Mineral- and vitamin-enhanced micronutrient powder reduces stunting in full-term low-birth-weight infants receiving nutrition, health, and hygiene education: a 2 × 2 factorial, cluster-randomized trial in Bangladesh[1,2]

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ABSTRACT

Background: The causes of stunting are complex but likely include prenatal effects, inadequate postnatal nutrient intake, and recurrent infections. Low-birth-weight (LBW) infants are at high risk of stunting. More than 25% of live births in low- and middle-income countries are at full term with low birth weight (FT-LBW). Evidence on the efficacy of specific interventions to enhance growth in this vulnerable group remains scant.

Objective: We investigated the independent and combined effects of a directed use of a water-based hand sanitizer (HS) and a mineral- and vitamin-enhanced micronutrient powder (MNP) (22 minerals and vitamins) to prevent infections and improve nutrient intake to reduce stunting in FT-LBW infants.

Design: The study was a prospective 2 × 2 factorial, cluster-randomized trial in 467 FT-LBW infants during 2 periods: from 0 to 5 mo postpartum (0−180 d postpartum) and from 6 to 12 mo postpartum (181−360 d postpartum) with the use of 48 clusters. All groups received the same general nutrition, health, and hygiene education (NHHE) at enrollment and throughout the 12 mo. Group assignments initially included the following 2 groups: no HS (control) group or HS from 0 to 5 mo postpartum. These assignments were followed by further divisions into the following 4 groups from 6 to 12 mo postpartum: *1*) no HS and no MNP (control), *2*) HS only, *3*) MNP only, and *4*) HS and MNP.

Results: When delivered in combination with NHHE, the use of an HS showed no additional benefit in reducing indicators of infection in the first or second half of infancy or the likelihood of stunting at 12 mo postpartum. FT-LBW infants who received the MNP (with or without the HS) were significantly less likely to be stunted at 12 mo than were controls (OR: 0.35; 95% CI: 0.15, 0.84; $P = 0.017$).

Conclusions: The use of a mineral- and vitamin-enhanced MNP significantly reduced stunting in FT-LBW infants in this high-risk setting. The use of a water-based HS did not have an additive effect. This trial was registered at clinicaltrials.gov as NCT01455636.
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Keywords: full-term low-birth-weight infant, hand hygiene, hand sanitizer, infants, infection, linear growth, low birth weight, micronutrient powder, minerals and vitamins, stunting

INTRODUCTION

Globally, 165 million children <5 y of age manifest stunting, which is a chronic form of undernutrition that results from some combination of prenatal and postnatal linear growth faltering (1, 2). Infants who are born with a low birth weight (LBW)[11] (<2500 g) are particularly vulnerable to frequent infections and malnutrition, which result in linear growth faltering and poor cognitive development (3, 4). In Bangladesh alone, more than 1 million LBW full-term infants were born in 2010 (1). Infections are associated with impaired nutrient absorption, impaired transport of nutrients to target tissues, and increased catabolic losses (5–7). If infections occur repetitively, their net effect on feeding, nutrient absorption and use, and ultimately growth can be substantial (7). Exclusive breastfeeding is recommended for the first 6 mo of life because it can best support the nutrient needs of most healthy infants (8) and provides protective immunologic benefits (9). However, during this period, even

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[11] Abbreviations used: FT-LBW, full-term with low birth weight; HNA, health and nutrition assistant; HS, hand sanitizer; ICC, intracluster correlation coefficient; LAZ, length-for-age z score; LBW, low birth weight; MNP, micronutrient powder; NHHE, nutrition, health, and hygiene education; WAZ, weight-for-age z score; WLZ, weight-for-length z score.

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exclusively breastfed infants are highly susceptible to infections particularly in resource-poor settings. In the second 6 mo of life and thereafter, the poor quality of complementary foods may lead to a deficiency of minerals and vitamins that are needed to support adequate linear growth (10). Any intervention that can decrease the number of episodes of infection in infants is likely to improve appetite, the ingestion of food, and the use of nutrients for linear and other growth.

A targeted use of handwashing with soap and water has been shown to be an effective strategy to prevent infections (11, 12). Although soap is widely available in many resource-poor settings, clean water is often scarce, thereby limiting appropriate handwashing. The use of hand sanitizers (HSs) has been shown to decrease iatrogenic infections in developed countries and in hospitals globally (13). Alcohol-based HSs are not totally safe for community use because they are highly flammable and toxic if inadvertently ingested (14), but there has been limited information on the efficacy of alcohol-free, water-based HSs particularly in resource-poor community settings (15). Water-based HSs contain benzalkonium chloride, which is a fast-acting biocidal agent (bacteriostatic or bactericidal according to its concentration) with a moderately long duration of action. Benzalkonium chloride is active against bacteria and some viruses, fungi, and protozoa. Gram-positive bacteria are generally more susceptible than are gram-negative bacteria (16).

Home fortification of complementary foods with micronutrient powders (MNPs) is a feasible and cost-effective strategy to prevent and treat micronutrient deficiencies globally (17–19). In the past, MNPs have included only those micronutrients that were needed to prevent or treat anemia or, alternatively, to provide a variety of minerals and vitamins to achieve the recommended dietary allowances for infants and young children. However, the formulations did not contain all of the minerals to potentially enhance bone growth (19). The inclusion of minerals such as calcium, phosphorus, magnesium, and manganese may enhance linear growth, and additional zinc in MNPs may improve appetite and total food intake (20). The objective of this trial was to investigate the effect of the directed use of a water-based HS and the effect of the HS combined with the provision of a mineral- and vitamin-enhanced MNP (22 minerals and vitamins) to prevent infections and reduce stunting in full-term LBW (FT-LBW) infants. The primary outcome of the study was the rate of stunting [length-for-age z score (LAZ) <-2] at age 12 mo. Secondary outcomes included the prevalence of moderate and severe stunting, signs of infections (e.g., diarrhea, upper respiratory tract infections, cough, and fever), dietary intake (not reported here), and hematologic status.

METHODS

Study subjects

The study was conducted in the following 2 adjacent rural upazilas (subdistricts): Palash in the Narsingdi district and Kaliganj in the Gazipur district within the Dhaka Division of Bangladesh, which is a country in South Asia with a very high rate of LBW and stunting (21, 22). The study was carried out in collaboration with BRAC, which is the largest nongovernment organization in Bangladesh. LBW infants were recruited as the study subjects and final targets of the intervention. Once infants were enrolled in the study after the receipt of parental consent, their biological mothers were provided with nutrition, health, and hygiene education (NHHE) as the intermediate targets of the intervention. Mothers also contributed as consenting participants by responding to the study questionnaires.

Study design

This study followed a prospective 2 × 2 factorial, community-based, cluster-randomized design to ensure better representativeness and prevent contamination in intervention groups (23). In the first 6 mo of infancy (0–5 mo of age), infants from all 48 clusters were allocated to either HS or no-HS groups. In the second 6 mo of infancy (6–12 mo of age), infants in each of the original 2 groups were randomly reallocated to either an MNP or a no-MNP group. For groups who were assigned to receive the HS, HS was continued throughout the 1-y study. All groups were provided with NHHE during the entire period of study (0–12 mo) by health and nutrition promoters and health and nutrition assistants (HNAs). The 48 clusters were randomized as follows: from 0 to 5 mo, no HS (control) or HS (n clusters = 24 for both); and from 6 to 12 mo, *1*) no HS or MNP, *2*) HS only, *3*) MNP only, and *4*) HS and MNP (n clusters = 12 for each group). This trial was registered at clinicaltrials.gov as NCT01455636.

