Lipid-Based Nutrient Supplements Do Not Affect the Risk of Malaria or Respiratory Morbidity in 6- to 18-Month-Old Malawian Children in a Randomized Controlled Trial

Charles Manganese, Per Ashorn, Kenneth Maleta, John Phuka, Chrissie Thakwalakwa, Kathryn Dewey, Mark Manary, Taneli Puunmalainen, and Yin Bun Cheung

Abstract

Background: There is evidence to support the use of lipid-based nutrient supplements (LNSs) to promote child growth and development in low-income countries, but there is also a concern regarding the safety of using iron-fortified products in malaria-endemic areas.

Objective: The objective of this study was to test the hypothesis that 6- to 18-mo-old rural Malawian children receiving iron-containing (6 mg/d) LNSs would not have excess morbidity compared with infants receiving no supplementation.

Methods: A randomized controlled trial allocated 840 children to receive daily supplementation with 54 g/d LNS with milk protein base (milk-LNS), 54 g/d LNS with soy protein base (soy-LNS), 71 g/d corn-soy blend (CSB), or no supplementation from 6 to 18 mo of age. Morbidity was compared using a non-inferiority margin set at 20% excess morbidity in supplemented groups compared with the nonsupplemented group.

Results: Baseline characteristics were similar across groups. The proportion of days with febrile illness between 6 and 18 mo was 4.9%, and there were no differences between the groups: 4.9% (95% CI: 4.3, 5.5%), 4.5% (95% CI: 3.9, 5.1%), 4.7% (95% CI: 4.1, 5.3%), and 5.5% (95% CI: 4.7–6.3%) in the milk-LNS, soy-LNS, CSB, and control groups, respectively. The proportion of days with respiratory problems and diarrhea between 6 and 18 mo also did not differ between groups. Compared with controls, the adjusted incident rate ratio (IRR) for clinical malaria was 0.80 (0.59, 1.09), 0.77 (0.56, 1.06), and 0.79 (0.58, 1.08) in milk-LNS, soy-LNS, and CSB, respectively, with 95% CIs confirming non-inferiority. The incidence of febrile episodes, diarrhea, respiratory problems or admission to hospital, prevalence of malaria parasitemia throughout the follow-up, and mean change in hemoglobin concentration from baseline were also similar between the groups.

Conclusions: Daily supplementation with 54 g of milk-based or soy protein–based LNS or 71 g of CSB did not result in increases in malaria or respiratory morbidity in children in a malaria-endemic setting. However, we could not conclude whether LNSs did or did not increase diarrheal morbidity. This trial was registered at clinicaltrials.gov as NCT00524446. J. Nutr. 144: 1835–1842, 2014.

Introduction

An estimated 165 million children aged <5 y were stunted and 100 million were underweight in 2011 (1). These same children are also at risk of micronutrient deficiencies, morbidity from infections, and death (1–4), in part due to complementary food diets that are very low in nutrient and energy densities (5,6). Home fortification of complementary foods with lipid-based nutrient supplements (LNSs) has emerged as a potential low-cost strategy for enrichment of local diets (7–9). Small-quantity LNSs allow delivery of energy, protein, essential FA, and micronutrients without displacing breast-milk intake (10–13). The products are also designed not to replace or displace local...
foods in the complementary diet, therefore providing the opportunity for dietary diversification (8).

There is ongoing concern regarding the use of iron-fortified supplements in malaria-endemic areas. Following the report by Sazawal et al. (14) on excess morbidity and mortality associated with iron supplementation in Tanzania, the risk of excess morbidity and mortality related to iron supplementation or iron-containing “home fortificants,” such as micronutrient powder (MNP), has been assessed in several studies (15). Previous studies on the use of home fortificants did not show adverse effects on morbidity (16), with 1 trial reporting a reduction in the proportion of children with diarrhea and incidence of fever (17). However, a recent large study in Pakistan reported excess diarrhea and respiratory illness (18) among children receiving iron-containing multiple MNPs for 12 mo. Another recent trial in Ghana found no increased risk of malaria, but it showed a significant increase in hospital admissions among children supplemented with iron-containing MNP (19). Four studies examined the effect of preventive LNS supplementation on morbidity; I found a reduction in fever and diarrheal illness (20), whereas the other 3 studies showed neither evidence of difference nor evidence of non-inferiority (21–23). However, the studies showed great variability especially with regard to the age of participants (from 6 to 60 mo), dose and duration of supplementation, and morbidity assessment (frequency of assessment, number of follow-up days, and morbidity assessed), making generalization of the findings difficult. Furthermore, only 1 of the studies assessed clinical malaria (22).

