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## Effects of community-based sales of micronutrient powders on morbidity episodes in preschool children in Western Kenya<sup>1,2</sup>

Parminder S Suchdev<sup>3,5,\*</sup>, O Yaw Addo<sup>5</sup>, Reynaldo Martorell<sup>5</sup>, Frederick KE Grant<sup>5</sup>, Laird J Ruth<sup>3</sup>, Minal K Patel<sup>4</sup>, Patricia C Juliao<sup>4</sup>, Rob Quick<sup>4</sup>, and Rafael Flores-Ayala<sup>3,5</sup>

<sup>3</sup>Nutrition Branch, CDC, Atlanta, GA

<sup>4</sup>Waterborne Diseases Prevention Branch, CDC, Atlanta, GA

<sup>5</sup>Hubert Department of Global Health, Emory University, Atlanta, GA

### Abstract

**Background**—Although the use of micronutrient powders (MNPs) is considered the preferred approach for childhood anemia control, concerns about iron-related morbidity from clinical trials have challenged programmatic scale-up.

**Objective**—We aimed to measure the effects of community-based sales of MNPs on diarrhea-, fever-, cough-, and malaria-morbidity episodes in children 6–35 mo of age.

**Design**—We conducted a cluster-randomized trial in rural Western Kenya where 60 villages were randomly assigned to either intervention or control groups. MNPs (containing iron, vitamin A, zinc, and 11 other micronutrients) and other health products (e.g., insecticide-treated bednets, soap, and water disinfectant) were marketed in 30 intervention villages from June 2007 to March 2008. Household visits every 2 wk were used to monitor self-reported MNP use and morbidity (illness episodes in the previous 24 h and hospitalizations in the previous 2 wk) in both groups. Iron, vitamin A, anemia, malaria, and anthropometric measures were assessed at baseline and at 12 mo of follow-up. Data were analyzed by intent-to-treat analyses.

**Results**—Of 1062 children enrolled in the study, 1038 children (97.7%) were followed (a total of 14,204 surveillance visits). Mean MNP intake in intervention villages was 0.9 sachets/wk. Children in intervention villages, compared with children in control villages, had ~60% fewer hospitalizations for diarrhea (0.9% compared with 2.4%, respectively;  $P = 0.03$ ) and 70% fewer hospitalizations for fever (1.8% compared with 5.3%, respectively;  $P = 0.003$ ) but no significant differences in hospitalizations for respiratory illness (1.1% compared with 2.2%, respectively;  $P = 0.11$ ) or malaria (3.1% compared with 2.9%, respectively;  $P = 0.82$ ). There were no differences between groups in the numbers of episodes of diarrhea, cough, or fever.

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\*To whom correspondence should be addressed. psuchde@emory.edu.

The authors' responsibilities were as follows—PSS: wrote the manuscript and had primary responsibility for the final content of the manuscript; PSS, OYA, RM, and RF-A: designed the analysis approach; PSS, FKEG, LJR, MKP, and PCJ: conducted the research; PSS, LJR, PCJ, and RQ: designed the research; OYA and FKEG: analyzed the data; and all authors: read and approved the final manuscript.

None of the authors reported a conflict of interest related to the study.

**Conclusions**—MNP use in Western Kenya through market-based community sales was not associated with increased infectious morbidity in young children and was associated with decreased hospitalizations for diarrhea and fever. An integrated distribution of MNPs with other health interventions should be explored further in settings with a high child malnutrition and infection burden. This trial was registered at [clinicaltrials.gov](http://clinicaltrials.gov) as NCT01088958.

### Keywords

anemia; malaria; micronutrient powders; morbidity; Kenya; hospitalizations

## INTRODUCTION

Anemia accounts for nearly 9% of the world's total disability. Children <5 y of age have the highest anemia burden, and its prevalence in that population is rising, in spite of a global decrease in prevalence from 1990 to 2010 (40.2% to 32.9%, respectively) (1). Nutrition interventions are an important component of anemia-control programs, and the WHO recommends universal supplementation with iron in young children as drops or syrups (2) or with micronutrient powders (MNPs),<sup>6</sup> which are added to prepared food as part of infant and young child feeding programs (3). Two recent systematic reviews showed that MNPs in young children significantly reduced the prevalence of anemia by 31–35%, of iron deficiency by 51%, and of iron deficiency anemia by 57%, but without positive effects on growth (4, 5). Because of their high acceptability and established efficacy, the use of MNPs has become the preferred approach to prevent and treat anemia and iron deficiency in young children and has been implemented in >40 countries worldwide (6).