Randomization and masking

The study area was divided into 48 clusters, and the clusters in all arms were equally distributed across the 2 subdistricts. All of our analyses accounted for clustering effects. Each cluster was defined as the geographical area covered by one HNA who provided service to ∼45–50 mothers. A cluster served as the unit of randomization, and an equal probability of allocation of the clusters was established with numbers that were randomly generated with the use of statistical software (SAS for Windows 9.1; SAS Institute Inc.) by the study statistician in Toronto, Canada. The study sampling frame was constructed by the investigators from a list of all married pregnant women who were identified through a household survey in Kaliganj and Palash districts. With the assumption that ≥20% of newborns would be born with LBW (21), a total of 2198 pregnant women were prospectively identified from 43,832 households in the 48 clusters. The required number of subjects was obtained after we assessed only 1295 of 2198 mother-infant pairs because the rate of LBW in our study was very high (36%); thus, 903 mothers were not approached for enrollment (**Figure 1**). All cluster randomization was performed before the recruitment began. However, the implementation of the interventions (with and without the HS and MNP) was done in 2 stages because all infants were meant to be exclusively breastfed for the first 6 mo of infancy, and the MNP intervention could only begin after 6 mo. It was not possible to mask infants who received the HS and MNP from those who did not; however, one team of fieldworkers recruited, enrolled, and provided supplies to infants (the recruitment team), and the other team (the evaluation team) collected outputs (e.g., weight, length, and health indexes). Although the recruitment team was aware of group allocations, the evaluation team was not.

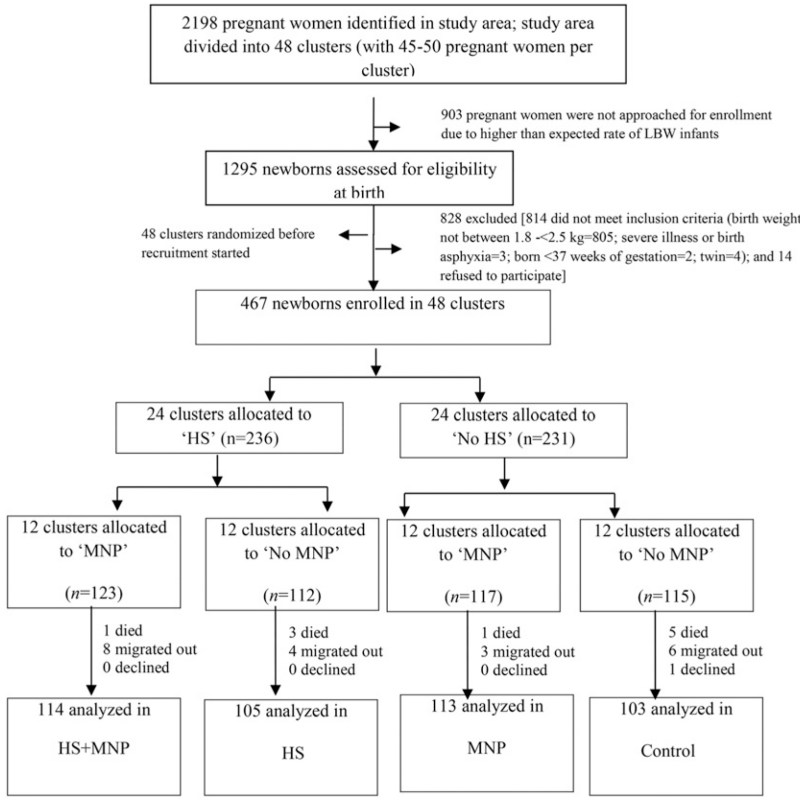

FIGURE 1 Trial profile of the study (0–12 mo). All families of enrolled infants received NHHE at enrollment and throughout the study. The control group received only NHHE and did not receive HS or MNP. All cluster randomization was performed before the recruitment began. The implementation of that random assignment was at birth and at 6 mo of age. HS, hand sanitizer; LBW, low birth weight; MNP, micronutrient powder; NHHE, nutrition, health, and hygiene education.

Sample size

The primary outcome was the rate of stunting, which was defined as an LAZ <-2 at the end of the intervention. On the basis of data from a previous study in rural Bangladesh (24), estimates of the required sample size were calculated with the assumption of a 20% reduction in the proportion of stunting (LAZ <-2) between the HS and MNP group and the control group (i.e., no HS and no MNP) by the end of the intervention. The intracluster correlation coefficient (ICC) was set low at 0.03, and cluster sizes [number of subjects in a cluster (m)] were expected to be $\geq$6 (25). The sample size was multiplied by a design effect (DE) of 1.15, which was calculated as DE = 1 + ICC (m – 1) to accommodate the clustering effect. We assumed a potential 20% loss to follow-up over 1 y and estimated that a total of 48 clusters inhabited by 480 LBW infants (120 infants/group) would have 80% power ($1 - \beta$) to detect a 20% reduction in the proportion of stunting at a 5% level of significance (α). Despite the long recruitment period, the dropout rate was lower than anticipated (6.4%), which resulted in a sample size of 436 that was sufficient for our analyses. On the basis of the data at baseline, our actual baseline ICC was 0.026 with 4 groups (which supported our initial assumption of an ICC of 0.03). Our actual ICC at 12 mo (at the end of the study) was 0.16.

Birth preparedness and notification

Each pregnant woman was visited at the eighth month of pregnancy, and a birth preparedness meeting was conducted in which education regarding essential newborn care, the use of the safe delivery kit (locally produced by the BRAC Health Program and provided free of charge), handwashing, the early initiation of breastfeeding, and exclusive breastfeeding was provided along with demonstrations. In addition, leaflets with clear messages on handwashing and breastfeeding were provided to the household head and literate members of the families.

Informed consent

Verbal consent to collect the weights and lengths of newborns within 24 h of birth was requested from all pregnant mothers and the male members of the family. For infants who met the eligibility criteria, written informed consent was requested from the biological mothers before enrollment.

Screening and enrollment

Within 24 h of a birth, each infant-mother dyad was visited by members of the recruitment team, which consisted of 2 trained field enumerators. The field enumerators were separated from the evaluation team throughout the study period by arranging separate administrative meetings and training sessions. Infants were eligible to be enrolled in the study according to the following inclusion criteria: *1*) born as singletons and at full term ($\geq$37 wk of gestation), *2*) birth weight from 1800 to $<$2500 g, and *3*) families planned to reside in the study area for $\geq$1 y. Exclusion criteria were as follows: *1*) severe illness, *2*) birth asphyxia, *3*) congenital abnormalities or severe malformations, and *4*) mother's health was significantly compromised during birth. During the 6 mo allocated for recruitment, a total of 467 infants were enrolled in the study and were to be followed for 12 mo.

NHHE

Throughout the 12-mo intervention period, caregivers in all groups received simple, standardized, and age- and culturally appropriate NHHE that aimed to improve infant feeding and prevent infections. The NHHE included *1*) kangaroo mother care, which is a technique that is used for the thermal protection of the newborn through skin-to-skin contact between the mother and newborn; *2*) the early initiation of breastfeeding; *3*) exclusive breastfeeding; *4*) timely, adequate, age-appropriate, and safe complementary feeding; *5*) responsive feeding and psychosocial stimulation; *6*) handwashing with soap; *7*) recognition of danger signs of common diseases and care during illness; and 8) the father's involvement and family support (26). In addition, mothers were informed how to use oral rehydration solutions and zinc tablets (provided free to study subjects for all diarrhea episodes).

