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Cost-effectiveness of Supplementation with iron syrups and Food fortification with iron-containing micronutrient powders for Anaemia among Young Children in Bangladesh

by

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A final report for

RESEARCH PROJECT IN PUBLIC HEALTH (POPH90284/90285)

Master of Public Health

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AFFIRMATION

The work presented in this report was undertaken to partially fulfil the requirements of the degree of Master of Public Health at The University of Melbourne.

The views expressed herein are those of the author and may not reflect the views of The University of Melbourne and/or the Melbourne School of Population and Global Health.

Edifofon Akpan

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ABSTRACT

OBJECTIVE: To compare the cost-effectiveness of iron interventions for anaemia among young children in Bangladesh.

PERSPECTIVE: Health system perspective.

SETTING: Cost-effectiveness analysis using data from Benefits and Risks of Iron interventionS in Children (BRISC) trial. The trial randomized 3300 children aged eight months to three months of *supplementation* with iron syrups, food *fortification* with iron-containing micronutrient powders (MNPs), or placebo.

METHODS: Data collected from the trial was used to assess the cost-effectiveness of *supplementation* and *fortification* compared to *doing nothing*. Costs and disability-adjusted life-years (DALY) were estimated over the trial follow-up period of 12-months. Cost-effectiveness analysis was performed using non-parametric bootstrapping method on multiply imputed data. Cost-effectiveness acceptability curves were constructed over a range willingness to pay (WTP) thresholds. A two-way sensitivity analysis investigated the impact of varying costs of active iron agents (syrups or MNPs) and programme delivery costs.

RESULTS: Mean DALYs and costs were expressed per 1,000 children. *Fortification* was estimated to avert 4.0 (95% confidence interval [CI] 3.7-4.3) DALYs over one year, while *supplementation* averted 5.2 (95% CI 4.9-5.4) DALYs, compared with doing nothing. Incremental mean costs were $7,355 (95% CI 7,301-7,403) for *fortification* vs *doing nothing* and $6,350 (6,299–

6,397) for *supplementation* vs *doing nothing*. The incremental cost-effectiveness ratio (ICER) was $1,852 per DALY averted and $1,229 per DALY averted for *fortification* and *supplementation*, respectively. The probability that *supplementation* is the optimal strategy was 0% at WTP thresholds of $200 and $985 (half GDP per capita) per DALY averted compared to *doing nothing*. Two-way sensitivity analyses indicated that both interventions were unlikely to be cost-effective, even at low programme delivery costs.

CONCLUSION: Using two plausible WTP thresholds for Bangladesh, *supplementation* with iron and *fortification* with iron-containing MNPs do not appear cost-effective for population-level control of anaemia among young children.

1. INTRODUCTION

1.1. Background

1.1.1. Definition and burden of anaemia in young children

Globally about 8.8% of the total years of life lived with disability (YLDs) is attributed to anaemia (1). In 2011, about 300 million (43%) of children under 5 years were anaemic with the greatest number affected residing in South Asia (2). In Bangladesh, the prevalence of anaemia among children under 2 years is very high. A longitudinal study in rural Bangladesh found the prevalence of anaemia up to 60% among children under 2 years (3). In the 2012 National Micronutrients Survey (4), the prevalence of anaemia in children under 2 years was 40% overall and 45% in rural areas.

Anaemia is a condition where oxygen-carrying capacity of circulating red blood cells are inadequate to meet the body's physiological needs (5, 6). The role of oxygen delivery is performed by Haemoglobin, a protein found in red blood cells (5). Impairment in this critical role explains the common symptoms of anaemia including fatigue, paleness of the conjunctiva and palms, heart palpitations, and problems with activities that require physical effort or deep concentration (7, 8). Conventionally, anaemia is diagnosed when the haemoglobin levels falls below a specific threshold, and this threshold is then used to estimate the prevalence in a population. (6). For instance, in children under 5 years, the prevalence of anaemia is the proportion of children with haemoglobin levels less than 110 grams per litre (g/l).

