Effect of Multiple Micronutrient Powder (MNP) and Anthelmintics on morbidity and nutritional status of extremely poor women and children: A cluster randomised trial in North-West Bangladesh

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Conflict of Interest: None.

Ethical Considerations and approvals: The study proposal was reviewed and approved (Ref: BMRC/NREC/2010-2013/791) by the National Research Ethics Committee (NREC) in Bangladesh and the London School of Hygiene and Tropical Medicine.

Contributor Statement: Md Masud Rana was the Principal Investigator for this study, while working for EEP/shiree as Nutrition Focal Point; as such, was involved in study design and was responsible for managing the surveys, training data collection staff, supervising the data collection and entry, and undertaking the analysis and report writing. Overall design was completed under the guidance of Professor Nicholas Mascie-Taylor from the University of Cambridge, who led the design team and undertook the sample size calculation and randomisation. He was also due to support the analysis. However, after completing data collection, Md Masud Rana changed his role within the organisation, so the analysis was put on hold. As such, he has undertaken data cleaning and analysis and produced this report (in part fulfilment of the requirements for the degree of MSc in Public Health in Developing Countries) under the supervision of Professor Joanna Schellenberg at London School of Hygiene & Tropical Medicine.

Professor Joanna Schellenberg was academic supervisor to the principal investigator and provided guidance to the data analysis and report production.

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ABSTRACT

Introduction: Growth failure among children and micronutrient deficiency among children and women is one of the major nutritional problems in Bangladesh. According to a 2011 estimate, half of the children and 40% women were anaemic, and the prevalence of stunting and underweight was 40% and 36% among children, while a quarter of non-pregnant adult women were chronically energy deficient. The problem was magnified among the extreme poor population. Previously, standalone initiatives have attempted to tackle undernutrition and micronutrient deficiency separately, but there have been few attempts to integrate these two approaches; and credible evidence from experimental studies was sought from the government and development partners to guide future policy and investment decisions.

Aims & Objectives: This study aimed to determine the effect of an intervention package, containing deworming at six-monthly intervals, daily multiple-micronutrient powder (MNP containing 15 ingredients) supplementation for twelve months, and flip flop (thong) shoes in reducing anaemia among extremely poor women and children under-five, as well as to assess the effect on growth failure.

Methods: The study employed a two-arm cluster randomised trial design involving 537 women and 168 under-five children in 21 clusters within the intervention arm, while the comparison clusters contained a total of 503 women and 139 under-five children in another 21 clusters. The implementation took place between December 2010 and December 2011. Anaemia prevalence was the primary outcome; growth failure (measured by anthropometry), the prevalence of diarrhoea, and passed worms were assessed as secondary outcomes. The analysis was conducted based on cluster-level summaries of mean and prevalence, and the differences between groups were compared using independent sample t-tests.

Results: The study detected a significant effect on anaemia. At endline, the prevalence of anaemia among the women in the intervention clusters was 52% less than the comparison clusters (mean difference 18.1%, 95% CI: 11.1% to 25.1%, P<0.001). Among the under-fives in the intervention clusters, anaemia prevalence was 58% lower (mean difference 18.4%, 95% CI: 7.2% to 29.6%, P=0.002). Mean haemoglobin concentration was also significantly higher among the children (mean difference 7.8 g/l, 95% CI: 5.0 to 10.7, P<0.001) and women (mean difference 4.8 g/l, 95% CI: 3.3 to 6.3, P<0.001) in the intervention clusters. However, there was no detectable effect on child growth failure (stunting, underweight, wasting and thinness), chronic energy deficiency among women, the prevalence of diarrhoea, or passed worms.

Conclusion: The study results suggest that the intervention package is effective in reducing anaemia among women and children under-five. However, the current evidence is insufficient to make a public health recommendation for using the intervention package, containing 15 component MNP, to replace the existing government and WHO recommendation for using 5 component MNP. Further investigation would be necessary to answer this important public health question.

Keywords: multiple micronutrient powder; MNP; anthelmintics; deworming; anaemia; haemoglobin; morbidity; stunting, underweight, wasting; children; women; Bangladesh.

INTRODUCTION

Background

Despite notable improvements over the past decade, poverty and undernutrition remain major challenges in Bangladesh. According to a recent (2010) estimate, 31% of Bangladeshis live below the poverty line, while 18% live below the lower poverty line (1). While the prevalence of stunting and underweight among under-five children declined by 10% and 7% respectively between 2004 and 2011, approximately 40% of children remained stunted and 36% underweight (2). In addition to this growth failure, the rate of micronutrient deficiency among under 5s remained very high; 51% of children were anaemic (2). Undernutrition among adult women was similarly widespread. In 2011, almost a quarter of all Bangladeshi women were chronically energy deficient, and 42% were anaemic.

The situation among the households in the lowest quintile was worse (2). In 2011, the prevalence of stunting among under 5 children was 14% higher than the national average, while underweight was 10% higher (2). Women from households in the lowest wealth quintile displayed 16% higher (40% vs 24%) prevalence of chronic energy deficiency and the anaemia prevalence was 10% higher than the national average (2). A similar level of nutritional inequality was also found among extreme poor women and children in other surveys conducted in Bangladesh (3, 4).

The proliferation of undernutrition among Bangladeshi women and under-five children in the poorest communities is to be expected, as poverty is the key underlying cause of under-nutrition (5). Micronutrient deficiency, which can derive either from lack of enough food or lack of enough micronutrients in food consumed, is an important factor behind poor nutritional status. Even with enough calories and protein in the diet, growth can falter due to insufficient micronutrients, a situation commonly known as ‘hidden hunger’ (6, 7). In the human body, micronutrients play a critical role in cell biology, growth, cognitive development, and work performance (8). Micronutrients also play an important role in the immune response to disease; lack of proper micronutrients weakens the immune system (9), and longer-term deficiency can lead to growth failure (10). Even when receiving sufficient nutrients through food consumption, intestinal parasite infection can lead to micronutrient deficiency, and anaemia. Nutritional causes of anaemia include iron deficiency and certain other micronutrient deficiencies (11). Conversely, micronutrient supplementation can enhance growth and appetite, counteract diseases like diarrhoea and pneumonia through strengthening the immune system, and even reduce mortality (12, 13).

Both the Bangladeshi Government (14) and development agencies (15-18) have made efforts to tackle these problems. However, early initiatives demonstrated that stand-alone nutrition interventions were unsustainable, while alleviating extreme poverty through raising incomes alone did not significantly improve nutritional status, especially among the most vulnerable – namely, women and children. Hence there was a clear need to combine efforts, leading to interest from the donor community in Bangladesh in integrating direct nutrition interventions within existing poverty reduction/livelihoods programming, to tackle multiple micronutrient deficiencies.