Randomized intervention components

Directed hand hygiene with HS

The active ingredient of the HS used in this study was benzalkonium chloride (alkyl dimethyl benzyl ammonium chloride). There has been good documentation of the efficacy of benzalkonium chloride in the literature. Benzalkonium chloride solutions are fast-acting biocidal agents with a moderately long duration of action. They are active against bacteria and some viruses, fungi, and protozoa. Bacterial spores are considered to be resistant. Solutions are bacteriostatic or bactericidal according to their concentrations. Gram-positive bacteria are generally more susceptible than are gram-negative bacteria. Activity is not greatly affected by pH but increases substantially at higher temperatures and prolonged exposure times (16). The product used in this study contained no alcohol, was produced in India by Hexagon Inc., and was delivered in 250-mL foam-producing plastic dispensers to the families in the study. Containers were replaced as required throughout the intervention period. Because the use of the HS was not meant to replace the practice of handwashing with soap and water, it was necessary to identify and separate the critical points for the use of the HS from that of washing hands with soap and water (**Table 1**). The instructions for the use of the product were informed by a formative research study that was completed before the intervention (with the use of focus-group discussions and interviews). All households received a poster that included pictorial messages describing critical points for the use of the HS and a practical demonstration of its use.

Mineral-enhanced MNP

From the beginning of the sixth month, infants in the MNP groups were assigned to receive one sachet of mineral- and vitamin-enhanced MNP/d for 6 mo (6–12 mo). A modified formulation of an MNP with 22 micronutrients was used (**Table 2**), which was designed for this study and was produced by a local pharmaceutical company (Renata Pharmaceuticals Ltd.). Caregivers were provided with information on the dosage, use, and possible side effects of the MNP through a 4-color picture flipchart and practical demonstrations followed by an in-home practice session to ensure appropriate use.

TABLE 1
Critical hand-hygiene opportunities identified in behavior-change communication messages

Action	Time to use
Advice on handwashing with soap and water (all 4 groups)[1]	Before touching the newborn[2]
	Before preparing food
	Before eating
	Before feeding a child
	After defecation
	After cleaning child's anus
	After cleaning house or handling waste
Advice on the use of hand sanitizer (2 hand sanitizer groups only)[3]	Before touching the newborn
	Before eating snacks
	After sneezing or coughing or picking nose
	After returning home from field or outside
	After handling animals
	At any other time of their choosing

[1]Separate critical points for the use of a hand sanitizer were identified on the basis of formative research completed before the start of the intervention. All groups received advice on handwashing with soap and water as part of nutrition, health, and hygiene education. Messages were included in existing behavior-change communication materials used by Alive and Thrive and BRAC Health Program. Because the use of the hand sanitizer was not meant to replace the practice of handwashing with soap and water, it was necessary to identify and separate the critical points for use of the hand sanitizer from washing hands with soap and water, which ran through every group. The use of the hand sanitizer was not an alternative to handwashing with soap and water.

[2]Both handwashing and use of hand sanitizers were recommended before touching a newborn.

[3]These messages were provided to the groups who received the hand sanitizer.

Intervention delivery

The behavior change communication package in NHHE was reformulated on the basis of the Alive and Thrive program (27). Although the intervention components were the same as those used in the Alive and Thrive program, according to the protocol of our study, different contact points were used. The first contact was made before childbirth (at 8 mo of pregnancy). Immediately after the infant was born, mothers and infants were visited by HNAs every day for the first week, weekly for the rest of first month, and monthly from 2 to 6 mo. Similarly, in the second phase, when complementary feeding (as well as the MNP) was initiated, HNAs visited daily for the first 7 d of the seventh month, weekly thereafter, and monthly from 8 to 12 mo. The health and nutrition promoters visited mothers and infants when a problem was identified and provided counseling as appropriate. Group sessions at the cluster level were held every 3 mo (at 3, 6, and 9 mo of intervention).

Indicators of infant growth and morbidity

All infants were followed from 0 to 12 mo to obtain data for the primary (stunting at 12 mo) and secondary outcomes (morbidity, infant and young child feeding practices, and hematologic status).

TABLE 2
Composition of mineral-enhanced MNPs[1]

	Composition of MNP		
Micronutrient	22-nutrient MNP[2]	15-nutrient MNP	5-nutrient MNP
Vitamin A,[3] μg RE	300	300	300
Vitamin D,[4] μg	5	5	—
Vitamin E,[5] mg α-TE	6	6	—
Vitamin C, mg	30	30	30
Thiamin, mg	0.5	0.5	—
Riboflavin, mg	0.5	0.5	—
Vitamin B-6, mg	0.5	0.5	—
Vitamin B-12, μg	0.5	0.9	—
Niacin, mg	6.0	6.0	—
Folic acid, μg	160	160	160
Iron, mg	10	10	12.5
Zinc,[6] mg	10	10	5
Copper, mg	0.5	0.3	—
Selenium, μg	20	—	—
Iodine, μg	90	50	—
Calcium,[7] mg	100	—	—
Magnesium,[7] mg	20	—	—
Phosphorus,[7] mg	100	—	—
Manganese,[7] mg	0.6	—	—
Vitamin K,[7] μg	20	—	—
Pantothenic acid,[7] mg	1.8	—	—
Biotin,[7] μg	6.0	—	—

[1]MNP, micronutrient powder; RDA, Recommended Dietary Allowance; RE, retinol equivalent; α-TE, α-tocopherol equivalent.
[2]Expanded MNP was targeted to deliver between 27% and 100% of the RDA of micronutrients (333% for zinc) for infants between 6 and 12 mo of age. Dose: 1 sachet/d.
[3]One RE of vitamin A = 3.3 IU.
[4]One microgram of vitamin D = 40 IU.
[5]One milligram of α-TE = 1.5 IU.
[6]Zinc in the 22- and 15-nutrient MNPs was provided at ∼3.5 times the RDA to potentially enhance growth.
[7]Additional minerals and vitamins that were incorporated in the expanded MNP compared with the standard 15-micronutrient formulation.

Information on demographics, socioeconomic status, and other covariates were collected at the individual level during enrollment. All study questionnaires were pretested in the field. Anthropometric data were collected monthly by members of the evaluation team who were working in pairs. Identical portable measuring equipment was used that was routinely checked for accuracy and precision. Morbidity surveillance data were collected weekly for 12 mo with the use of structured questionnaires.

Standardized procedures were used to measure recumbent length to the nearest 1 mm on a locally constructed, high-quality length board (with digit-counter readings precise to 1 mm). Infants were measured independently by 2 members of the evaluation team at each visit; the paired measurements were compared, and if they differed by more than the threshold values (7 mm for length and 100 g for weight), a second set of measurements was performed. If the second pair differed by more than the threshold values, the procedure was repeated a third time. Unclothed infants were weighed with the use of an electronic infant-weighing scale (Tanita HD-314; Tanita Corp.), and weights were recorded to the nearest 10 g. Midupper arm circumference and head circumference were measured with the use of nonstretchable plastic tape measures (Lasso-o Tape; Harlow Printing Ltd.). All measuring devices were calibrated monthly. For anthropometric measurements, we followed the anthropometric protocol as described by the WHO Multicentre Growth Reference Study Group (28).