However, recent evidence from 2 large clinical trials suggested that iron-containing MNPs may increase infectious morbidity. In Pakistani children, iron-containing MNPs with or without zinc were associated with small but significant increases in diarrhea and respiratory infections (7). In Ghana, children who received MNPs with iron showed a higher number of hospital admissions during the 5-mo intervention but a decreased malaria incidence compared with children who received MNPs without iron (8). These findings have left policy makers with an unresolved dilemma on the safety of MNPs, in particular in areas with a high coexisting malnutrition and infectious disease burden (9).

We previously evaluated the effectiveness of a market-based community MNP distribution in Western Kenya as part of the Nyando Integrated Child Health and Education (NICHE) project and reported that, despite a low and infrequent use, the distribution of MNPs reduced iron deficiency, vitamin A deficiency, and recovery from anemia in children aged 6–35 mo (10). Because additional evidence is needed on the safety of MNP in programmatic settings, we aimed to perform secondary analyses of the NICHE data to evaluate the effects of the distribution of MNPs on diarrhea-, fever-, cough-, and malaria-morbidity episodes.

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<sup>6</sup>Abbreviations used: AGP,  $\alpha$ -1-acid glycoprotein; CRP, C-reactive protein; MNP, micronutrient powder; NICHE, Nyando Integrated Child Health and Education; PR, prevalence ratio; RBP, retinol-binding protein.

## METHODS

### Enrollment, intervention, and follow-up procedures

The data for the current study were from the NICHE project, which aimed to evaluate the effectiveness of a market-based community distribution of health products in the rural Nyando Division (population: 80,000) of the Nyanza Province, Kenya (11). This setting is characterized by endemic malaria transmission, high rates of diarrheal diseases because of poor access to safe water, and anemia (11). Details of the study methodology, including the promotion and monitoring of the interventions and effects on primary nutrition outcomes have been published elsewhere (10, 12, 13). Formative research on cultural conceptions of morbidity has also been previously reported (14).

In the current study, a 2-stage cluster-sampling strategy was used to select 30 intervention and 30 control villages and children aged 6–35 mo from the Nyando Division. Three months after a baseline survey in March 2007, MNPs were promoted and distributed alone or with other health products including sodium hypochlorite as a water disinfectant, soap, insecticide-treated bednets, and condoms in intervention villages; however, vendors were not prevented from selling products, including MNPs, in control villages. More details of the market-based distribution of MNPs have been previously reported (12). The composition of each 2-g sachet of MNPs (Sprinkles; Sprinkles Global Health Initiative) included encapsulated ferrous fumarate (12.5 mg), zinc gluconate (5 mg), vitamin A (375  $\mu\text{g}$ ), iodine (50  $\mu\text{g}$ ), copper (0.6 mg), vitamin C (35 mg), cholecalciferol (5  $\mu\text{g}$ ), vitamin B-12 (0.9 mg), thiamine (0.5 mg), riboflavin (0.5 mg), vitamin B-6 (0.5 mg), vitamin E (6.0 mg), niacin (6.0 mg), and folic acid (150 mcg). MNPs were sold retail for 2 Kenya shillings/sachet (~US \$0.03/sachet) and were promoted for daily use (1–2 sachets/wk to achieve health benefits) to families with children aged 6–59 mo.

From July 2007 through March 2008, home visits were conducted every 2 wk to intervention and control village households to assess product use and the occurrence of diarrhea, respiratory illness, or fever. A follow-up survey was conducted in March 2008 to measure the nutritional effect, after which project interventions were expanded to control villages. Children with hemoglobin concentrations  $<7.0$  g/dL were referred to the nearest clinic for the treatment of severe anemia, and children with active diarrhea were given free oral rehydration salts.

Written informed consent was obtained from all participating households. Children were excluded if they were unavailable for enrollment on 3 separate household visits or if parents refused to give informed consent. The Ethics Committee of the Kenyan Medical Research Institute, Nairobi, Kenya (protocol 1176), and the Institutional Review Board of the CDC, Atlanta, Georgia (protocol 5039), approved the study. This trial was registered at [clinicaltrials.gov](http://clinicaltrials.gov) as NCT01088958.