1.1.2. Iron deficiency as a major cause of anaemia in young children

The main causes of anaemia are iron deficiency; deficiencies in other micronutrients like folic acid, vitamin A, vitamin B2 and vitamin B12; infections such as malaria; and genetic disorders that affect red blood cells (1, 9). Iron deficiency occurs when body iron stores become depleted, and is defined as serum ferritin less than 12 micrograms per litre (*µ*g/l) in young children (10). Iron deficiency anaemia occurs when there is concurrent anaemia and iron deficiency. An estimated 50% of all anaemia globally (9), and in rural Bangladesh (3) are due to iron deficiency.

Children aged 6 to 23 months are particularly susceptible to iron deficiency because of iron requirements needed for growth (10). Infants usually have adequate iron stores from birth which make them iron sufficient until about 4-6 months of age (11). Beyond 6 months these stores become depleted as a child grows rapidly and maintaining sufficient levels will require intake of complementary iron-rich foods (10, 12). At the population level, the prevalence of iron deficiency anaemia peaks around 18 months, due to rapid growth and low dietary iron content and during the first year (13, 14). After this period, the prevalence falls as iron requirements decline and iron intake is increased through complementary foods (14). Therefore, it is important to address anaemia within the critical window from 6 months to 2 years of age.

1.1.3. Iron interventions for population control of anaemia in young children

The WHO recommends two universal iron interventions (supplementation and fortification) for population-level control of anaemia among children between 6 - 23 months (15, 16). The term *universal* implies all children are provided the intervention whether they have anaemia or not). Where anaemia prevalence is

above 40%, all children are to be provided daily iron *supplementation* in form of syrups or drops (15). Where anaemia prevalence is above 20%, the recommendation is home *fortification* of food with iron-containing micronutrient powders (MNPs) (16). The contents of MNP sachets are to be applied to a child's prepared meals at home (hence the term home fortification).

Available evidence indicates iron interventions are effective and could be rationalized when considering the high proportion of anaemia due to iron deficiency. Estimates suggest that about 41% of anaemia cases in South Asia are responsive to iron interventions (9). Systematic reviews have examined the effect of iron supplementation (17, 18) and home fortification of food (19, 20) interventions on key health outcomes. All reviews concluded that taking these interventions significantly reduced the risk of anaemia. However, whether they improved cognitive development and other functional outcomes in children below 2 years was uncertain. This is important because, despite the limited data on effectiveness, iron interventions have been promoted based on presumed benefit in the improvement of cognitive development in children under 2 years (13, 21). In 2019, 58 countries implemented home fortification programmes with support from UNICEF (22).

1.1.4. Cost-effectiveness for public health interventions

In addition to the health effects, it is also necessary to evaluate whether public health interventions like iron interventions provide value for money by conducting formal cost-effectiveness analysis. This could be done by assessing the epidemiological evidence (effectiveness), and identify, measuring and valuing the extent of resource use (costs) associated with implementing such interventions. Then by dividing the additional costs of the intervention by the

additional health effects, we can get the incremental cost-effectiveness ratio (ICER), which is the incremental costs per additional unit of health effects compared to the status quo or doing nothing).

When using cost effectiveness methods, costs are measured in monetary terms and the outcomes in natural units such as number of anaemia cases prevented or an aggregate measure such as disability adjusted life years (DALYs) averted. Using DALYs enables us to assess the impact of an intervention on both the length and quality of life. This then facilitates comparison of benefits across different interventions within the same disease area and even across diseases. When a decision maker sets a maximum willingness to pay (WTP) threshold, interventions that cost less than this threshold per DALY averted can be termed cost-effective or of good value for money. Even in health systems where no explicit threshold value is defined, the ICER can be converted to net monetary benefits (NMB) and assessed using a range of different threshold values. At a particular threshold, interventions with higher NMB have higher value for money.

1.2. Review of published studies

Ovid MEDLINE and CabDirect Global Health was searched on 27th April 2021 for economic evaluations of iron interventions in young children. Details of the search string for the two databases is provided in Appendix 1.1.1. Both cost-effectiveness analyses conducted alongside clinical studies and modelling studies based on data from literature were included. Review articles or studies that did not describe the sources or methodology for estimating costs and outcomes were excluded. Studies where an intervention targeted pregnant

women and outcomes were measured in young children were excluded, as effects of those interventions are within the first 6 months of age.

