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A Fortified Food Can Be Replaced by Micronutrient Supplements for Distribution in a Mexican Social Protection Program Based on Results of a Cluster-Randomized Trial and Costing Analysis

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ABSTRACT

Background: Despite positive nutrition impacts, the prevalence of malnutrition among beneficiaries of Mexico's conditional cash transfer (CCT) program remains high. Greater nutrition impact may have been constrained by the type of nutritional supplements provided.

Objective: The objective of this study was to inform a potential modification to the supplements distributed to pregnant and lactating women and children.

Methods: Impact was assessed using 2 cluster-randomized trials (pregnant women, children) run simultaneously. Communities ($n = 54$) were randomly assigned to the fortified foods provided by the program (Nutrivida women, Nutrisano children) or alternatives: tablets (women), syrup (children), or micronutrient powders for women (MNP-W) and children (MNP-C). Each supplement for women/children contained the same micronutrients based on the formulations of Nutrivida and Nutrisano, respectively. Pregnant women (aged >18 y) were recruited before 25 weeks of gestation and followed to 3 mo postpartum. Children aged 6–12 mo were recruited and followed to age 24 mo. Primary outcomes were anemia for women and length growth for children. Statistical analyses appropriate for cluster-randomized designs were used, and structural equation modeling to estimate dose-response effects. Supplement costs per beneficiary (daily dose for 18 mo) were estimated for production and distribution.

Results: There was no significant difference in change of anemia prevalence between supplement groups in women, or in length growth between groups in children. One daily dose of any supplement was associated with 0.8 cm greater length growth. From baseline to age 24 mo, the prevalence of anemia in the Nutrisano, syrup, and MNP-C groups decreased by 36.7, 40.8, and 37.9 percentage points, respectively (within-group, $P < 0.05$; between groups, $P > 0.05$). Costs per beneficiary ranged from $12.1 (MNP-C) to $94.8 (Nutrivida).

Conclusions: The CCT program could distribute alternative supplements at lower cost per beneficiary without compromising potential for impact. Acceptance among beneficiaries should also be considered in choice of alternatives. This trial was registered at www.clinicaltrials.gov as NCT00531674. *J Nutr* 2019;149:2302S–2309S.

Keywords: fortified food, micronutrient powders, micronutrient syrup, growth, anemia, implementation research, 1000 days

Introduction

There is a growing body of evidence for the long-term benefits of nutrition during the first 1000 days of life (from conception through 2 y) on intellectual functioning (1) and economic productivity (2). Aligned with their long-term goal of increasing human capital, several conditional cash transfer programs therefore, include actions specifically designed to address undernutrition in this period. In the case of the Progresa Program in Mexico (later named The Oportunidades Program for Human Development, then The Prospera Program of Social Inclusion, referred to here as CCT-POP), the health component

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included the free distribution and promotion of a fortified drink for pregnant and lactating women (Nutrivida), and a fortified pap for children aged 6–23 mo, and 2–4 y with low weight-for-age (Nutrisano). The foods formed the cornerstone of the program's approach to improving nutritional outcomes and represented an important contributor to programmatic costs.

Impact evaluation found significant positive impact on child growth (3, 4). Despite these promising results, after almost 10 y of operation (2005) the prevalence of stunting was still 17–38%, and anemia 24–35% among beneficiary children aged <5 y across various states (5). Minimal impact was found on other nutritional outcomes including anemia in lactating women and children (3–5). Impact on the nutritional status of pregnant women was not assessed because of logistical challenges (5). We have reported previously that greater impact may have been constrained because of low consumption of the fortified foods resulting from sharing in the household, among other reasons (5). We have also shown that several programmatic (6) and sociocultural (7) factors underpin this pattern of supplement consumption and that the program was not effective as originally designed to modify this pattern.

A second challenge in Mexico has been the changing epidemiology of nutrition since the program's inception in 1997. At the national level and even among program beneficiaries, the prevalence of stunting in children aged <5 y has decreased substantially, and the prevalence of wasting at population level is within the range expected in a healthy population (<2%) (8). On the other hand, the prevalence of anemia persists at moderate level in women and children and has recently shown an increase among women of reproductive age (9). Overweight and obesity across all ages and segments of the population is high, and recent survey results show further increases among children and adolescents in rural areas (10).