### Data collection

Data were collected by trained fieldworkers at enrollment and during 17 household visits every 2 wk to monitor diarrhea, cough or difficulty breathing, and fever in the previous 24 h. Diarrhea was defined as  $\geq 3$  loose stools in the past 24 h or hospital or clinic visits for

diarrhea within the past 2 wk; respiratory illness was defined as a reported cough or difficulty breathing in the past 24 h or hospital or clinic visits for respiratory illness within the past 2 wk; malaria was defined as any hospital or clinic visit for malaria within the past 2 wk. All morbidity measures were based on caretaker's reports. Baseline assessments included household sociodemographic characteristics, the history of child-feeding practices, anthropometric measurements, and capillary blood collections.

Details of the laboratory analyses have been described in detail elsewhere (15). In summary, capillary blood was obtained at baseline and at 12 mo of follow-up for determinations of hemoglobin, ferritin, C-reactive protein (CRP),  $\alpha$ -1-acid glycoprotein (AGP), and retinol-binding protein (RBP). Hemoglobin concentrations were determined with the use of HemoCue photometers; children with hemoglobin concentrations  $<11.0$  g/dL were classified as anemic. Two drops of blood were placed on a microscope slide (Thermo Fisher Scientific Inc.) for thick and thin malaria smears for the detection of malaria parasitemia by the CDC Kenya laboratory. Frozen plasma samples were transported to Germany (VitA-Iron Laboratory), which measured concentrations of ferritin, RBP, CRP, and AGP with the use of a sandwich ELISA (16). The following thresholds were used to define abnormal values for these biochemical indicators: ferritin concentration  $<12$   $\mu$ g/L, RBP concentration  $<0.7$   $\mu$ mol/L, CRP concentration  $>5$  mg/L, and AGP concentration  $>1$  g/dL. Iron deficiency and vitamin A deficiency were adjusted for the effect of inflammation with the use of a correction-factor approach to adjust values of ferritin and RBP on the basis of the elevated acute-phase proteins CRP and AGP as described previously (15, 17). Correction factors for ferritin and RBP were as follows: 0.64 and 1.28, respectively, for early inflammation (elevated CRP and normal AGP), 0.31 and 1.38, respectively, for early convalescent inflammation (elevated CRP and AGP), and 0.64 and 1.09, respectively, for late convalescent inflammation (elevated AGP and normal CRP).

### Data management and statistical analyses

Data were recorded in the field with the use of Dell Axim personal digital assistants (Dell) by trained field workers. Data were entered in customized electronic forms with the use of Visual CE software (version 10.0; Syware) and stored in an Access 2007 database (Microsoft Corp.) on a daily basis. Individual MNP use was estimated by dividing the reported household MNP purchases or gifts every 2 wk by the number of children aged 6–59 mo who were living in that household (12). Baseline anthropometric measures were calculated with the use of WHO child-growth standards for underweight (weight-for-age  $z$  score  $<-2$ ), stunting (height- and length-for-age  $z$  score  $<-2$ ), and wasting (weight-for-height and -length  $z$  scores  $<-2$ ) (18). To classify respondents by socioeconomic status, we used a principal component analysis to categorize households into quintiles within the study population on the basis of household assets (19). Low socioeconomic status was defined as the lowest 2 quintiles.

Primary analyses were conducted as intent-to-treat analyses. Morbidity information was presented in the following ways by treatment arm: 1) total cumulative sum of all sick visits, and 2) proportion of children ever sick. The total number of sick visits was estimated as the total count of surveillance visits in which a child was recorded as having been sick or

hospitalized. All repeated visits over the study period for each child were entered in a time series of computational do loops for each illness in the creation of a child-specific illness index, which was used to create ever-sick or ever-hospitalized variables. Ever sick or hospitalized were quantified as at least one recorded sickness or hospitalization (or nonzero illness index) visit per child over the entire follow-up period by treatment arm. This quantification of morbidity enabled us to detect more transient changes in morbidity because the analytic effective sample was based on the total number of illness-related surveillance visits ( $n = 14,204$ ) rather than only the number of children ( $n = 1038$ ). If the caregiver was absent during a visit by the fieldworker, that surveillance period was excluded from the analysis because of the absence of both morbidity and MNP-use data ( $n = 1619$  visits were excluded or 11.2% of total visits). Survey chi-square and Wilcoxon's median-rank tests were used to examine differences in measures of morbidity between study arms.