Diarrhea was defined as >3 loose stools in a 24-h period. An upper respiratory tract infection was diagnosed if the mother reported symptoms in her child of a stuffy or runny nose, whereas a cough was diagnosed if the child reported to have any sort of cough or difficulty breathing. In addition, body temperature data were recorded with the use of an axillary thermometer. With the aid of a pictorial calendar, mothers recorded daily whether a child had diarrhea, a cough, fever, or any other symptom of common childhood illnesses. Fieldworkers verified the information on the calendar every week through a recall interview.

Compliance

Compliance was assessed by counting the total number of bottles of HS and MNP sachets used by families at the end of each month with the use of structured data-collection forms.

Data management and quality control

Data were entered twice into a custom-designed Microsoft Access 2010 database program (Microsoft Corp.) and were electronically checked for extreme values considering biological plausibility and corrected after range and mismatch checks. Selection bias was minimized by strictly following the eligibility criteria. Measurement bias was minimized by following standard procedure in training the fieldworkers by the same set of trainers and with the use of structured questionnaires and standard methods. On the basis of the methods described in the WHO's multicenter growth reference study (29), interobserver variation was categorized into 3 categories as small, medium, and large. In the quality-assurance measurements done by the evaluators for height and weight, nearly all measurements fell into the small category. For the few measurements that were in the medium category, the training was continued or repeated until all measurements fell into the small category. All questionnaires and data forms were reviewed for accuracy, consistency, and completeness. To ensure data quality, the study supervisors and investigators made random spot checks. In addition, a 10% sample of study children were reinterviewed and remeasured ≤48 h of the original interview by 2 data collectors for quality control to provide continuous feedback on the quality of data. In addition, data collectors received refresher training every month. Quantitative and qualitative data were collected on the quality of training, intervention delivery, and supply of intervention components.

Ethics

The Research Ethics Committees of the Hospital for Sick Children, Canada, and the James P Grant School of Public Health, BRAC University, Bangladesh, provided ethical oversight of the study.

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Statistical analysis

Length, weight, and age were used to calculate standardized scores for the LAZ, weight-for-age *z* score (WAZ), and weight-for-length *z* score (WLZ) that were compared with WHO Child Growth Standards (29) with the use of ANTHRO 2011 software (2011 SAS igrowup package; SAS Institute Inc.). The analyses were performed with the use of SAS software (version 9.3; SAS Institute Inc.) on an intention-to-treat basis. The primary outcome of the study was the rate of stunting (LAZ <-2) at age 12 mo. Secondary outcomes included the prevalence of moderate and severe stunting, signs of infections (e.g., diarrhea, upper respiratory tract infections, cough, and fever), dietary intake (not reported here), and hematologic status. Baseline characteristics of the different intervention groups were examined for group comparability at enrollment. Generalized linear mixed models were used for all analyses to account for clustering effects. The weekly prevalence of symptoms between 2 groups (control and HS groups) during the first 5 mo and the differences across 4 groups for the LAZ over the 12-mo duration were examined. All tests were 2-sided with a significance level set at 5%.

RESULTS

Between 14 October 2010 and 30 April 2011, 1295 infants were born in the study area and were assessed for enrollment (Figure 1). The study ended 1 y later (30 April 2012). In these newborns, 828 infants were excluded. Of these 828 infants, 814 newborns did not meet the eligibility criteria (805 infants had birth weight <1.8 or >2.5 kg; 3 infants had a severe illness or birth asphyxia; 2 infants were born at <37 wk of gestation; and 4 infants were twins), and the families of 14 eligible infants declined to participate. The remaining 467 newborns were preassigned to one of 48 clusters by the locations of their residences, were then randomly assigned into 2 intervention groups [HS or control (no HS)] at birth (in 24 clusters), and were further

TABLE 3
Comparison of selected maternal and socioeconomic characteristics at enrollment and infant characteristics at birth by intervention group[1]

Descriptor	Intervention group				*P*
	Control[2] (*n* = 115)	HS (*n* = 112)	MNP (*n* = 117)	HS and MNP (*n* = 123)	
Socioeconomic status					
Ownership of house, %	91.2	92.0	96.6	96.7	0.21
Use electricity, %	78.9	74.3	78.6	79.7	0.86
Area of main house, ft^2	160.8 ± 93.3[3]	155.7 ± 96.2	138.5 ± 66.8	151.0 ± 88.1	0.275
Area of owned land, decimal[4]	76.0 ± 99.9	43.9 ± 61.8	68.7 ± 177.2	79.6 ± 126.0	0.229
Expenditure on food in the past month, $	57.8 ± 27.9	61.7 ± 29.8	61.8 ± 36.1	57.4 ± 30.2	0.812
Water sanitation, %					
Access to a tube well at the home premise	57.0	48.7	56.4	70.7	0.047
Access to a sanitary latrine at home[5]	21.1	24.8	16.2	14.6	0.32
Washed hands before feeding children	39.5	35.4	41.0	36.6	0.86
Maternal characteristic					
Age (y), %					0.314
<20	21.1	25.7	24.8	24.4	—
20–24	46.5	35.4	33.3	40.7	—
25–29	16.7	22.1	24.8	24.4	—
≥30	15.8	16.8	17.1	10.6	—
BMI, kg/m^2	20.5 ± 2.8	21.0 ± 2.7	21.0 ± 2.8	20.4 ± 2.8	0.759
Educational level, %					0.037
None or only primary schooling	53.5	48.6	37.1	36.5	—
Secondary or further	46.5	51.3	62.9	63.4	—
ANC visits, *n*	2.7 ± 1.9	2.7 ± 1.9	2.8 ± 1.9	2.6 ± 1.6	0.929
Received iron supplementation, %	57.0	45.1	53.8	56.1	0.510
Delivered infant at home, %	78.9	82.3	75.2	82.1	0.60
Infant characteristic					
Male, %	50.4	36.6	42.7	51.2	0.26
Birth weight, kg	2.2 ± 0.2	2.2 ± 0.2	2.2 ± 0.2	2.2 ± 0.2	0.56
Birth length, cm	43.9 ± 1.9	44.0 ± 1.7	44.1 ± 1.8	44.3 ± 1.8	0.46
Head circumference, cm	32.4 ± 0.9	32.3 ± 1.0	32.5 ± 1.1	32.6 ± 1.2	0.12
Length-for-age *z* score	−3.0 ± 0.8	−3.0 ± 0.9	−2.9 ± 1.0	−2.8 ± 1.1	0.28
Weight-for-age *z* score	−2.5 ± 0.4	−2.4 ± 0.4	−2.4 ± 0.4	−2.4 ± 0.4	0.34
Weight-for-length *z* score	−1.4 ± 0.9	−1.2 ± 0.9	−1.3 ± 0.7	−1.5 ± 0.8	0.258
Stunting at birth, %	82.6	84.5	82.9	74.9	0.20

[1]Significance was assessed with the use of generalized linear mixed models for all analyses to account for clustering effects. ANC, antenatal care; HS, hand sanitizer; MNP, micronutrient powder.

[2]Control group received no HS and no MNP.

[3]Mean ± SD (all such values).

[4]Decimal = 0.01 acres (40.4 m^2).

[5]Sanitary latrine was defined in the BRAC report (30).

randomly assigned into 4 intervention groups at the end of 5 mo (in 12 clusters). All random assignments took place before completion of recruitment. On the basis of the data at baseline, our actual baseline ICC was 0.026 with 4 groups (which supported our initial assumption of an ICC of 0.03). Our actual ICC at 12 mo (at the end of the study) was 0.16.

