# Prenatal supplementation with multiple micronutrient supplements or medium-quantity lipid-based nutrient supplements has limited effects on child growth up to 24 months in rural Niger: a secondary analysis of a cluster randomized trial

Lilia Bliznashka[1], Christopher R. Sudfeld[1,2], Souna Garba[3], Ousmane Guindo[3], Issaka Soumana[3], Irène Adehossi[4], Céline Langendorf[5], Rebecca F. Grais[5], Sheila Isanaka[1,2,5]

**Author affiliations:**

[1] Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[2] Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[3]Epicentre, Niamey, Niger
[4] National Pediatric Hospital, Niamey, Niger
[5]Department of Research, Epicentre, Paris, France

**Corresponding author:** Sheila Isanaka
Email: sheila.isanaka@epicentre.msf.org
Address: 14-34 Avenue Jean Jaurès
75019 Paris, France
Phone: + 33 (0)1 4021 5498

**Running title:** Prenatal supplementation and child growth

**Conflict of interest:** The authors have no conflicts of interest.

**Funding**: Funding for this study was provided to Epicentre by Médecins Sans Frontières-Operational Center Geneva and the Kavli Foundation, Norway. The funders had no role in the study implementation, data collection, data analysis, data interpretation, or writing of the manuscript.

**Abbreviations:** BEP, balanced energy and protein; BMI, body mass index; IFA, iron-folic acid supplementation; LAZ, length-for-age Z-scores; LMICs, low- and middle-income countries; MD, mean differences; MMS, multiple micronutrient supplementation; MQ-LNS medium quantity lipid-based nutrient supplementation; MUAC, mid-upper arm circumference; RCT, randomized controlled trial; RDA, recommended daily allowance; RR, relative risks; WASH, water, sanitation, and hygiene; WAZ, weight-for-age Z-scores; WLZ, weight-for-length Z-scores.

**Registration:** The trial was registered with clinicaltrials.gov, number NCT02145000.

## Abstract

**Background:** Prenatal multiple micronutrient supplementation (MMS) and lipid-based nutrient supplementation (LNS) can improve birth outcomes relative to iron-folic acid supplementation (IFA); however, effects on child postnatal growth remain unclear.

**Objective:** To compare the effect of prenatal MMS, medium-quantity LNS (MQ-LNS), and IFA on child growth up to 2 years of age.

**Design:** We conducted a cluster-randomized controlled trial of prenatal nutritional supplementation in Madarounfa, Niger. Villages were randomly assigned for pregnant women to receive IFA (17 villages, 1,105 women), MMS (18 villages, 1,083 women) or MQ-LNS (18 villages, 1,144 women). Pregnant women received nutritional supplements weekly until delivery, and children were followed up monthly from 6-8 weeks to 24 months of age. We assessed the effect of prenatal MMS and MQ-LNS compared to IFA and the effect of prenatal MMS compared to MQ-LNS on child length-for-age Z-scores (LAZ), weight-for-age Z-scores (WAZ), and weight-for-length Z-scores (WLZ) at 24 months of age using generalized linear models. In secondary analyses, we used mixed effects models to assess the trajectory of anthropometric Z-scores longitudinally from 6-8 weeks to 24 months.

**Results:** Compared to IFA, MMS and MQ-LNS had no effect on child LAZ, WAZ, or WLZ at 24 months of age (p-values >0.05). Children in the MQ-LNS arm had significantly higher MUAC at 24 months than children in the MMS arm: mean difference 0.50 cm (95% CI 0.10, 0.91). WAZ and WLZ trajectories were more negative in the MQ-LNS arm compared to IFA and MMS, with lower Z-scores from 14 to 20 months of age. However, WAZ and WLZ trajectories converged after 20 months of age, and there were no differences by 24 months of age.

**Conclusions:** Prenatal MMS and MQ-LNS had limited effect on anthropometric measures of child growth up to 24 months of age as compared to IFA in rural Niger.

**Keywords:** child growth; multiple micronutrient supplementation; prenatal supplementation; lipid-based nutrient supplements; Niger





## Introduction

Maternal undernutrition in pregnancy is a major risk factor for poor child growth (1–3). In low- and middle-income countries (LMICs), 14% of child stunting is attributable to fetal growth restriction (4), and low maternal body mass index (BMI) in pregnancy is a leading risk factor for child wasting (5). Multiple concurrent micronutrient deficiencies and macronutrient deficiency are common among pregnant women in LMICs due to low dietary intake and increased nutrient demands in pregnancy (6,7). Although data on micronutrient deficiencies among pregnant women is sparse, data on women of reproductive age in Africa suggest that ~40% are folate or zinc deficient, 30% are iodine deficient, and 20% are vitamin B12 deficient (6). In addition, 14% of pregnant women in LMICs are macronutrient deficient, as defined by low body mass index (BMI <18.5 kg/m$^2$) (3). Supplementation with multiple micro- and/or macronutrients could improve maternal nutrition in pregnancy in LMICs where pregnant women are at risk of undernutrition.

Prenatal multiple micronutrient supplementation (MMS) is one strategy to address maternal micronutrient deficiencies during pregnancy and improve birth outcomes (8,9). Compared to iron and folic acid supplementation (IFA), MMS reduces the risk of stillbirth, low

birth weight, small-for-gestational age, and preterm birth (6,10–12). Although MMS has been shown to reduce adverse birth outcomes, which may contribute to poor postnatal child growth outcomes (4), evidence on the effect of MMS on postnatal child growth remains limited. Meta-analyses and systematic reviews suggest no overall effect of prenatal MMS on child stunting, wasting, or underweight as compared to IFA; however, only seven trials were identified in the most recent meta-analysis (8,12–14). In certain contexts, individual trials have demonstrated small-to-medium sized benefits on anthropometric Z-scores and large reductions in child stunting (15–17), suggesting heterogeneity of effects across settings.

Another strategy to address both macro- and micronutrient deficiencies during pregnancy is prenatal supplementation with lipid-based nutrient supplements (LNS). LNS are ready-to-use supplements, which typically contain many of the same vitamins and minerals as MMS, but also provide energy, protein, and fatty acids (18). Prenatal LNS can improve birth outcomes, such as birth weight, birth length, and newborn stunting, as compared to IFA (19); however, effects on postnatal child linear or ponderal growth have not been demonstrated compared to IFA (19) or MMS (20).

Given the high burden of maternal undernutrition in LMICs and its potential consequences for child outcomes, more evidence is needed on the effect of prenatal nutritional supplementation on improving child outcomes in infancy. In this study, we assessed the effect of prenatal supplementation with MMS or LNS as compared to routine IFA on child growth outcomes in the first two years of life in rural Niger. In this setting, MMS and LNS supplementation had no effect on low birthweight (LBW) and had a limited effect on gestational weight gain (21).

## Materials and Methods

*Study setting*

This study was conducted in the Madarounfa Health District, Maradi region of south-central Niger. Maternal and child nutritional status in the region were poor, with 54% of children <5 years stunted, 19% wasted, and 43% underweight (22). About 20% of women of reproductive age were underweight (BMI <18.5 kg/m$^2$) and 43% were anemic (22).

*Study design, participants, and enrollment procedures*

We conducted a double-blind, placebo-controlled randomized phase III clinical trial to assess the efficacy of Rotasiil (Serum Institute of India, Pvt Limited), a live, oral rotavirus vaccine against severe rotavirus gastroenteritis (23). Details on the study design, participants, and procedures of the vaccine efficacy trial have been previously published (23). Given evidence of lower efficacy of oral vaccines in high-mortality settings and the potential of nutritional supplementation to boost immunogenicity (24,25), we nested a cluster randomized controlled trial (RCT) within the parent vaccine trial to test the effect of the type of prenatal nutritional supplementation on infant immune response to three doses of a live, oral rotavirus vaccine (immunogenicity trial) (26). By design, the nested immunogenicity trial was conducted concurrently to the parent vaccine trial, drawing from the same population but with separate enrollment and outcome assessment (**Figure 1**). The unit of randomization in the immunogenicity trial was the village (n=53). Randomization of village clusters in the immunogenicity trial was stratified by village size (< 100; 100-249; ≥ 250 non-pregnant women

of reproductive age) and block randomization with permutated blocks of random sizes was used to allocate villages in a 1:1:1 ratio to one of three prenatal supplementation arms: (1) IFA, (2) MMS, and (3) LNS. After providing consent for village participation, the head of each village selected the name of one of the three supplements from a jar, which served as randomized village assignment. Non-pregnant women of reproductive age in participating villages provided informed consent for monthly pregnancy surveillance. Women with a confirmed pregnancy (based on a urine test) were screened for eligibility to enroll in the immunogenicity trial and begin prenatal supplementation. Inclusion criteria for pregnant women in the immunogenicity trial were: < 30 weeks gestation at the time of enrollment; intended to remain in the study area through delivery and for 2 years thereafter; and did not have a chronic health condition, severe illness, evident pregnancy complications (moderate to severe oedema, hemoglobin < 7 g/dL, or diastolic blood pressure > 90 mmHg), or known peanut allergy at the time of enrollment. Eligible women who provided informed consent were enrolled and received the supplement until pregnancy outcome. Women were enrolled into the immunogenicity trial from March 2015 to November 2016.