Illness and hospitalizations within the previous 24 h and 2 wk of any visit, respectively, were used as binary outcomes to conduct a complex survey multiple logistic analysis with the use of the treatment arm as the key predictor to derive adjusted prevalence ratios (PRs) and 95% CIs for morbidity between the 2 arms (with the control arm as the reference). These models were stratified by baseline anemia and iron-deficiency status and adjusted for household socioeconomic status and water treatment.

Complex survey models with adjustment for the village-sampling cluster were used in all analyses. Although 7.4% of households had more than one child enrolled in the study, a test of clustering effects that was conducted by using the household as a random intercept in a mixed model with a classical sandwich covariance matrix indicated no significant clustering (intraclass correlation coefficient: 0.02%;  $P = 0.44$ ). All data analyses were done with SAS 9.2 software (SAS Institute Inc.) and R software, version 3.2.0 (R Foundation for Statistical Computing).  $P < 0.05$  was considered significant for hypothesis testing.

## RESULTS

### Study participants

Of 1420 children selected as potential study participants, 1062 children (74.8%) were enrolled in the study (560 children in intervention villages and 502 children in control villages) (Figure 1). Of 358 children who were not enrolled, 61.6% of them were not available on 3 attempted household visits, 35.3% of them were outside of the age range, and 3.1% of them did not receive parental consent. A total of 1038 children (97.6%) had surveillance data available and were included in the analysis. There were 14,204 total surveillance visits for these children for the 9-mo follow-up period (7189 and 7015 visits in intervention and control villages, respectively). The median (IQR) number of visits per child was 9.0 (5.0–13.0) with no significant differences in the numbers of visits between intervention and control groups.

At baseline, the mean age of enrolled children was 20.0 mo, 51.8% of the children were boys, ~2 of 3 children were anemic, and one of 2 children was iron deficient. A majority of households reported the use of malaria bednets and soap. Baseline characteristics of children in intervention and control groups were similar overall, except for a higher proportion of

households in the lowest 2 socioeconomic quintiles in control villages compared with in intervention villages (46.8% compared with 36.5%, respectively;  $P=0.03$ ) and a higher proportion of households that reported the treatment of drinking water in intervention villages than in control villages (70.7% compared with 61.8%, respectively;  $P=0.03$ ) (Table 1).

### MNP use

In intervention villages, nearly all children (88.3%) used MNPs; however, most children consumed <2 sachets/wk (Table 2). Mean estimated MNP intake per child was 0.9 sachets/wk (median: 0.5 sachets/wk). More than one-third of children (35.7%) in control villages also reported the use of MNPs because of vendors selling outside their own villages; however, median MNP intake was 0 sachets/wk.

### Morbidity findings

The total number of surveillance visits across study arms with a reported illness in the past 24 h was 589 visits for diarrhea, 2184 visits for cough, and 2395 visits for fever. Approximately 43% of children were ever sick with diarrhea, 63% of children were ever sick with cough, and 76% of children were ever sick with fever. There were no differences between intervention and control groups regarding the total number of sick visits or percentage of children ever sick (Table 3). In children in the intervention group, the percentage of children who were ever hospitalized or who had a clinic visit was 0.9% for diarrhea, 1.1% for a cough or respiratory illness, 1.8% for fever, and 3.1% for malaria. Compared with children in control villages, children in intervention villages were 60% less likely to have hospitalizations for diarrhea (crude PR: 0.4; 95% CI: 0.1, 0.9) and 70% less likely to have hospitalizations for fever (PR: 0.3; 95% CI: 0.2, 0.7). There were also significantly fewer total hospitalizations for fever in the intervention arm than in the control arm ( $n=75$  compared with 329, respectively;  $P=0.004$ ) and a trend toward fewer hospitalizations for diarrhea ( $n=46$  compared with 199, respectively;  $P=0.06$ ). There were no differences between arms for hospitalizations of respiratory illness or malaria. These findings did not change when we controlled for baseline differences in socioeconomic status and the use of treated water (data not shown).

Although formal tests of interactions (treatment arm  $\times$  baseline anemia and treatment arm  $\times$  low ferritin concentration) indicated no significance at  $\alpha=0.10$  with each morbidity outcome, we conducted a secondary, stratified analysis because previous studies have indicated that malarial morbidity is more likely to occur in individuals who are iron sufficient and not anemic (20, 21). Children who were iron deficient at baseline were less likely to be ever sick with a cough or fever than were children who were not iron deficient at baseline [adjusted PRs: 0.7 (95% CI: 0.5, 0.95) and 0.5 (95% CI: 0.3, 0.9), respectively] (Table 4). No other significant differences in morbidity in subgroups of children were observed.