The persistent prevalence of micronutrient deficiency provides the justification for inclusion of a supplement in the program (5), but the changing nutritional profile of the population raised 2 questions. First, whether the distribution of a food supplement to women is appropriate given the high overweight/obesity prevalence. Second, whether sufficient food (e.g., macronutrients) is still a limiting factor for child growth. As part of the implementation research activities, we sought to test whether lower cost micronutrient-only supplements would be more appropriate. The objective of the cluster-randomized trial was therefore *1*) to inform a decision to change Nutrivida and if so, to which supplement (tablets or micronutrient powders) based on consumption pattern and impact during pregnancy, taking into consideration the cost of the products, and 2) based on similar criteria, to determine whether Nutrisano should be changed to a micronutrient-only supplement comparing 2 alternatives, micronutrient syrup and micronutrient powders.

Methods

Design and primary outcomes of the cluster-randomized trials

We conducted 2 cluster-randomized trials, 1 with pregnant women (objective 1) and 1 with children (objective 2). The trials were designed and implemented simultaneously in the same communities. For simplicity we describe them together in methods, distinguishing when needed between data and methods for women and for children. Communities were assigned to 1 of 3 nutritional supplements: the fortified foods Nutrivida for women and Nutrisano for children; micronutrient tablets for women and syrup for children; and a micronutrient powder (MNP) for women (MNP-W) and children (MNP-C). The unit of randomization was the community, and the trial was unblinded given supplement presentation differences. The tablets, syrup, and MNP-W, MNP-C were developed using the same combination and dose of micronutrients as those added as fortificants to Nutrivida and Nutrisano (**Supplemental Table 1**). The content for each micronutrient is close to 100% of recommended dietary intakes for pregnant women and children, respectively (11), except for vitamin C, which was increased to promote iron absorption (5).

The primary outcome for women was change in hemoglobin concentration and anemia prevalence from baseline to 37 weeks of gestation, and 1 and 3 mo postpartum. Weight changes from baseline to each follow-up were secondary outcomes. For children, growth in length and weight from baseline to age 24 mo was the primary outcome. We also report change in length-for-age to illustrate degree of growth retardation. Change in hemoglobin concentration and anemia prevalence from baseline to each follow-up point (after 2, 4, 10 mo supplementation and at age 24 mo) were secondary outcomes.

The study took place in 4 states in southern Mexico (Tabasco, Veracruz, Oaxaca, and Puebla). All communities in the states with at least 20,000 inhabitants and at least 70% of the population beneficiaries of the CCT-POP program were considered eligible. We used a block-randomized design considering relevant community-level factors (degree of marginalization, population size, geographic proximity of communities). Degree of marginalization and community size were based on national population statistics (12). Communities within blocks were randomly assigned to 1 supplement using the "rand" command in Microsoft Excel.

Ethics, recruitment, and supplement delivery

The study was reviewed and approved by the Research, Ethics, and Biosecurity Commissions at the National Institute of Public Health, Mexico, and written permission was obtained from national and state-level health authorities. We were granted permission to re-recruit all children who had dropped out, for a 1-time anthropometric assessment at age 24 mo, to strengthen the robustness of our intent-to-treat analysis. Written informed consent was obtained individually from those willing to participate after receiving full details of the study. The study was registered before recruitment began on the Clinical Trial Registry (www.clinicaltrials.gov; NCT00531674).

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Supplemental Tables 1–4 and Supplemental Figures 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/.

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Abbreviations used: CCT, conditional cash transfer; CCT-POP, conditional cash transfer program—Progresa-Oportunidades-Prospera; MNP, multiple micronutrient powder; MNP-C, multiple micronutrient powder(s) for children; MNP-W, multiple micronutrient powder(s) for women.

Recruitment continued from November 2005 to January 2006 and field work was finished in October 2007. The women's cohort included adult women (aged >18 y) identified at <25 weeks of gestation, without known pregnancy complications. Children aged 6–12 mo at baseline without congenital anomalies were included. Exclusion criteria for both women and children included multiple pregnancies and severe anemia (hemoglobin <90 g/L). Eligible women and children were identified through beneficiary listing at the corresponding health center and were recruited individually.

Supplementation continued from baseline until 3 mo postpartum for women, and until age 24 mo for children. Supplements were delivered daily, 6 d/wk for the first 6 mo by trained field workers. We then switched to once-weekly supplement delivery to reduce respondent burden.

Data collection

Gestational age of women was assessed by recall of last menstrual period using methods previously validated by us (13). Height, weight, and hemoglobin concentration were measured at baseline, and weight and hemoglobin re-assessed at 37 weeks of gestation and at 1 and 3 mo postpartum.

For children, recumbent length, weight, and hemoglobin were assessed at baseline, after 2, 4, and 10 mo of supplementation and at age 24 mo of the child (the endpoint of the study) by highly trained and standardized field staff (14). Length was measured using a portable infantometer (ShorrBoard®) with standard procedures (15).