Families of infants in all groups received NHHE throughout the study. At the infant age of 6 mo, the groups included a no-HS and no-MNP (control) group (n = 115), an HS group (n = 112), an MNP group (n = 117), and an HS and MNP group (n = 123). There were ~8–14 infants/cluster. The 31 infants who dropped out did not differ in their enrollment characteristics from those of infants who completed the trial at 12 mo of age (data not shown). In infants who completed the study, at birth, 379 newborns were stunted of whom 205 infants (47.0%) were severely stunted and 174 infants (39.9%) were moderately stunted. The remaining 57 infants (13%) were not stunted at birth. WAZs and WLZs were similar at birth (**Table 3**) and at 6 and 12 mo across the 4 groups [WAZ: from −1.4 to −1.6 at 6 mo (P = 0.71) and from −1.0 to −1.4 at 12 mo (P = 0.543); WLZ: from 0.0 to 0.1 at 6 mo (P = 0.25) and from 0.0 to −0.5 at 12 mo (P = 0.86)].

No significant differences between the control and 3 intervention groups were observed in maternal and household socioeconomic characteristics at enrollment and infants at birth with the exception of maternal education and access to a tube well at home (Table 3). In addition, we compared baseline sample characteristics in the 2 groups (HS compared with no HS) and showed no significant differences.

At enrollment, the mean birth weight of the infants was 2.2 kg, and the mean birth length was 44.1 cm. Approximately 80% of the infants were born at home.

Morbidity events of full-term LBW infants during the first 6 mo (0–5 mo of age) and second 6 mo by intervention group are shown in **Tables 4** and **5**. The proportion of morbidity symptoms (e.g., fever and cough) in the first or second 6 mo was not different between groups.

At the end of 12 mo, the proportion of moderately (LAZ of ≥−3 and <−2) and severely stunted (LAZ <−3) infants was significantly lower in both the MNP and HS and MNP groups than in the no-MNP groups (**Figure 2**, **Table 6**). Both groups who received the MNP (with and without HS) had lower proportions of infants with LAZs <−2 at 12 mo. This difference in LAZs largely emerged between 6 and 12 mo (**Figures 3** and **4**). Infants who received any MNP were less likely to be stunted at 12 mo (OR: 0.35; 95% CI: 0.15, 0.84) (Table 6). Note that there was a reduction in the prevalence of both moderate and severe stunting with age (Figure 2) such that, in the control group from birth to 12 mo, the percentage of nonstunted infants changed from ~20% to ~45%, whereas in the MNP group, the change was from ~20% to ~65%.

Mean hemoglobin concentrations in infants and the proportion of infants who had anemia at 6 and 12 mo respectively, within each group are shown in **Figure 5**. Groups who received the MNP had significantly higher hemoglobin concentrations at 12 mo than at 6 mo ($P < 0.01$) and lower proportions of anemia ($P < 0.05$).

The general patterns of feeding were similar across study groups throughout the study. For example, there were no differences in rates of exclusive breastfeeding at ages 6, 9, and 12 mo by study group (data not shown). Similarly, no difference was shown across groups in terms of handwashing with soap and water in mothers at different handwashing opportunities (e.g., before eating or preparing food and after defecation or disposal of waste) (data not shown).

The study was not powered to evaluate differences in infant mortality rates, but rates were lower than Bangladesh Demographic and Health Survey rates in all intervention groups (21). The control group had the highest incidence of child deaths (n = 5), whereas the number of deaths in HS, MNP, and HS and MNP groups were 3, 1, and 1, respectively (Figure 1). Findings from verbal autopsies suggested that the major causes of death were pneumonia and severe respiratory illnesses followed by gastrointestinal-related causes (severe diarrhea and vomiting). Three infants died in the neonatal period because of complications during delivery.

TABLE 4
Morbidity events of full-term low-birth-weight infants during the first 6 mo (0–180 d) by intervention group[1]

	Intervention group		
	Control[2] (5307 child-weeks)	HS (5436 child-weeks)	P
URTI	34.4 (1827)	30.2 (1644)	0.116
Cough	12.8 (681)	10.9 (591)	0.249
Fever	4.5 (241)	4.0 (220)	0.269
Diarrhea	0.8 (43)	0.6 (32)	0.330

[1]All values are proportions of infants who had any reported infectious morbidity during the previous week in the 6-mo period; n children with a reported illness in 24 wk (6 mo) in parentheses. Significance was assessed with the use of generalized linear mixed models for all analyses to account for clustering effects. HS, hand sanitizer; URTI, upper respiratory tract infection.

[2]Control group received no HS.

DISCUSSION

We investigated the independent and combined effect of a directed use of a water-based HS and a mineral- and vitamin-enhanced MNP to prevent infections and improve nutrient intake to reduce stunting in FT-LBW infants whose mothers were supported with NHHE. The daily home fortification of complementary foods with an MNP that contained 22 micronutrients significantly reduced stunting at 12 mo. The use of the water-based HS did not have an additive effect. Similar to the results of previous studies, infants who received the MNP had higher hemoglobin concentrations and lower rates of anemia.

Recent estimates are that 27% of live births in low-and middle-income countries are born small-for-gestational age, and 10.6 million infants are born at FT-LBW (32). The main cause of LBW (at term) is intrauterine growth restriction, which is associated with maternal and environmental factors such as chronic undernutrition, multiple pregnancies, placental insufficiency, pregnancy complications (e.g., pre-eclampsia), infections, and other toxic exposures (33). Each of these known causes affected women at an unusually high prevalence in the study population. Two-thirds of small-for-gestational-age infants are born in Asia (17.4 million infants are born in South Asia), most of whom are born in India, Pakistan, and Bangladesh and in sub-Saharan Africa, mainly in Nigeria, where the implementation of effective

TABLE 5
Morbidity events of full-term low-birth-weight infants during the second 6 mo (181–360 d) by intervention group[1]

	Intervention groups				
	Control[2] (2424 child-weeks)	HS (2570 child-weeks)	MNP (2509 child-weeks)	HS and MNP (2734 child-weeks)	*P*
URTI	28.7 (648)	27.9 (716)	30.1 (755)	26.7 (784)	0.730
Cough	10.1 (246)	10.5 (270)	11.1 (279)	10.1 (275)	0.872
Fever	9.2 (222)	8.6 (220)	8.1 (204)	7.4 (202)	0.795
Diarrhea	1.3 (31)	1.4 (37)	1.7 (43)	2.0 (54)	0.575

[1]All values are proportions of infants who had any reported infectious morbidity during the previous week in the 6-mo period; *n* children with a reported illness in 24 wk (6 mo) in parentheses. Significance was assessed with the use of generalized linear mixed models for all analyses to account for clustering effects. HS, hand sanitizer; MNP, micronutrient powder; URTI, upper respiratory tract infection.

[2]Control group received no HS and no MNP.

interventions is an "urgent priority to increase survival and reduce disability," especially in resource-poor rural communities (33–35). To our knowledge, this trial is the first study to investigate the independent and combined efficacy of a water-based HS and a mineral-enhanced MNP in combination with a package of nutrition, health, and hygiene messages to improve growth and reduce stunting in full-term LBW infants.