We aimed to determine the effect of provision of 54 g/d milk-based or soy protein-based LNSs, a quantity larger than used in several recent large-scale LNS trials (24), on the incidence of malaria and other common childhood illnesses among children residing in a high malaria-burden area. Malaria is endemic throughout Malawi, with an estimated 6 million cases occurring annually (25). Approximately 49% of children aged <5 years are estimated as residing in high-transmission intensity areas (26).

We reported previously that daily supplementation of a complementary local diet for 1 y with milk powder-containing LNSs could reduce linear growth faltering among at-risk children aged 6-18 mo compared with corn-soy blend (CSB) or the local complementary diet (27). In the current article, we report on the effect of daily consumption of LNSs on the secondary outcomes of morbidity in infants and young children using an non-inferiority analysis. In view of the recent accumulating evidence that raises concern about the safety of iron administration in highly malaria-endemic areas (18,19), the objective of the analysis was to evaluate the safety of providing an iron-containing LNS. We hypothesize that supplementation of the local complementary diet with fortified milk-based or soy protein-based LNSs would not result in excess morbidity.

Methods

Study setting. We performed the study in 2 rural health facility catchment areas, Lungwena and Malindi in Mangochi district, southern Malawi, from 28 January 2008 to 25 May 2009. Malindi is ~17 km from Mangochi town and had on average a more educated population and better access to electricity, clean water, and sanitation than Lungwena, a more rural site ~32 km from the town. Both sites have functional health facilities and are broadly representative of rural Malawi. All of Mangochi district had a high prevalence of infant stunting, underweight, and poor food security (28). Almost all children are breast-fed up to age 2 y; however, the duration of exclusive breastfeeding is generally no more than 1–2 mo. The principal complementary food is a thin maize-based porridge (29). The area has a holo-endemic malaria transmission pattern that peaks during the rainy season (November to March). An estimated 86% of the population in the district is under high-transmission intensity (26).

Study design and intervention. The study was designed as a community-based randomized trial comparing 3 nutritional supplementation groups and 1 control group. The protocol was described in detail previously (27). Briefly, 840 children aged 5.50–6.50 mo were randomly assigned into 4 treatment groups: 1) control; 2) micronutrient-fortified LNSs with milk protein base (milk-LNS); 3) micronutrient-fortified LNSs with soy protein base (soy-LNS); and 4) micronutrient-fortified CSB. Blocked randomization was used with each block containing 16 allocations evenly distributed for the 4 groups. The group allocation was masked to the investigators. However, fieldworkers and guardians knew whether their child was receiving supplementation with LNSs or CSB or was in the control group.

Children were supplemented with either 54 g/d milk-LNS, or 54 g/d soy-LNS or 71 g/d CSB, or were allocated to a control group that were not administered any supplemental complementary food in the initial 12-mo period but were given supplementation from ages 18–36 mo. Guardians were advised to offer the children daily either 10 spoonfuls of CSB, cooked into a complementary porridge, or 8 spoonfuls of milk-LNS or soy-LNS, divided into 2–4 daily servings mixed with a small amount of porridge. The daily LNS dose provided ~280 kcal and 6 mg of both iron and zinc (Supplemental Table 1). The daily CSB dose provided similar energy but lower iron (5.46 mg) and zinc (3.6 mg). Participants were followed every 2 wk between 6 and 18 mo and were provided with a 14-d supply of supplemental food. Child diet, feeding practices, and LNS use were also assessed at these visits.

The LNSs were produced locally by Project Peanut Butter from peanut paste, milk powder or soy flour, soybean oil (contributed ~57% of fat in the products), sugar, and a multiple micronutrient mixture (Nutriset).

Outcome measurements. Morbidity was assessed by trained field-workers every 2 wk using standardized data-collection instruments and guidelines. Throughout the study, the guardians were asked to record on a daily basis the presence or absence of illness symptoms in picture calendars that were provided every 2 weeks. The calendar had separate rows for different days up to 2 weeks and separate columns for the following symptoms: 1) fever; 2) cough; 3) diarrhea (≥3 stools/d); and 4) other. The first 3 symptom columns had pictures describing them to assist the guardians in identifying the correct area to record the information. The guardian reports on the calendars did not include the recording of temperature for fever or the number of stools for diarrhea. The recorded information was reviewed and cross-checked by fieldworkers at each 2 weekly food-delivery visit for completeness.