The "Improvement of nutrient intake through crop varieties and supplements" project under the UKaid-funded EEP/shiree (www.shiree.org) programme was one such initiative, designed to both ‘improve the nutritional status and strengthen the livelihood opportunities of 1,055 extreme poor households in Bogra district by 2011’(19). The extreme poor participant households suffered from chronic vulnerability and food insecurity, seasonally exacerbated during the *monga* (indicates periods of seasonal food insecurity; usually between September-November and March-April) periods, when income-generating opportunities are especially scarce. The project aimed to lift beneficiaries out of

extreme poverty within three years, by supporting them to produce diversified crops for both household consumption and sale. Specific nutrition interventions were integrated through a 'nutrition package', comprising micronutrient supplementation and provision of de-worming tablets and flip-flops (thong shoes). The introduction of such a package into a livelihood project focused on the extreme poor in Bangladesh was novel, meaning a lack of credible evidence existed surrounding this approach from randomised trials. Hence this specific intervention was introduced as an experiment, to gather robust evidence for future scale-up and policymaking.

Aims and Objectives

The overall aim of the study was to evaluate the effectiveness of the intervention package (i.e. micronutrient supplements, deworming tablets and use of flip-flops) in improving maternal and child nutritional status among an extremely poor population in rural Bangladesh. The primary objective of the study was to assess the effect of the intervention on the anaemia status of children below five years and non-pregnant adult (>15 years) women. In addition, this study aimed at assessing the effect of the intervention package on:

- child under-nutrition (measured by weight for height, height for age and weight for age of children under five).
- nutritional status of women (measured by chronic energy deficiency / body mass index of non-pregnant adult women)
- maternal and child morbidity (worm infestation and diarrhoea)

METHODS

Study design and setting: The study was a two-arm cluster randomised trial, conducted among the extreme poor population of Bogra district in North-West Bangladesh. It was designed to test the effectiveness of the intervention in a 'real world' setting. The trial was part of a larger project aimed at alleviating extreme poverty and improving the nutritional status of extreme poor women and children (19). All households (both intervention and comparison) received support for vegetable cultivation, and awareness-raising training on essential health, hygiene and nutrition. All this support started before the trial and continued after it was completed (until August 2012).

Participants: The essential enrolment criteria for participant households in the livelihoods project (19) were as follows: (i) income < 1500 BDT per month; (ii) lack of cultivable land; and (iii) lack of access to microfinance institutions (20), which reflected project's definition of extreme poverty. Based on these criteria, 1,055 households were selected, all of whom were later trained and supported with livelihoods interventions. All 1,055 households participating in the trial were screened for eligible participants, i.e. non-pregnant women aged > 15 years, and children <five years, but > 6 months old, at time of enrolment. As the study was a cluster randomised trial and the unit of randomisation was 'mothers' groups', eligibility criteria were also set for groups – namely, (i) groups must consist of project beneficiaries only; and (ii) groups must be functional – i.e. members had to meet at least monthly.

Intervention package and delivery: The intervention package included deworming at six-monthly intervals, daily micronutrient supplementation (using new so-called "sprinkles" powder with 15 ingredients) for twelve months and pairs of flip flops for women and children. For the deworming intervention, a single dose of Albendazole 400 mg was used for adults and children over 2 years, while for children under 2 years, Albendazole 200 mg suspension was used. For the micronutrient supplementation intervention, micronutrient sprinkles with 15 micronutrients were distributed (21, 22). The intervention started in December 2010 (two months after the baseline survey).

Mothers and children in intervention group were dewormed (exposure to the intervention was measured by direct observation) at the beginning of the intervention, and then again six months later; the trial ended in December 2011. This meant participants were dewormed twice during the trial period. The recommended dose of micronutrient supplements for both women and under-fives was one sachet daily. The required number of sachets were delivered to households at the beginning of every month, and adherence to the regimen was estimated by counting empty sachets at months-end. Additionally, two pairs of flip-flops were provided to every mother and under-five child in intervention group.

Outcomes: The primary outcome measures assessed were anaemia status and haemoglobin concentration for both mothers and children. Cut-off values of haemoglobin concentration for children under 5 was <110 g/l and for non-pregnant adult women it was <120, as per the WHO definition of anaemia (23). Blood haemoglobin level was measured using HemoCue Hb-301 at baseline, midline and endline, by trained measurers.

Secondary outcome measures for children were stunting, underweight, wasting and thinness, calculated from height for age, weight for age, weight for height and body mass index (BMI) for age z-scores. These anthropometric indicators were calculated using the 2006 WHO reference growth standards (24). The secondary outcome measure for women was to determine whether women were chronically energy deficient (CED, i.e. BMI<18.5) or not. Prevalence of diarrhoea and maternal identification of passed worms were also considered as secondary outcome measures, for both women and children. Prevalence of each was measured according to three different timescales – (i) on the day of the survey (ii) over the previous 7 days, and (iii) over the previous 30 days.

Sample size: In order to detect an improvement in haemoglobin of 4 g/l, (an alpha of 0.05, a power of 0.80, and assuming a design effect of 2 for cluster randomisation), a sample size of about 400 households in 20 clusters was found to be required for each arm of the intervention. For practical reasons, and increased study power, all 1,055 project beneficiary households (which were divided into 42 clusters) was included in the study.

Randomisation

Sequence generation: Based on baseline data, all 42 mother groups were allocated to either the intervention or comparison group using restricted randomisation to ensure baseline balance between intervention and comparison groups with respect to mean haemoglobin concentration (g/l) and proportion of anaemia among mothers and under 5 children. Baseline survey variables were used to generate two samples: (i) a set of 21 clusters containing 537 households, and (ii) another set of 21 clusters with 503 households, which respectively formed the intervention and comparison groups.

Open allocation: The mothers' groups were formed 1 year before the baseline survey, while the random sequence allocating each group to either intervention or comparison was generated after baseline. All members (both women and children) from each mothers' group included in the trial were fixed – i.e. individuals didn't change group during the study period. After randomisation, group participants and the programme team delivering the interventions were made aware of which treatment arm they belonged to, since some of the interventions could not be concealed. However, survey enumerators (who filled out the questionnaire) and measurers (those in charge of anthropometry and blood haemoglobin measurement) were unaware which group the households they surveyed belonged to.

Implementation: After the randomisation, all under 5 children from the intervention group and non-pregnant women over 15 years old received the intervention package, delivered by NGO (National Development Programme) field staff on a monthly basis, and participants were also trained on the treatment regimen.

Data Collection

Overview: Field data collection was undertaken at three points in time. Baseline data were collected in September-October 2010, two months before the actual intervention started. Six months after the intervention commenced, a midline survey was conducted (in May-June 2011), while the endline survey commenced in December 2011 and was completed on 4 January 2012. All 1,040 households (excluding 15 project households who were excluded from the study) were visited during all three surveys to collect demographic, anthropometric data.