## DISCUSSION

We showed that the distribution of MNPs through integrated market-based community sales in a malaria-endemic setting was not associated with increased infectious morbidity in young children and may have decreased hospitalizations for diarrhea and fever. Although the uptake of the intervention was low (mean of 0.9 sachets consumed/wk), in children in intervention villages compared with in control villages, we previously showed a significant improvement in primary nutrition outcomes of child hemoglobin concentrations (+0.9 compared with +0.6 g/dL, respectively), iron (decrease in deficiency by 19.3% compared with 5.3%, respectively), and vitamin A status (decrease in deficiency by 7.5% compared with increase by 2.5%, respectively) (10).

Our findings of no increases in infectious morbidity are in contrast to results of recent studies that have shown increased morbidity from iron supplementation including the daily use of 12.5 mg iron-containing MNPs (7, 8). In Pakistan, although MNP use in children 6–18 mo of age led to large 75–80% reductions in iron-deficiency anemia, there were small but significant increases in diarrhea and chest indrawing (6.6% compared with 5.7% of days with diarrhea and 0.08 higher incidence rate per child year of chest indrawing in treatment than in the control groups) (7). In Ghana, the use of daily MNPs with iron in children aged 6–35 mo compared with the use of MNPs without iron did not result in increased malaria incidence; however, during the 5 mo of intervention, there were a higher number of hospitalizations that were due to diarrhea in the intervention group (8). There have also been studies with results that are consistent with our morbidity findings. A 2006 study in Pakistan showed an 11% reduction in the longitudinal prevalence of diarrhea with the use of iron plus zinc MNPs than with a placebo (22). In a noninferiority safety trial in Bangladesh, there was no difference in diarrhea or lower-respiratory infection with the use of iron plus zinc-containing MNPs than with a placebo (23).

Several mechanisms could explain the inconsistent findings of iron-containing MNP and infectious morbidity. First, in Kenya, the diet or intermittent intake of MNPs may have optimized the absorption and use of zinc and vitamin A, thereby leading to beneficial impacts on diarrhea and respiratory illness. Although the Pakistan study showed no effect of MNPs on serum zinc or retinol (7), in Kenya, we showed significant improvements in vitamin A deficiency and positive associations between MNP use and vitamin A status (10); we did not assess zinc status. Zinc deficiency has direct effects on the gastrointestinal tract including the impairment of the intestinal brush border, increased secretion in response to bacterial enterotoxins, and modifications in intestinal permeability (24, 25). Data from systematic reviews have shown that preventive zinc supplementation is associated with a 13% reduction in the incidence of diarrhea and a 19% reduction in the pneumonia morbidity (26). Preventive zinc supplementation has also been shown to reduce rates of fever in Tanzanian preschool children (27) as we showed in our trial. Adequate vitamin A status is essential for maintaining the integrity of the epithelial barrier with adequate vitamin A stores being positively associated with measures of innate immune activity, which suggests protection against diverse pathogens (28, 29). Therefore, the prevention of diarrhea and pneumonia by optimizing intakes of micronutrients including zinc and vitamin A may be biologically plausible. However, in our study, the dose of zinc was low at 5 mg/sachet and

was coadministered with 12.5 mg Fe. Esamai et al. (30) recently reported low zinc absorption from MNPs in Kenyan infants regardless of whether iron was added, which suggested that higher doses of zinc are needed to meet physiologic requirements.

Second, in contrast to published daily iron-MNP-supplementation studies, intermittent dosing in Kenya likely ameliorated the potential harmful effects of iron on gut flora. Furthermore, the MNP composition in Kenya contained additional micronutrients that favored beneficial gut flora. In a recent trial in US children aged 9–24 mo who were receiving therapeutic iron supplementation for iron deficiency, the addition of vitamin E to the iron supplement beneficially affected the gut microbiome, including a decrease in the relative abundance of *Bacteroides* and an increase in the beneficial butyrate producers *Lachnospiraceae* and *Roseburia* (31). These findings suggest that the addition of antioxidants, prebiotics, or probiotics to MNPs may overcome the proinflammatory changes in the intestine and microbiota that have been shown with iron supplementation (32–34).

