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An integrated infant and young child feeding and micronutrient powder intervention does not affect anemia, iron status, or vitamin A status among children 12-23 months in Eastern Uganda

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Abstract

Background: Micronutrient powders (MNP) can reduce iron deficiency and anemia in children.

Objective: We evaluated the impact of an integrated infant and young child feeding (IYCF) – MNP intervention on anemia and micronutrient status among children 12–23mo in Eastern Uganda. The intervention focused on MNP distribution, IYCF education, and caregiver behavior change.

Methods: Population-based cross-sectional surveys representative of children 12–23mo in Amuria (intervention) and Soroti (non-intervention) districts were collected in June/July 2015 at baseline (n=1,260) and 12 months after implementation at endline in 2016 (n=1,490). From pooled capillary blood, we assessed hemoglobin (Hb), malaria, ferritin, retinol binding protein (RBP), C-reactive protein, and alpha-1 acid glycoprotein. Ferritin and RBP were regression-adjusted to correct for inflammation. Caregivers reported sociodemographic characteristics and MNP knowledge and practices. Linear regression estimated the difference-in-difference (DiD) effect of MNP on Hb, ferritin, and RBP and logistic regression estimated DiD effect of MNP on anemia (Hb <11.0 g/dL), iron deficiency (ferritin <12.0 μg/L), iron deficiency anemia (Hb <11.0 g/dL and

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ferritin <12.0 μg/L), and vitamin A deficiency (VAD) (RBP equivalent to <0.70 μmol/L retinol: <0.79 μmol/L at baseline and RBP <0.67 μmol/L at endline).

Results: In Amuria, 96% of children had ever consumed MNP vs. <1% of children in Soroti. Fifty-four percent of caregivers reported organoleptic changes when MNP were added to foods cooked with soda ash. Adjusting for age, sex, malaria, recent morbidity, and household-level factors, the intervention was associated with −0.83 g/dL lower Hb (95% CI −1.36, −0.30 g/dL; *P*=0.003) but not with anemia, ferritin, iron deficiency, iron deficiency anemia, RBP, or VAD.

Conclusion: Despite high program fidelity, the intervention was associated with reduced Hb concentrations but not with change in anemia or micronutrient status among children 12–23 months in Eastern Uganda. Contextual factors, like cooking with soda ash, might explain the lack of effectiveness.

Keywords

Anemia; Iron Deficiency; Vitamin A Deficiency; Micronutrient Powders (MNP)

Introduction

In settings where the prevalence of anemia is ≥20%, the WHO recommends home fortification with micronutrient powder (MNP) to prevent anemia and iron deficiency among children 6–23mo (1). The single-dose sachets of vitamins and minerals can be mixed into any ready-to-eat semi-solid food (2). According to UNICEF, MNP are most effective in improving diet quality among children 6–23mo when introduced as part of a comprehensive infant and young child feeding (IYCF) strategy (3). Of the 65 countries with MNP interventions in 2015, 53 were implemented as integrated IYCF-MNP programs (3).

The 2011 Uganda Demographic Health Survey (DHS) suggests that Ugandan children have a high burden of anemia and potentially other micronutrient deficiencies, reporting that 49% of children 6–59mo had anemia while 38% had vitamin A deficiency (VAD) (4). In 2015, the Uganda Ministry of Health in collaboration with the United Nations World Food Programme (WFP) implemented a pilot program to promote and distribute MNP with IYCF counseling in Amuria and Katakwi districts in Eastern Uganda. The pilot aimed to improve IYCF practices and reduce the prevalence of anemia and other micronutrient deficiencies among children 6–23mo.

Although MNP interventions have been shown to reduce anemia and iron deficiency in a variety of contexts worldwide (5), some recent program evaluations have shown that MNP interventions may not be efficacious or effective in all settings (6–8). To understand the context-specific effectiveness of the MNP intervention and identify lessons learned for scaling up the intervention in other districts in Uganda, the implementing partners planned an evaluation of the pilot project.

The objectives of these analyses were to determine the impact of the pilot program on: *1*) hemoglobin, ferritin, and retinol binding protein (RBP) concentrations; and *2*) the prevalence of anemia, iron deficiency, iron deficiency anemia, and VAD.

Methods

Pilot program integrating MNP into an IYCF Program

The yearlong IYCF/MNP pilot project started in July 2015, and was implemented in Amuria and Katakwi districts, with support from Andre Food Consults, an implementing partner contracted by WFP. The intervention focused on caregiver behavior change to generate demand for MNP and to increase knowledge and motivation for optimal IYCF practices for children under 2y. Two producers (Hexagon Nurition and DSM Nutritional Products) supplied MNP for the intervention. The MNP contained 15 vitamins and minerals with slightly different formulations (Supplemental Table 1). Supported by Andre Food Consults, health facility staff and village health team volunteers carried out monthly MNP distribution at facilities (government outposts and health centers) and in communities (central locations in villages and home delivery). MNP was distributed free of charge to children 6–23mo according to a schedule of one box of 30 sachets every two months. Messaging suggested giving the child one sachet mixed into their food every other day. During distribution, caregivers received counseling on the preparation of food mixed with MNP including food preparation demonstrations, the MNP dosing schedule, and locally tailored optimal IYCF practices. Caregivers received program materials including ration and adherence cards. The pilot also used mass media (radio jingles, brochures, stickers, posters), and partnerships with women groups, and others to disseminate messages about MNP and IYCF.