Quality assurance: Data quality was assured through intensive training and maintenance of a strict data collection protocol. Emphasis was given to correct anthropometric measurement. To check measurement quality during training, technical error of measurement (TEM) and coefficient of reliability (R) were used. Both intra- and inter- observer technical error of measurement were used to check if measurers were taking accurate measurements. During data collection, two measurements were taken for each participant, and if the difference between the two was >0.5 kg for weight, or >1cm for height, a third measurement were taken. Finally, the average between the two closest measurements was entered for later analysis. When administering the questionnaire, lack of error in transferring anthropometric data from the measurement sheet to the questionnaire was ensured by double-checking. Special attention was given to the assessment of child date of birth. In addition, a subsample (usually 4-6, out of an average of 50) of questionnaires were redone by supervisors every day, to check the accuracy of data collected by enumerators. If any differences were found, a third visit would verify which data were correct. All questionnaires were thoroughly checked for missing data, and in the event of any confusion or any blank spaces, households were revisited.

Data management: Data were entered (single entry) into a computer the day after collection. A data entry form was developed in 'Microsoft Access 2007', including logical condition at the time of entry. During data cleaning, range and consistency checks were performed to identify outliers and whether responses or anthropometric measurements were consistent with previous information.

Statistical analysis

The statistical analysis was performed using IBM SPSS version 21. Anthropometric indicators for child data were calculated using WHO Anthro Plus, using the WHO 2006 reference population data (27, 28).

Baseline comparability: Baseline data were compared across both the main outcome indicators and other indicators. No statistical test was performed to see if the two treatment arms were different from each other; as the mother groups (clusters) were randomly assigned to intervention and comparison arms, any difference would be due to chance; hence the null hypothesis of the two arms not being different would be true (29).

Primary outcome analysis: The unit of analysis in analysing the primary outcome was the cluster, which was also the unit of randomisation. The primary outcome was analysed in two stages: (i) cluster-specific mean was calculated from the individual level data; then (ii) cluster-specific means were compared between the two treatment arms using an independent sample t-test, as recommended for cluster randomised trials with a small number of clusters per treatment arm (30, 31, 32). Mean, and

standard deviation of cluster-specific means is presented for both comparison and intervention clusters, and mean difference is also presented, with a 95% confidence interval. Given that the analysis was undertaken at the cluster-level, each group or cluster provided a single data point; hence the concept of the intra-cluster correlation was deemed less relevant. Therefore, the intra-cluster correlation coefficient (ICC) is not presented for primary outcomes (32).

Secondary Outcome analysis: The same approach was undertaken as for the primary outcome analysis. Cluster-level means for continuous variables (such as height for age z scores, or BMI) and prevalence for categorical variables (such as stunting, or chronic energy deficiency) were calculated for each mother group at baseline, midline and end-line, and cluster-level means were then compared between intervention and comparison groups using an independent sample t-test. Means (standard deviation) are presented for both comparison and intervention groups, as well as mean difference (with 95% confidence interval) at the three survey points. P-values of the t-test are also presented in the tables. Repeated measures analysis of variance was conducted to analyse changes over time.

Ethical Considerations: Before the baseline survey and randomisation, informed consent was taken from all mother groups (clusters) and all groups agreed to participate. Written consent was also taken from individual participants - for children, consent was taken from both parents. Participants informed that they had the option to quit at any stage of the trial. The study proposal was reviewed and approved (Ref: BMRC/NREC/2010-2013/791) by the National Research Ethics Committee (NREC) in Bangladesh and the London School of Hygiene and Tropical Medicine in the UK.

RESULTS

Participant flow

All 42 mother groups and all potential participants were assessed for eligibility and asked for their permission to be included in the study (Figure 1). All groups had met the inclusion criteria; however, 5 households did not meet inclusion criteria, and 10 households chose not to participate. A total of 42 mother groups (considered as 42 clusters, which included 1,040 non-pregnant women and 307 under 5 children) were randomly assigned to either intervention or comparison group, with each group containing 21 clusters. Intervention clusters had a total of 537 women (mean 25.57, range 17-34) and 168 under 5 children (mean 8.0, range 1-17), while comparison clusters had a total of 503 women (mean 24.0, range 11-32) and 139 under 5 children (mean 6.62, range 1-12).

There was no loss of cluster from either group at either midline or endline. However, during the one-year trial period, individual attrition took place. 67 (12.5%) mothers and 17 (10.1%) children from the intervention group and 89 (17.7%) mothers and 13 (9.4%) children from the comparison group were lost during follow-up (details in Figure 1). In the final analysis, both trial arms had 21 clusters, while 470 women and 151 children from the intervention and 414 women and 126 children from the comparison group were included.

Baseline Characteristics

At baseline, there were no noticeable differences in primary and secondary outcome indicators for mothers or children between intervention and comparison clusters (see Table 1). As shown in Table 1, the haemoglobin concentration 108.3 g/l (SD 11.17) for children and 118 g/l (SD 3.6) for women for the overall sample. In the overall sample, 51.6% of children and 53% of mothers were anaemic at baseline. Almost half of the children were stunted and underweight, almost one in every three children was wasted, and a quarter (22.9%) of all children were thin for their age.

Figure 1: Schematic view of the randomization process and participant's flow during the trial period.