Finally, the findings of a lack of harm and decreased hospitalizations for fever in our study may not have been due to MNPs alone because the MNPs were distributed as part of a health-product package, which included insecticide-treated bednets, soap, and point-of-use water treatment, many of which have proven efficacy in preventing infections (35, 36). However, bednet use and soap use were high in both groups at all times during the study (>85%) and therefore were unlikely to have been associated with any differences in malaria or diarrhea incidence. Although more households in intervention villages reported treating their water, there was no difference in the percentage of children with diarrhea in households with measured free chlorine in stored water (an indicator of point-of-use water treatment) and households with no chlorine residual (2.1% compared with 1.8%, respectively; OR: 1.2; 95% CI: 0.8, 1.6) (NICHE project; M Patel, P Juliao, R Quick, unpublished data).

Our null findings of MNPs on malaria morbidity are consistent with those of the systematic review of Ojukwu et al. (37) in which iron supplementation did not increase risk of malaria when adequate malaria surveillance and treatment services were provided. In our study, insecticide-treated net use was high, and MNPs were taken with food and therefore likely contributed lower peak concentrations of plasma iron (38). In vitro studies have shown that *Plasmodium falciparum* infects iron-deficient erythrocytes less efficiently, suggesting protective effects of iron deficiency on malaria susceptibility (21). We showed that iron-replete children, as defined by normal ferritin concentrations corrected by inflammation, did not have increased hospitalizations or clinic visits for malaria, which was consistent with the findings in the Ghana MNP trial (8). This outcome could have been due to the iron biomarker used to define iron deficiency, the high coverage of bednets in the study area (>80%), and the lack of data on malaria incidence or transient changes in iron status over the course of the study.

This study had several limitations. First, the study was limited to one division in the Nyanza Province, and thus, its findings may not be generalizable to other populations including those with a low prevalence of micronutrient deficiency or those with a high prevalence of wasting. Second, because there was a spillover of MNP use in the control villages, we may have biased our findings toward an underestimate of the intervention's effectiveness or a



difference in reported morbidity. Third, morbidity was self-reported by caregivers, and we lacked active hospital-based surveillance, which may have led to an underreporting of morbidity. Fourth, the incidence of illness and the overall sample size were low and were not powered for changes in morbidity, which may have limited our ability to show an effect modification by iron status. Sample-size estimates were based on the primary study aim of the change in anemia prevalence. On the basis of the final sample size of 1038 children included in the analysis, we were able to detect a minimal difference in morbidity of 13.5% between study arms (2-sided  $\alpha = 5\%$  and 80% power, which accounted for an intracluster correlation as high as 20%). The strengths of the study included the community-based distribution of MNPs in intervention communities by vendors, which was applicable to a real-world setting. In addition, active household surveillance enabled a closer look at MNP uptake and morbidity with the use of this distribution model.

In conclusion, we have shown that a market-based community distribution of MNPs in a resource-poor, malaria-endemic area is not associated with increased infectious morbidity and may decrease hospitalizations for diarrhea and fever. These findings suggest the need for ongoing infectious disease surveillance in the context of MNP programs as they are scaled up globally as part of childhood-anemia control programs. A detailed analysis of risks and benefits of iron interventions, especially in areas with high malnutrition and infectious disease burden, is needed to inform policy makers.

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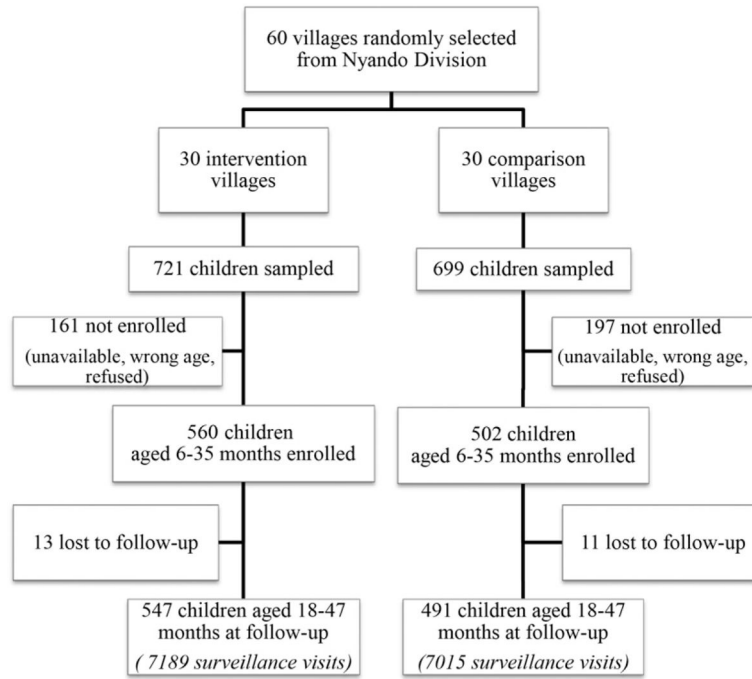
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**FIGURE 1.**  
Trial profile.