Study population

The impact evaluation used pre-post, cross-sectional, population-based surveys representative of children 12–23mo in intervention (Amuria) and non-intervention (Soroti) districts. Following a pre-survey field visit, Soroti district was selected as the most suitable comparison due to geographic proximity and similarities in ethnicity, cultural, and socio-economic profiles. Because Amuria district is rural while Soroti has a few urban areas, this evaluation is representative only of rural areas in Soroti district.

Because no anemia or iron data were available for Amuria or Soroti districts prior to the baseline survey, sample sizes were based on 60% anemia and 25% iron deficiency - the national prevalences among children 12–23 month in the 2011 DHS (4). A 2013 meta-analysis of 17 studies of MNP interventions found that MNP significantly reduced prevalences of anemia and iron deficiency by 34% (Risk Ratio [RR] 0.66; 95% CI: 0.57, 0.77) and 57% (RR 0.43, 95% CI 0.35, 0.52), respectively (9). The survey samples were designed to detect a more conservative 10.0 and 9.1 percentage point changes in the prevalence of anemia and iron deficiency, respectively. The sample size estimation was based on two sequential, clustered cross-sectional surveys (pre- and post-intervention) of equal sample size (10) with the following assumptions: two-sided α of 0.05, 80% power, an individual response rate of 75%, and a design effect of 1.56 based on the design effect for the rural sample for anemia in children 6–59mo in the 2011 DHS (4). The resultant sample size was 833 children 12 to 23 months per district, or 1,666 for the 2 districts and included a 30% increase in the number of participants to reflect the potential prevalence of inflammation and possible need to exclude for inflammation during data analyses

(ultimately a regression correction was applied instead of exclusion). This sample size was also adequate to detect a change of ~8.2% in VAD as defined by RBP.

Baseline data were collected in June-July 2015, and endline data were collected in June-July 2016, 12 months after pilot program implementation. Makerere University School of Food Technology, Nutrition and Bio-Engineering led the surveys with technical assistance from the United States CDC and oversight of the WFP and the Ministry of Health.

Similar protocols were followed for both the baseline and endline surveys. Using a multi-stage cluster sampling design, we randomly selected 38 census enumeration areas in Amuria (all rural) and Soroti (rural areas only) without replacement using probability proportional to population size. Enumerators completed a census in each selected cluster and then randomly selected without replacement 22 children ages 12–23mo from each cluster. Of the 3,046 eligible children in the selected clusters at baseline and endline combined, 2,818 (92.5%) caregivers consented to participate (89.5% at baseline and 95.1% at endline). We excluded children for missing ferritin (n=36, 1.2%) and for missing information on covariates (n=33, 1.2%) for a final analytic sample of 2,749 children.

Data collection

Data were collected from caregivers using a pre-tested interviewer-administered questionnaire on child's sex, age, food group consumption the day preceding the survey, two week morbidity recall, sociodemographic characteristics, household assets and housing characteristics, food security, IYCF and MNP knowledge and practices, and experiences with the MNP pilot, including organoleptic changes to foods mixed with MNP.

In each cluster, blood samples were collected at a central location to assess micronutrient, inflammation, and infection status. Trained laboratory technicians collected two 250-μL finger stick capillary blood samples following standard procedures. They analyzed hemoglobin (HemoCue® Hb 301 analyzer) and malaria (malaria antigen rapid test kit for *Plasmodium falciparum*) at the point of collection. Samples were processed 3–4 h after collection and temporarily stored at a regional level laboratory in a −20°C freezer before being transported to Makerere University and stored in a −86°C freezer until analysis, maintaining cold chain. VitMin Lab (Willstaett, Germany) assessed RBP, serum ferritin, transferrin receptor (sTfR), c-reactive protein (CRP), and α-1-acid glycoprotein (AGP) using a sandwich ELISA (11). To correct for inflammation, we regression-adjusted ferritin, and RBP to a pooled country reference using CRP and AGP (12).

Variable specification

Outcomes: Anemia was defined as altitude-adjusted Hb <11.0 g/dL (13). Iron deficiency was defined as adjusted ferritin <12.0 μg/L (13). Iron deficiency anemia was classified as adjusted Hb <11.0 g/dL and adjusted ferritin <12.0 μg/L (13). VAD was defined as adjusted RBP <0.79 μmol/L at baseline and adjusted RBP <0.67 μmol/ at endline. To find the population-specific RBP cut-off for each time point, we regressed RBP on retinol to determine the RBP equivalent of retinol <0.70 μmol/L (14), based on the randomly selected subsample of 39 children for whom modified relative dose response and serum retinol were

assessed using HPLC from a second blood draw approximately 4 hours after the first blood draw.