Our results lend empirical support to recent calls for integrated packages of interventions targeting young children to reduce stunting (35). In the current study, ∼80% of FT-LBW infants were stunted at birth. Our finding of significant effects of the MNP on linear growth in later infancy is consistent with those of a meta-analysis of trials that tested multiple micronutrients to improve linear growth in children <5 y of age, although they

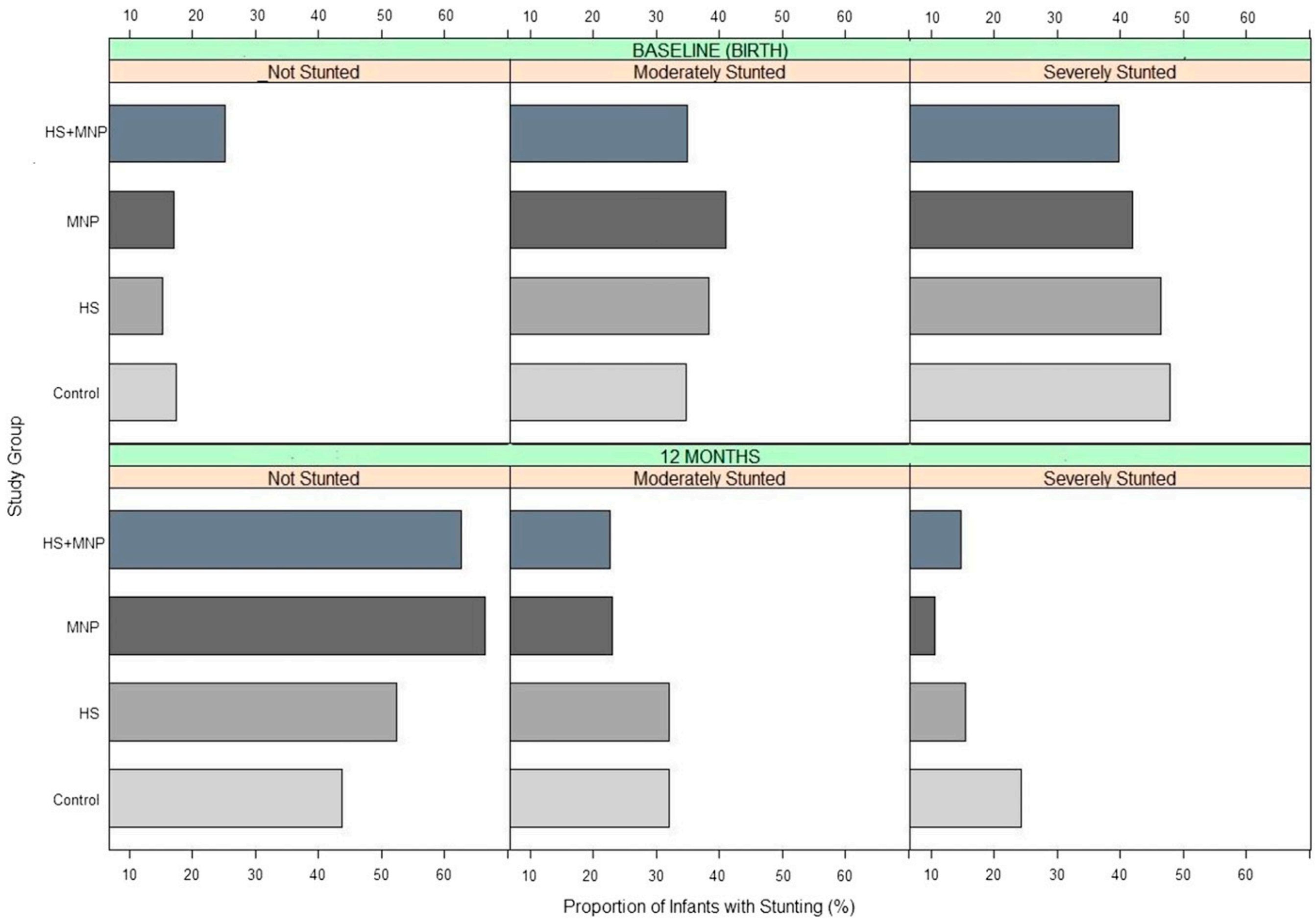

FIGURE 2 Proportions of full-term low-birth-weight infants with severe stunting (length-for-age *z* score <−3), moderate stunting (length-for-age *z* score ≥3 and <−2), and no stunting at baseline (birth) and at the end of the 12-mo intervention by intervention group. At the end of 12 mo, the proportions of moderately and severely stunted infants were significantly lower in both the MNP and HS+MNP groups than in the control group. All parents of infants in each of the 4 groups received NHHE. The control group received NHHE only and did not receive HS or MNP. Significance was assessed with the use of generalized linear mixed models for all analyses to account for clustering effects. HS, hand sanitizer; MNP, micronutrient powder; NHHE, nutrition, health, and hygiene education.

TABLE 6
Effect of intervention components on ORs of stunting in full-term low-birth-weight infants at 12 mo of age[1]

	OR[2] (95% CI)	*P*
HS[3]	0.69 (0.29, 1.64)	0.48
MNP[4]	0.35 (0.15, 0.84)	0.017
HS × MNP[5]	1.81 (0.54, 6.11)	0.335
Stunted at birth	1.42 (0.81, 2.46)	0.217
Sex, M	1.44 (0.94, 2.21)	0.097

[1]Significance was assessed with the use of generalized linear mixed models for all analyses to account for clustering effects. HS, hand sanitizer; MNP, micronutrient powder.

[2]Adjusted odds (for district, cluster, sex, stunting status at baseline, mother's education, and access to a tube-well).

[3]Two groups who received HS (with or without MNP).

[4]Two groups who received MNP (with or without HS).

[5]Interaction between HS and MNP.

were inconsistent with many of our previous studies that used 5 or 15 MNPs (35, 36). All previous studies have generally pooled full-term and preterm appropriate-for-gestational-age and small-for-gestational-age infants for inclusion, follow-up, and analyses. An unmeasured but likely small proportion of these infants may have been FT-LBW infants. Therefore, it is possible that the lack of a previous effect may also have been attributable to the status of infants at birth.

Of the factors that contributed to the reduction of stunting in the MNP groups, the provision of a wider range of minerals (calcium, phosphorus, magnesium, and manganese) and vitamins (vitamin K, pantothenic acid, and biotin) in the MNP formulation may have contributed greater substrate for linear growth during the normal period of complementary feeding, thereby reducing rates of stunting in FT-LBW infants. When we speak of linear growth we are describing the growth of long bones in the body. The role of minerals in bone growth has been well described (37). The accretion of minerals, including calcium, phosphate, and magnesium, is most rapid in the first 2 y of life and during adolescence. In exclusively breastfed infants, it is expected that the minerals present in milk will meet mineral needs for growth. We are not aware of other studies that have added additional minerals to complementary foods to enhance linear growth in FT-LBW infants. Once complementary foods are introduced at age 6 mo, the combination of human milk and food is expected to meet the mineral needs for growth. On the basis of current knowledge, it is plausible to expect that adequate intake of foods that contain additional sources of minerals, such as dairy products and fish, during later infancy would enable FT-LBW infants to achieve catch-up linear growth. However, a decade ago, the WHO raised concerns about the ability of local complementary foods to meet the dietary requirements for iron, calcium, and zinc (38), and these concerns have been highlighted in recent reviews (39).