Participants who visited the Lungwena and Malindi health centers, the only formal health facilities in the study area, were assessed and treated according to the Integrated Management of Childhood Illness guidelines (30) by separate teams of clinicians and nurses unrelated to the study and unaware of which intervention was allocated to which participants. Data were retrieved from these health facilities. Diagnoses were coded and recorded into 6 major categories: 1) clinical malaria; 2) clinical pneumonia; 3) diarrhea; 4) trauma; 5) other respiratory illness; and 6) other illnesses.

Weight and length measurements were obtained at 12-wk intervals from enrollment up to 18 mo of age. The weight of unclothed infants was measured to the nearest 10 g using an electronic infant weighing scale from enrollment up to 18 mo of age. The weight of unclothed infants was measured to the nearest 1 mm using a high-quality length board (Kiddimetre; Raven Equipment). Anthropometric indexes, including length-for-age, weight-for-age, and weight-for-length, were calculated using WHO Child Growth Standards (STATA igrowup package) (31).

Diarrhea was defined as the passage of ≥3 loose or watery stools in a 24-h period. An acute respiratory illness (ARI) episode was defined as a minimum of 2 d with cough and fever. Febrile illness was defined as unusually high body temperature observed by the mother, in the absence of diarrhea or ARI. Recovery from an illness episode was considered if the child was free of symptoms for ≥3 consecutive days according to
definitions used in similar studies (32,33). Rapid breathing was defined as an elevated respiratory rate above the age-specific cutoff values of 50 breaths/min in infants and 40 breaths/min in older children. Clinical pneumonia was defined as a combination of cough with either rapid breathing or crepitations or bronchial breathing by auscultations or lower chest indrawing. Suspected severe pneumonia was defined as pneumonia associated with $\geq 1$ of the following features: 1) convulsions; 2) extreme lethargy; 3) inability to drink or feed; 4) restlessness or irritability; or 5) abnormal sleeping as per the WHO Integrated Management of Childhood Illness guidelines (30). Clinical malaria was defined as a child with fever (axillary temperature $>37.5^\circ C$ or reported a fever within the past 48 h) and a confirmed laboratory diagnosis of malaria parasitemia (at any parasite density).

Blood samples were obtained at baseline from all children and every 12 wk during the follow-up period. Malaria status, including parasite specification and count, was determined via microscopy. Thin films were fixed with methanol, and both thick and thin films were stained with Giemsa. Each smear was read twice by independent microscopists, and discordant results were re-read by a third microscopist. Blood hemoglobin concentration was measured from a venous sample using cuvettes and a reader (HemoCue). Malaria treatment was provided according to the national guidelines to all participants with clinical malaria. All participants found to have a blood hemoglobin concentration $<80$ g/DL were treated with iron supplementation in accordance with the national treatment guidelines (1–6 mg/kg body weight/d for 1 month).

**Statistical analysis.** Sample size calculation was based on the primary study outcome: the prevalence of severe stunting. Assuming a prevalence of severe stunting of 15% in the control group and 5% in the intervention groups and allowing for an attrition rate of 10%, the targeted sample size per group was estimated at 210 participants to achieve 85% power and control type I error rate at 5%. For this analysis, a non-inferiority margin ($\Delta$) predefined in the statistical analysis plan of no more than 20% increase in geometric mean of longitudinal prevalence, incidence rates in a) incident or b) clinical morbidity, or proportion with malaria parasitemia in the intervention groups vs. the control group was used. We assumed that an increase in morbidity of $\geq 20\%$ in the LNS groups relative to the control group would be clinically substantial with negative consequences to overall health and well-being of the children. There is no commonly agreed definition of non-inferiority in this context. Our definition is based on another non-inferiority safety trial that assessed the effects of supplementation of children aged 12–24 mo with an iron-containing MNP on infectious morbidities (34). Non-inferiority was established if the 2-sided 95% CIs of the geometric mean ratio (GMR), incidence rate ratio (IRR), or RR for an intervention group compared with the control group fell entirely below 1.2.