Covariates: Covariates were selected *a priori* by identifying sociodemographic and health characteristics that might affect the trajectory of change in the outcomes. Child age group was categorized as 12–17mo vs. 18–23mo. Caregiver education measured in years of schooling was classified as less than a primary education (< 5 years) vs. primary or higher education (≥ 5 years). Severe household food insecurity was defined as households who reported often cutting back on meal size or number of meals and/or ever experiencing any of the three most severe conditions (no food to eat of any kind in the household because of lack of resources to get food; any household member goes to sleep at night hungry because there was not enough food; and any household member goes a whole day and night without eating anything because there was not enough food) during the 12 months preceding the survey (15). We created a household wealth index based on a principal components analysis of household assets, housing characteristics, and service amenities, per the guidelines for the Uganda DHS, and divided household wealth into tertiles (4). Improved water source was defined as having piped water, tube well borehole, protected well or spring, stone tap, rainwater, or bottled water (16). We included severe household food insecurity, improved water source, malaria, and caregiver report of morbidity (fever, diarrhea) during the two weeks preceding the survey as binary variables (yes/no).

Statistical analyses

To evaluate whether the MNP-IYCF intervention had an effect on biological indicators of anemia, iron and vitamin A status, we used an intent-to-treat difference-in-difference (DiD) modeling approach (17). The DiD method quantified the additive impact of the MNP-IYCF intervention in the intervention district (Amuria) relative to the non-intervention district (Soroti) from 2015 to 2016 net of differences attributable to district-level differences or other period effects. We calculated the average intervention effect using generalized linear mixed models, using cluster as a random effect and applying sampling weights to account for complex sampling design. The average intervention effects are the interaction terms for intervention assignment and time and are presented as adjusted mean differences for continuous outcomes (Hb, ferritin, RBP) and adjusted prevalence differences (APDiD) for binary outcomes (anemia, iron deficiency, iron deficiency anemia, VAD).

The base models included a variable to account for the fixed effects of district and intervention assignment (Amuria vs. Soroti), a variable for time (post-[2016] vs. pre-[2015] pilot implementation), the interaction between the intervention and time, and adjustment for sex and age group. Adjusted models additionally controlled for household wealth tertile, caregiver schooling level, improved water source, severe household food insecurity, malaria, caregiver report of recent fever, and caregiver report of recent diarrhea. We conducted all analyses using SAS v.9.4 (SAS Institute Inc., Cary, North Carolina). Two-sided $P < 0.05$ were considered statistically significant.

The Uganda National Council for Science and Technology granted research clearance. The School of Biomedical Sciences Higher Degrees, Research and Ethics Committee, College of

Health Sciences, Makerere University gave ethical approval for this survey. Enumerators obtained informed consent from all participating caregivers for their child(ren).

Results

The survey population was characterized by high burden of infection. At baseline, more than 70% of caregivers reported that their child had a fever during the two weeks preceding the survey and half of children had a positive malaria test (Table 1).

At baseline, prevalences of anemia, iron deficiency, iron deficiency anemia, and VAD were similar across districts (Table 1). For both districts combined at baseline, 47.9% (95% CI 45.3, 50.6) of children had anemia (data not shown). More than one-third of children (36.6%, 95% CI 33.9, 39.2) had iron deficiency and 17.7% (95% CI 15.7, 19.8) had iron deficiency anemia. Five percent (95% CI 3.8, 6.2) of children had VAD.

At endline, 95.5% (95% CI 93.3, 97.7) of caregivers in Amuria reported that their child had ever received MNP compared to four caregivers in Soroti (<1%). More than half (53.5%, 95% CI 47.8, 59.3) reported receiving the 2011 WHO-recommended number of sachets during the pilot year. Among children in Amuria, 65.5% (95% CI 61.0, 70.0) consumed MNP during the two weeks preceding the endline survey.

In the fully adjusted multivariable model, the MNP intervention was associated with −0.83 g/dL lower hemoglobin concentrations (95% CI −1.36, −0.30 g/dL; P=0.003) (Table 2); however, there was no intervention effect on anemia prevalence (Table 3).

Similarly, there was no intervention effect on serum ferritin concentrations, serum RBP concentrations, or prevalences of iron deficiency, iron deficiency anemia, or VAD. Results for ferritin and RBP concentrations unadjusted for inflammation are presented in Supplemental Table 2. Results for iron deficiency, iron deficiency anemia, and vitamin A deficiency unadjusted for inflammation are presented in Supplemental Table 3. The findings did not differ from those presented in the main analyses.

In terms of caregiver experiences with the MNP, 54.0% (95% CI 48.5, 59.5 of caregivers reported organoleptic changes when MNP were added to foods cooked with soda ash; most (87.2%; 95% CI 82.6, 91.7) reported the food turned black (Table 1).

Discussion

Using an intent-to-treat DiD approach, we modeled the impact of an integrated MNP-IYCF pilot intervention on hemoglobin and biomarkers of iron and vitamin A status among children 12–23mo in Eastern Uganda. The intervention was associated with −0.83 g/dL lower hemoglobin concentrations; however, we found no intervention effect on mean ferritin or RBP concentrations or on prevalences of anemia, iron deficiency, iron deficiency anemia, or VAD.