In Bangladesh, only 20% of children aged 6–24 mo are in compliance with the infant and young-child feeding recommendations that include the consumption of breast milk or other milk products, thereby achieving a minimum dietary diversity score and the adequate meal-frequency recommendations (40). Typical complementary foods are cereal based and, thus, are not a good source of minerals, and the minerals present in the foods are not highly bioavailable because of high amounts of phytates, oxalates, dietary fiber, and polyphenols, all of which are known inhibitors of mineral absorption. Combs and Hassan (41) and other authors (42) previously published data on estimated

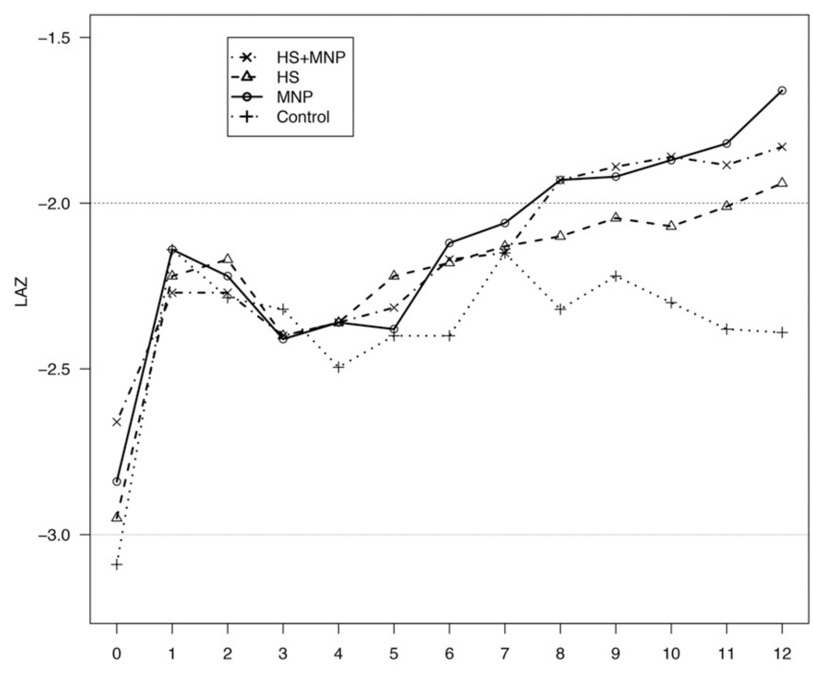

FIGURE 3 LAZs of full-term low-birth-weight infants from 0 to 12 mo of age by study group. Each curve represents the median (50th percentile of a given age). Both groups who received MNP (with and without HS) had lower proportions of infants with LAZs <-2 at 12 mo. This difference in LAZs largely emerged between 6 and 12 mo. Infants who received any MNPs were less likely to be stunted at 12 mo. The control group received nutrition, health, and hygiene education only and did not receive HS or MNP. HS, hand sanitizer; LAZ, length-for-age *z* score; MNP, micronutrient powder.

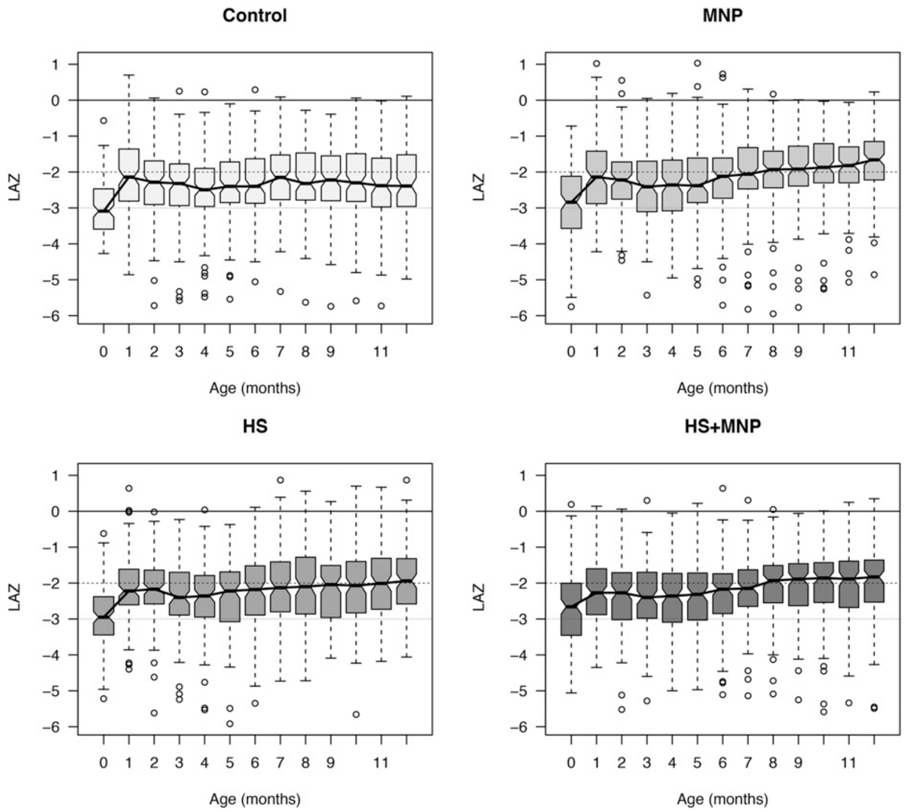

FIGURE 4 Boxplot (31) for age-specific LAZ of full-term low-birth-weight infants from 0 to 12 mo of age by study group. *z* Scores were calculated with the use of WHO Growth Standards. Boxes contain 50% of the data (25th to 75th percentiles), and the lines in the boxes indicate median values of the data. Ends of the vertical lines or whiskers indicate the minimum and maximum data values unless outliers are presented, in which case the whiskers extend to a maximum of 1.5 times the IQR. Points outside the ends of the whiskers are suspected outliers. The control group received nutrition, health, and hygiene education only and did not receive HS or MNP. HS, hand sanitizer; LAZ, length-for-age *z* score; MNP, micronutrient powder.

calcium intakes from a combination of breast feeding and complementary foods for infants and young children in Bangladesh. Compared with an Adequate Intake estimate for calcium of 270 mg (from 7 through 12 mo of age), average intake is in the range of 150 mg/d. Thus, the provision of an additional 100 mg Ca through the MNP provided in the current study would bring total intake to approximately the Adequate Intake range. Other minerals and vitamins that are needed for bone growth and were included in the MNP formulation used in the current study include phosphate, magnesium, and vitamin K for γ-carboxylation of osteocalcin and vitamin D.

The water-based HS did not significantly reduce the symptoms of infections in the first 6 mo of life. Our design assumed that the results from handwashing and the use of the HS would be better than the results from handwashing alone (13, 15). It would have been inappropriate and unethical to recommend that participants stop the practice of washing their hands with soap and water, but the addition of the HS was not powerful enough to differentiate its effect from that of handwashing. This outcome is similar to that of a recently published study that compared handwashing with HS use in a daycare setting. The primary outcome was the number of absence episodes because of any illness in 2443 follow-up children whose caregivers were telephoned after each absence from school. There was no significant difference in absence episodes (43). Other studies in Bangladesh included the use of alternatives to soap and water, such as ash and soil, and one study examined the concentration of fecal-indicator bacteria with alcohol-based HSs, but none of the studies examined changes in clinical signs of infection (44, 45). Because, in many previous studies, recurrent infections and their concurrent morbidity seemed to have been an etiologic component that was linked to stunting, the finding that the promotion of a water-based HS showed no additional effect in reducing infant stunting when caregivers were already receiving health and hygiene messaging that included the promotion of handwashing deserves further investigation (46). Note that the relatively low prevalence of diarrhea across groups suggested that the fecal-oral transmission of pathogens may have been well controlled in this sample, which may explain the limited impact of the HS in this trial.