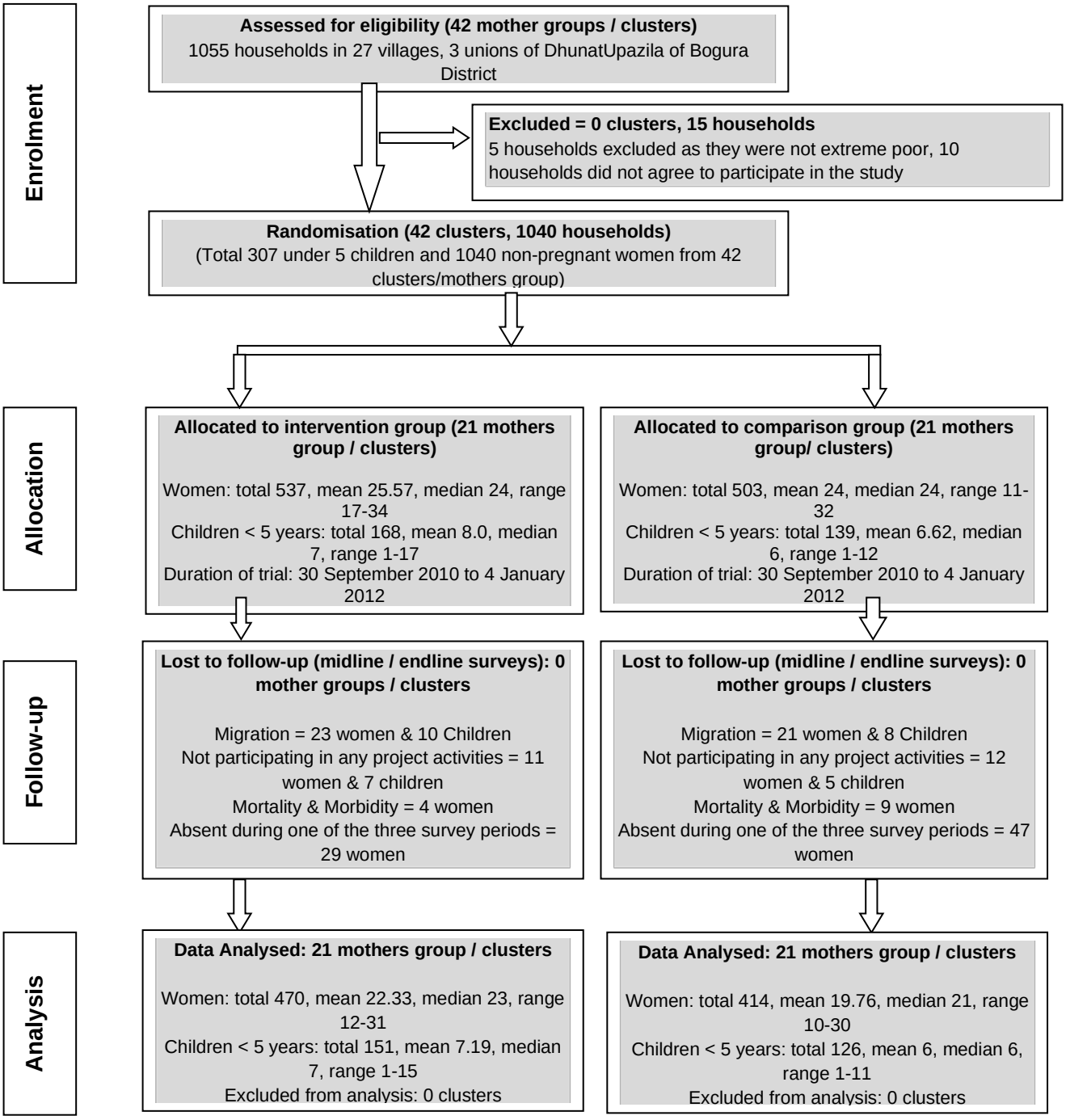


Table 1: Baseline comparison of the intervention and comparison group

		Indicators	Intervention Group (n = 21 clusters)	Comparison Group (n = 21 clusters)	Total (n = 42 clusters)
Children under-five years old	Mean[a] (SD)	Age (months)	33.1 (8.7)	35 (7.5)	34.1 (8.1)
		Height (cm)	85.3 (5.0)	86 (5.8)	85.7 (5.4)
		Weight (Kg)	10.3 (1.1)	10.6 (1.3)	10.4 (1.2)
		Height for Age (HAZ)	-1.6 (1.0)	-1.7 (0.6)	-1.7 (0.8)
		Weight for Age (WAZ)	-2.0 (0.5)	-2.0 (0.5)	-2.0 (0.5)
		Weight for Height (WHZ)	-1.6 (0.5)	-1.4 (0.5)	-1.5 (0.5)
		BMI for Age (BAZ)	-1.4 (0.5)	-1.3 (0.6)	-1.3 (0.5)
		Haemoglobin level (g/l)	108.9 (5.9)	108.6 (4.9)	108.8 (5.3)
	Prevalence[b] (SD)	Stunting (HAZ<-2SD)	43.3% (26.1)	51.5% (21.9)	47.4% (24.2)
		Underweight (WAZ<-2SD)	45.5% (24.1)	50.1% (20.0)	47.8% (22.0)
		Wasting (WHZ<-2SD)	28.5% (24.6)	32.5% (17.7)	30.5% (21.3)
		Thinness (BAZ<-2SD)	19.1% (22.6)	26.7% (17.0)	22.9% (20.1)
		Anaemia (Hb<110 g/l)	50.9% (29.2)	52.3% (23.3)	51.6% (26.1)
		Female Child	58.4% (21.6)	52.5% (25.7)	55.5% (23.6)
Women (non-pregnant)	Mean[a] (SD)	Age (years)	44.4 (5.3)	45.1 (3.9)	44.7 (4.6)
		Height (cm)	148.2 (1.9)	147.5 (2.2)	147.8 (2.0)
		Weight (Kg)	40.3 (1.8)	39.7 (1.6)	40.0 (1.7)
		Body mass index (BMI)	18.2 (0.7)	18.1 (0.7)	18.2 (0.7)
		Haemoglobin level (g/l)	118.3 (3.7)	118.0 (3.6)	118.1 (3.6)
	Prevalence[b] (SD)	Chronic energy deficiency (BMI<18.5)	58.0% (13.3)	63.1% (13.7)	60.6% (13.6)
		Anaemic (Hb<120 g/l)	54.1% (9.6)	52.0% (14.7)	53.1% (12.3)
		Female household head	50.1% (13.2)	59.7% (14.8)	54.9% (14.7)

[a]Arithmetic mean of cluster-specific means of 21 intervention and 21 comparison clusters; [b]Arithmetic mean of cluster-level prevalence of 21 intervention and 21 comparison clusters

Anaemia and Haemoglobin Concentration

Cluster-level anaemia and haemoglobin response of children during the trial period are given in Table 2 and Figure 2, and of non-pregnant women over 15 years old in Table 3 and Figure 3. Results are presented as the means (SD) of cluster-level prevalence for anaemia and cluster-level means for haemoglobin concentration (g/l) for 21 intervention and 21 comparison clusters.