The findings were unexpected because MNP interventions are reportedly efficacious in reducing anemia across a variety of contexts worldwide. Although a 2013 meta-analysis of

17 studies of MNP interventions reported that MNP significantly reduced prevalences of anemia and iron deficiency (9), recent studies have reported that MNP was inefficacious or ineffective in reducing iron deficiency and anemia. A trial of daily home fortification with multiple micronutrients among children 12–36mo in Kenya did not improve hemoglobin or iron status (6). Similarly, a cluster RCT of daily MNP among children 12–24mo in Colombia reported no impact on hemoglobin or anemia (8). An evaluation 3y after national scale-up of an MNP program in Kyrgyzstan reported no change in anemia and increases in VAD among children 6–2mo, while iron deficiency and iron deficiency anemia declined (7).

Although we used intent-to-treat analyses, we found no evidence to suggest that the lack of effectiveness might have been due to poor program implementation, low adoption, or poor adherence (19). Based on program monitoring reports, we found no evidence of stock outs or limited stock. Only two caregivers reported experiencing limited MNP supply. In Amuria, 95.5% of children ever received MNP. Of those, 96.7% had consumed at least one MNP sachet (data not shown). Further, 53.5% reported receiving the 2011 WHO-recommended dose during the pilot (18). Reported recent intake was high. Sixty-five percent of children in Amuria consumed MNP during the two weeks preceding the endline survey. Except for ferritin, we found no difference in mean concentrations of biomarkers or prevalences of deficiency by either MNP sachet coverage or recent MNP intake (Supplemental Table 4). Finally, there was little crossover of MNP intervention into Soroti where <1% reported caregivers reported that their child ever received MNP.

Dosage and intake regimen might influence MNP effectiveness. Each MNP sachet contained either 10 mg iron as ferrous fumarate (Hexagon Nutrition) or 11.0 mg iron as elemental iron and NaFe(III)EDTA (DSM Nutritional Products), which are both within the 10–12.5 mg range suggested by the WHO (1). Further, the Uganda MNP had higher vitamin A (400 μg for Hexagon MNP; 500 μg for DSM MNP vs. 300 μg) compared to the WHO suggested formulation (1). The Salem et al. meta-analysis (9) included multiple dosing regimens, and a study of MNP containing low dose iron (6 mg) reported significant improvements in hemoglobin and anemia among infants 9–12mo in Ethiopia (20). The suggested dosing at the time of the pilot was 60 sachets every six months, the expected minimum dose required to see an impact (18). In 2016, the WHO updated its dosing recommendations to 90 sachets every six months based on the poor nutritional quality of complementary feeding in many contexts (1). In Amuria, we found no difference in mean concentrations of biomarkers or prevalences of deficiency at endline by MNP sachet coverage according to the updated 2016 dosing recommendations (Supplemental Table 5).

Quality of MNP premix, sachet packaging, and storage could affect effectiveness. Both MNP suppliers have ISO certifications for quality. Pilot monitoring reports did not indicate that sachets were expired or that packaging was damaged or of poor quality. MNP should be stored in cool (below 30° C) and dry conditions. Average temperatures in Amuria range from 18° to 35° C. We have no evidence that implementation staff stored MNP improperly although we do not know how caregivers stored the sachets. MNP education stressed proper storage and encouraged caregivers to check sachets for evidence of spoilage. No caregivers reported that powders were clumped or had changed color. We did not test the premix at the

lab to confirm its content, which is a limitation to understanding why the intervention was not effective despite good program fidelity.

Inappropriate preparation of MNP do not appear to explain program ineffectiveness. Among those who had ever heard of MNP, 75.7% knew they should be introduced at age 6mo, 90.5% knew that a child should receive one sachet in a day, and 96.0% knew that each child should have his or her own sachet of MNP (data not shown). Further, we found no evidence that MNP displaced nutrient-rich foods in the diet. In fact, the intervention had a positive effect on most IYCF practices measured in the evaluation including children consuming vitamin A-rich fruits and vegetables, animal-flesh foods, and minimum acceptable diet (21). Evaluations of integrated IYCF-MNP programs reported improved minimum dietary diversity and acceptable diet among children 6–23mo (22–24).

The MNP-IYCF pilot may have been ineffective in reducing anemia if anemia were due to reasons other than iron deficiency. Factors such as deficiency in micronutrients other than iron, infection, and blood disorders contribute to anemia (13). Nevertheless, the study population had a high co-existence of anemia and iron deficiency, suggesting that at least some of the anemia burden might be reduced with improved iron status. Although the MNP contained 15 micronutrients including vitamin A, the pilot had no effect on either RBP concentrations or VAD. There is a dearth of evidence to suggest that MNP is efficacious or effective in reducing deficiencies other than iron. A 2013 systematic review based on few studies with moderate outcome-specific quality of evidence found that MNP significantly reduced the risk of VAD (retinol) by 21% (95% CI 0.64, 0.89) but had no reported effects on either serum retinol or zinc deficiency among children (9).

Although infection and inflammation can contribute to anemia, we do not believe they explain the ineffectiveness of the MNP pilot. Ferritin and RBP were regression corrected to account for the role of inflammation. Models adjusted for malaria, caregiver report of recent fever and diarrhea, and household water source to account for differences in disease burden that could affect trajectory of change. Finally, the 2011 Cochrane Review of MNP reported that MNP was efficacious in settings with different prevalences of malaria endemicity (5), suggesting that malaria would not preclude MNP effectiveness.