At 6-8 weeks after birth, infants were screened for eligibility for enrollment in the parent double-blind, placebo-controlled phase III vaccine trial (23). Infant inclusion criteria for the vaccine trial were: 6-8 weeks of age, able to swallow and no history of vomiting within the past 24 hours, parent/guardian intended to remain in the study area for 2 years, and parent/guardian provided written informed consent. Infants enrolled in the vaccine trial were followed-up monthly until they reached 24 months of age.

*Study supplements*

Women in the IFA arm received tablets containing 60 mg iron and 400 μg folic acid (Remedica Ltd; Limassol, Cyprus) as the standard of care. Women were instructed to take one tablet daily. Women in the MMS arm received capsules containing a daily dose of 30 mg iron, 400 μg folic acid, and 20 other micronutrients (DSM Nutritional Products; Isando, South Africa). The capsules provided two times the Recommended Daily Allowance (RDA) for each micronutrient, except for iron, folic acid, calcium, phosphorous, potassium and magnesium. This dose was more effective in improving birth weight in Guinea Bissau as compared to routine IFA relative to one RDA compared to IFA (27). Women in the LNS arm received a daily 40 g sachet of fortified, ready-to-use food made of peanuts, oil, dried skimmed milk powder, and sugar (Nutriset S.A.S; Malaunay, France). The LNS contained the same 22 micronutrients as the MMS. Due to its size, the product is classified as a medium-quantity LNS (MQ-LNS) (18). Detailed nutritional composition of the three study supplements is shown in **Supplementary Table 1**. Formative work conducted prior to the start of the trial showed that the three supplements were well accepted by the communities and pregnant women (28).

A study midwife provided the first package of supplements and instructions for use and storage at the time of enrollment. Community health assistants thereafter conducted weekly home visits to distribute a 10-day supply of the supplements: 7 days' supply to be consumed until the next scheduled weekly home visit and 3 days' extra supply. The extra supply was provided in case of loss, damage or unexpected delay until the next home visit and was returned to the community health assistant at the next home visit if unused. Each week, the community

health assistants reviewed supplement adherence, discussed health events and concerns since the last distribution, and provided the next 10-day supply. Since supplements were not identical in appearance, participants and study staff were not blinded to intervention allocation. Data analysts remained blinded to intervention allocation until the analysis was completed.

*Data collection and measures*

At enrollment, a study midwife collected data on maternal and household socio-economic and demographic characteristics, conducted a physical and obstetric exam, and assessed maternal anthropometry, hemoglobin, and malaria infection. Maternal weight was assessed using an electronic scale, and underweight defined as body mass index <18.5 kg/$m^2$. Maternal hemoglobin (Hb) concentration was assessed from a finger prick sample using a HemoCue machine (HemoCue Hb 301, Angelholm, Sweden), and anemia was defined as Hb<11 g/dL. Malaria infection was assessed using a rapid diagnostic test (SD Bioline Malaria Ag *Pf* (HRP-2)). Adherence to the supplementation regimen was defined as the mean percentage of supplements consumed by the woman, based on used supplement counts made by community health assistants during each home visit, divided by the total number of supplements that should have been consumed from enrollment into the trial until delivery. A household wealth index was constructed using principal components analysis of 10 items describing asset and livestock ownership, and housing quality. Food security was assessed using the household hunger scale (29). Improved sanitation was defined as household having access to a flush toilet, improved pit latrine, or slab latrine. Improved water source was defined as household using covered or protected ground well for drinking water.

At infant enrollment in the vaccine trial at 6-8 weeks of age, study staff assessed child growth at the health facilities. From 3 to 24 months of age, community health assistants conducted monthly home visits to assess child growth, health, and nutrition. Child weight, length, and mid-upper arm circumference (MUAC) were assessed using standard protocols (30). Child weight was measured to the nearest 0.1 kg using a SECA scale until 6 months and Salter scale thereafter. Recumbent length was measured to the nearest 0.1 cm using a wooden height board. We calculated anthropometric Z-scores according to the 2006 WHO child growth standards (31): length-for-age Z-score (LAZ), length-for-weight Z-score (WLZ), and weight-for-age Z-score (WAZ). Extreme values (<-6 Z or >6 Z) for all anthropometric Z-scores were excluded. Stunting was defined as LAZ <-2, underweight as WAZ < -2, and wasting as WLZ <-2 (31).

*Ethics*

The study was approved by the Comité Consultatif National d'Ethique in Niger, the Comité de Protection des Personnes in France, the Commission d'Ethique de la Recherche sur l'Etre Humain, Hôpitaux Universitaires de Genève in Switzerland, the Research Ethics Review Committee of the World Health Organization in Switzerland, and the Western Institutional Review Board in Olympia, WA. An independent Data Safety and Monitoring Board, established prior to the start of the parent trial, conducted safety reviews for adverse and serious adverse events after half the pregnancies were enrolled and every 6 months thereafter. The parent trial was registered with ClinicalTrials.gov, identifier NCT02145000.

*Sample size*

The primary endpoint of the immunogenicity trial designed to test the effect of prenatal nutritional supplementation on infant immune response was anti-rotavirus IgA sero-conversion, defined as ≥ 3-fold rise in serum titer of anti-rotavirus IgA from Rotasiil dose 1 to 28 days post Rotasiil dose 3. The immunogenicity trial's sample size was based on power calculations to detect a 20% absolute difference in the proportion of children that sero-convert between nutritional supplements with 90% power and 0.05 alpha, assuming a 30% sero-conversion rate in the IFA arm, 20% non-accessibility, and 30% exclusion due to detection of rotavirus disease between Rotasiil doses (26).

*Statistical Analysis*

In our primary analysis, we evaluated the effect of prenatal MMS and MQ-LNS compared to IFA and the effect of prenatal MQ-LNS compared to MMS on postnatal growth of singleton children at 24 months of age. Multiple births were excluded from the analysis. We used generalized linear models to assess differences in continuous LAZ, WLZ, and WAZ at 24 months of age and log-binomial models to assess the relative risk of stunting, wasting, and underweight at 24 months of age. We present unadjusted mean differences (MD) for continuous outcomes and relative risks (RR) for binary outcomes with their 95% CIs. All models accounted for clustering at the village level using cluster-robust standard errors.

In secondary analyses, we examined differences in LAZ, WAZ, and WLZ trajectories from 6-8 weeks to 24 months of age using linear mixed effects models. Trajectory analyses included

all singleton live births with at least one anthropometric measurement after birth. The models included the intervention arm, month of assessment, and an interaction term between these variables. The trajectory models accounted for clustering by village and a compound symmetry correlation structure for within-subject correlation. We tested for difference in trajectory over time for each group comparison: MMS vs. IFA, MQ-LNS vs. IFA, and MQ-LNS vs. MMS. If the test for difference in trajectory for a group comparison (interaction of intervention arm and assessment month) was statistically significant, we presented differences in mean Z-scores at each month of assessment from 6-8 weeks to 24 months. Differences were tested applying a Tukey-Kramer adjustment for multiple comparisons.

As a sensitivity analysis of the primary and secondary analyses, we estimated multivariate models to account for potential imbalance between randomized arms at enrollment and to potentially increase precision (32). We controlled for the following pre-specified covariates which are known predictors of child growth: household wealth, size, and food security; maternal age, education, and underweight; and child age and sex. We also controlled for maternal anemia, malaria infection, and whether the woman was enrolled into the immunogenicity trial during the hunger season (May-September). Multivariate models also accounted for whether the child was randomly assigned to the vaccine or placebo group of the parent vaccine trial.

Finally, we explored potential effect modification of MMS and MQ-LNS, relative to IFA, on postnatal growth outcomes by pre-specified enrollment factors: maternal education, anemia, underweight, and season of enrollment into the trial; household wealth, food security, improved sanitation, and improved water source; child sex; and adherence to supplements. Interactions were considered statistically significant at $p<0.10$ based on a Wald test. All analyses used the intention to treat principle and were conducted in Stata Version 16 (33).