We analyzed data on an intention-to-treat basis, using Stata (version 11.2, StataCorp). Proportions, means, and SDs were presented for the baseline variables and compared between groups by using ANOVA for continuous variables and a chi-square test for proportions. Longitudinal prevalence of an illness was defined as the percentage of all days of observation that the child suffered the illness (35). GMRs were calculated to compare the longitudinal prevalence of illness in the 3 intervention groups with the control group. For analyses of disease incidence, we used negative binomial regression modeling to obtain IRRs (36). The RR for prevalence of malaria parasitemia was estimated. Interactions between intervention and the child's sex, study site, baseline length-for-age, and baseline hemoglobin were explored but not shown because of nonsignificant findings. The difference in morbidity between the 2 catchment areas was also explored through stratified analyses and calculation of rate ratios. No differences in morbidity were found between the sites (details not shown). Changes in anemia prevalence within intervention groups from 6 to 18 mo were analyzed by using McNemar's test. We assessed the proportion of children having used a bed net in the previous 24 h and participant compliance to intervention (in terms of scheduled visit attendance, food sharing, and observed leftovers) at each 2-week visit. Bed net usage and compliance to intervention were analyzed using the generalized linear model with Huber-White robust SE to allow for correlated data (multiple visits per child) (37). Statistical tests were considered significant if $P < 0.05$.

All collected data were recorded on paper forms, transcribed to paper case report forms, and double entered into a custom-made database (Microsoft Access 2003; Microsoft). The 2 entries were electronically compared, and extreme or otherwise suspicious values were confirmed or corrected. The study was approved by the University of Malawi College of Medicine Research and Ethics Committee and the ethics committee of Pirkannaa Hospital District (Finland). During the enrollment session, guardians were given detailed information on the trial contents and a consent form in the local language. A signed consent form was required for inclusion of a subject in the study. This trial was registered at clinicaltrials.gov as NCT00524446.

**Results**

A total of 1385 infants were screened, and 840 of them were enrolled. The recruitment, group allocation, reasons for exclusions, and dropouts are shown in Figure 1. The demographic, anthropometric, and environmental characteristics of the study population were similar between the groups at baseline (Table 1). Almost all the children were still breast-fed, 36.7% were stunted, 14.1% were underweight, and 1.7% were wasted. The prevalence of anemia and malaria parasitemia at baseline was similar between the groups. There was limited variability in the sample in drinking water source or toilet availability and type.

A total of 25 children (3.0%) died, and 68 (8.1%) dropped out during the study. The proportion of participants who died and dropped out was similar in the different study groups ($P = 0.54$ and $P = 0.99$, respectively) (Fig. 1). The completion rate for all the study visits was also balanced between the groups ($P = 0.19$).

Throughout the intervention period, reported adherence to the use of supplementary products was good in all the supplementation groups. During the 2-wk home visits, leftovers were found in only 1.3, 1.3, and 0.7% of the visits in the milk-LNS, soy-LNS, and CSB groups, respectively ($P = 0.01$). Diversion of any portion to someone other than the intended beneficiary was reported at only 69 of 18,906 (0.36%) supplement-delivery interviews; 29 in the milk-LNS, 19 in the soy-LNS, and 21 in the CSB groups ($P = 0.52$). The reported bed-net usage by participant in the previous night was 80.8, 78.5, 79.1, and 78.8% in the milk-LNS, soy-LNS, CSB, and control groups, respectively, across all the home visits ($P = 0.79$).

Longitudinal prevalence of febrile illness, cough, ARI, or diarrhea, or any reported morbidity was 5.5, 6.1, 1.4, 4.5, and 14.5%, respectively, in the control group and was similar to the 3 intervention groups (Table 2). Relative to the control group, the GMR (95% CI) for the longitudinal prevalence of febrile illness was 0.91 (0.73, 1.09) in the milk-LNS, 0.90 (0.72, 1.08) in the soy-LNS, and 0.91 (0.73, 1.09) in the CSB groups. The GMRs for longitudinal prevalence of cough, ARI, or any reported morbidity were also similar for all 3 intervention groups (Table 2); all 95% CIs confirmed non-inferiority. For diarrhea, the GMR (95% CI) was 1.06 (0.87, 1.25) in the milk-LNS, 0.99 (0.81, 1.17) in the soy-LNS, and 1.05 (0.86, 1.24) in the CSB groups. Because the 95% CIs for the milk-LNS and CSB groups crossed the non-inferiority margin of 1.2, non-inferiority could not be established for diarrhea.