Anaemia and haemoglobin response among children under 5 years

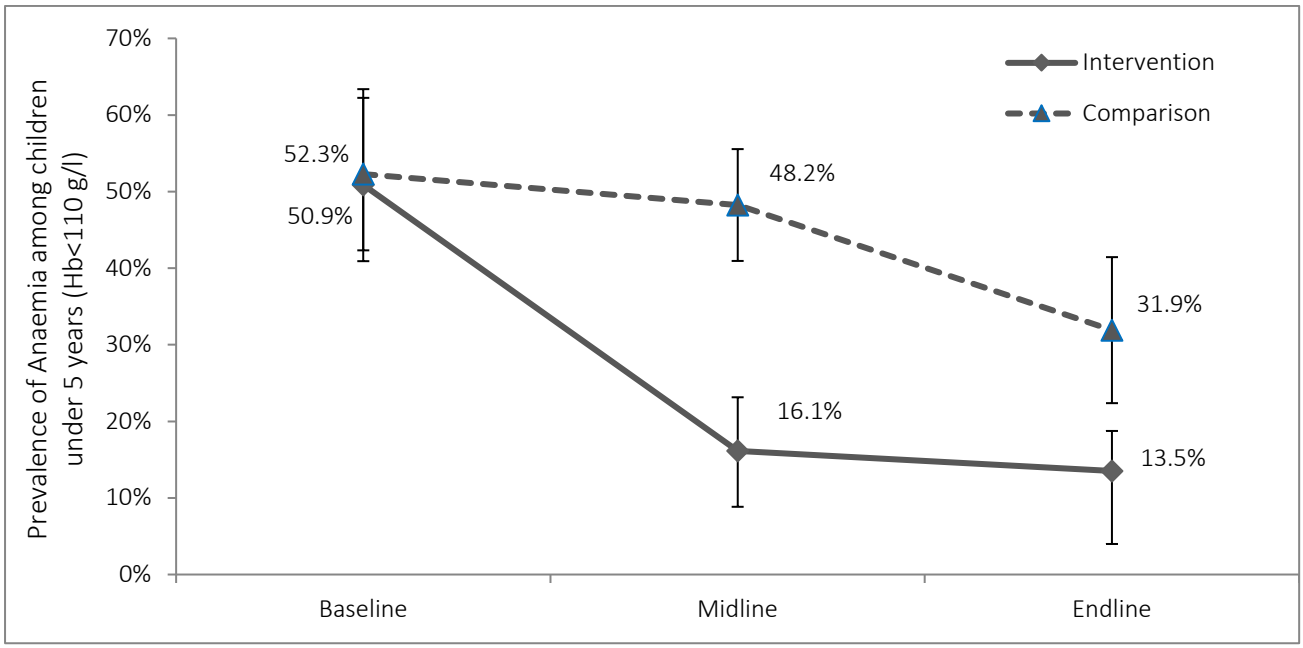
As demonstrated in Table 2 and Figure 2, prevalence of anaemia among children declined sharply (from 51% to 16%) after six months of the intervention (i.e. between baseline and midline), among intervention clusters; however, the prevalence of anaemia among comparison clusters remained almost the same (52% at baseline and 48% at midline). During the next six months, the prevalence declined more in the comparison area. After the full twelve months of the intervention period, intervention clusters had an 18.4% reduction in anaemia prevalence among children compared to the comparison clusters. There was strong evidence that the difference in anaemia prevalence between comparison and intervention clusters is statistically significant at both the midline ($P < 0.001$) and endline ($P = 0.002$).

Table 2: *Cluster-level haemoglobin concentration (g/l) of children under 5 years at baseline, midline and endline surveys*

	Intervention Group (n=21)	Comparison Group (n=21)	Difference (95% CI)[a]	P-value[b]
		Haemoglobin concentration, mean (SD), g/l		
Baseline	108.9 (5.9)	108.6 (4.9)	0.3 (-3.0 to 3.7)	
Midline	116.9 (5.0)	110.4 (3.7)	6.4 (3.7 to 9.2)	<0.001
Endline	119.3 (5.6)	111.5 (3.2)	7.8 (5.0 to 10.7)	<0.001

[a]Mean difference (g/l for haemoglobin and 95% confidence interval); [b]P value from independent sample t-test

Figure 2: *Change in the prevalence of anaemia (blood haemoglobin level<110 g/l) among children under-five years*



Both intervention and comparison clusters showed an increase in blood haemoglobin concentration; however, the increase among the intervention group was greater. By midline, children in the intervention group had seen a 6.4 g/l (95% CI: 3.7 to 9.2) greater improvement in mean than the comparison clusters. By the end of the trial period, the intervention group had shown a 7.8 g/l (95% CI: 5.0 to 10.7) greater increase than the comparison group. Mean changes between groups were statistically significant both at the midline (P<0.001) and endline (P<0.001).

Anaemia and haemoglobin response among non-pregnant women

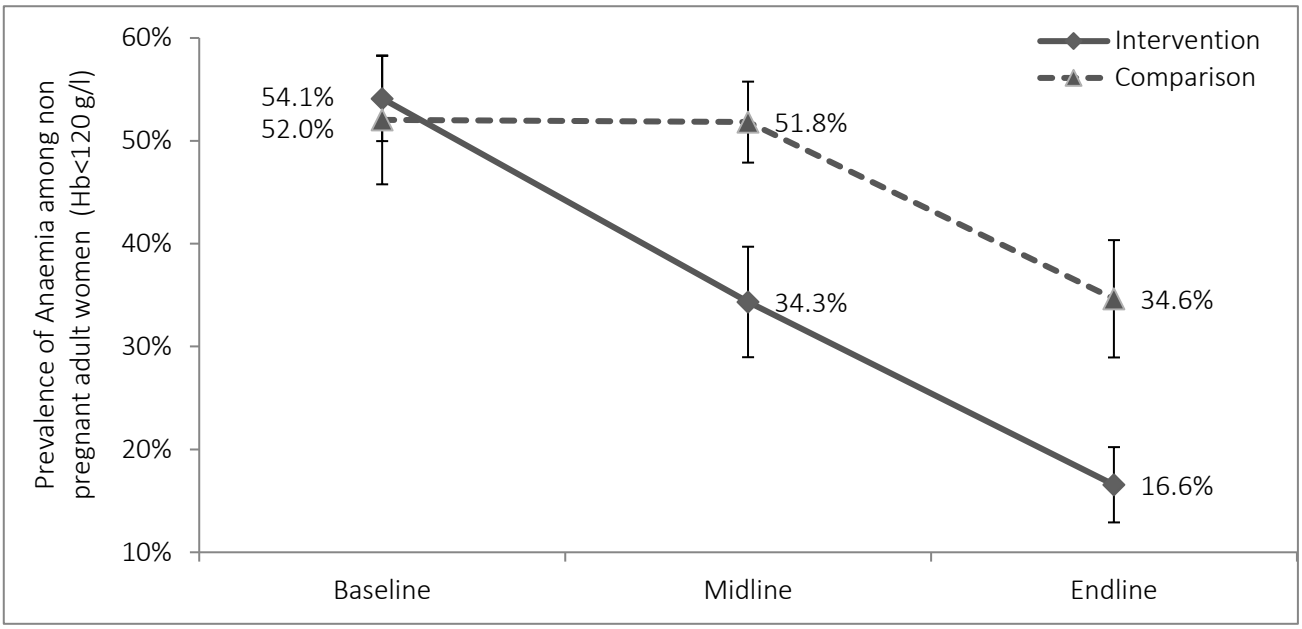
As demonstrated in Figure 3 (and Table 3), between baseline and midline, there was a dramatic fall in anaemia among women in intervention clusters (54% to 34%), whereas anaemia prevalence in the comparison clusters remained the almost same (approximately 54% and 52%). Both declined at about the same rate in the second six months. At the end of the trial, anaemia prevalence had shown an 18.1% (95% CI: 11.1% to 25.1%, P<0.001) greater reduction in intervention group than in the comparison group.