Weight was measured for women and children using an electronic scale (Tanita Corp.), with tarring function for children. Hemoglobin was measured on a single capillary blood sample (second drop) on a HemoCue B-Hemoglobin system (HemoCue AB). Family demographics and economic status was collected at baseline and updated at endline. Dietary intake of women and children was estimated using a semiquantitative FFQ (16) referring to the previous 7 d at each follow-up visit, as well as a feeding practice questionnaire for children. Supplement consumption was observed daily for the first 6 mo then recalled weekly and noted with approximate portion consumed (in quarters). Morbidity symptoms (diarrhea, cough and respiratory illness, fever) recall for the previous 24 h (then previous 7 d) was noted during each supplement visit.

Sample size, variable creation, and statistical analyses

A sample of 238 women per group was estimated to compare change in prevalence of anemia with a 2-sided test, 80% power, and significance level of 5%. For children, a sample of 300 (20 children each in 15 communities) was estimated to achieve 80% statistical power to detect a difference in mean length of 0.4 cm (17) between 2 study groups, assuming loss-to-follow up of 20%, and intra-cluster correlation coefficient for length of 0.118 [based on data from previous studies (4)]. We increased the number of communities to 18 per supplement in case of difficulty to recruit 20 children per community and for potential dropout of an entire community from the trial. Data were double entered (Epi Info 2000) at the National Institute of Public Health offices. Data management and statistical analyses were performed with SAS 8.2 (SAS Institute Inc, 2001) and Stata 15 (StataCorp).

A household index of relative economic status was obtained through use of principal component analysis of household materials, services, and possessions (18). Eligibility for the CCT-POP program is established based on economic criteria and represents the poorest 20% of the Mexican population (19).

Supplement consumption for women and children was estimated as the total number of days that supplement consumption was recorded (even if the amount consumed was 0), and as the total number of doses consumed (combining partial doses). There was no significant difference in mean consumption when supplements were delivered daily or weekly, so data are reported together. Daily mean dose consumed was calculated as total number of doses consumed divided by the number of days offered.

The z scores for children were calculated from the 2006 WHO reference standards for age and sex (20). Hemoglobin concentration was adjusted for altitude of residence (when >1000 m) (21). Anemia was diagnosed as hemoglobin concentration <110 g/L for pregnant women, and <120 g/L at 1 and 3 mo postpartum, and <110 g/L for children (22).

Intent-to-treat analyses provide an estimate of the relative effectiveness of each supplement and were performed for women and children. Mixed effects models were applied for continuous outcomes including indicator variables of supplement group with blocks modelled as fixed effects. Nutrivida/Nutrisano were the reference supplement groups, and random effects at community level were included to capture data dependencies. Change in prevalence of anemia was obtained from a fractional logistic regression model. Change response was mapped onto the [0,1] interval before estimation and returned to the original scale for predictive margin calculations, SEs in the original scale were obtained through the Delta method (23). z Statistics were performed for each pairwise comparison, with statistical significance set at 5%.

Because this trial does not have a placebo control group the intent-to-treat analysis does not permit any inferences of whether the supplements improved outcomes relative to no supplement. To provide insight into the latter for children only, we used structural equation modelling to approximate a dose-response analysis (24). The model includes an equation for mean change in the outcome (child length, cm; hemoglobin concentration, g/L) and an equation for the fraction of consumed doses. The equation of change in outcome included as predictors the fraction of doses consumed, age at baseline and endline, sex, and indicator variables of study group and design blocks. The equation of fraction of consumed doses per day included indicator variables of study group and design blocks as predictors. Fraction of doses per day acts as a mediator variable between supplement group and change in outcome in this system of equations. Differences in the dose-response relation by supplement type were tested as an interaction term between supplement type and fraction of doses consumed. SEs were obtained with an extension of the robust Huber/White/sandwich estimator to account for clustering (25). To obtain estimates for the reference category of the study group (Nutrisano), all other predictors were set at their means. To estimate differences in the mean length/hemoglobin change among supplement groups exclusively related to fraction of doses consumed, we set all predictors at their means in the outcome change equation except fraction of dose consumption and obtained the predicted mean change. We also tested whether inclusion of factors that may be related to both length/hemoglobin change and supplement consumption, particularly economic status modified the results of the model.