We suspect the lack of effectiveness might be explained by contextual factors such as cooking practices. Parts of Uganda, including Amuria, cook greens and beans with soda ash (sodium carbonate) to reduce cooking time (25). Soda ash can influence both micronutrient bioavailability and absorption. HCl in the stomach is crucial for absorption of non-heme iron (26). Changes to intestinal pH from soda ash can lead to reduced iron absorption (26). Soda ash can also directly affect iron bioavailability by forming ternary, insoluble compounds with iron (27). In alkaline environments, vitamin C has a buffering reaction with copper, resulting in in lower ascorbic acid content, further influencing iron bioavailability (27). Studies of stomach acid suppression via antacids and proton-pump inhibitors found associations with reduced iron absorption and anemia (28–30). Sodium carbonate can also reduce absorption of vitamin B_{12}, which is required for hemoglobin synthesis (31–34).

Caregiver experiences with MNP reported at endline suggest that soda ash might have affected the bioavailability of micronutrients in the MNP. When prepared correctly, MNP should not alter the color of food (1). However, during the pilot, the evaluation team became aware that mixing MNP into foods that were cooked with soda ash caused foods to turn dark. Based on these reports, the behavior change component was adapted to motivate continued use despite color changes, and questions about soda ash were included in the endline survey. Although data on the prevalence of soda ash use are not available, more than half of caregivers reported changes to foods cooked with ash. Color changes result from the buffering reaction between vitamin C and copper and the ternary complexes formed with iron and other molecules in the presence of bicarbonate (27). Even though 84% of caregivers who reported changes to food still served the food to their child, the ability of the child to absorb the micronutrients in the MNP might have been compromised by cooking methods.

To our knowledge, only one study has explored the role of cooking with soda ash on micronutrient bioavailability. Mamiro et al. (35) found that traditional African dishes cooked with ash had reduced iron and zinc bioavailability, and the authors cautioned that communities should be informed of the negative nutritional effects of this cooking technique. WHO MNP guidelines do not address cooking practices and how practices might affect the organoleptic properties of foods with MNPs or how cooking practices might influence micronutrient bioavailability. Further, research is needed to understand whether soda ash use is susceptible to change.

This impact evaluation used a pre-post cross-sectional design where secular, period, and cohort changes were accounted for by the non-intervention district. Our analyses adjusted for a range of potential confounders. Two suppliers produced MNP for this intervention with slightly different formulations and iron compounds. We do not know which formulation children consumed; however, both formulations contained at or above the recommended concentrations of iron and vitamin A. Although we were unable to measure blood disorders, MNP has been effective in reducing iron deficiency and anemia in other similar contexts in sub-Saharan Africa (36). We were unable to assess potential effect modification by iron, anemia, and inflammation status. Future research might explore the biological mechanisms underlying heterogeneity in response to micronutrient supplementation including genetic factors, differences in microbiome, and potential interaction with inflammation.

An integrated MNP-IYCF program was associated with lower hemoglobin concentrations and did not affect anemia, iron status, or vitamin A status among children 12–23mo in Eastern Uganda. While we cannot definitively conclude that cooking with soda ash is responsible for the lack of improvement in biomarkers of nutrient status, existing evidence suggests the relationship between soda ash consumption and poor nutrient absorption is biologically plausible. Future research might explore how cooking practices might influence micronutrient bioavailability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflict of Interest and Funding Disclosure:

The Government of Uganda, Ministry of Health and World Food Programme Uganda Country Office supported the implementation of the pilot intervention. World Food Programme Uganda funded an external agency (Makerere University) to conduct the baseline survey. The U.S. Centers for Disease Control and Prevention (CDC) provided technical assistance for this survey through a Memorandum of Agreement with the World Food Programme. Nicole D. Ford, Laird J Ruth, Sarah Ngalombi, Abdelrahman Lubowa, Siti Halati, Martin Ahimbisibwe, Rhona Baingana, Ralph D. Whitehead Jr., Carine Mapango, and Maria Elena Jefferds do not report any conflicts of interest.

Abbreviations:

AGP	α-1-acid glycoprotein
APDiD	adjusted prevalence difference-in-difference
CRP	C-reactive protein
DHS	Demographic and Health Survey
DiD	difference-in-difference
Hb	hemoglobin
IYCF	Infant and Young Child Feeding
MNP	micronutrient powder
RBP	retinol binding protein
RR	risk ratio
sTfR	transferrin receptor
VAD	vitamin A deficiency
WFP	United Nations World Food Programme

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Table 1.