## Results

A total of 3,332 pregnant women were enrolled in the immunogenicity trial (**Figure 2**). At enrollment, mothers' socio-economic and demographic characteristics were similar across intervention arms (**Table 1**). The current analysis of child growth outcomes included 2,410 children with at least one anthropometric measurement, of which 2,095 (87%) had a measurement at 24 months of age. Median adherence (Q1, Q3) to the supplementation regimen was 84% (70%, 93%) in the IFA arm, 86% (73%, 93%) in the MMS arm, and 88% (76%, 94%) in the MQ-LNS arm (p-value for differences across arms = 0.395). Results showed per protocol efficacy of 66.7% (95% CI 49.9, 77.9) (23).

Overall, at 24 months of age, 69% of children were stunted, 41% were underweight, and 12% were wasted. MMS and MQ-LNS had no effect on any of the child anthropometric outcomes at 24 months of age, relative to IFA (**Tables 2 and 3**). When comparing MQ-LNS to MMS, children in the MQ-LNS arm had significantly higher MUAC at 24 months of age: MD 0.50 cm (95% CI 0.10, 0.91). Multivariate-adjusted estimates showed similar intervention effects (**Supplementary Table 2**).

We examined trajectories in anthropometric Z-scores from 6-8 weeks to 24 months of age (**Figures 3, 4, and 5**). Mean LAZ and WAZ over time were significantly lower in the MQ-LNS arm relative to IFA (p-value for difference in trajectory <0.001, Figure 3, and p-value for difference in trajectory <0.001, Figure 4, respectively), although we observed no statistically significant differences in LAZ or WAZ between intervention arms at individual time points (**Supplementary Tables 3 and 4**). The mean change in WLZ was significantly different in both the MMS and MQ-LNS arms (both p-values for difference in trajectory <0.001), relative to IFA

(Figure 5). Although children in the MQ-LNS arm had significantly higher WLZ at 1 month of age compared with children in the IFA arm, they had lower WLZ from 16 to 19 months of age (**Supplementary Table 5**). In addition, we found significant differences in mean LAZ, WAZ, and WLZ trajectories when comparing the MQ-LNS to MMS arms (all three p-values for difference in trajectory <0.001). Relative to MMS, children in the MQ-LNS arm had significantly lower WAZ from 16 to 18 months of age and lower WLZ from 14 to 20 months of age (**Supplementary Tables 4 and 5**).

In exploratory analyses to assess potential effect modifiers, we found that maternal anemia at enrollment modified the effect of MQ-LNS relative to IFA on LAZ and stunting at 24 months of age. Specifically, the effect of MQ-LNS on LAZ as compared to IFA was MD -0.11 (95% CI -0.38, 0.16) among children of pregnant women who were anemic at enrollment and MD 0.12 (95% CI -0.16, 0.41) among children of pregnant women who were not anemic at enrollment (p-value for interaction 0.02). The effect of MQ-LNS on stunting as compared to IFA was RR 1.05 (95% CI 0.89, 1.25) among children of pregnant women who were anemic at enrollment and RR 0.94 (95% CI 0.80, 1.10) among children of pregnant women who were not anemic at enrollment (p-value for interaction 0.08). In addition, we found that enrollment during the hunger season modified the effect of MQ-LNS relative to IFA on wasting at 24 months of age: RR 2.13 (95% CI 0.79, 5.77) among children of pregnant women enrolled during the non-hunger season (October-April) and RR 1.12 (95% CI 0.49, 2.55) among children of pregnant women enrolled during the hunger season (p-value for interaction 0.08). Lastly, we found that child sex and household sanitation modified the effect of MMS relative to IFA on wasting at 24 months. Specifically, the effect of MMS on wasting as compared to IFA was RR 0.74 (95% CI 0.37, 1.48) among boys and RR 1.50 (95% CI 0.90, 2.49) among girls (p-value for interaction 0.05).

The effect of MMS on wasting as compared to IFA was RR 1.48 (95% CI 0.91, 2.41) among children in households without an improved latrine at enrollment and RR 0.85 (95% CI 0.48, 1.49) among children in households with an improved latrine at enrollment (p-value for interaction 0.05).

**Discussion**

In this cluster RCT conducted in rural Niger, prenatal MMS and MQ-LNS supplementation had no effect on child anthropometric measures at 24 months of age relative to IFA. MQ-LNS improved MUAC at 24 months as compared to MMS. MQ-LNS also improved WLZ at 1 month of age relative to IFA. However, relative to both IFA and MMS, MQ-LNS led to more negative WAZ and WLZ trajectories in the second year of life, although differences in trajectories did not persist to 24 months of age.

Prior studies to test the effect of prenatal MMS relative to IFA are few and have shown limited effect on child growth outcomes up to 24 months of age. Several meta-analyses suggest that prenatal MMS does not improve child growth up to 9 years of age as compared with routine IFA (8,12–14). However, individual trials in Burkina Faso, Nepal, and Vietnam have demonstrated small-to-medium sized benefits on anthropometric Z-scores and large reductions in child stunting (15–17). Likewise, prior trials suggest that prenatal LNS supplementation appears to have no effect on postnatal child growth as compared with IFA, though the latest meta-analysis pooled only four studies (19). In undernourished population, balanced energy and protein (BEP) supplementation, which typically provides more calories and protein than MQ-LNS, is recommended for improved birth outcomes (34). Although positive effects on small-for-gestational age and birth weight were found in eight RCTs that used BEP supplements

containing 417 to 1017 kcal with 7 to 40 g of protein per day (35,36), one meta-analysis showed that BEP supplementation did not increase child weight or length at 1 year of age, relative to IFA, based on one RCT that used supplements containing 470 kcal with 40 g of protein per day (35). However, the varying macronutrient composition of individual BEP supplements used in these RCTs and this study's MQ-LNS formulation, as well as differences in the study populations, make the evidence difficult to compare.

Several explanations for the lack of effect of MMS and MQ-LNS as compared to IFA on LAZ, WLZ, and WAZ at 24 months are plausible. First, findings from the immunogenicity trial suggested that MMS and MQ-LNS reduced the LBW risk by 17% and 7% respectively, relative to IFA; however, these findings were not statistically significantly. There was also a limited effect on gestational weight gain (21). These results suggest that MMS and MQ-LNS supplementation in this study population did not meaningfully improve maternal undernutrition or fetal growth, which may have been expected to be on the pathway to improved child growth assessed in this analysis (4). Second, given the poor nutrient status in the region, it was hypothesized that the prenatal supplements may correct pre-existing micronutrient deficiencies (37). Although one RDA may be sufficient to improve micronutrient status but insufficient to eliminate micronutrient deficiencies as shown in one trial among pregnant women in rural Bangladesh (38), it is possible that two RDAs provided by the MMS and MQ-LNS in this study were sufficient to reduce underlying deficiencies in the mother but may have still been insufficient to channel nutrients to the fetus needed for sustained improvements in child growth. Third, frequent acute or chronic infections during pregnancy, which can be prevalent in LMICs (39), can lead to nutrient losses and nutrient sequestration in the mother (27), which in turn may have limited the quantity of nutrients available to the fetus. Our study did not have complete data

on maternal infection throughout pregnancy, but if prevalent in this setting, acute or chronic infection may have reduced the effective micronutrient dose provided to the mother through the study supplements. Likewise, acute or chronic infection in the child could have limited the potential benefits from the micronutrients received by the fetus during pregnancy. Lastly, IFA supplementation (60 mg iron and 400 μg folic acid) has been shown to be effective to reduce low birth weight and is associated with reduced risk of stunting and higher LAZ (8,40). However, the iron content of the MMS and MQ-LNS supplements in our study was lower (30 mg), such that we were simultaneously testing a reduced iron dose with the addition of macro- and micronutrients. Several trials have compared prenatal MMS and IFA with equal iron content (60 mg) and also shown no difference in child growth (41–43), indicating that the difference in iron content between nutritional supplements in our study might not explain the lack of effects on child growth observed later in infancy.

While we found no effect on indicators of child growth at 24 months of age, except for MUAC when comparing MQ-LNS to MMS, we unexpectedly found that MQ-LNS led to transiently lower WAZ and WLZ from 14 to 20 months of age as compared to IFA and MMS. One potential explanation for the observed transient deficit in WAZ and WLZ in late infancy is that infants exposed to MQ-LNS in utero had better nutritional conditions and may have been more sensitive to suboptimal postnatal environmental and nutrition factors. In a trial in Burkina Faso, which found that prenatal LNS led to greater declines in LAZ in the first year of life, as compared to MMS, Lanou et al. hypothesized these results were due to a mismatch between a better nutritional environment in utero (as evidenced by larger placentas in pregnant women who received LNS) and a poorer nutritional environment postnatally (20). Our findings that MQ-LNS improved WLZ at 1 month of age relative to IFA are consistent with this hypothesis of a better

nutritional environment in utero. Another potential explanation is that there was a higher propensity to share MQ-LNS with other household members or substituting it for food (28) and therefore the actual micronutrient intake in the MQ-LNS arm may have been lower than planned. Additional research is needed to understand the mechanisms that may lead to transient differences in anthropometric outcomes in children whose mothers receive prenatal MQ-LNS as compared to MMS or IFA.