TABLE 1

Baseline characteristics by treatment group, Nyando District, Kenya ( $n = 1062$ )<sup>1</sup>

	Intervention ( $n = 560$ )	Control ( $n = 502$ )	<i>P</i>
Mothers and households			
Maternal age, y	26.7 ± 0.3 <sup>2</sup>	26.2 ± 0.4	0.15
Did not complete primary education, %	55.0	54.4	0.90
Poor, <sup>3</sup> %	36.5	46.8	0.03
No electricity, %	99.4	99.2	0.98
Malaria bednet use, %	83.5	83.2	0.93
Soap use, %	93.1	91.4	0.38
Treated drinking water, %	70.7	61.8	0.03
Children			
Age, mo	20.4 ± 0.4	19.3 ± 0.4	0.49
Boys, %	50.4	53.4	0.25
Anthropometric measure			
Underweight, WAZ less than -2, %	12.3	14.0	0.52
Stunted, HAZ less than -2, %	30.2	25.9	0.11
Wasted, WHZ less than -2, %	5.0	5.5	0.83
Breastfed yesterday, %	55.4	58.7	0.39
Malaria parasitemia, %	20.3	17.3	0.41
Anemia, hemoglobin concentration <11.0 g/dL, %	66.2	67.3	0.75
Inflammation, <sup>4</sup> %	30.8	25.2	0.24
Low ferritin concentration, <12 µg/L, %	37.5	40.1	0.51
Iron deficiency, <sup>5</sup> %	53.9	56.8	0.47
Low RBP concentration, <0.7 µg/L, %	23.8	22.1	0.65
Vitamin A deficiency, <sup>5</sup> %	10.7	12.4	0.51

<sup>1</sup> *P* values were computed with the use of the Rao-Scott chi-square test for differences in proportions and the survey *t* test for differences in means accounting for complex survey-design effects. RBP, retinol-binding protein; HAZ, height-for-age z score; WAZ, weight-for-age z score; WHZ, weight-for-height z score.

<sup>2</sup> Mean ± SE (all such values).

<sup>3</sup> Lowest 2 socioeconomic status quintiles.

<sup>4</sup> Elevated C-reactive protein concentration (>5 mg/L) or  $\alpha$ -1-acid glycoprotein concentration (>1 g/L).

<sup>5</sup> Adjusted for inflammation with the use of correction factors.

**TABLE 2**MNP use by treatment group, Nyando District, Kenya ( $n = 1062$ )<sup>1</sup>

	Intervention ( $n = 560$ )	Control ( $n = 502$ )	<i>P</i>
MNP ever use, %	88.3	35.7	<0.001
Sachets consumed/wk, <i>n</i>			
Mean $\pm$ SE	0.9 $\pm$ 0.1	0.2 $\pm$ 0.03	<0.001
Median (IQR)	0.5 (0.2, 1.0)	0.0 (0.0, 0.1)	<0.001
MNP use/wk, %			<0.001
No use, 0 sachets	12.0	64.2	
Infrequent, >0–2 sachets	78.0	35.1	
Regular, >2 sachets	9.9	0.6	

<sup>1</sup>*P* values were computed with the use of the Rao-Scott chi-square test for difference in proportions. The complex survey extension for the *t* test and Wilcoxon's median-rank test were used to test for differences in means and median MNP use with the *svyrankest* and *svyttest* functions (R survey package, version 3.2.0; R Foundation for Statistical Computing). MNP, micronutrient powder.

