Author’s response to reviews

Title: Effect of micronutrient powder supplementation for two and four months on hemoglobin level of children 6-23 months old in a slum in Dhaka: a community based observational study

Authors:
Mustafa Mahfuz (mustafa@icddrb.org)
Mohammed Alam (mashraful@icddrb.org)
MMunirul Islam (mislam@icddrb.org)
Dinesh Mondal (din63d@icddrb.org)
MIqbal Hossain (ihossain@icddrb.org)
AM Ahmed (a.ahmed@uq.net.au)
Nuzhat Choudhury (nuzhat@icddrb.org)
Mohammad Raihan (raihan@icddrb.org)
Rashidul Haque (rhaque@icddrb.org)
Tahmeed Ahmed (tahmeed@icddrb.org)

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COMMENTS OF REVIEWERS AND RESPONSES

Reviewer 1#

General:
This study compares the impact on anaemia prevalence and Hb concentration of 4 vs 2 months MMP supplementation in young children living in Dhaka, Bangladesh. This has been done as part of a large programme. The authors have found evidence that 4 months intervention has a larger impact on haemoglobin concentrations and on anaemia prevalence compared with 2 months, and may reduce the risk of some infections.

Specific comments:

1. My concern with this paper is the risk of confounding in this observational study, as there are some differences at baseline between children whom received 2 vs 4 months iron in terms of variables which could directly influence anaemia, iron status or risk of infection - the 4 month duration children seem better off in terms of stunting, risk of wasting, baseline Hb, and food security. Thus, I think it is crucial for the authors to look at confounding variables; although they report the infection model accounts for covariates, these would need to include the key variables which are different between the groups (as above). For example, it is plausible that younger children would respond less well to iron in terms of Hb whereas older children might respond better because of slowing growth. So I'd suggest both age stratified reporting of Hb response to MMPs, and also a multivariate approach to adjust for these factors in the analysis. So for both the Hb response and infection analysis, I'd suggest incorporating multivariate analyses to adjust for baseline confounders, to see if MMP duration remains a significantly associated variable.

Response: Many thanks for your valuable suggestions. We have reanalyzed the data accordingly. In the difference in difference analysis, we now included the confounding variables in the regression model using the variables those were significant at baseline. As per your suggestion we initially used base line hemoglobin, gender, stunting, wasting, food security and vitamin A supplementation status between two groups: 6-11 months and 12-23 months. The following regression model was used:

\[ Y_{it} = \beta_0 + \beta_1 Time + \beta_2 Group + \delta (Time \times Group) + \beta_3 Gender + \beta_4 Food security + \beta_5 Stunted + \beta_6 Wasted + \beta_7 Underweight + \beta_7 (Vitamin A capsule given) + \epsilon \]

Where,

\[ Y_{it} = \text{Outcome variable of interest for individual } i \text{ at time } t \]

\[ Time = (1) \text{ if endline and (0) if baseline} \]
Group = (1) if 4 months MNP supplementation and (0) if 2 months MNP supplementation

δ = The effect of the 4 months MNP supplementation

ε = Error term

The overall effect was significantly better for 4 months supplementation, however, when we categorized by age groups only 6-11 months groups showed significant superiority for 4 months MNP supplementation. Considering the problem with co-linearity, we then removed the wasting and underweight from the model, however, there has been no change of result after doing so. So, the final model we used in the manuscript was:

\[ Y_{it} = \beta_0 + \beta_1 \text{Time} + \beta_2 \text{Group} + \delta (\text{Time} \times \text{Group}) + \beta_3 \text{Gender} + \beta_4 \text{Food security} + \beta_5 \text{Stunted} + \beta_6 (\text{Vitamin A capsule given}) + \epsilon \]

For infection analysis we also adjusted the confounding variables in both studies including non-intervene cohort. Incidence Rate Ratios were estimated with generalized linear models with a Poisson distribution. All are now adjusted by gender, stunting, wasting and food security status.

2. Comparative data are provided from a non-intervened cohort for the infection data. Are Hb data likewise available? This would be useful to determine the efficacy of even 2 months Hb. It is possible Hb is declining in this group without intervention.

Response: The time points of hemoglobin measurements in available data from non-intervened cohort do not match with the MNP supplementation data. Therefore, we could not compare between two studies.

3. It would be useful to have iron biochemistry. With collection of venous blood, this should be achievable.

Response: Thank you again for this important observation. MNP is an intervention for anemia in children. Since it contains different micronutrients, it is believed to act on anemia through different means. Therefore, our focus is on anemia as measured by hemoglobin, and not on iron status.

4. AML doesn't cause brain 'metastases' - was this leptomeningal disease?
Response: We completely agree with you. We have rechecked our record. It was not clearly written in the hospital report. Probably this was a leptomeningeal disease. Now we have re-written this as death due to complication of AML.

5. Bangladesh is known to have an unusual anaemia epidemiology situation with high levels of groundwater iron perhaps influencing iron deficiency rates and contribution to anaemia - this is not discussed here - do the authors feel this may influence impact of MMPs?

Response: We have now included a discussion on the high levels of ground water contamination of iron with the prevalence of anemia. It can be noted that our team recently published a paper on this (Rahman S. Public Health Nutrition 2016) based on Bangladesh national micronutrient survey that we have conducted in 2011. We found that natural iron level in slum areas is not that high and this current study has taken place in a slum of Dhaka city. Moreover, according to British geological survey, ground water iron level was low in the Dhaka city (<0.15 to 1.00 mg L-1).

Reviewer 3#

Several strategies have been shown to be effective in resolving micronutrient deficiencies in children. WHO recommends that in settings where the prevalence of anaemia in children under 2 years or under 5 years of age is 20% or higher, home fortification of foods with multiple micronutrient powders is recommended to improve iron status and reduce anaemia among infants and children 6-23 months of age. Home fortification technical advisory group of WHO recommended that 60-180 sachets of MNP should be made available to target groups (children 6-23 months) over a period of 6 months. However data on optimum duration for MNP to be given to children aged 6-24 months is limited among Bangladeshi population. This study examined the relative efficacy of MNP provided for 2 and 4 months on improving plasma Hb levels among children 6-23 months.

Overall, a well organized, well written and nice paper

I have only a few minor comments.
Introduction

-Page 5 line 4: The sentence "Home fortification technical advisory group of WHO recommended that 60-180 sachets MNP sachets should be made available to target groups (children 6-23 months) over a period of 6 months" needs to be reworded to "Home ---- that 60-180 sachets of MNP should be ------".

Methods

-Page 6 line 12: In a sentence "MNP was provided in sachets, with daily allowance of one sachet per children,----", 'one sachet per children' is to be corrected to 'one sachet per child'.

-Page 7 line 29-31 (Methods) and Page 9 line 42-45 (Results): Hb results were available for 818 children at baseline and 511 children at endline. This information is getting repeated twice in methods and results section; I would suggest to give at one place.

-Table 1: Reference to footnote '†' and 'a' is not there in table-1.

Results

-Was the adherence to intervention similar in the 2 months and 4 months MNP supplementation groups?

Response: Thank you very much for your positive review and suggestions regarding this manuscript. We have accepted all your inputs and modified our manuscript accordingly.

Adherence to intervention was similar across the groups (85.2% for 2 months vs. 86.9% 4 months MNP groups). We now included this information in the result section.