We understand that targeting is a major challenge if an MNP program were to be scaled up specifically in a unique population of FT-LBW infants. In Bangladesh, data have suggested that the prevalence of FT-LBW infants is in the range of 30–35% of all live-born infants, and thus, the target population is quite large. However, with many infants born at home, without having a scale to weigh babies, it would be difficult to identify LBW infants. We do not have a definitive solution to this problem; however, there are very small, inexpensive scales that are available that could be used by skilled (or even unskilled) birth attendants so that LBW infants could be identified and potentially targeted. At this time, the public health adoption of MNPs specifically for LBW infants is not yet feasible.

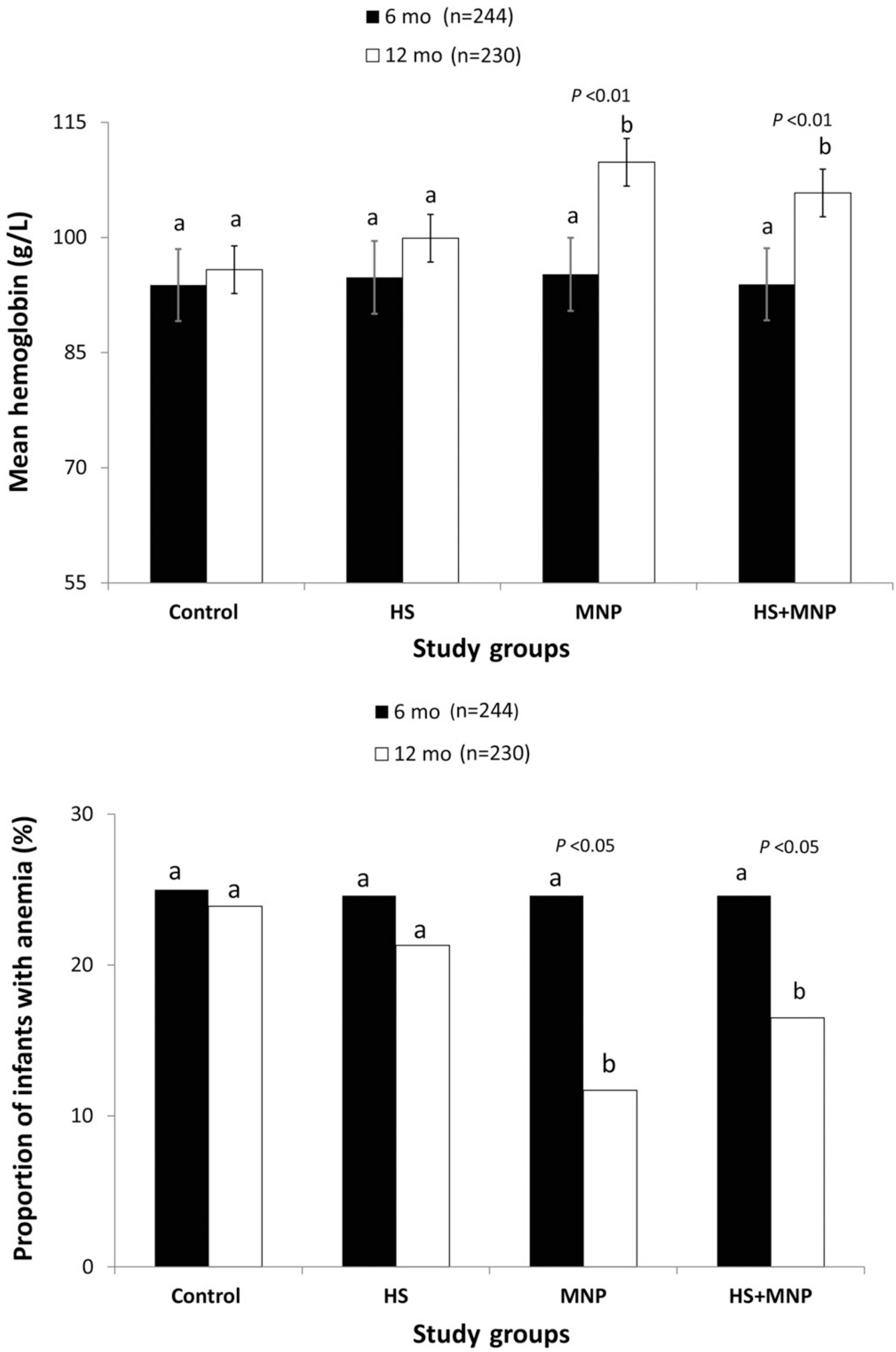

FIGURE 5 Mean (95% CI) hemoglobin concentrations in full-term low-birth-weight infants at 6 and 12 mo are presented by study group (upper panel). The control group received nutrition, health, and hygiene education only and did not receive HS or MNP. Proportions of anemia (hemoglobin concentration $<$110 g/L) in full-term low-birth-weight infants at 6 and 12 mo are presented by study group (lower panel). *P* values of tests for differences within groups (assessed with the use of generalized linear mixed models for all analyses to account for clustering effects) are represented by different lowercase letters, which indicate significant differences within groups. HS, hand sanitizer; MNP, micronutrient powder.

Possible limitations of the study include the estimation of weekly infant morbidity by maternal recall rather than by direct observation, which could have resulted in recall bias and the underreporting of infectious morbidity (47). Nevertheless, the study design was strong in several key ways. Trial bias was unlikely because of the cluster randomization to prevent contamination in the intervention groups (23), the broad inclusion criteria, the random group allocation, the similarity of the intervention groups at enrollment, the separation of the recruitment from the evaluation team, and the comprehensive follow-up. Data quality was ensured through rigorous routine field supervision and ongoing training in data collection. Before the study began, we completed a formative study of HS acceptability and uptake to design appropriate messages. For example, we used separate messages for handwashing with soap and water and the use of the HS so that HS use was not meant to replace or compete with the regular handwashing practices of the households. Nevertheless, we delivered handwashing education but did not directly observe what transpired with regard to handwashing or HS use; thus, we had to assume that our behavior change communication messages concerning hand hygiene were followed. We do not know what actually occurred in terms of handwashing.

In conclusion, the daily home fortification of complementary foods with an MNP that contained 22 micronutrients reduced stunting at 12 mo in infants born FT-LBW in rural Bangladesh. It is likely that the improved availability of essential nutrients for linear growth in the second half of infancy accounted for the reduced stunting. Because no safety issues were identified that were associated with the new micronutrient formulation and because of the small cost differential between MNP formulations of 22 compared with 15 micronutrients, additional research is warranted to validate these findings. The study showed no evidence that the directed use of a water-based HS was more effective for improving FT-LBW infant length gain than was the promotion of handwashing with soap and water in this setting.

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The authors' responsibilities were as follows—SS, DWS, and SHZ: designed the research; SS, CSJ, and SPJ: conducted the research; SS and WL: analyzed the data and performed the statistical analysis; SS, DWS, WL, and SHZ: wrote the manuscript; SHZ: had primary responsibility for the final content of the manuscript, had full access to all of the data in the study, and had the final responsibility for the decision to submit the manuscript for publication; and all authors: read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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