Finally, we found evidence that maternal anemia at enrollment modified the effect of prenatal MQ-LNS relative to IFA on LAZ and stunting at 24 months of age. Other studies have also demonstrated that maternal anemia during pregnancy modified the effect of MQ-LNS and MMS on birth outcomes, with larger benefits among anemic women (11,44,45). In this study, although we found statistical evidence of effect modification, we could not determine whether benefits were larger among anemic or non-anemic women given our wide confidence intervals. Apart from direct improvements in maternal hemoglobin, non-hemoglobin pathways of impact of the supplements on child growth may include reductions in maternal and child inflammation and improvements in oxidative metabolism (11). In addition, we also found evidence of modification of the effect of MQ-LNS relative to IFA on wasting by season of enrollment into the trial, and of the effect of MMS relative to IFA on wasting by household sanitation and child sex. However, similar to maternal anemia at enrolment, we observed wide confidence intervals and could not determine which sub-groups may have benefited more from MQ-LNS or MMS. Previous studies have also shown significant interactions of the effect of prenatal LNS with other maternal characteristics at enrollment, such as maternal underweight (BMI <18.5 kg/m$^2$), age, parity, and short stature (44,45). Together with ours, these findings suggest future interventions may target specific sub-groups of pregnant women who might benefit most from prenatal LNS.

Our trial and the existing evidence suggest that in the context of LMICs prenatal supplementation alone is not sufficient to prevent child growth faltering (8,12–14,19). In our trial, nutritional supplementation started in pregnancy and therefore it is possible that preconception nutritional supplementation may confer greater benefits on child growth. Nevertheless, one trial conducted in four LMICs found that starting MQ-LNS supplementation prior to conception, did not yield additional benefits on child linear growth at birth relative to starting MQ-LNS supplementation in pregnancy (46). As a result, evidence on preconception nutrition interventions in LMIC settings remains limited and it is not clear if initiation of MMS and MQ-LNS prior to conception would provide greater effects. In contrast, evidence suggests that combined pre- and postnatal supplementation might be an alternative strategy to improve child growth (47–52). Evidence on combining child micronutrient supplementation with water, sanitation, and hygiene (WASH) interventions is growing, but effects on child growth have been limited (53) and no trials to date have assessed the combination of prenatal micronutrient supplementation and WASH on postnatal child growth. For potentially more durable effects on child growth, future studies could therefore assess the effectiveness of interventions that combine prenatal micronutrient supplementation with postnatal interventions that improve child nutrition (through improved breastmilk quality or complementary feeding) and reduce environmental stressors such as WASH.

Our trial is subject to several limitations. First, we lacked data on maternal biomarkers and were therefore unable to directly assess intermediate effects of the study supplements on maternal micronutrient status. However, we observed high adherence (84% in the IFA arm, 88% in the MQ-LNS arm, and 86% in the MMS arm) and acceptability of the supplements (28), indicating improvements in micronutrient status were possible. Second, we lacked data on

maternal infection and could not determine the extent to which maternal infection may have influenced nutrient availability. Third, child growth was only assessed through anthropometry. Data on child body composition might have provided a more complete picture of the effect of prenatal supplementation on child growth than anthropometry alone.

In conclusion, we found limited effect of prenatal MMS and MQ-LNS on child growth at 24 months of age in rural Niger. MQ-LNS increased MUAC at 24 months as compared to MMS but appeared to lead to temporary but more negative WAZ and WLZ trajectories relative to IFA and MMS during the period of 14 and 20 months of age, despite improving WLZ at 1 month of age relative to IFA. It is important to note that while we identified some transient differences in child growth between the prenatal supplementation arms, this study suggests that MMS and MQ-LNS were insufficient to prevent growth faltering for children in rural Niger at 24 months of age. Future research should evaluate alternative nutritional support strategies that may improve child growth, such as combined pre- and postnatal supplementation and/or combining prenatal nutritional supplementation with interventions that reduce infections, environmental stressors and other factors that may influence child growth in rural Niger for a more durable impact.

**Conflict of interest:** The authors have no conflicts of interest.

**Authors' contributions:** SI, CL, and RFG designed the research; SG, OG, and IS conducted the research; LB and CRS analyzed the data; LB wrote the first draft of the manuscript; all authors provided important intellectual contributions, edited the manuscript, and ensured its final contents.

## References


1. Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, Mathers C, Rivera J. Maternal and child undernutrition: global and regional exposures and health consequences. Lancet. 2008;371:243–60.
2. Black RE, Victora CG, Walker SP, Bhutta Z a., Christian P, de Onis M, Ezzati M, Grantham-McGregor S, Katz J, Martorell R, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet. 2013;382:427–51.
3. Victora CG, Christian P, Vidaletti LP, Gatica-Domínguez G, Menon P, Black RE. Revisiting maternal and child undernutrition in low-income and middle-income countries: variable progress towards an unfinished agenda. Lancet. 2021;
4. Danaei G, Andrews KG, Sudfeld CR, Fink G, McCoy DC, Peet E, Sania A, Smith Fawzi MC, Ezzati M, Fawzi WW. Risk Factors for Childhood Stunting in 137 Developing Countries: A Comparative Risk Assessment Analysis at Global, Regional, and Country Levels. Tumwine JK, editor. PLOS Med. 2016;13:e1002164.
5. Li Z, Kim R, Vollmer S, Subramanian S V. Factors Associated With Child Stunting, Wasting, and Underweight in 35 Low- and Middle-Income Countries. JAMA Netw Open. 2020;3:e203386.
6. Bourassa MW, Osendarp SJM, Adu-Afarwuah S, Ahmed S, Ajello C, Bergeron G, Black R, Christian P, Cousens S, Pee S, et al. Review of the evidence regarding the use of antenatal multiple micronutrient supplementation in low- and middle-income countries. Ann N Y Acad Sci. 2019;1444:6–21.
7. Bailey RL, West Jr. KP, Black RE. The Epidemiology of Global Micronutrient Deficiencies. Ann Nutr Metab. 2015;66:22–33.
8. Keats EC, Das JK, Salam RA, Lassi ZS, Imdad A, Black RE, Bhutta ZA. Effective interventions to address maternal and child malnutrition: an update of the evidence. Lancet Child Adolesc Heal. 2021;
9. Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S, Webb P, Lartey A, Black RE. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? Lancet. 2013;382:452–77.
10. Keats EC, Haider BA, Tam E, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. Cochrane Database Syst Rev. 2019;
11. Smith ER, Shankar AH, Wu LS-F, Aboud S, Adu-Afarwuah S, Ali H, Agustina R, Arifeen S, Ashorn P, Bhutta ZA, et al. Modifiers of the effect of maternal multiple micronutrient supplementation on stillbirth, birth outcomes, and infant mortality: a meta-analysis of individual patient data from 17 randomised trials in low-income and middle-income countries. Lancet Glob Heal. 2017;5:e1090–100.
12. Oh C, Keats EC, Bhutta ZA. Vitamin and Mineral Supplementation During Pregnancy on Maternal, Birth, Child Health and Development Outcomes in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis. Nutrients. 2020;12:491.
13. Devakumar D, Fall CHD, Sachdev HS, Margetts BM, Osmond C, Wells JCK, Costello A, Osrin D. Maternal antenatal multiple micronutrient supplementation for long-term health benefits in children: a systematic review and meta-analysis. BMC Med. 2016;14:90.
14. Lu W-P, Lu M-S, Li Z-H, Zhang C-X. Effects of Multimicronutrient Supplementation during Pregnancy on Postnatal Growth of Children under 5 Years of Age: A Meta-Analysis of Randomized Controlled Trials. Baradaran HR, editor. PLoS One.