Table 3: Cluster-level haemoglobin concentration of non-pregnant women at baseline, midline and endline surveys

	Intervention Group (n=21)	Comparison Group (n=21)	Difference (95% CI)[a]	P-value[b]
Haemoglobin concentration, mean (SD), g/l				
Baseline	118.3 (3.7)	118.0 (3.6)	0.3 (-2.0 to 2.6)	
Midline	122.7 (3.5)	118.8 (2.6)	3.9 (2.0 to 5.8)	<0.001
Endline	126.4 (2.6)	121.6 (2.1)	4.8 (3.3 to 6.3)	<0.001

[a]Mean difference (g/l for haemoglobin and 95% confidence interval); [b]P value from independent sample t-test

Figure 3: *Change in the prevalence of anaemia among non-pregnant women (aged over 15 years)*



Both intervention and comparison clusters had seen an increase in maternal haemoglobin concentration; however, the increase in the intervention group was greater (see Table 3 and Figure 3). By midline, women in the intervention group had seen a 3.9 g/l (95% CI: 2.0 to 5.8, P<0.001) improvement in mean haemoglobin level compared with comparison clusters. In the second six months, the comparison increased almost as much as the intervention group. At endline, the intervention group had a significantly higher haemoglobin concentration (mean difference 4.8 g/l, 95% CI: 3.3 to 6.3, P<0.001) compared with the comparison group.

Anthropometry

Children under-five years

As demonstrated in Table 4, between baseline and endline, stunting prevalence had increased slightly for both treatment (43% to 47%) and comparison (51% to 53%). Underweight decreased slightly from 46% to 38% in the treatment group, and 50% to 46% in the comparison group. However, wasting and thinness both fell sharply. However, the changes were comparable between the trial arms, and there was no statistically significant difference between intervention and comparison clusters across any of the child anthropometric indicators at any survey.

Table 4: *Changes in anthropometric indicators of children under 5 years during the trial period*

	Intervention Group (n=21)	Comparison Group (n=21)	Difference (95% CI)[a]	P-value[b]
Height for Age z-score (HAZ), mean (SD)				
Baseline	-1.6 (1.0)	-1.7 (0.6)	0.12 (-0.38 to 0.63)	
Midline	-1.7 (0.8)	-2.0 (0.6)	0.28 (-0.15 to 0.70)	0.197
Endline	-1.9 (0.6)	-2.0 (0.5)	0.14 (-0.20 to 0.47)	0.418
Weight for Age z-score (WAZ), mean (SD)				
Baseline	-2.0 (0.5)	-2.0 (0.5)	0.00 (-0.3 to 0.31)	
Midline	-2.0 (0.4)	-2.1 (0.4)	0.16 (-0.09 to 0.41)	0.200
Endline	-1.8 (0.4)	-2.0 (0.4)	0.14 (-0.11 to 0.38)	0.262
Weight for Height z-score (WHZ), mean (SD)				
Baseline	-1.6 (0.5)	-1.4 (0.5)	-0.13 (-0.41 to 0.16)	
Midline	-1.4 (0.5)	-1.4 (0.5)	0.04 (-0.27 to 0.35)	0.809
Endline	-1.0 (0.4)	-1.2 (0.5)	0.15 (-0.16 to 0.45)	0.338
BMI for Age z-score (BAZ), mean (SD)				
Baseline	-1.4 (0.5)	-1.3 (0.6)	-0.12 (-0.44 to 0.20)	
Midline	-1.2 (0.6)	-1.2 (0.5)	-0.02 (-0.35 to 0.31)	0.889
Endline	-0.9 (0.5)	-1.0 (0.5)	0.06 (-0.22 to 0.35)	0.659
Stunting (HAZ<-2) , mean prevalence (SD)				
Baseline	43.3 (26.1)	51.5 (22.0)	-8.2 (-23.2 to 6.8)	
Midline	41.1 (24.2)	55.8 (21.4)	-14.8 (-29.0 to -0.5)	0.043
Endline	46.8 (25.2)	53.1 (22.9)	-6.4 (-21.4 to 8.6)	0.397
Underweight (WAZ<-2) , mean prevalence (SD)				
Baseline	45.5 (24.1)	50.1 (20.0)	-4.6 (-18.4 to 9.2)	
Midline	47.1 (23.0)	54.2 (19.8)	-7.0 (-20.4 to 6.4)	0.295
Endline	38.2 (24.9)	44.5 (19.6)	-6.3 (-20.3 to 7.7)	0.367
Wasting (WHZ<-2) , mean prevalence (SD)				
Baseline	28.5 (24.6)	32.5 (17.7)	-4.0 (-17.4 to 9.4)	
Midline	20.0 (22.1)	26.5 (20.9)	-6.5 (-19.9 to 6.9)	0.336
Endline	10.8 (14.7)	16.2 (18.8)	-5.4 (-15.5 to 5.1)	0.306
Thinness (BAZ<-2) , mean prevalence (SD)				
Baseline	19.1 (22.6)	26.7 (17.0)	-7.6 (-20.0 to 4.9)	
Midline	17.2 (23.8)	19.4 (16.0)	-2.3 (-14.9 to 10.4)	0.718
Endline	8.8 (11.6)	12.0 (12.0)	-3.2 (-10.6 to 4.1)	0.382

[a]Mean difference (g/l for haemoglobin and percentages for anaemia and 95% confidence interval); [b]P value from independent sample t-test

Non-pregnant women

There was no significant difference in mean body mass index (BMI) or prevalence of chronic energy deficiency (CED), between comparison and intervention clusters at midline or endline (Table 5). Both intervention and comparison group had seen an approximate 7% decrease in CED between baseline and endline, and at endline the prevalence of CED was 51% and 56% respectively.

Table 5: *Changes in anthropometric indicators of women*

	Intervention Group (n=21)	Comparison Group (n=21)	Difference (95% CI)[a]	P-value[b]
Body Mass Index (BMI), mean (SD)				
Baseline	18.2 (0.7)	18.1 (0.7)	0.11 (-0.33 to 0.55)	
Midline	18.7 (0.8)	18.4 (0.7)	0.32 (-0.15 to 0.79)	0.176
Endline	18.8 (0.8)	18.4 (0.8)	0.37 (-0.13 to 0.87)	0.143
Chronic energy deficiency (BMI<18.5), mean prevalence (SD)				
Baseline	58.0 (13.3)	63.1 (13.7)	-5.1 (-13.5 to 3.4)	
Midline	51.3 (12.6)	57.2 (12.3)	-5.8 (-13.6 to 1.9)	0.136
Endline	50.8 (13.3)	55.6 (14.4)	-4.8 (-13.4 to 3.8)	0.269

[a]Mean difference (g/l for BMI and percentages for CED and 95% confidence interval); [b]P value from independent sample t-test

Morbidity

Comparison between cluster-specific prevalence of worm infestation is presented in Table 6 while prevalence of diarrhoea among intervention and comparison clusters is presented in Table 7.