Table 3 shows incidence and rate ratios for guardian-reported febrile illness, cough, ARI, and diarrheal episodes for the 3 treatment groups. During the 12-mo intervention period, overall incidence of reported febrile episodes was 5.6/child-year. Consistent with the findings on longitudinal prevalence, all except 1 of the 95% CIs of IRRs fell entirely below the non-inferiority margin. The exception was, again, for diarrhea in the

Lipid-based nutrient supplements and morbidity
milk-LNS group, for which IRR was 1.12 (95% CI: 0.95, 1.32), crossing the non-inferiority margin of 1.2.

A total of 2706 nonscheduled visits were made by study participants to health facilities in the study area for medical consultation and treatment. Table 4 summarizes data for clinical malaria, respiratory problems, and diarrhea recorded at the clinic visits for the 4 groups. A total of 418 clinical malaria episodes were recorded during clinic visits, for an overall incidence of 0.54 episodes/child-year. All 3 intervention groups had lower incidence rate (IRR ranging from 0.77 to 0.80) than the control group; all 3 95% CIs fell entirely below the non-inferiority margin of <1.2. Similarly, non-inferiority of the 3 interventions in terms of rapid breathing was also established. The CSB group (IRR: 0.87; 95% CI: 0.68, 1.11) was non-inferior to the control group in clinical pneumonia incidence. Milk-LNS was marginal, with the IRR of clinical pneumonia at 0.95 (95% CI: 0.75, 1.20), just touching the non-inferiority margin. However, for chest indrawing, diarrhea, and hospital admission, neither inferiority nor non-inferiority could be concluded.

The overall proportion of children with malaria parasitemia during the intervention period was 12.4%. The proportion was slightly lower in the milk-LNS (11.0%) and soy-LNS (12.1%) groups than in the control (13.3%) and CSB (13.4%) groups. The 95% CIs of the RRs compared with the control group were as follows: 1) milk-LNS: 0.63, 1.06; 2) soy-LNS: 0.71, 1.17; and 3) CSB: 0.78, 1.28. Milk-LNS and soy-LNS were non-inferior; CSB was not.

At 18 mo, there were no significant differences between the intervention groups in mean hemoglobin concentration (10.2 g/dL in the control group, 10.3 g/dL in the milk-LNS group, 10.1 g/dL in the soy-LNS group, and 10.3 g/dL in the CSB group; P = 0.43). There were also no significant differences between the intervention groups in the mean gain in hemoglobin concentration between ages 6 and 18 mo (0.8 g/dL in the control group, 0.6 g/dL in the milk-LNS group, 0.8 g/dL in the soy-LNS group, and 0.7 g/dL in the CSB group; P = 0.45). There was a significant reduction in the proportion of children with anemia (defined as hemoglobin <11 g/dL) between 6 and 18 mo in all 4 groups (all P < 0.05) from 84.4% to 65.1% in the control group, 82.5% to 63.4% in the milk-LNS group, 83.7% to 73.8% in the soy-LNS group, and 83.6% to 63.5% in the CSB group.

**Discussion**

We reported the effect of supplementation with 54 g/d iron-containing milk-based or soy protein–based LNSs on the risk of...
common infections in young children in rural Malawi. The 2 tested formulations of LNSs were shown to be non-inferior to no supplementation with respect to several morbidities. Using different sources of information, the data consistently showed that LNSs with 6 mg/d iron would not result in excess morbidity from malaria or respiratory illness. However, there was no conclusive evidence on whether LNSs would or would not increase diarrhea morbidity.

The WHO expert panel in 2007 postulated that iron given with foods, either as home fortificants or centrally processed foods, would be a safe iron-delivery strategy in malaria-endemic areas (38). To our knowledge, this is the first study that assessed the non-inferiority of complementary diet supplementation with LNSs on excess morbidity. Our findings suggest that the use of LNS products that are fortified with iron at this amount and fed to children aged 6–60 mo (22). Our findings are consistent with most previous studies (21–23). In Chad facility during the study period and prevalence of malaria parasitemia at 12-week intervals. In Niger, there was no increased risk of malaria associated with a 3-mo preventive supplementation with a 92-g/d dose of LNSs among healthy children aged 6–60 mo (22). Our findings are consistent with those results. A previous study reported a significant increase in malaria cases in groups supplemented with a tablet containing 12.5 mg/d iron once a day or half of a tablet if aged <1 y (14). The present study used a lower dosage of iron, and the LNS intake was in smaller amounts throughout the day, which may food, with 9 mg/d iron, for 4 mo compared with a control group on a local diet. However, their participants had a mean weight-for-height Z-score of −1.1 at baseline, whereas the mean weight-for-height among children in this study was −0.45 at baseline. Furthermore, the participants in the Chad study were, on average, aged 24 mo at enrollment, older than the present target population. Their finding may suggest that, in more wasted children and/or in older children (even after the first 1000-d window), LNSs could reduce morbidity.