Supplement costing analysis

Production and distribution costs were estimated for each type of supplement for women and for children in 2007. Costs were provided by Liconsa (Nutrivida and Nutrisano), and Zerboni Laboratories (tablets and syrup). For MNP we used estimated production and shipping costs to Mexico from large-scale producers of the product (Bangladesh and India). All costs were estimated based on likely purchase volumes to meet programmatic needs for 2007, estimated at 2 million children and 362,000 pregnant and lactating women. Several factors that might influence costs over time (e.g., change in the price of milk, exchange rates) were taken into consideration in the estimations. The costs of distribution were estimated in collaboration with Diconsa, the organization responsible for distribution of Nutrivida and Nutrisano to health centers, considering volume variability (e.g., size and number of boxes), and the need for special shipping considerations (e.g., for glass syrup flasks). Costs are expressed in US dollars using the July 2018 exchange rate (26).

Results

Pregnant and lactating women

A total of 723 pregnant women were identified as eligible for the study, of whom 715 were measured at baseline and 628 began supplementation (Nutrivida $n = 220$; tablets $n = 226$;

TABLE 1 Mean changes in hemoglobin concentration, anemia prevalence, and weight from baseline to follow-up at 37 weeks of gestation, and 1 and 3 mo postpartum, by supplement group[1]

	Nutrivida		Tablets		MNP-W	
	n	Mean (95% CI)	*n*	Mean (95% CI)	*n*	Mean (95% CI)
Baseline assessment						
Hemoglobin, g/L	198	120 (118, 122)	205	121 (120, 123)	192	122 (120, 124)
Anemia,[2] %	198	24.9 (18.8, 31.1)	205	17.9 (12.9, 22.9)	192	18.4 (14.1, 22.7)
Weight, kg	189	60.5 (59.0, 62.0)	197	59.8 (58.3, 61.2)	178	59.3 (57.8, 60.9)
Change in hemoglobin concentration from baseline to each follow-up, g/L						
37 weeks of gestation	150	+0.7 (−1.8, 3.3)	165	+0.6 (−1.9, 3.0)	155	− 0.1 (−2.7, 2.4)
1 mo postpartum	184	+8.8 (6.2, 11.3)	196	+9.8 (7.3, 12.4)	177	+6.3 (3.7, 8.9)
3 mo postpartum	184	+11.7 (9.4, 14.1)	196	+10.9 (8.5, 13.2)	166	+9.7 (7.2, 12.2)
Change in anemia prevalence from baseline to each follow-up, percentage points						
37 weeks of gestation	150	− 5.3 (−13.4, 2.7)	165	− 1.7 (−8.5, 5.1)	155	− 2.7 (−10.3, 4.8)
1 mo postpartum	184	+3.4 (−2.8, 9.6)	196	+2.7 (−4.6, 10.0)	177	+7.6 (2.9, 12.3)
3 mo postpartum	184	− 3.6 (−9.2, 2.1)	196	− 4.1 (−10.3, 2.0)	166	− 3.2 (−8.2, 1.8)
Change in weight from baseline to each follow-up, kg						
37 weeks of gestation	142	+6.3 (+5.7, 6.9)	159	+6.5 (+6.0, 7.1)	143	+6.3 (+5.8, 6.9)
1 mo postpartum	185	− 0.9 (−1.4, −0.4)	193	− 1.0 (−1.5, −0.5)	174	− 0.7 (−1.2, −0.2)
3 mo postpartum	182	− 0.3 (−0.8, 0.3)	193	− 0.6 (−1.1, 0.0)	166	− 0.2 (−0.8, 0.4)

[1] There were no statistically significant differences ($P > 0.05$) between study groups. MNP-W, micronutrient powders for women.
[2] Anemia in pregnancy <110 g/L; at 1 and 3 mo post-partum <120 g/L.

MNP-W $n = 236$) (**Supplemental Figure 1**). With 118 women lost to follow-up or excluded because of missing data, 597 women were included in the intent-to-treat analysis. Women excluded from the analysis were from less poor households and had 1.6-wk lower gestational age at recruitment ($P < 0.05$) (**Supplemental Table 2**).

The number of days that supplement consumption was recorded did not differ by group. Up to 37 weeks of gestation, women had consumed 85 ± 36, 74 ± 36, 83 ± 38 doses of Nutrivida, tablets, and MNP-W, respectively ($P > 0.05$). By 3 mo postpartum, total doses were 156 ± 43, 154 ± 43, 162 ± 43, respectively ($P > 0.05$). There was no difference between groups in change in hemoglobin concentration or prevalence of anemia from baseline to 37 weeks of gestation or 1 or 3 mo postpartum (Table 1). There was no difference in the change in weight from baseline to 37 weeks of gestation, 1 or 3 mo postpartum between groups.

