.15	2.39 ± 0.16	0.70
Diarrhea[7]	0.26 ± 0.05	0.30 ± 0.06	0.16 ± 0.03	0.16 ± 0.03	0.038
Occurrence[3]					
High fever	16.5	19.8	16.5	18.1	0.24
AURI	29.1	29.1	30.3	31.5	0.75
ALRI	10.4	13.7	9.9	12.7	0.11
Diarrhea	8.3	9.3	6.5	6.0	0.07
Number of episodes[4]					
Cough and nasal discharge	2.51 ± 0.07	2.71 ± 0.08	2.73 ± 0.08	2.73 ± 0.08	0.13
Rapid or difficult breathing plus cough and nasal discharge	0.34 ± 0.03	0.33 ± 0.04	0.32 ± 0.03	0.32 ± 0.03	0.97
Diarrhea[8]	0.42 ± 0.03[a,b]	0.45 ± 0.03[a]	0.36 ± 0.02[a,b]	0.33 ± 0.02[b]	0.007
18–24 mo					
Days of illness[2]					
High fever	0.37 ± 0.04	0.51 ± 0.06	0.41 ± 0.04	0.48 ± 0.05	0.18
Nasal discharge	4.05 ± 0.20	4.26 ± 0.21	4.21 ± 0.20	4.48 ± 0.22	0.54
Cough	1.87 ± 0.13	2.02 ± 0.15	1.89 ± 0.14	2.31 ± 0.17	0.17
Diarrhea	0.11 ± 0.03	0.10 ± 0.03	0.05 ± 0.02	0.07 ± 0.02	0.30
Occurrence[3]					
High fever	15.1	18.8	15.9	18.1	0.17
AURI	28.8	27.5	29.5	32.5	0.23
ALRI	8.5	10.0	7.6	9.3	0.45
Diarrhea	4.2	4.6	2.3	2.6	0.06
Number of episodes[4]					
Cough and nasal discharge	2.25 ± 0.07	2.22 ± 0.07	2.11 ± 0.06	2.26 ± 0.07	0.40
Rapid or difficult breathing plus cough and nasal discharge	0.20 ± 0.02	0.18 ± 0.02	0.19 ± 0.02	0.19 ± 0.02	0.87
Diarrhea	0.21 ± 0.02	0.22 ± 0.02	0.17 ± 0.02	0.17 ± 0.02	0.15

[a,b]Groups that do not share a common superscript letter differ, $P < 0.05$.

[1]ALRI, acute lower respiratory infection; AURI, acute upper respiratory infection; IFA, iron and folic acid supplement; IRR, incidence rate ratio; LNS, lipid-based nutrient supplement; MNP, micronutrient powder.

[2]Number of days of illness (mean ± SD) reported in the last 2 wk.

[3]Occurrence (%) of illness reported in the last 2 wk.

[4]AURI between IFA-LNS and IFA-Control: OR: 0.74; 95% CI: 0.56, 0.99; $P = 0.040$.

[5]Number of reported episodes of illness during the 6-mo period (mean ± SD).

[6]Diarrhea between IFA-LNS and IFA-Control: IRR: 1.38; 95% CI: 1.02, 1.86; $P = 0.033$.

[7]None of the pairwise group differences were significant.

[8]Diarrhea between IFA-LNS and IFA-Control: IRR: 1.36; 95% CI: 1.06, 1.75; $P = 0.011$.

in the IFA-Control group at 12 mo; and *3*) a higher number of reported episodes of diarrhea from 6 to 12 and from 12 to 18 mo in the IFA-LNS group than in the IFA-Control group.

The lower prevalence of AURI in the maternal LNS group at 6 mo might be due to chance, or could be related to the exposure of those infants to the additional nutrients provided by LNS-PL during gestation and via breastfeeding, as their mothers received LNS-PL until 6 mo postpartum. During gestation, essential fatty acids, vitamins, and minerals are transported to the fetus through the placenta (31). During lactation the type and amount of fat in the woman's diet (32) and intake of certain vitamins and minerals (33) influence breast-milk composition and infant status. Essential fatty acids are required for immune cell phospholipids, and thus may affect immune function by altering membrane functions, signal transduction pathways, and bioactive lipids (12). Other nutrients provided by LNS-PL (but not IFA) also play a role in immune function, including vitamin A (6), vitamins B-6 and B-12 (7), vitamin C (7), vitamin D (6, 8), vitamin E (7), zinc (7, 9, 10), selenium (7), and copper (7). We are unable to compare our findings regarding the effect of both pre- and postnatal maternal nutrient supplementation on infant morbidity in the first 6 mo of life to previous research because we did not locate any similar studies. However, there is evidence that perinatal zinc deficiency is related to acquisition of maternal antibodies and development of natural immunity in the infant (34, 35) and zinc supplementation during pregnancy reduced the risk of diarrhea and dysentery at 6 mo of age among low-birth-weight infants (21).