2014;9:e88496.
15. Roberfroid D, Huybregts L, Lanou H, Ouedraogo L, Henry M-C, Meda N, Kolsteren P. Impact of prenatal multiple micronutrients on survival and growth during infancy: a randomized controlled trial. Am J Clin Nutr. 2012;95:916–24.
16. Vaidya A, Saville N, Shrestha BP, de L Costello AM, Manandhar DS, Osrin D. Effects of antenatal multiple micronutrient supplementation on children's weight and size at 2 years of age in Nepal: follow-up of a double-blind randomised controlled trial. Lancet. 2008;371:492–9.
17. Huy N Do, Hop LT, Shrimpton R, Hoa CV. An Effectiveness Trial of Multiple Micronutrient Supplementation during Pregnancy in Vietnam: Impact on Birthweight and on Stunting in Children at around 2 Years of Age. Food Nutr Bull. 2009;30:S506–16.
18. Arimond M, Zeilani M, Jungjohann S, Brown KH, Ashorn P, Allen LH, Dewey KG. Considerations in developing lipid-based nutrient supplements for prevention of undernutrition: Experience from the International Lipid-Based Nutrient Supplements (iLiNS) Project. Matern Child Nutr. 2015;11:31–61.
19. Das JK, Hoodbhoy Z, Salam RA, Bhutta AZ, Valenzuela-Rubio NG, Weise Prinzo Z, Bhutta ZA. Lipid-based nutrient supplements for maternal, birth, and infant developmental outcomes. Cochrane Database Syst Rev. 2018;
20. Lanou H, Huybregts L, Roberfroid D, Nikièma L, Kouanda S, Van Camp J, Kolsteren P, Nikiema L, Kouanda S, Van Camp J, et al. Prenatal Nutrient Supplementation and Postnatal Growth in a Developing Nation: An RCT. Pediatrics. 2014;133:e1001–8.
21. Rattigan SM, Garba S, Plikaytis B, Sudfeld CR, Guindo O, Soumana I, Langendorf C, Grais RF, Isanaka S. Effect of prenatal supplementation with multiple micronutrients and medium-quantity lipid-based nutrient supplements on maternal weight gain and birth weight in rural Niger: a cluster randomized trial.
22. Institut National de la Statistique (INS), ICF International. Enquête Démographique et de Santé et à Indicateurs Multiples du Niger 2012. Calverton, Maryland, USA; 2013.
23. Isanaka S, Guindo O, Langendorf C, Matar Seck A, Plikaytis BD, Sayinzoga-Makombe N, McNeal MM, Meyer N, Adehossi E, Djibo A, et al. Efficacy of a Low-Cost, Heat-Stable Oral Rotavirus Vaccine in Niger. N Engl J Med. 2017;376:1121–30.
24. Church JA, Parker EP, Kirkpatrick BD, Grassly NC, Prendergast AJ. Interventions to improve oral vaccine performance: a systematic review and meta-analysis. Lancet Infect Dis. 2019;19:203–14.
25. Armah GE, Sow SO, Breiman RF, Dallas MJ, Tapia MD, Feikin DR, Binka FN, Steele AD, Laserson KF, Ansah NA, et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled trial. Lancet. 2010;376:606–14.
26. Isanaka S, Garba S, Plikaytis B, Malone McNeal M, Guindo O, Langendorf C, Adehossi E, Ciglenecki I, Grais RF. Immunogenicity of an oral rotavirus vaccine administered with prenatal nutritional support in Niger: A cluster randomized clinical trial. Tumwine JK, editor. PLOS Med. 2021;18:e1003720.
27. Kæstel P, Michaelsen KF, Aaby P, Friis H. Effects of prenatal multimicronutrient supplements on birth weight and perinatal mortality: a randomised, controlled trial in Guinea-Bissau. Eur J Clin Nutr. 2005;59:1081–9.
28. Clermont A, Kodish S, Matar Seck A, Salifou A, Rosen J, Grais R, Isanaka S. Acceptability and Utilization of Three Nutritional Supplements during Pregnancy:

Findings from a Longitudinal, Mixed-Methods Study in Niger. Nutrients. 2018;10:1073.
29. Ballard, Terri; Coates, Jennifer; Swindale A; Deitchler M. Household Hunger Scale (HHS): Indicator Definition and Measurement Guide. 2011.
30. Lohman T, Roche A, Martorell R. Anthropometric standardization reference manual. Champaign (IL): Human Kinetics Books; 1988.
31. WHO Multicentre Growth Reference Study Group. WHO child growth standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Geneva; 2006.
32. Streiner DL. Best (but oft-forgotten) practices: the multiple problems of multiplicity—whether and how to correct for many statistical tests. Am J Clin Nutr. 2015;102:721–8.
33. StataCorp L. Stata Statistical Software: Release 16. College Station, TX; 2019.
34. World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience. Geneva: World Health Organization; 2016.
35. Ota E, Hori H, Mori R, Tobe-Gai R, Farrar D. Antenatal dietary education and supplementation to increase energy and protein intake. Cochrane Database Syst Rev. 2015;
36. Stevens B, Buettner P, Watt K, Clough A, Brimblecombe J, Judd J. The effect of balanced protein energy supplementation in undernourished pregnant women and child physical growth in low- and middle-income countries: a systematic review and meta-analysis. Matern Child Nutr. 2015;11:415–32.
37. Christian P, Jiang T, Khatry SK, LeClerq SC, Shrestha SR, West KP. Antenatal supplementation with micronutrients and biochemical indicators of status and subclinical infection in rural Nepal. Am J Clin Nutr. 2006;83:788–94.
38. Schulze KJ, Mehra S, Shaikh S, Ali H, Shamim AA, Wu LS-F, Mitra M, Arguello MA, Kmush B, Sungpuag P, et al. Antenatal Multiple Micronutrient Supplementation Compared to Iron–Folic Acid Affects Micronutrient Status but Does Not Eliminate Deficiencies in a Randomized Controlled Trial Among Pregnant Women of Rural Bangladesh. J Nutr. 2019;149:1260–70.
39. Dauby N, Goetghebuer T, Kollmann TR, Levy J, Marchant A. Uninfected but not unaffected: chronic maternal infections during pregnancy, fetal immunity, and susceptibility to postnatal infections. Lancet Infect Dis. 2012;12:330–40.
40. Nisar Y Bin, Aguayo VM, Billah SM, Dibley MJ. Antenatal Iron-Folic Acid Supplementation Is Associated with Improved Linear Growth and Reduced Risk of Stunting or Severe Stunting in South Asian Children Less than Two Years of Age: A Pooled Analysis from Seven Countries. Nutrients. 2020;12:2632.
41. Gernand AD, Schulze KJ, Nanayakkara-Bind A, Arguello M, Shamim AA, Ali H, Wu L, West KP, Christian P. Effects of Prenatal Multiple Micronutrient Supplementation on Fetal Growth Factors: A Cluster-Randomized, Controlled Trial in Rural Bangladesh. Scott JG, editor. PLoS One. 2015;10:e0137269.
42. Christian P. Effects of alternative maternal micronutrient supplements on low birth weight in rural Nepal: double blind randomised community trial. BMJ. 2003;326:571–571.
43. Johnson W, Darboe MK, Sosseh F, Nshe P, Prentice AM, Moore SE. Association of prenatal lipid-based nutritional supplementation with fetal growth in rural Gambia. Matern Child Nutr. 2017;13:e12367.
44. Adu-Afarwuah S, Lartey A, Okronipa H, Ashorn P, Zeilani M, Peerson JM, Arimond M, Vosti S, Dewey KG. Lipid-based nutrient supplement increases the birth size of infants of