Children

In total, 988 children were recruited (Nutrisano $n = 288$; syrup $n = 348$; MNP-C $n = 352$), of whom 61 were never supplemented (**Supplemental Figure 2**). Of all children recruited, 151 (15%) were excluded from analyses because of a lack of valid anthropometric assessment at baseline and/or age 24 mo. There was no significant difference in rate (14–17%) or reasons for loss to follow-up by supplementation group. We were able to re-recruit many of those lost to follow-up for age 24 mo measurement and therefore included 837 children in our intent-to-treat analyses.

Children included in the intent-to-treat analyses had 1.6-y older mothers than those excluded (**Supplemental Table 3**). Children included in the analysis were aged 8.2 ± 2.5 (±SD) mo at recruitment and 48.0% were male. Overall, the prevalence of stunting was moderate (17.8%) and wasting prevalence was low (1.1%). There were no significant differences in age or anthropometric measures at baseline by supplement group.

The number of days supplement consumption was registered was higher ($P < 0.05$) in the Nutrisano group (363 ± 136 d) than the syrup group (330 ± 133 d), but did not differ from the MNP-C (358 ± 120 d). The total number of doses consumed over the duration of the trial was significantly ($P < 0.05$) higher in the MNP-C group (306 ± 118 doses) then the other 2 groups (Nutrisano 268 ± 129; syrup 262 ± 127).

There was no difference in the change in length or weight from baseline to age 24 mo among supplement groups (Table 2). Height deficit, defined as the change in length-for-

TABLE 2 Indicators of nutritional status at baseline and change from baseline to age 24 mo, including all children in intent-to-treat sample ($n = 837$)[1]

	Nutrisano ($n = 239$)	Syrup ($n = 299$)	MNP-C ($n = 299$)
Length, cm			
Baseline	67.0 (66.5, 67.6)	67.2 (66.7, 67.7)	67.3 (66.8, 67.8)
Change from baseline to age 24 mo	+16.7 (16.2, 17.1)	+16.1 (15.7, 16.5)	+16.4 (16.0, 16.8)
Weight, kg			
Baseline	7.9 (7.7, 8.1)	7.9 (7.8, 8.1)	7.9 (7.7, 8.1)
Change from baseline to age 24 mo	+3.5 (3.3, 3.7)	+3.4 (3.2, 3.5)	+3.5 (3.3, 3.6)
Length-for-age *z* score			
Baseline	− 1.00 (−1.15, −0.85)	− 1.06 (−1.19, −0.92)	− 1.07 (−1.21, −0.94)
Change from baseline to age 24 mo	− 0.06[ab] (−0.16, 0.04)	− 0.12[b] (−0.21, −0.03)	+0.01[a] (−0.07, 0.10)

[1] Data are means (95% CIs). Different letters within rows indicate statistically significant differences ($P < 0.05$) between supplement groups. MNP-C, micronutrient powders for children.

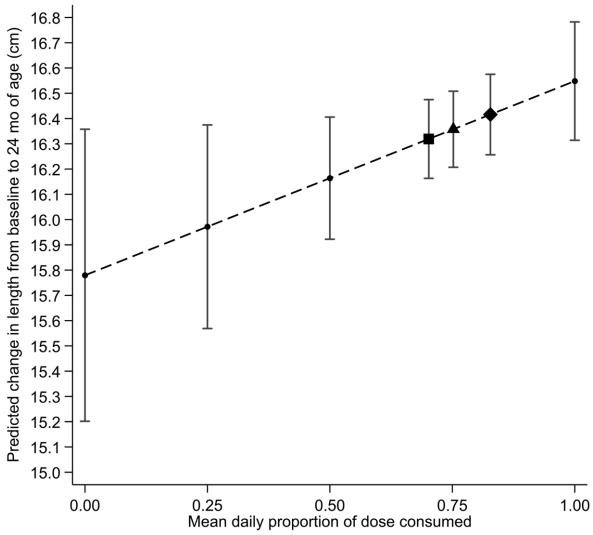

FIGURE 1 Change in child length (cm) from baseline (mean 8.2 mo) to age 24 mo exclusively associated with supplement consumption, by proportion of daily dose consumed (from 0 to 1 dose). The small dots and trend line show the relationship modeled using all data available from the trial. For reference, the mean proportion of a daily dose consumed throughout the trial is shown for the Nutrisano (square, 0.70), syrup (triangle, 0.75), and micronutrient powders (diamond, 0.83) groups. Results obtained from structural equation modeling (model details in Supplemental Table 4).

age from baseline to 24 mo was larger ($P < 0.05$) in the syrup than in the MNP-C and Nutrisano groups, but the magnitude of the difference was small (syrup compared with MNP-C −0.13; syrup compared with Nutrisano −0.06 z scores). The structural equation modeling suggests that consumption of any supplement favored linear growth (see **Supplemental Table 4** for model details), but we found no evidence of a significant difference in the magnitude of this relation among supplement types ($P = 0.558$). Length at age 24 mo was 0.8 cm greater ($P < 0.05$) among those who had consumed 1 dose daily than those who did not consume. This relation did not change when adjusted for economic status of the household (results not shown). Supplement consumption was higher in the MNP-C group than in the Nutrisano or syrup groups, resulting in a slightly larger, but non-significant change in length that can be associated exclusively with the supplement. **Figure 1** shows the estimated change in length for various consumption levels, with the mean daily portion of dose consumed in each supplement group indicated.