Prevalence of passed worms fell sharply during the trial period for both women and children (see Table 6), and the reduction was proportionate between intervention and comparison clusters with no statistically significant difference detected between groups. The reported prevalence of diarrhoea also fell among both women and children during the trial period (see Table 7); however, there was no statistically significant difference between intervention and comparison clusters.

DISCUSSION

Comments on the study findings

In this trial, both the intervention and comparison arms of the study were receiving a substantive set of interventions throughout the trial period. The intervention group received some additional inputs in the form of provision of daily micronutrient powder (MNP), semi-annual deworming, and the provision of flip flops.

Overall, this additional intervention was more effective than the comparison intervention in reducing anaemia prevalence and improving haemoglobin concentration among both children and women. Despite the difference in micronutrient composition and the duration of the study, similar results were found for children from studies in India (33, 34), China (35), Kenya (36), Cambodia (37) and Pakistan (38). There are various trials and systematic review that found positive impact of MNP supplementation during pregnancy (with or without deworming) on birth outcome and maternal nutrition (39, 40), but the study team could not find trials that tested the effect of MNP (with or without deworming) on non-pregnant women (41). As far as the study team was concerned, this was the first randomised trial in Bangladesh (and possibly elsewhere) that tested the effectiveness of MNP and deworming (and flip-flops) on the nutritional status of non-pregnant adult women.

At the end of the trial period, there was 58% less anaemia (mean difference 18.4%, 95% CI: 7.2% to 29.6%) among children in intervention clusters. A recent systematic review by Rehana et al. (41), reported that MNP reduced anaemia by 34% (RR: 0.66, 95% CI: 0.57-0.77) among children. This

Table 6: *Changes in maternal observation of passed worms among children and women*

		Intervention Group (n=21)	Comparison Group (n=21)	Difference (95% CI)[a]	P- value[b]
Children under 5 years	*Passed worm on the day of survey*				
	Baseline	20.3 (16.7)	15.1 (17.0)	5.2 (-5.3 to 15.7)	
	Midline	10.2 (11.8)	7.3 (10.0)	2.9 (-3.9 to 9.8)	0.390
	Endline	2.0 (5.3	2.4 (6.3)	-0.4 (-4.1 to 3.2)	0.822
	Passed worm in past 7 days				
	Baseline	53.4 (29.5)	41.0 (25.8)	12.4 (-4.9 to 29.7)	
	Midline	29.9 (24.3)	23.1 (24.1)	6.8 (-8.3 to 21.9)	0.369
	Endline	8.7 (13.6)	8.3 (14.5)	0.4 (-8.4 to 9.1)	0.930
	Passed worm in past 30 days				
	Baseline	64.1 (26.3)	54.4 (25.6)	9.6 (-6.6 to 25.8)	
	Midline	36.3 (26.4)	29.2 (24.1)	7.1 (-8.7 to 22.8)	0.370
	Endline	17.4 (23.6)	12.4 (16.7)	5.0 (-7.7 to 17.7)	0.433
Women (non-pregnant)	*Passed worm on the day of survey*				
	Baseline	20.8 (10.6)	20.4 (15.7)	0.4 (-8.0 to 8.8)	
	Midline	10.2 (7.6)	14.2 (8.9)	-4.0 (-9.2 to 1.2)	0.127
	Endline	4.2 (5.7)	4.5 (5.4)	-0.3 (-3.8 to 3.1)	0.846
	Passed worm in past 7 days				
	Baseline	47.9 (16.2)	48.9 (20.1)	-1.0 (-12.4 to 10.4)	
	Midline	20.1 (10.8)	23.4 (13.6)	-3.3 (-11.0 to 4.3)	0.386
	Endline	9.2 (7.8)	11.2 (9.5)	-1.9 (-7.4 to 3.5)	0.475
	Passed worm in past 30 days				
	Baseline	59.9 (14.2)	66.4 (17.2)	-6.5 (-16.3 to 3.4)	
	Midline	25.8 (11.2)	31.1 (14.4)	-5.3 (-13.4 to 2.7)	0.189
	Endline	12.0 (9.3)	15.4 (9.8)	-3.4 (-9.4 to 2.5)	0.251

[a]Mean difference (percentages and 95% confidence interval); [b]P value from independent sample t-test

outcome is slightly less impressive than that of the current study; however, the intervention covered in the systematic review was MNP alone. The present trial involved the use of a micronutrient powder providing 10 mg or iron per day, which is lower than that used in most of the studies in the

Table 7: *Changes in diarrhoea prevalence among children and women, as per maternal recall*

		Intervention Group (n=21)	Comparison Group (n=21)	Difference (95% CI)[a]	P-value[b]
Children under 5 years	*Diarrhoea on the day of survey*				
	Baseline	7.6 (13.7)	7.8 (13.4)	-0.2 (-8.7 to 8.2)	
	Midline	4.7 (8.8)	9.1 (24.1)	-4.5 (-15.8 to 6.9)	0.431
	Endline	2.9 (6.7)	5.5 (8.5)	-2.6 (-7.4 to 2.2)	0.272
	Diarrhoea in past 7 days				
	Baseline	38.6 (23.7)	32.6 (27.7)	6.0 (-10.0 to 22.1)	
	Midline	24.8 (22.3)	30.0 (25.9)	-5.2 (-20.3 to 9.8)	0.486
	Endline	24.6 (25.6)	22.9 (22.6)	1.7 (-13.3 to 16.8)	0.817
	Diarrhoea in past 30 days				
	Baseline	57.4 (28.0)	47.3 (27.2)	10.1 (-7.1 to 27.3)	
	Midline	36.4 (25.3)	42.9 (28.1)	-6.5 (-23.2 to 10.2)	0.435
	Endline	33.5 (24.0)	39.3 (29.5)	-5.8 (-22.6 to 11.0)	0.489
Women (non-pregnant)	*Diarrhoea on the day of survey*				
	Baseline	7.8 (5.1)	9.8 (9.1)	-2.0 (-6.6 to 2.6)	
	Midline	3.4 (3.2)	6.3 (4.2)	-2.9 (-5.2 to -0.6)	0.016
	Endline	6.0 (6.4)	6.1 (4.4)	-0.1 (-3.5 to 3.3)	0.948
	Diarrhoea in past 7 days				
	Baseline	34.8 (15.2)	29.2 (13.0)	5.5 (-3.3 to 14.3)	
	Midline	20.7 (11.9)	25.0 (12.3)	-4.3 (-11.9 to 3.2)	0.256
	Endline	22.4 (12.0)	23.5 (12.6)	-1.1 (-8.7 to 6.6)	0.781
	Diarrhoea in past 30 days				
	Baseline	46.3 (16.6)	43.4 (12.9)	2.9 (-6.4 to 12.2)	
	Midline	32.5 (12.6)	39.4 (13.5)	-6.9 (-15.1 to 1.2)	0.093
	Endline	33.1 (13.5)	34.4 (12.9)	-1.3 (-9.6 to 6.9)	0.743