Select Sociodemographic and Health Characteristics of Children 12–23 months at Baseline (2015) and Endline (2016) in Amuria (Intervention) and Soroti (Non-Intervention) Districts, Micronutrient Powder/Infant and Young Child Feeding Intervention Survey, Uganda, 2016 (*n*=2,749)[1]

		Amuria (Intervention District) at Baseline, 2015 (*n*=571)		Amuria (Intervention District) at Endline, 2016 (*n*=747)		Soroti (Non-Intervention District) at Baseline, 2015 (*n*=672)		Soroti (Non-Intervention District) at Endline, 2016 (*n*=759)	
Characteristic		***n***	**Mean or % (95% CI)**	***n***	**Mean or % (95% CI)**	***n***	**Mean or % (95% CI)**	***n***	**Mean or % (95% CI)**
Female, %		264	46.2 (42.5,50.0)	352	47.1 (43.9,50.4)	326	48.5 (44.7,52.3)	356	46.9 (43.6,50.2)
Age group, %									
	12–17 mo	261	45.7 (40.8,50.6)	449	60.1 (57.0,63.2)	320	47.6 (44.0,51.3)	452	59.6 (55.7,63.4)
	18–23 mo	310	54.3 (49.4,59.2)	298	39.9 (36.8,43.0)	352	52.4 (48.7,56.0)	307	40.4 (36.6,44.3)
Household wealth tertile[2], %									
	Poorest	219	38.4 (32.5,44.2)	256	34.3 (28.9,39.6)	199	29.6 (25.2,34.0)	222	29.2 (25.5,33.0)
	Middle	198	34.7 (30.2,39.1)	261	34.9 (31.4,38.5)	217	32.3 (28.6,36.0)	254	33.5 (29.5,37.4)
	Wealthiest	154	27.0 (21.7,32.2)	230	30.8 (25.0,36.5)	256	38.1 (34.0,42.2)	283	37.3 (32.0,42.6)
Caregiver has less than a primary education, %		419	73.4 (68.5,78.2)	530	71.0 (66.4,75.5)	484	72.0 (68.1,76.0)	533	70.2 (66.6,73.8)
Improved water source[3], %		530	92.8 (87.6,98.1)	700	93.7 (89.6,97.8)	644	95.8 (93.3,98.4)	732	96.4 (94.6,98.3)
Severe household food insecurity[4], %		23	4.0 (2.0,6.0)	97	13.0 (10.3,15.7)	14	2.1 (0.8,3.4)	89	11.7 (9.0,14.4)
Two-week morbidity recall, %									
	Fever	470	82.3 (78.7,85.9)	577	77.2 (73.3,81.2)	483	71.9 (68.2,75.5)	581	76.5 (73.5,79.6)
	Cough	352	61.6 (56.1,67.2)	383	51.3 (47.5,55.1)	407	60.6 (56.6,64.6)	450	59.4 (55.4,63.4)
	Diarrhea	344	60.2 (55.4,65.0)	327	43.8 (40.3,47.2)	368	54.8 (50.7,58.8)	371	48.9 (44.8,52.9)
Malaria (RTK), %		300	52.5 (46.1,58.9)	350	46.9 (41.3,52.4)	309	46.0 (40.8,51.2)	382	50.3 (45.7,55.0)
Hemoglobin[5], g/dL		571	11.2 (10.8,11.6)	747	10.7 (10.6,10.9)	672	10.6 (10.3,10.9)	759	10.8 (10.7,10.9)
Anemia[6], %		273	47.8 (40.9,54.7)	378	50.6 (47.0,54.2)	323	48.1 (41.8,54.3)	372	49.0 (45.4,52.6)
Anemia severity[7], %									
	No anemia	298	52.2 (45.3,59.1)	369	49.4 (45.4,53.4)	349	51.9 (45.7,58.2)	387	51.0 (47.6,54.4)
	Mild	156	27.3 (22.4,32.2)	201	26.9 (23.2,30.6)	158	23.5 (20.3,26.8)	231	30.4 (27.6,33.3)
	Moderate	114	20.0 (15.7,24.2)	169	22.6 (18.5,26.8)	150	22.3 (16.9,27.8)	133	17.5 (14.6,20.4)
	Severe	3	0.5 (0.0,1.1)	8	1.1 (0.3,1.8)	15	2.2 (0.8,3.7)	8	1.1 (0.4,1.7)