After 2 mo of supplementation, the change in hemoglobin was larger in the syrup (+4.8 g/L) and MNP-C (+4.1 g/L), than the Nutrisano group (+0.9 g/L) ($P < 0.05$ for syrup or MNP-C vs. Nutrisano, **Table 3**). This pattern persisted after 4 mo supplementation, but between-group differences were no longer statistically significant after 10 mo supplementation. At age 24 mo, hemoglobin had increased 12.2, 14.1, and 13.0 g/L, and the prevalence of anemia was 11.3%, 9.7%, and 8.2% in the Nutrisano, syrup, and MNP-C groups, respectively ($P < 0.05$ for all within-group comparisons; $P > 0.05$ for all between-group comparisons). Structural equation modelling similarly suggests a significant ($P < 0.05$) dose-response relation between supplement consumption and hemoglobin, the magnitude of which did not vary by supplement type over the study period ($P = 0.473$). One daily dose of any of the 3 supplements resulted in a hemoglobin increase of ∼9 g/L from baseline to age 24 mo, with no difference between supplement types ($P > 0.05$).

Supplement cost estimations

For all supplements, production was the primary cost driver. Among supplements for women, the total cost of production and distribution for Nutrivida was $0.173/dose, for tablets $0.056/dose, and MNP-W $0.023/dose (**Table 4**). Considering the program recommendation of supplementation for 18 mo, a switch from Nutrivida to MNP-W would result in a saving per beneficiary of $82.2, translating into a yearly saving of $29 million (given 362,000 women receiving supplements at the time of the study). For children, the cost of syrup was $0.147/dose, for Nutrisano $0.118/dose, and MNP-C $0.022/dose. The cost of production of syrup was at least in part driven by the need for high-cost packaging (tinted glass bottles). Again, considering the 18 mo supplementation for children, the change from Nutrisano to MNP-C would result in a per beneficiary saving of $52.6, or a yearly saving of $105 million (based on the estimated distribution of supplements to 2 million children each year).

Discussion

This study provided evidence that changing supplements for pregnant and lactating women and for children may have potential to optimize the investment in nutritional supplements provided by the CCT-POP program.

Supplements for pregnant and lactating women

We found no evidence of higher weight gain during pregnancy or weight retention up to 3 mo postpartum with consumption of Nutrivida compared to the micronutrient-only supplements. Consistent with a previous analysis of the dietary data from this study (27), this suggests that women beneficiaries of CCT-POP are not food insufficient.

Given the study design, we cannot conclude directly whether the supplements improved hemoglobin concentration. At baseline, the prevalence of anemia in our study (20.5%) was not unlike that found in a 2006 nationally representative sample of women of reproductive age in the lowest wealth tertile (19.5%) (9). The relatively low prevalence of anemia at 3 mo postpartum (13.3%) and the significant increase in hemoglobin concentration within each supplement group at 1 and 3 mo postpartum suggests that all supplements may have favored iron status. We previously published evidence from a qualitative research study that MNP-W was the least favored by women in this trial (28). This is consistent with a previous trial where MNP-W consumption was lower than other supplement types (29). Thus, while our cost analyses showed that MNP-W were substantially cheaper than Nutrivida or tablets, their generally poor acceptance may limit consumption and ultimately potential for impact.

Supplements for children aged 6–24 mo

Recent papers have encouraged the use of indicators in addition to linear growth to detect impact of nutritional outcomes on children (30, 31). We report here the impact on anemia and child growth (weight and length) and have previously published results for dietary intake (32), and physical activity (33). Together these results suggest that in the context of urban Mexico, the provision of Nutrisano, a fortified pap does not provide measurable benefits over and above micronutrient-only

TABLE 3 Change in hemoglobin concentration and anemia prevalence in children from baseline to follow-up at 2, 4, and 10 mo of supplementation and at age 24 mo, by supplement group[1]