primiparous women in Ghana. Am J Clin Nutr. 2015;101:835–46.
45. Huybregts L, Roberfroid D, Lanou H, Menten J, Meda N, Van Camp J, Kolsteren P. Prenatal food supplementation fortified with multiple micronutrients increases birth length: a randomized controlled trial in rural Burkina Faso. Am J Clin Nutr. 2009;90:1593–600.
46. Hambidge KM, Westcott JE, Garcés A, Figueroa L, Goudar SS, Dhaded SM, Pasha O, Ali SA, Tshefu A, Lokangaka A, et al. A multicountry randomized controlled trial of comprehensive maternal nutrition supplementation initiated before conception: the Women First trial. Am J Clin Nutr. 2019;109:457–69.
47. Christian P, Kim J, Mehra S, Shaikh S, Ali H, Shamim AA, Wu L, Klemm R, Labrique AB, West KP. Effects of prenatal multiple micronutrient supplementation on growth and cognition through 2 y of age in rural Bangladesh: the JiVitA-3 Trial. Am J Clin Nutr. 2016;104:1175–82.
48. Adu-Afarwuah S, Lartey A, Okronipa H, Ashorn P, Peerson JM, Arimond M, Ashorn U, Zeilani M, Vosti S, Dewey KG. Small-quantity, lipid-based nutrient supplements provided to women during pregnancy and 6 mo postpartum and to their infants from 6 mo of age increase the mean attained length of 18-mo-old children in semi-urban Ghana: A randomized controlled trial. Am J Clin Nutr. 2016;104:797–808.
49. Ashorn P, Alho L, Ashorn U, Cheung YB, Dewey KG, Gondwe A, Harjunmaa U, Lartey A, Phiri N, Phiri TE, et al. Supplementation of Maternal Diets during Pregnancy and for 6 Months Postpartum and Infant Diets Thereafter with Small-Quantity Lipid-Based Nutrient Supplements Does Not Promote Child Growth by 18 Months of Age in Rural Malawi: A Randomized Controlled Tria. J Nutr. 2015;145:1345–53.
50. Villamor E, Saathoff E, Bosch RJ, Hertzmark E, Baylin A, Manji K, Msamanga G, Hunter DJ, Fawzi WW. Vitamin supplementation of HIV-infected women improves postnatal child growth. Am J Clin Nutr. 2005;81:880–8.
51. Mridha MK, Matias SL, Chaparro CM, Paul RR, Hussain S, Vosti SA, Harding KL, Cummins JR, Day LT, Saha SL, et al. Lipid-based nutrient supplements for pregnant women reduce newborn stunting in a cluster-randomized controlled effectiveness trial in Bangladesh. Am J Clin Nutr. 2016;103:236–49.
52. Galasso E, Weber AM, Stewart CP, Ratsifandrihamanana L, Fernald LCH. Effects of nutritional supplementation and home visiting on growth and development in young children in Madagascar: a cluster-randomised controlled trial. Lancet Glob Heal. 2019;7:e1257–68.
53. Pickering AJ, Null C, Winch PJ, Mangwadu G, Arnold BF, Prendergast AJ, Njenga SM, Rahman M, Ntozini R, Benjamin-Chung J, et al. The WASH Benefits and SHINE trials: interpretation of WASH intervention effects on linear growth and diarrhoea. Lancet Glob Heal. 2019;7:e1139–46.
54. Ballard T, Coates J, Swindale A, Deitchler M. Household Hunger Scale: Indicator definition and measurement guide. Washington, D.C.: Food and Nutrition Technical Assistance II Project, FHI 360; 2011. p. 23.

**Table 1** Socio-economic and demographic characteristics of women enrolled in the trial at the time of enrollment[1]

| | IFA (N=1,105) | MMS (N=1,083) | MQ-LNS (N=1,144) |
|---|---|---|---|
| *Household characteristics* | | | |
| Wealth index[2] | 0.1±1.6 | 0.2±1.8 | -0.3±1.6 |
| Number of children <5 y | 2.2±1.9 | 2.4±2.0 | 2.5±1.9 |
| Number of household members | 10.5±6.8 | 10.0±6.5 | 10.1±6.6 |
| Access to an improved latrine[3] | 694 (63.3) | 605 (56.2) | 585 (51.3) |
| Access to an improved water source[4] | 258 (23.4) | 267 (24.7) | 312 (27.3) |
| Little-to-no hunger in the past month[5] | 974 (88.4) | 985 (91.2) | 1091 (95.8) |
| *Maternal characteristics* | | | |
| Age, y | 26.5±6.8 | 26.8±6.8 | 27.0±7.2 |
| Completed primary or higher education (≥6 years) | 61 (5.5) | 80 (7.4) | 66 (5.8) |
| Married or cohabitating | 1081 (97.9) | 1068 (98.6) | 1128 (98.6) |
| Anaemic[6] | 320 (32.5) | 317 (32.7) | 397 (38.4) |
| Underweight[7] | 39 (3.9) | 37 (3.7) | 62 (5.9) |
| Malaria infection[8] | 162 (16.2) | 150 (15.3) | 229 (21.9) |
| Enrolled in the hunger season (May-September) | 482 (43.7) | 363 (33.5) | 573 (50.1) |
| Gestational age, weeks | 18.1±3.9 | 18.3±4.1 | 17.7±3.9 |

[1] Values are mean ± SD or N (%) unless otherwise specified. IFA, iron and folic acid; MMS, multiple micronutrient supplement; MQ-LNS, medium quantity lipid-based nutrient supplement.
[2] Constructed using principal components analysis of 10 items describing asset and livestock ownership, and housing quality.
[3] Improved sanitation was defined as household having access to a flush toilet, improved pit latrine or slab latrine.
[4] Improved water source was defined as household using covered or protected ground well for drinking water.
[5] Based on the Household Hunger Scale (54).
[6] Anemia defined as hemoglobin < 11 g/dL.
[7] Underweight defined as body mass index <18.5 kg/m$^2$.
[8] Malaria infection based on a positive rapid diagnostic test.

**Table 2** Unadjusted effects of prenatal multiple micronutrient supplements (MMS), medium-quantity lipid-based nutrient supplement (MQ-LNS), and iron-folic acid (IFA) on continuous child growth outcomes at 24 months of age[1]

| | IFA (n=718)[2] | MQ-LNS (n=735)[2] | MMS (n=642)[2] | MQ-LNS vs. IFA[3] | MMS vs. IFA[3] | MQ-LNS vs. MMS[3] |
|---|---|---|---|---|---|---|
| LAZ | -2.53±0.99 | -2.49±0.96 | -2.60±1.06 | 0.04 (-0.22, 0.30) | -0.07 (-0.33, 0.18) | 0.11 (-0.15, 0.38) |
| WAZ | -1.75±1.06 | -1.87±1.09 | -1.80±1.08 | -0.12 (-0.44, 0.19) | -0.05 (-0.29, 0.18) | -0.07 (-0.38, 0.25) |
| WLZ | -0.59±1.08 | -0.80±1.32 | -0.64±1.14 | -0.21 (-0.69, 0.26) | -0.05 (-0.25, 0.15) | -0.16 (-0.64, 0.32) |
| MUAC (cm) | 13.69±1.13 | 14.03±1.12 | 13.52±1.10 | 0.34 (-0.05, 0.73) | -0.16 (-0.48, 0.15) | 0.50 (0.10, 0.91) |

[1] IFA, iron and folic acid; LAZ, length-for-age Z-score; MMS, multiple micronutrient supplement; MQ-LNS, medium quantity lipid-based nutrient supplement; MUAC, mid-upper arm circumference; WAZ, weight-for-age Z-score; WLZ, weight-for-length Z-score.
[2] Values are mean ± SD or N (%).
[3] Values are mean differences (95% CI) derived from generalized linear models. All estimates were unadjusted. SEs were clustered at the village-level.

**Table 3** Unadjusted effects of prenatal multiple micronutrient supplements (MMS), medium-quantity lipid-based nutrient supplement (MQ-LNS), and iron-folic acid (IFA) on binary child growth outcomes at 24 months of age[1]

| | IFA (n=718)[2] | MQ-LNS (n=735)[2] | MMS (n=642)[2] | MQ-LNS vs. IFA[3] | MMS vs. IFA[3] | MQ-LNS vs. MMS[3] |
|---|---|---|---|---|---|---|
| Stunted, LAZ < -2 | 499 (69.6) | 498 (67.9) | 447 (70.0) | 0.98 (0.84, 1.14) | 1.01 (0.88, 1.14) | 0.97 (0.83, 1.13) |
| Underweight, WAZ < -2 | 277 (38.6) | 311 (42.4) | 268 (41.8) | 1.10 (0.86, 1.41) | 1.08 (0.86, 1.36) | 1.01 (0.78, 1.32) |
| Wasted, WLZ < -2 | 67 (9.3) | 113 (15.4) | 67 (10.5) | 1.65 (0.67, 4.05) | 1.12 (0.71, 1.77) | 1.47 (0.62, 3.47) |

[1] IFA, iron and folic acid; LAZ, length-for-age Z-score; MMS, multiple micronutrient supplement; MQ-LNS, medium quantity lipid-based nutrient supplement; MUAC, mid-upper arm circumference; WAZ, weight-for-age Z-score; WLZ, weight-for-length Z-score.
[2] Values are mean ± SD or N (%).
[3] Values are relative risks (95% CI) derived from log-binomial models. All estimates were unadjusted. SEs were clustered at the village-level.