After 6 mo, there were few differences between the intervention groups in terms of morbidity outcomes. However, the occurrence of AURI in the last 2 wk before 12 mo was lower among the children in the IFA-LNS group than among those in the IFA-Control group, which is consistent with the difference in AURI observed at 6 mo. Occurrence of AURI in the 2 wk before 12 mo did not differ between the LNS-LNS and IFA-LNS groups, both of which received LNS-C, but the difference compared with the IFA-Control group was significant only in the latter. This indicates that the difference is not due to LNS-PL because the IFA-LNS group did not receive LNS-PL. Direct receipt of nutrients via LNS-C by the children could have influenced immune function and thereby occurrence of AURI. For example, the essential fatty acids provided by LNS-C, and the higher content of zinc compared with the amount in the MNP, may have played a role. At 18 and 24 mo, the occurrence of AURI no longer differed significantly between intervention groups. Because of the rapid development of the immune system in infancy, it is possible that a morbidity response to nutrient supplementation would be more evident in the first year of life. Alternatively, the difference in AURI at 12 mo could have been due to chance, given that another randomized controlled trial on the effect of LNS-C among children in Malawi at 6–18 mo of age did not show any group differences in respiratory illness (18).

The number of episodes of diarrhea reported in the last 6 mo was low at all time points, but was significantly higher in the IFA-LNS group than in the IFA-Control group at 12 and 18 mo. However, there was no difference at 24 mo, and values for the LNS-LNS and IFA-MNP groups did not differ from those of the IFA-Control group at any time point. In some studies using nutrient supplements or MNPs, iron has been implicated with regard to potentially increasing the risk of diarrhea in children (4, 16, 17). Iron may increase diarrhea by altering the microbiota to favor pathogenic organisms, increasing permeability of the intestinal wall due to oxidative effects (36, 37), and/or inducing gut inflammation (17). However, a systematic review of iron supplementation in children 4–23 mo of age did not indicate any increase in risk of diarrhea (5). In our study, the lack of any differences in diarrhea in the MNP and LNS-LNS groups, compared with IFA-Control, suggests that iron was not the cause of the difference in the IFA-LNS group, because all 3 groups received similar amounts of iron (10 mg in MNP, 9 mg in LNS). In Malawi, a randomized trial in which LNS (with 6 mg Fe) was provided from 6 to 18 mo of age did not show any effects on diarrhea (20). Thus, the reason for the slightly higher number of episodes of diarrhea (+0.12 to +0.13 episodes per 6 mo) in the IFA-LNS group than in the IFA-Control group at 12 and 18 mo in our study is unclear and could be due to chance. Nonetheless, future studies should include measures of diarrhea to determine if these findings can be replicated.

Neonatal mortality did not differ between intervention groups, but post-neonatal mortality was significantly lower in the IFA-LNS group than in IFA-Control. Given that children in both the IFA-LNS and the LNS-LNS groups received LNSs, it is not clear why mortality was significantly lower only in the IFA-LNS group. This study was not powered for detection of differences in child mortality, so further research with larger sample sizes is needed.

Strengths of this study include the following: *1*) its large sample size; *2*) its randomized design with 16 clusters per arm; *3*) morbidity data collection by a well-trained and standardized team; and *4*) a low rate of attrition in all intervention groups at all data collection time points. A key limitation is that all of the morbidity outcomes were based on maternal or caregiver recall of symptoms, with a recall period of 2 wk for the main outcomes and 6 mo for the secondary outcomes, and there may be recall errors and misclassification particularly in distinguishing between AURI and ALRI. However, recall error should be similar across intervention groups so should not be a major source of bias. Other key limitations are *1*) the inability to blind participants to the type of supplement provided because of differences in supplement appearance and taste; *2*) morbidity recall data were collected by the "home visit team" in the study participants' homes, so those data collectors might have seen study supplements and become unblinded; and *3*) because of greater loss to follow-up of infants who were born preterm or with low birth weight (partly due to greater mortality among those infants), maternal and child characteristics of this sample of children differ from those of the original study sample enrolled, so generalizability is limited. In addition, the definition of diarrhea for the 2-wk recall periods in our study was more restrictive than that of other studies, i.e., >3 (rather than ≥3) abnormally loose or watery stools in a 24-h period. Also, adherence was assessed based on qualitative data reported retrospectively by caregivers which could be biased. Reported adherence in a subsample of participants who were visited by a separate team of interviewers was somewhat lower than in the full sample (38, 39). Lastly, some sharing of supplements was reported, although mainly within a household and not across clusters (38, 39).

We conclude that providing LNSs to women or LNSs or MNP to children generally did not increase or decrease common childhood illnesses. Further research is needed to evaluate whether the beneficial effects of LNSs on AURI that we observed can be replicated in other settings and, if so, to investigate potential mechanisms. Although some group differences in diarrhea were observed, they were very small and not consistent,

so they are not likely to be of clinical importance. Evaluation of nutrition interventions should take into account multiple outcomes, including growth, development, and morbidity in the context of the health and nutritional status of the study population, to allow for informed decision-making for program implementation.

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