Characteristic	Amuria (Intervention District) at Baseline, 2015 (*n*=571)		Amuria (Intervention District) at Endline, 2016 (*n*=747)		Soroti (Non-Intervention District) at Baseline, 2015 (*n*=672)		Soroti (Non-Intervention District) at Endline, 2016 (*n*=759)	
	n	**Mean or % (95% CI)**	***n***	**Mean or % (95% CI)**	***n***	**Mean or % (95% CI)**	***n***	**Mean or % (95% CI)**
CRP, mg/L	571	2.86 (2.39,3.43)	747	2.90 (2.37,3.55)	672	2.27 (1.92,2.69)	759	2.61 (2.25,3.03)
AGP, g/L	571	1.37 (1.30,1.45)	747	1.25 (1.18,1.34)	672	1.24 (1.16,1.31)	759	1.10 (1.27,1.33)
Inflammation[8], %	394	69.0 (65.4,72.6)	488	65.3 (60.8,69.9)	430	64.0 (59.4,68.6)	409	53.9 (49.1,58.7)
Inflammation adjusted serum ferritin[9], µg/L	571	14.8 (13.6,16.2)	747	19.6 (18.5,20.7)	672	14.7 (13.8,15.7)	759	18.4 (17.3,19.6)
Iron deficiency[10], %	207	36.3 (31.0,41.5)	159	21.3 (17.7,24.8)	248	36.9 (32.9,40.9)	164	21.6 (17.6,25.7)
Iron deficiency anemia[11], %	99	17.3 (13.5,21.2)	65	8.7 (6.6,10.8)	122	18.2 (14.2,22.2)	75	9.9 (7.0,12.8)
Unadjusted serum ferritin, µg/L	571	41.9 (37.1,47.4)	747	51.3 (46.8,56.2)	672	37.8 (34.7,41.0)	759	43.8 (40.3,47.5)
Serum RBP[9], µg/L	571	1.26 (1.22,1.29)	747	1.30 (1.27,1.33)	672	1.26 (1.24,1.29)	759	1.32 (1.29,1.35)
Vitamin A deficiency[12], %	33	5.8 (3.6,7.9)	4	0.5 (0.0,1.0)	28	4.2 (2.6,5.7)	10	1.3 (0.6,2.0)
Unadjusted RBP, µg/L	571	0.95 (0.93, 0.98)	747	0.98 (0.95, 1.01)	672	0.98 (0.96, 1.01)	759	1.01 (0.99, 1.03)
Currently breastfeeding, %	330	57.8 (53.1,62.4)	398	53.3 (48.3,58.2)	431	64.1 (61.5,66.8)	464	61.2 (56.7,65.7)
Introduced complementary foods at age 6 months, %	240	42.0 (37.8,46.3)	498	66.7 (62.1,71.3)	384	57.1 (52.3,61.9)	447	58.9 (55.4,62.4)
Prior day food consumption, %								
Flesh, organ, or blood-based foods	70	12.3 (8.2,16.3)	183	24.5 (20.5,28.5)	167	24.9 (20.0,29.7)	208	27.4 (24.4,30.5)
Green, leafy vegetables	135	23.6 (17.4,29.8)	393	52.6 (49.2,56.0)	284	42.3 (36.1,48.4)	307	40.7 (37.2,44.1)
Vitamin A-rich fruits or vegetables	179	31.3 (24.7,38.0)	654	87.6 (82.8,92.3)	394	58.6 (52.4,64.9)	676	89.2 (86.0,92.3)
Ever received MNP, %	-	-	678	95.5 (93.3,97.7)	-	-	4	0.5 (0.0,1.0)
High MNP sachet coverage -, 2011 WHO recommendation[13], %	-	-	400	53.5 (47.8,59.3)	-	-	1	0.1 (0.0,0.4)
High MNP sachet coverage – 2016 recommendation[14], %	-	-	154	20.6 (17.2,24.0)	-	-	1	0.1 (0.0,0.4)
Recent MNP intake[15], %	-	-	444	65.5 (61.0,70.0)	-	-	0	-
Experienced organoleptic changes to foods cooked with soda ash and mixed with MNP, %	-	-	366	54.0 (48.5,59.5)	-	-	-	-
Food cooked with soda ash turned black when mixed with MNP[16], %	-	-	319	87.2 (82.6,91.7)	-	-	-	-

[1]Ns are unweighted. Values presented are geometric mean (95% CI) or percent (95% CI). All estimates account for weighting and complex sampling design.

[2]Household wealth index was based on a principal components analysis of household assets, housing characteristics, and service amenities, per the guidelines for the Uganda DHS, and divided household wealth into tertiles (4).

[3] Water source based on self-report. Improved water source defined as piped water, tubewell borehole, protected well or spring, stone tap, rainwater, or bottle water (16).

[4] Severe household food insecurity was defined as households who reported often cutting back on meal size or number of meals and/or ever experiencing any of the three most severe conditions (no food to eat of any kind in the household because of lack of resources to get food; any household member goes to sleep at night hungry because there was not enough food; and any household member goes a whole day and night without eating anything because there was not enough food) during the 12 months preceding the survey (15).

[5] Hemoglobin adjusted for altitude (13).

[6] Anemia defined as altitude-adjusted Hb <11.0 g/dL (13).

[7] Anemia severity categorized as mild (adjusted Hb 10.0–10.9 g/dL), moderate anemia (adjusted Hb 7.0–9.9 g/dL), and severe (adjusted Hb<7.0 g/dL) (13).

[8] Inflammation defined as elevated CRP (>5 mg/L) or elevated AGP (>1 g/L) (12).

[9] Biomarker was regression-adjusted to a pooled country reference to adjust for inflammation, using CRP and AGP (12).

[10] Iron deficiency defined as inflammation-adjusted serum ferritin <12.0 μg/L (13).

[11] Iron deficiency anemia defined as altitude-adjusted Hb <11.0 g/dL and inflammation-adjusted serum ferritin <12.0 μg/L (13).

[12] Vitamin A deficiency was defined as adjusted RBP <0.79 μmol/L at baseline and adjusted RBP <0.67 μmol/L at endline. To find the population-specific RBP cut-point, we regressed RBP on retinol in a subsample of 39 children for whom serum retinol was assessed using HPLC from a second blood draw to determine the assay- and matrix-specific RBP equivalent to retinol <0.70 μmol/L (14).

[13] High MNP sachet coverage was defined as having reported receiving at least 60 sachets (2 boxes) every six months during the 12-month pilot - the minimum recommended dose per the 2011 WHO guideline (18).

[14] High MNP sachet coverage was defined as having reported receiving at least 90 sachets (2 boxes) every six months during the 12-month pilot - the minimum recommended dose per the updated 2016 WHO guideline (1).