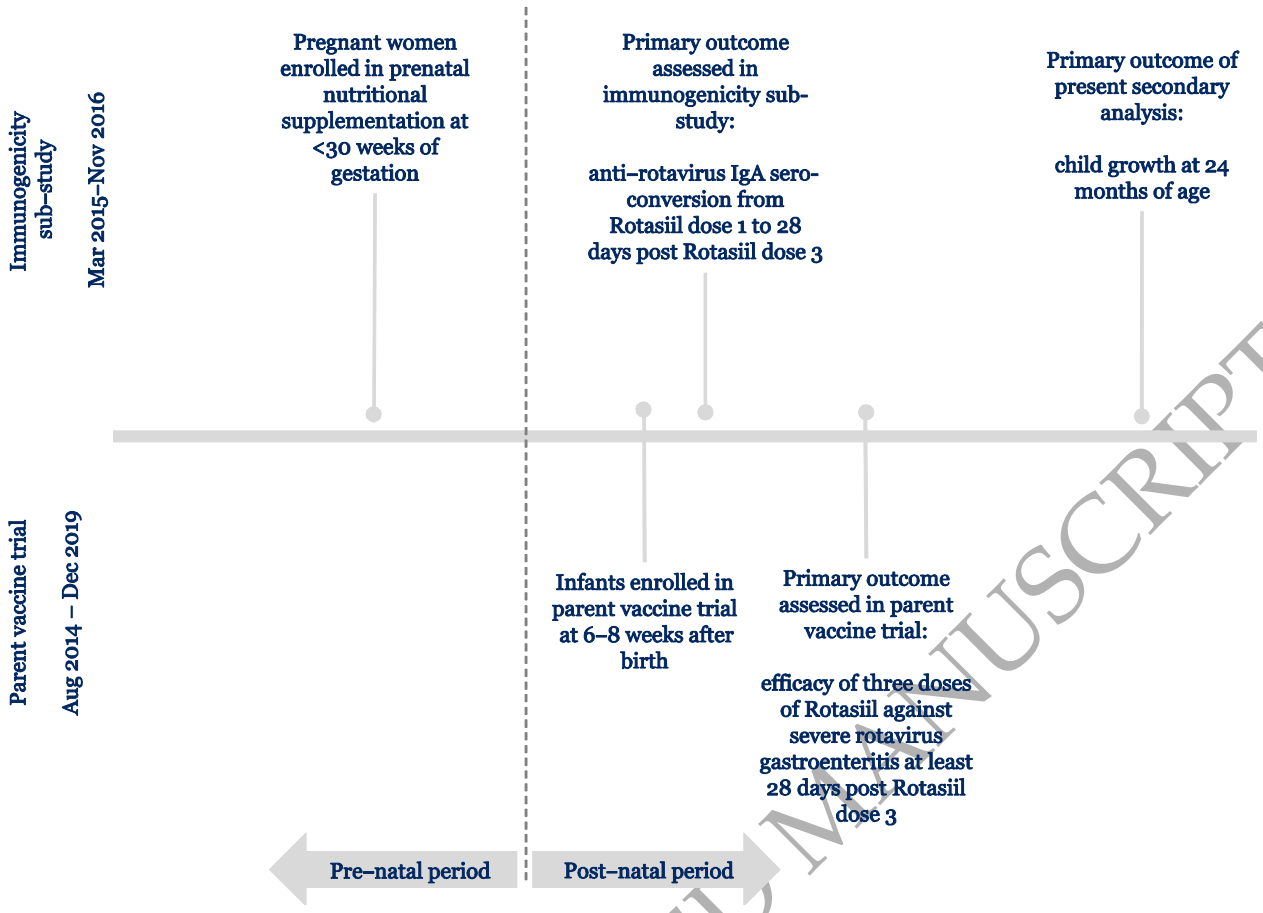


**Figure 1** Sequence of events in the parent vaccine trial and the immunogenicity sub-study

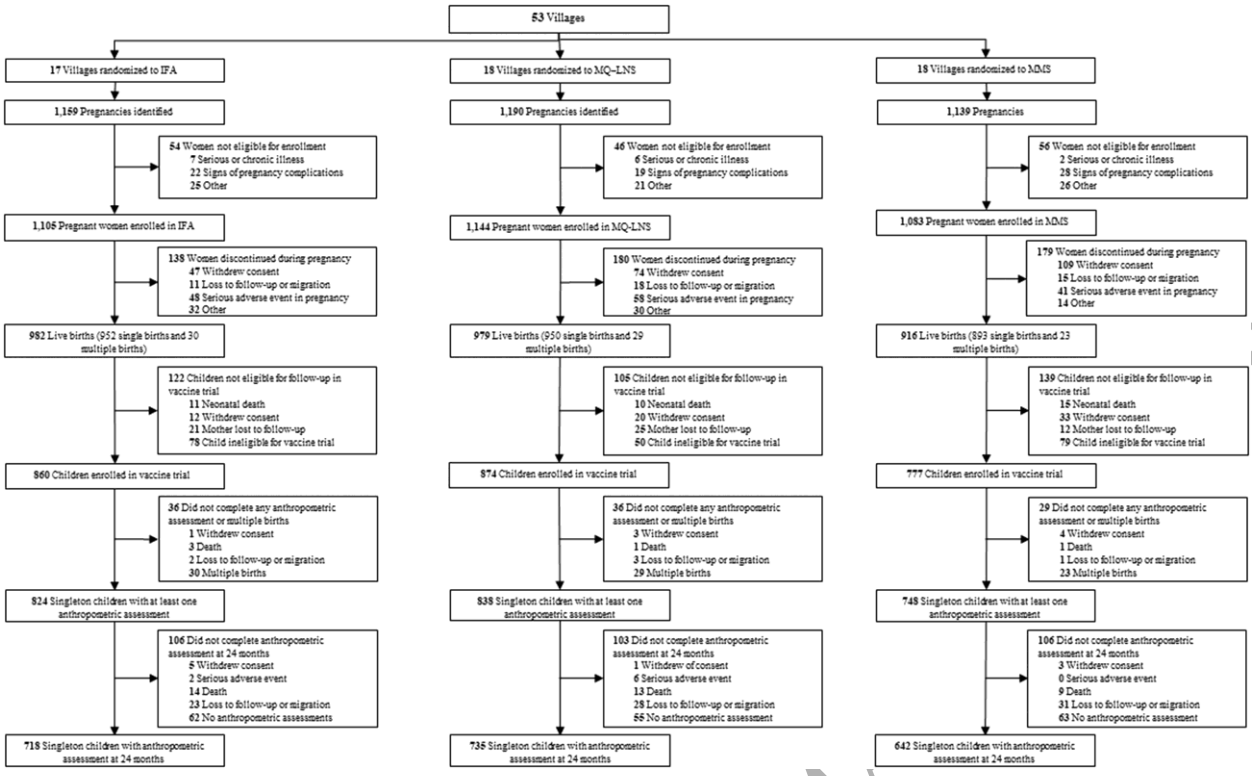


**Figure 2** Study profile of the randomized trial of prenatal supplementation with iron and folic acid (IFA), multiple micronutrient supplements (MMS), and medium quantity lipid-based nutrient supplements (MQ-LNS).

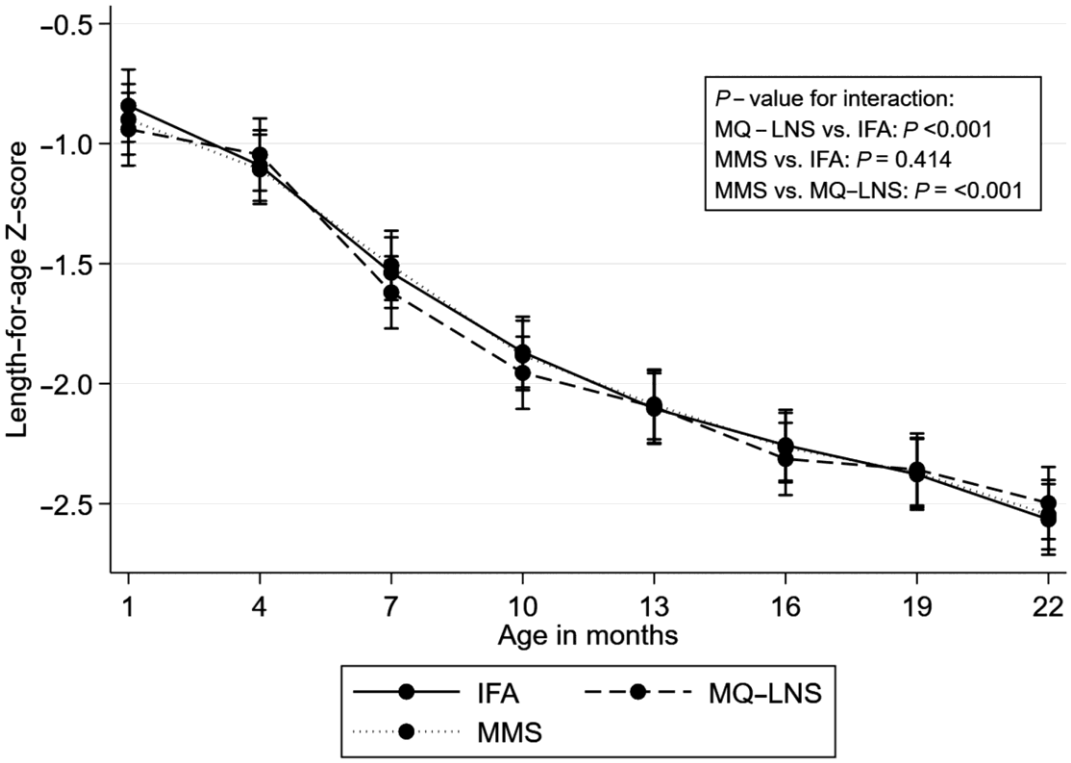


**Figure 3** Unadjusted effect of daily prenatal supplementation with multiple micronutrient supplements (MMS) or medium-quantity lipid-based nutrient supplement (MQ-LNS) as compared to iron and folic acid (IFA) on child length-for-age Z-score from 6-8 weeks to 24 months of age. N=824 in IFA arm, N=748 in MMS arm, and N=838 in MQ-LNS arm. Curves were derived from a linear mixed effects model. Bars represent 95% CIs for each intervention arm at each time point. P-values were derived from the interaction term between intervention arm and child age. IFA, iron and folic acid; MMS, multiple micronutrient supplement; MQ-LNS, medium quantity lipid-based nutrient supplement.