We assessed for the important morbidity outcomes of incidence of malaria among children who ever visited a health facility during the study period and prevalence of malaria parasitemia at 12-week intervals. In Niger, there was no increased risk of malaria associated with a 3-mo preventive supplementation with a 92-g/d dose of LNSs among healthy children aged 6–60 mo (22). Our findings are consistent with those results. A previous study reported a significant increase in malaria cases in groups supplemented with a tablet containing 12.5 mg/d iron once a day or half of a tablet if aged <1 y (14). The present study used a lower dosage of iron, and the LNS intake was in smaller amounts throughout the day, which may

### Table 1
Baseline characteristics of the participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 209)</th>
<th>Milk-LNS (n = 212)</th>
<th>Soy-LNS (n = 210)</th>
<th>CSB (n = 209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mo</td>
<td>6.02 ± 0.23</td>
<td>6.02 ± 0.25</td>
<td>6.04 ± 0.25</td>
<td>6.03 ± 0.24</td>
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<tr>
<td>Male infants, %</td>
<td>53.1</td>
<td>50.5</td>
<td>49.1</td>
<td>46.9</td>
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<tr>
<td>Breast-fed, %</td>
<td>100.0</td>
<td>99.5</td>
<td>100.0</td>
<td>100.0</td>
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<tr>
<td>Anthropometric status</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stunted, &lt; −2 LAZ WHO, %</td>
<td>34.0</td>
<td>34.0</td>
<td>39.1</td>
<td>39.7</td>
</tr>
<tr>
<td>LAZ</td>
<td>−1.64 ± 0.97</td>
<td>−1.59 ± 1.05</td>
<td>−1.68 ± 1.11</td>
<td>−1.72 ± 0.97</td>
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<tr>
<td>Underweight, &lt; −2 WAZ WHO, %</td>
<td>13.4</td>
<td>10.4</td>
<td>14.3</td>
<td>18.2</td>
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<tr>
<td>WAZ</td>
<td>−0.80 ± 1.06</td>
<td>−0.70 ± 1.10</td>
<td>−0.80 ± 1.12</td>
<td>−0.85 ± 1.21</td>
</tr>
<tr>
<td>Wasted, &lt; −2 WHZ WHO, %</td>
<td>1.9</td>
<td>0.9</td>
<td>2.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Weight-for-length Z-score</td>
<td>0.41 ± 1.05</td>
<td>0.50 ± 1.05</td>
<td>0.46 ± 1.00</td>
<td>0.42 ± 1.1</td>
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<tr>
<td>Hemoglobin concentration, g/d</td>
<td>9.4 ± 1.7</td>
<td>9.6 ± 1.7</td>
<td>9.3 ± 1.7</td>
<td>9.5 ± 1.2</td>
</tr>
<tr>
<td>Proportion anemic (Hb &lt; 110 g/dL), %</td>
<td>84.4</td>
<td>82.5</td>
<td>83.7</td>
<td>83.6</td>
</tr>
<tr>
<td>Proportion with malaria parasitemia, %</td>
<td>17.1</td>
<td>10.1</td>
<td>13.7</td>
<td>10.9</td>
</tr>
<tr>
<td>Household characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children aged &lt;5 y the household, n</td>
<td>1.6 ± 0.7</td>
<td>1.6 ± 0.8</td>
<td>1.6 ± 0.7</td>
<td>1.7 ± 0.9</td>
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<td>Maternal years of education, n</td>
<td>3.6 ± 3.4</td>
<td>4.0 ± 3.7</td>
<td>3.0 ± 3.1</td>
<td>3.7 ± 3.1</td>
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<tr>
<td>Piped drinking water, %</td>
<td>4.0</td>
<td>5.4</td>
<td>2.9</td>
<td>4.4</td>
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<td>Availability of latrine, %</td>
<td>92.5</td>
<td>94.2</td>
<td>93.6</td>
<td>92.7</td>
</tr>
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</table>

1 Values are means ± SDs or percentages. CSB, corn-soy blend; Hb, hemoglobin; LAZ, length-for-age Z-score; milk-LNS, lipid-based nutrient supplement with milk protein base; soy-LNS, lipid-based nutrient supplement with soy protein base; WAZ, weight-for-age Z-score; WLZ, weight-for-length Z-score.