[15] Recent MNP intake defined as consumed MNP during the two weeks preceding the endline survey.

[16] Among those who reported changes to foods cooked with soda ash and mixed with MNP.

Abbreviations: AGP, α-1 acid glycoprotein; CRP, C-reactive protein; Hb, hemoglobin; MNP, micronutrient powder; RBP, retinol binding protein; RTK, rapid test kit.

Table 2.

Difference-in-difference in mean hemoglobin, inflammation-adjusted ferritin, and inflammation-adjusted RBP concentrations among children 12–23 months between intervention (Amuria) and non-intervention (Soroti) districts, Micronutrient Powder and IYCF Intervention Baseline Survey 2015 and Endline Survey 2016, Amuria and Soroti districts, Uganda 2015–16[1]

	β (95% CI)	*P*
Hemoglobin[2], g/dL		
Base Model	−0.74 (−1.29, −0.20)	0.008
Adjusted Model	−0.83 (−1.36, −0.30)	0.003
Serum ferritin[3], μg/L		
Base Model	0.65 (−1.78, 3.08)	0.6
Adjusted Model	1.53 (−0.70, 3.76)	0.2
Serum RBP [4], μmol/L		
Base Model	−0.01 (−0.07, 0.05)	0.7
Adjusted Model	−0.007 (−0.07, 0.05)	0.8

[1]Unweighted sample sizes are 2782 (hemoglobin) and 2749 (ferritin and RBP). Base model estimates are the beta coefficients and 95% confidence intervals for the interaction term specifying exposure to the MNP intervention controlling for: fixed effects of district (Amuria vs. Soroti), year (2016 vs. 2015), child sex, and child age group (12–17mo vs. 18–2mo). Adjusted models additionally control for household wealth tertile, caregiver schooling level (no formal or some primary education vs. other education level), improved water source, malaria (assessed by rapid test kit), and caregiver report of fever in the two weeks preceding the survey, and caregiver report of diarrhea in the two weeks preceding the survey. Confidence intervals account for weighting and complex sampling design.

[2]Hemoglobin adjusted for altitude.

[3]Biomarker was regression-adjusted to a pooled country reference to correct for inflammation, using CRP and AGP (12).

Abbreviations: Abbreviations: AGP, α-1 acid glycoprotein; CRP, C- reactive protein; MNP, micronutrient powder; RBP, retinol binding protein.

Table 3.

Adjusted difference-in-difference in the prevalence (APDiD) of anemia and inflammation-adjusted iron deficiency, iron deficiency anemia, and vitamin A deficiency among children 12–23 months between intervention (Amuria) and non-intervention (Soroti) districts, Micronutrient Powder and IYCF Intervention Baseline Survey 2015 and Endline Survey 2016, Amuria and Soroti districts, Uganda 2015–16[1]

	APDiD (95% CI)	*P*
Anemia[2]		
Base Model	3.0 (−7.2, 13.3)	0.6
Adjusted Model	5.2 (−4.8, 15.2)	0.2
Iron deficiency[3,4]		
Base Model	−0.4 (−8.6, 7.8)	0.9
Adjusted Model	−2.6 (−10.0, 4.9)	0.5
Iron deficiency anemia[3,5]		
Base Model	−0.2 (−6.7, 6.3)	0.9
Adjusted Model	−0.9 (−7.3, 5.5)	0.8
Vitamin A deficiency[3,6]		
Base Model	−2.3 (−5.1, 0.4)	0.09
Adjusted Model	−2.1 (−4.9, 0.6)	0.1

[1]Unweighted sample sizes are 2782 (anemia) and 2749 (iron deficiency, iron deficiency anemia, and vitamin A deficiency). Base model estimates are the difference in the prevalence (95% CI) for exposure to the MNP intervention controlling for: fixed effects of district (Amuria vs. Soroti), year (2016 vs. 2015), sex, and age group (12–17 months vs. 18–23 months). The adjusted model additionally controls for household wealth tertile, caregiver schooling level (no formal or some primary education vs. other education level), improved water source, malaria (assessed by rapid test kit), and caregiver report of fever and/or diarrhea in the two weeks preceding the survey. Confidence intervals account for weighting and complex sampling design.

[2]Anemia was defined as altitude-adjusted Hb <11.0 g/dL (13).

[3]Biomarker was regression-adjusted to a pooled country reference to correct for inflammation, using CRP and AGP (12).

[4]Iron deficiency was defined as inflammation- adjusted ferritin <12.0 μg/L (13).

[5]Iron deficiency anemia was classified as altitude-adjusted Hb <11.0 g/dL and inflammation-adjusted ferritin <12.0 μg/L (13).

[6]Vitamin A deficiency was defined as inflammation-adjusted RBP <0.79 μmol/L in the baseline sample and RBP <0.67 μmol/L in the endline sample. To find the population-specific RBP cut-point for each survey, we regressed RBP on retinol to determine the RBP equivalent of retinol <0.70 μmol/L based on the subsample of 39 children for whom serum retinol was assessed using HPLC from a second blood draw (14).

Abbreviations: AGP, α-1 acid glycoprotein; APDiD, adjusted prevalence difference-in-difference; CRP, C- reactive protein; MNP, micronutrient powder; RBP, retinol binding protein.