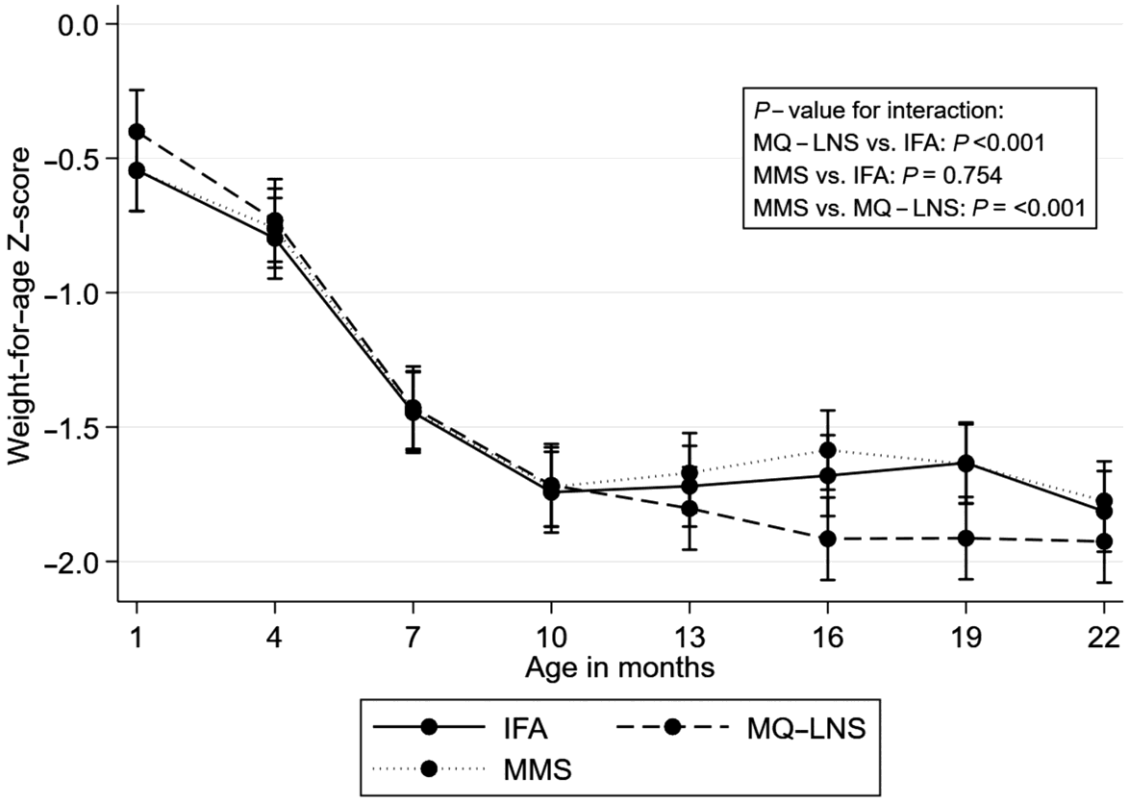


**Figure 4** Unadjusted effect of daily prenatal supplementation with multiple micronutrient supplements (MMS) or medium-quantity lipid-based nutrient supplement (MQ-LNS) as compared to iron and folic acid (IFA) on child weight-for-age Z-score from 6-8 weeks to 24 months of age. N=824 in IFA arm, N=748 in MMS arm, and N=838 in MQ-LNS arm. Curves were derived from a linear mixed effects model. Bars represent 95% CIs for each intervention arm at each time point. P-values were derived from the interaction term between intervention arm and child age. IFA, iron and folic acid; MMS, multiple micronutrient supplement; MQ-LNS, medium quantity lipid-based nutrient supplement.

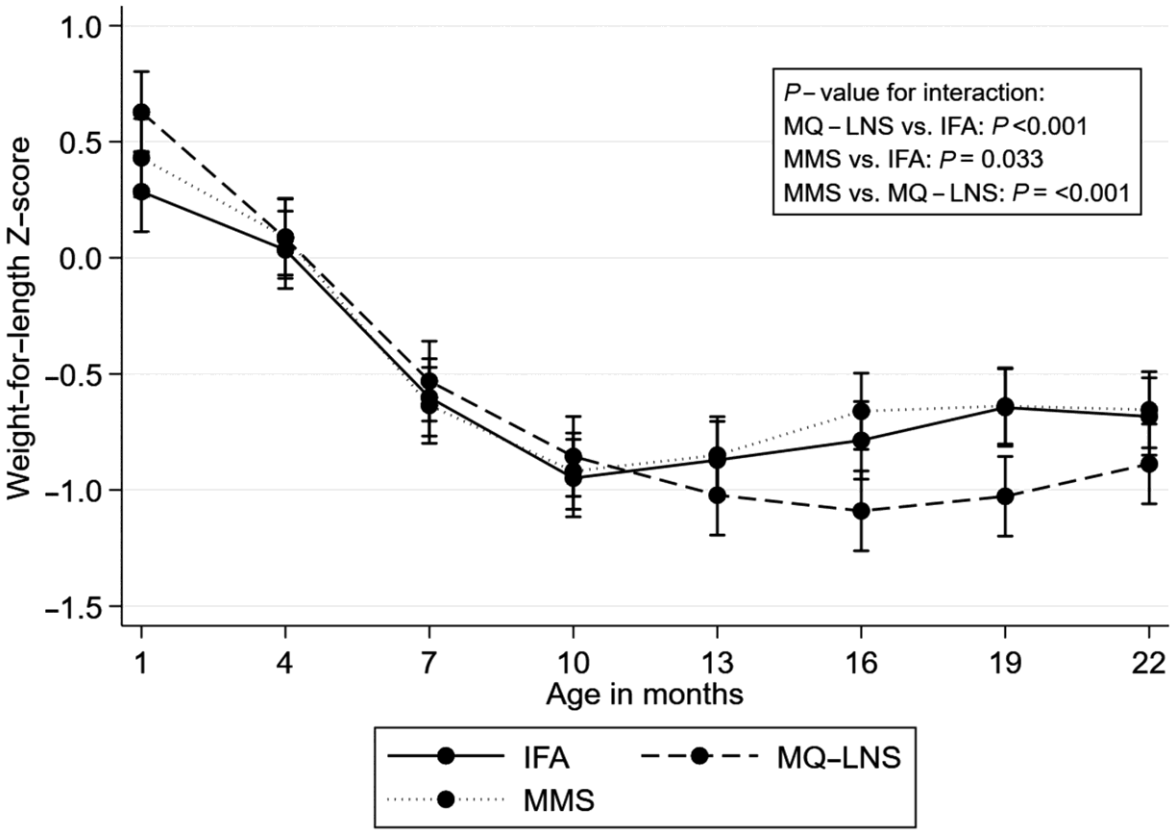


**Figure 5** Unadjusted effect of daily prenatal supplementation with multiple micronutrient supplements (MMS) or medium-quantity lipid-based nutrient supplement (MQ-LNS) as compared to iron and folic acid (IFA) on child weight-for-length Z-score from 6-8 weeks to 24 months of age. N=824 in IFA arm, N=748 in MMS arm, and N=838 in MQ-LNS arm. Curves were derived from a linear mixed effects model. Bars represent 95% CIs for each intervention arm at each time point. P-values were derived from the interaction term between intervention arm and child age. IFA, iron and folic acid; MMS, multiple micronutrient supplement; MQ-LNS, medium quantity lipid-based nutrient supplement.