TABLE 3

Reported infectious morbidity per child by treatment group, Nyando District, Kenya<sup>1</sup>

	Intervention ( <i>n</i> = 7189 visits, 547 children)	Control ( <i>n</i> = 7015 visits, 491 children)	<i>P</i>	Crude prevalence ratio
Illness in the previous 24 h				
Diarrhea				
Total sick visits, <i>n</i>	294 (195, 393)	295 (199, 391)	0.25	—
Ever sick, %	41.9 (37.7, 46.0)	43.7 (39.1, 48.4)	0.53	0.95 (0.8, 1.1)
Cough				
Total sick visits, <i>n</i>	1071 (747, 1395)	1113 (776, 1450)	0.54	—
Ever sick, %	61.1 (55.6, 66.5)	65.9 (61.5, 70.5)	0.16	0.9 (0.8, 1.0)
Fever				
Total sick visits, <i>n</i>	1105 (769, 1441)	1290 (897, 1683)	0.20	—
Ever sick, %	73.5 (69.1, 77.9)	78.8 (74.8, 82.8)	0.07	0.9 (0.9, 1.0)
Hospitalizations in the previous 2 wk				
Diarrhea				
Total hospitalizations, <i>n</i>	46 (4, 89)	199 (9, 407)	0.06	—
Ever hospitalized, %	0.9 (0.2, 1.7)	2.4 (1.2, 3.7)	0.03	0.4 (0.1, 0.9)
Respiratory illness				
Total hospitalizations, <i>n</i>	41 (9, 73)	84 (24, 143)	0.17	—
Ever hospitalized, %	1.1 (0.3, 1.9)	2.2 (0.9, 3.6)	0.11	0.5 (0.2, 1.2)
Fever				
Total hospitalizations, <i>n</i>	75 (23, 127)	329 (79, 578)	0.004	—
Ever hospitalized, %	1.8 (0.7, 2.9)	5.3 (3.4, 7.2)	0.003	0.3 (0.2, 0.7)
Malaria				
Total hospitalizations, <i>n</i>	126 (45, 207)	126 (48, 203)	0.74	—
Ever hospitalized, %	3.1 (1.3, 4.9)	2.9 (1.4, 4.3)	0.82	1.1 (0.5, 2.3)

<sup>1</sup> All values in parentheses are 95% CIs. The total number of sick visits was estimated as a total count of surveillance visits in which a child was recorded to be sick or hospitalized. Ever sick or hospitalized was quantified as at least one recorded sickness or hospitalization per child over the entire follow-up period. *P* values for the median difference in total sick visits or total hospitalizations were calculated from a complex-survey Wilcoxon's median-rank test. *P* values for differences in ever sick or ever hospitalized proportions across study arms were calculated with a complex survey chi-square test.

TABLE 4

Effects of treatment on reported infectious morbidity by baseline iron status and anemia<sup>1</sup>

Morbidity intervention compared with control	Baseline anemia status		Baseline iron status	
	Hemoglobin concentration <11.0 g/dL (n = 674)	Hemoglobin concentration 11.0 g/dL (n = 353)	Ferritin concentration <12 µg/L (n = 498)	Ferritin concentration 12 µg/L (n = 403)
Illness in previous 24 h, ever sick				
Diarrhea	0.9 (0.7, 1.3)	1.1 (0.7, 1.9)	1.0 (0.7, 1.3)	0.9 (0.6, 1.3)
Cough	0.8 (0.5, 1.1)	1.0 (0.6, 1.6)	0.7 (0.5, 0.95)	1.0 (0.6, 1.6)
Fever	0.7 (0.5, 1.03)	0.9 (0.5, 1.7)	0.5 (0.3, 0.9)	0.8 (0.5, 1.4)
Hospitalization in previous 2 wk, ever hospitalized				
Diarrhea	0.4 (0.1, 1.1)	0.5 (0.1, 3.3)	0.4 (0.1, 1.5)	0.4 (0.1, 1.8)
Respiratory illness	0.8 (0.2, 2.9)	0.4 (0.1, 1.6)	0.4 (0.1, 1.7)	0.6 (0.2, 2.0)
Fever	0.4 (0.2, 0.99)	0.3 (0.1, 1.3)	0.5 (0.2, 1.6)	0.2 (0.1, 0.8)
Malaria	1.0 (0.4, 2.2)	2.0 (0.5, 8.6)	1.0 (0.4, 2.7)	0.9 (0.3, 2.9)

<sup>1</sup>All values are adjusted prevalence ratios; 95% CIs in parentheses. Complex survey models were adjusted for household socioeconomic status and water treatment. Ferritin values were further adjusted for inflammation with the use of correction factors. Missing observations: baseline hemoglobin, *n* = 35; baseline ferritin, *n* = 161.