	Nutrisano		Syrup		MNP-C	
	n	Mean (95% CI)	*n*	Mean (95% CI)	*n*	Mean (95% CI)
Baseline assessment						
Hemoglobin, g/L	239	111 (109, 112)	298	110 (108, 111)	299	111 (109, 113)
Anemia, %	239	48.3 (43.7, 52.9)	298	50.5 (43.7, 57.3)	299	46.4 (39.3, 53.4)
Changes in hemoglobin concentration from baseline to each follow-up, g/L						
2 mo follow-up	221	+0.9[a] (−1.1, 2.9)	249	+4.8[b] (2.8, 6.8)	281	+4.1[b] (2.2, 5.9)
4 mo follow-up	208	+0.1[a] (−2.5, 2.6)	259	+4.4[b] (2.0, 6.8)	268	+5.1[b] (2.7, 7.5)
10 mo follow-up	196	+10.2 (7.7, 12.7)	234	+13.2 (10.9, 15.5)	243	+11.9 (9.7, 14.2)
Age 24 mo	238	+12.2 (10.3, 14.1)	296	+14.1 (12.4, 15.9)	295	+13.0 (11.3, 14.7)
Changes in anemia prevalence from baseline to each follow-up, percentage points						
2 mo follow-up	221	− 6.1[a] (−13.3, 1.0)	249	− 17.7[b] (−26.6, −8.7)	281	− 11.5[b] (−18.1, −4.9)
4 mo follow-up	208	− 2.2[a] (−9.3, 4.8)	259	− 14.6[b] (−25.2, −3.9)	268	− 18.1[b] (−27.9, −8.3)
10 mo follow-up	196	− 32.7 (−37.8, −27.6)	234	− 39.7 (−47.4, −31.9)	243	− 36.6 (−46.2, −26.9)
Age 24 mo	238	− 36.7 (−42.2, −31.2)	296	− 40.8 (−49.1, −32.6)	295	− 37.9 (−45.1, −30.7)

[1] The endpoint of the trial was 24 mo of child age, regardless of age at recruitment, mean duration of supplementation at age 24 mo was 16 mo. Different letters within a row indicate statistically significant differences ($P < 0.05$) between supplement groups. MNP-C, micronutrient powders for children.

supplement. Including a placebo control group would have improved the study design, but it was considered unethical to withhold some type of supplement for research purposes in this programmatic context.

Because we do not have a placebo control group, it is important to determine whether the large reductions in the prevalence of anemia are reflective of supplement impact or other factors, perhaps an age effect. The national prevalence of anemia among children aged 12–23 mo at the time of our study was 40.5% (34), 3–4 times higher than the 24 mo prevalence in our trial. The dose-response analysis also showed a strong relation between the consumption of any supplement and hemoglobin. We therefore conclude that it is highly likely that all 3 supplements were effective to control anemia, with a much faster response for syrup and MNP-C than Nutrisano. Qualitative research with trial participants suggested that all 3 supplements were acceptable, but mothers had a preference for MNP-C over syrup (35).

Over the past years several studies have reported adverse effects of excess iron intake including impaired growth and increased infectious disease among children who are iron replete (36). One trial with micronutrient powders in Pakistan (37) reported a higher proportion of days with morbidity, particularly diarrhea, in the micronutrient powder group than in the control group. Previously, we reported no difference among supplement groups for total days ill or days ill with diarrhea during the first 4 mo of the trial (38). It is possible that the potential negative effects of iron are mitigated in populations with lower risk of infectious disease and generally better health status. For example, the population in Pakistan had a high prevalence of wasting and limited contact with the health system (37). In contrast, our population in Mexico had little to no wasting and high usage of routine and curative health services, facilitated through the CCT-POP program (5).

Our structural equation modeling suggests that daily supplement consumption resulted in a small but statistically significant improvement in linear growth, the magnitude of which did not vary by supplement type. Supplement consumption was significantly higher in the MNP-C than other groups, but given the magnitude of association with growth, this translated into a negligible nonsignificant difference in length. We previously reported that Nutrisano tended to replace less nutrient-dense foods in the diet resulting in no net contribution to energy intake (32). Previous studies comparing the growth impact of different types of fortified complementary food products to MNPs have been mixed. Population characteristics might

TABLE 4 Estimated production and distribution costs of 3 types of supplements for pregnant and lactating women and children[1]

	Estimated costs ($)				
Product	Production	Distribution	Total per dose, mean (range)	Total per beneficiary	Annual to program (million $)
Supplements for pregnant and lactating women					
Nutrivida	0.165	0.008	0.173 (0.172–0.231)	94.8	34
Tablets	0.056	0.000	0.056 (0.042–0.057)	30.7	11
MNP-W	0.022	0.000	0.023 (0.023–0.025)	12.6	5
Supplements for children					
Nutrisano	0.111	0.006	0.118 (0.117–0.156)	64.7	129
Syrup	0.147	0.001	0.147 (0.111–0.148)	80.6	161
MNP-C	0.021	0.000	0.022 (0.022–0.024)	12.1	24