[a]Mean difference (percentages and 95% confidence interval); [b]P value from independent sample t-test

review (41), whereas all studies in the review (except one) used MNPs with 12.5mg of iron in the form of ferrous fumerate. However, the MNP used in this study had 15 micronutrients and was combined with the use of deworming and flip-flops. The combined effect of the intervention package in our study may have had a stronger effect on anaemia reduction. Prevalence of anaemia among women in the intervention clusters was 52% less (mean difference: 18.1%, 95% CI: 11.1% to 25.1%) than those in comparison clusters, which shows the intervention package had a similar effect in reducing anaemia in both children and women. However, after one year of intervention, the intervention package resulted in 4.8g/l higher haemoglobin among women, whereas the improvement was greater (7.8 g/l) among children. The greater improvement in haemoglobin concentration and anaemia status in the intervention than in the comparison group can be attributed to the increased iron consumption through MNP and also perhaps partially due to the reduction of worm load through deworming (41). The substantive improvements in the comparison groups may have been due to the other ongoing interventions taking place in this district at the same time.

Child anthropometric indicators, on the other hand, did not show significant improvement in the intervention compared to the comparison group during the trial. While stunting got slightly worse across both comparison and intervention groups, wasting improved in both. Studies evaluating the

effect of MNPs in other countries (41) did not find any significant impact on child growth, which is consistent with the findings in this study.

In terms diarrhoeal incidence, some studies have reported increase in diarrhoea incidence related to micronutrient supplementation among children (34, 41, 42). However, this study did not find any such outcome; a similar reduction in overall diarrhoea prevalence during the course of the study was observable across both groups, while women showed a parallel trend. Given that the association between increased diarrhoea with iron supplementation is well recognized in the literature, this outcome was perhaps unexpected. The study team hypothesized that the reduced dosage of iron in the MNP used in this trial compared to other trials in combination with the provision of zinc in the 15 component MNP might have helped reduce the risk of diarrhoea.

As part of the intervention package included semi-annual deworming, it was expected to see a significant reduction in reported worm passing during defecation in the intervention group. While there was a sharp fall in reported worm infestation for both women and children during the course of the study period, there were no statistically significant differences between the comparison and intervention clusters. As there was a huge nationwide campaign promoting child deworming linked with vitamin A supplementation, organised by UNICEF Bangladesh and the Government of Bangladesh (43), during the trial period, we have reason to believe children in comparison clusters were also exposed to deworming, hence explaining the decline in both groups and lack of significant difference between trial arms. There is no concrete explanation for the lack of impact among women. Increased national awareness about worm infestation generated through the aforementioned campaign might have played a role in changing behaviours among women, meaning women in the comparison group might have procured and consumed deworming tablets.

Limitations and methodological considerations

Although standard guidelines for cluster randomised trials (32) were followed, this study nevertheless had some methodological and implementation issues that need to be considered.

There was no provision for double data entry - data were entered only once during all three surveys. The second design issue was loss of participants during follow-up, which can affect the power of any study (44, 45); however, no full cluster was lost. The study still had adequate power as the sample size calculation allowed for some attrition. The attrition bias (loss during follow-up) can potentially cause another bias, (i) imbalance between the trials arms, and (ii) the participants lost during follow-up might be different from those who complied (44, 46). The loss of participants was proportionate in the two arms. Since they were comparable in various baseline characteristics, there is a minimum risk of imbalance.

It was not possible to blind participants, as there was no placebo. Firstly, there was no placebo available for micronutrient sprinkles and deworming drugs in Bangladesh, and secondly, it was considered unethical to provide a placebo, as the aim of the trial was to determine the effectiveness, not the efficacy of the intervention. The implementers were not blinded either, as they were delivering the intervention at the field level, so needed to be aware which clusters and participants were included in the intervention group.

The analysis was conducted on data from participants who took part in all three surveys) and did not include those lost during follow up. It was assumed during the analysis that all participants received the full dose of the treatment (intervention), but due to the lack of compliance data, this article could not reveal the extent to which participants adhered to the intervention.

Adherence to the treatment protocol, especially the MNP consumption, was assessed only by counting the empty sachets at the end of the month. Consumption could not be confirmed by observation. Furthermore, the detection of worm infestation was a self-reported count of passed worms by the mother based on casual observation, which is less accurate than microscopic stool examination. This was adopted due to resource limitations.

Finally, the readers should keep in mind that the anaemia prevalence detected by HemoCue in this study can be slightly different than the he gold standard, the direct cyanmethaemoglobin method. However, due to the nature of data collection settings, and very high level of reliability of HemoCue, this method was used.

Generalisability

Generally, the internal validity in randomised trials is strong, but external validity (generalisability) can be limited. However, the applicability of the findings of this study is not limited to the study population. Although the study was geographically limited to a single district in Northwest Bangladesh, the selected samples have similar socio-economic characteristics to other extreme poor populations in the country. As such, the results could be generalisable beyond the study sample, at least to the poorest communities in Bangladesh. However, before generalising the results beyond Bangladesh, the socio-economic, cultural, as well as the basic baseline characteristics of the study population need to be considered.

CONCLUSIONS

We found that daily supplementation of MNP coupled with deworming and practice of wearing flip-flops was effective in reducing anaemia among non-pregnant women and children under five. However, this study did not find any evidence of an effect on child growth (e.g. stunting, underweight, wasting and thinness) or chronic energy deficiency (CED) among women, which suggests that a package of MNP, deworming and flip-flops alone cannot enhance growth or weight gain among women and children in a population already receiving a substantial package of interventions (Shiree).

The study findings alone cannot provide enough evidence to recommend the use of this intervention for improving child growth or reducing CED among adult women. While the intervention package led to significant improvements in anaemia status among both non-pregnant women and under-five children these study findings alone are not enough to make a policy recommendation to the Ministry of Health in Bangladesh. There are a few issues that we need to consider. Firstly, the variation in the iron content in different MNPs (47), and in this study did not assess whether this might make any difference. Secondly, it was also outside the scope of this study to assess the comparative advantage of 15 micronutrients versus 5 micronutrients, which is the current WHO recommendation (47-49). Nevertheless, results from this study can inform donor and government policy on integrating MNP and anthelmintic treatment into livelihood projects, to tackle micronutrient deficiency. Furthermore, if anaemia reduction is the only benefit, other interventions such as food fortification might be more cost effective than MNP.

This study adds credible information to the evidence base by evaluating the effect of the use of MNP and deworming on nutritional status of non-pregnant women and children under five. However, further research would be required to evaluate the effect of the individual intervention (MNP vs deworming) in comparison to the combined effect, as well as the effect of using 15 component MNP versus 5 component MNP, in order to make a strong public health recommendation.

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