### Table 2
Longitudinal prevalence of guardian-reported fever, respiratory illness, and diarrhea in Malawian children aged 6–18 mo given LNSs, CSB, or no supplement

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (n = 209)</th>
<th>Milk-LNS (n = 212)</th>
<th>Soy-LNS (n = 210)</th>
<th>CSB (n = 209)</th>
<th>Milk-LNS vs. control</th>
<th>Soy-LNS vs. control</th>
<th>CSB vs. control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile illness</td>
<td>5.5 (4.7, 6.3) (3855)</td>
<td>4.9 (4.3, 5.5) (3523)</td>
<td>4.5 (3.9, 5.1) (3208)</td>
<td>4.7 (4.1, 5.3) (3207)</td>
<td>0.91 (0.73, 1.09)</td>
<td>0.90 (0.72, 1.08)</td>
<td>0.91 (0.73, 1.09)</td>
</tr>
<tr>
<td>Cough alone</td>
<td>6.1 (5.2, 7.0) (4116)</td>
<td>5.7 (4.9, 6.5) (4066)</td>
<td>5.3 (4.5, 6.0) (3762)</td>
<td>5.5 (4.5, 6.5) (3666)</td>
<td>0.98 (0.86, 1.10)</td>
<td>0.95 (0.87, 1.03)</td>
<td>0.88 (0.67, 1.04)</td>
</tr>
<tr>
<td>ARI</td>
<td>1.6 (1.2, 1.9) (988)</td>
<td>1.3 (1.0, 1.6) (881)</td>
<td>1.2 (0.9, 1.5) (874)</td>
<td>0.9 (0.7, 1.2) (688)</td>
<td>0.82 (0.61, 1.03)</td>
<td>0.98 (0.63, 1.09)</td>
<td>0.73 (0.54, 0.92)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.5 (3.9, 5.1) (3155)</td>
<td>4.9 (4.3, 5.5) (3480)</td>
<td>4.5 (3.9, 5.0) (3165)</td>
<td>4.4 (3.8, 5.0) (3072)</td>
<td>1.06 (0.87, 1.25)</td>
<td>0.98 (0.81, 1.17)</td>
<td>1.05 (0.86, 1.24)</td>
</tr>
<tr>
<td>Any morbidity</td>
<td>14.5 (13.0, 16.0) (9969)</td>
<td>13.9 (12.5, 15.2) (9999)</td>
<td>13.0 (11.7, 14.3) (9289)</td>
<td>13.7 (12.0, 15.4) (9396)</td>
<td>0.97 (0.81, 1.14)</td>
<td>0.91 (0.75, 1.06)</td>
<td>0.90 (0.74, 1.05)</td>
</tr>
</tbody>
</table>

1 Values are percentages (95% CIs) or geometric mean ratios (95% CIs). ARI, acute respiratory illness; CSB, corn-soy blend; LNS, lipid-based nutrient supplement; milk-LNS, lipid-based nutrient supplement with milk protein base; soy-LNS, lipid-based nutrient supplement with soy protein base.
2 The non-inferiority margin for the geometric mean ratio compared with control is 1.2.
3 The number of days with illness.
4 Non-inferiority is concluded.

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help to minimize the adverse risk effect of iron (15). In the recent report from Ghana described previously (19), there was an increase in hospitalizations in children receiving iron-containing MNP but no associated increase in the risk of malaria.

We observed similar mean hemoglobin concentrations and prevalence of anemia at the end of the intervention between the groups. Previous studies in Chad (20), Ghana (21), and Malawi (39) showed substantial effects of LNS interventions on both mean hemoglobin concentration and prevalence of anemia compared with nonsupplemented controls. However, the iron content in our LNS daily dose was lower (approximately half of that in the previous Ghana and Malawi studies and 75% of that in the Chad study) and may not have been enough to increase hemoglobin concentration and resolve anemia due to iron deficiency. The proportion of anemia due to iron deficiency is unknown because hemoglobin was the only biomarker measured. The high prevalence of anemia at 18 mo of age (65% in the control group) suggests the coexistence of other etiologic causes of anemia not amenable to iron supplementation, given that the background rate of iron deficiency anemia among children aged <5 y in Malawi in 2009 was estimated at 30.6% (40).