[1] Values are cost (shown in 2018 $) based on program requirements and information provided at the time of the analysis. The mean and range of total cost takes into consideration potential variability because of differences in ingredient costs and production volumes using 2 scenarios per type of supplement. Total cost per beneficiary estimated based on the program recommendation of 1 dose/d for 18 mo for women (approximately 6 mo of pregnancy and 1 y postpartum) and for children (age 6–24 mo). Costs to program are calculated based on the number of beneficiaries at the time of the study estimated at 2 million children, and 362,000 pregnant and lactating women (personal communication). MNP-C, micronutrient powders for children; MNP-W, micronutrient powders for women.

at least in part explain these differences. For example, in Ghana (39) a lipid-based nutrient supplement (Nutributter) was found to improve growth in young children, whereas micronutrient powders or dispersible micronutrient tabs did not. The prevalence of stunting was low in Ghana (<10% in all groups, with mean length-for-age *z* score approximately −0.3), but the prevalence of wasting was relatively high (3.1–7.8%) in the different supplementation groups at baseline. In this context, macronutrients may more likely be limiting for linear growth. The recent PROCOMIDA evaluation in Guatemala also found a small but positive impact on child growth when micronutrient powders were provided together with family rations (40). Unfortunately, several previous trials with micronutrient powders may have had little potential to detect growth impacts given low power and/or short duration (see, e.g., 41, 42). An older meta-analysis of zinc supplements with and without other micronutrients found growth effects for zinc only without other micronutrients over a wide range of zinc content (3–20 mg/d) (43). Our micronutrient supplement contained 10 mg of zinc per dose, higher than many trials with multiple micronutrients. Interestingly, the trial previously mentioned from Pakistan also found a small but significant growth impact using a micronutrient powder with 10 mg of zinc (0.56 cm) or without zinc (0.31 cm) compared to a nonplacebo control group (37).

We believe that the situation in Mexico, where the prevalence of zinc and other micronutrient deficiencies is high (44) but there is no evidence of wasting truly represents "hidden hunger," or micronutrient malnutrition in the absence of macronutrient insufficiency in the diet. Under this scenario, micronutrients may be limiting for growth and their provision from any of the 3 types of supplements provided in this study may have been beneficial to promote growth. Micronutrient supplements alone, however, cannot address linear growth faltering in this context, first because it is too late. At age 8 mo length deficit was already evident (mean, SD length-for-age *z* score -1.05 ± 1.05). This suggests that linear growth faltering likely begins in utero, as has been suggested previously (45). Second, the small magnitude of impact (+0.8 cm among daily consumers from an average age of 8 to 24 mo) is insufficient to overcome that deficit.

Costing analysis

The production and distribution cost analysis provided an estimate of the potential cost-saving for the CCT-POP program to change from Nutrivida/Nutrisano to other nutritional supplements. We acknowledge that the costing did not include several potential sources of variability in cost (e.g., opportunity costs). This may result in an underestimation of total costs, but given that the distribution channel and accompanying activities within the program remain constant with any of the supplements, we do not anticipate that it will modify the comparison among them. We also acknowledge that we did not use comprehensive program costing methodologies as reported by others (46), which may limit comparability to other costing analyses in the nutrition literature (47). In the context of the CCT-POP program, however, the simple supplement comparison provided the information required for decision making.

Conclusions

The ultimate purpose of this trial was to provide evidence that could support the Mexican CCT-POP program in decision making related to the most appropriate supplement for distribution in the program. The cluster-randomized trials provided evidence that Nutrivida for women and Nutrisano for children did not provide nutritional benefits over and above what might be achieved with lower-cost micronutrient-only supplements. Taking into consideration the previously published evidence of acceptance (28, 35), we recommended a modification to tablets for women, and micronutrient powders for children. We also recommended that the provision of a supplement should be only part of a comprehensive approach to nutrition promotion across the life course, with focus on prevention of undernutrition and weight management, given the high prevalence of overweight in the population. Finally, we recommended that both components, supplements and nutrition education required a well-developed strategy and intensive training for health workers for its effective implementation. These recommendations were passed to the program who convened an expert committee to review them. The recommendations were used as the basis for the development of the Integrated Strategy for Attention to Nutrition (EsIAN)—the subject of the final 2 papers in this supplement (6, 48).

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