This study has several limitations. First, we had no measures of iron status among the participants. Second, the sample size was calculated based on the primary outcome of the trial (linear growth) and not the morbidity outcomes. However, as Feinstein and Concato (41) maintained, after the completion of a trial, the intervention effect should be determined by CIs without power calculation. This study yielded CIs that were precise enough to conclude non-inferiority of LNSs in most aspects of morbidity. Third, the study participants were not masked with respect to the intervention assignment because of the type of supplement (paste, flour) provided to children, leading to possible differential reporting by guardians on morbidity occurrence. However, objective measures (malaria parasitemia) and incidence based on diagnosis obtained from health facilities indicated similar results, showing robustness in the findings. Despite the above limitations, our study has several strengths: 1) we had broad inclusion criteria for participants to the study; 2) their allocation to intervention groups was random; and 3) the groups were similar on a wide range of participant characteristics at baseline. Additionally, success to follow-up visits was high with no differences between the groups, drop-out rate was low, and reported adherence to the supplements was good. Furthermore, data collection on morbidity information was done prospectively and regularly, and guardian-reported illness was documented using a morbidity calendar that was shown to improve data completeness and accuracy by minimizing recall errors compared with cross-sectional recall interviews (42).

In summary, our study showed that, in a population of rural children aged 6–18 mo in a malaria-endemic area where anemia is prevalent, provision of 54 g/day milk-based or soy protein–based LNSs containing 6 mg/d iron did not increase the risk of malaria or respiratory morbidity. However, because of insufficient power, we cannot confirm the non-inferiority of the intervention with respect to hospital admissions or death, which would need to be evaluated in larger studies.

### Table 3: Incidence of guardian-reported fever, respiratory illness, and diarrhea in Malawian children aged 6–18 mo given LNSs, CSB, or no supplement

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Incidence per child-year (n episodes)</th>
<th>Incidence rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (189.8 child-years)</td>
<td>Milk-LNS (198.0 child-years)</td>
</tr>
<tr>
<td></td>
<td>Febrile illness alone</td>
<td>5.88 (1116)</td>
</tr>
<tr>
<td></td>
<td>Cough alone</td>
<td>5.82 (1104)</td>
</tr>
<tr>
<td></td>
<td>ARI</td>
<td>1.49 (282)</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>4.44 (843)</td>
</tr>
</tbody>
</table>

^1 The non-inferiority margin for incidence rate ratio compared with control is 1.2. Incidence per child-year was calculated as the number of episodes divided by child-years in a group.
^2 Non-inferiority is concluded.

### Table 4: Incidence of malaria, acute respiratory problems, and diarrhea in Malawian children aged 6–18 mo given LNSs, CSB, or no supplement

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Incidence per child-year (n episodes)</th>
<th>Incidence rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (189.8 child-years)</td>
<td>Milk-LNS (198.0 child-years)</td>
</tr>
<tr>
<td></td>
<td>Clinical malaria</td>
<td>0.64 (122)</td>
</tr>
<tr>
<td></td>
<td>Rapid breathing</td>
<td>1.18 (223)</td>
</tr>
<tr>
<td></td>
<td>Chest indrawing</td>
<td>0.10 (19)</td>
</tr>
<tr>
<td></td>
<td>Clinical pneumonia</td>
<td>0.96 (183)</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>0.15 (29)</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>12 (0.06)</td>
<td>7 (0.04)</td>
</tr>
</tbody>
</table>

^1 The non-inferiority margin for the incidence rate ratio compared with control is 1.2. Data are from clinician’s diagnosis at a health facility during unscheduled visits from any illness. Incidence per child-year was calculated as the number of episodes divided by child-years in a group. CSB, corn-soy blend; LNS, lipid-based nutrient supplement; milk-LNS, lipid-based nutrient supplement with milk protein base; soy-LNS, lipid-based nutrient supplement with soy protein base.
^2 Non-inferiority is concluded.

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Acknowledgments
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References