Seven studies met the inclusion criteria (23-29). Only one study assessed supplementation using iron syrups (23), but in a region of Tanzania where malaria is endemic and a major contributor to the burden of anaemia. Therefore, the findings would not apply to non-malaria endemic settings. The first published study on cost-effectiveness of MNPs evaluated a food security program in Peru (24). Micronutrients were provided to children aged 6 months to 4 years, women of reproductive age, and teenage girls. The results were reported in cost per 1% of prevented anaemia per community resident (24). Whether MNPs were cost-effective in young children only was not assessed.

Three studies have evaluated whether iron-containing MNPs could improve cognitive development thereby averting productivity losses or increasing earnings (25-27). All three studies reported that MNPs were of good value for money. Two of these studies involved providing subsidies to caregivers for purchasing MNPs for Pakistani (26) and Indian (27) children. The ICER was estimated as the difference between subsidy costs and future productivity costs avoided divided by DALYs (societal perspective). The interventions were “cost-saving”. When productivity losses averted were not considered (health system perspective), the costs per DALY averted ranged from $354 to $3341. These studies did not incorporate costs of delivering the price subsidies. Additionally, benefits of MNPs in improving cognitive development and therefore averting productivity losses have not been confirmed by systematic reviews

Two studies published in 2020 have reported the cost-effectiveness of MNPs for Bangladeshi children (28, 29). The BRAC home fortification programme sold MNPs to caregivers of children 6–59 months in Bangladesh and assessed the prevalence of anaemia before and after the programme. Using this data, Ahmed and colleagues (28), estimated the effects in DALYs and estimated the cost-effectiveness. The incremental cost per DALY averted was $ 159. Finally, Pasricha *et al* (29) developed a microsimulation model to estimate DALYs due to anaemia, malaria, and diarrhoea by providing MNPs to 6-month old children. For Bangladesh, the incremental cost per DALY averted was above $ 1,500 at 100% coverage.

1.3. Research gaps and study rationale

Undertaking this study is important because resources in the health sector in many LMICs is limited, even when supplemented by donors (30). There is therefore the need to trade-off between potentially beneficial options to maximize health gain or avert DALYs. These options could be for the same condition (such as iron interventions for anaemia) as well as comparing interventions across health conditions. The prevalence of anaemia in Bangladesh and many LMICs is high in young children, therefore any *universal* iron intervention that is funded will have huge budget impact because of the absolute number of people to pay for.

In settings like Bangladesh where the prevalence of anaemia is above 40% in children aged 6-23 months, the two WHO guidelines on iron interventions are applicable (15, 16). Previous studies have examined the value-for-money of either supplementation with iron syrups or home fortification with MNPs under

5years of age in many population settings. However, our review of literature did not find any published cost-effectiveness studies that directly compared both supplementation and fortification in any setting. This study will be the first direct comparison of both interventions. In malaria-endemic areas, WHO strongly recommends that providing iron supplementation be done in combination with malaria prevention or curative measures (15). Only one study assessed iron supplementation, but this was in a malaria-endemic area. This study will be the first appraisal of iron supplementation in a non-malaria-endemic setting.

The **B**enefits and **R**isks of **I**ron Intervention**S** in **C**hildren (BRISC) trial compared 3 months of *iron supplements* or *MNPs* with *placebo* in children less than 2 years on cognitive development and other secondary outcomes (31). The three-arm design of the BRISC trial enables a direct comparison of cost-effectiveness of both interventions recommended in WHO guidelines for children below 2 years. Children were observed from 8 months (screening) to 20 months (end of follow-up). This age cohort falls within the period of 6 to 23 months where anaemia is most prevalent among young children (13, 14), and where the two WHO guidelines on iron interventions apply. This cost-effectiveness study focuses on only health outcomes that have been shown to have effect – previous systematic reviews and the BRISC trial showed no meaningful difference in cognitive development, so this is excluded from assessment of outcomes for cost-effectiveness study.

1.4. Research question and objectives

Therefore, the research question for this study was

From a healthcare system perspective, is universal provision of i) daily supplementation with iron syrup or ii) home fortification of foods with iron-containing micronutrient powders (MNPs) cost-effective compared to doing nothing for population-level control of anaemia among children under 2 years of age in Bangladesh?

The specific objectives of this study are:

I. To estimate the total healthcare costs of supplementation and fortification strategies compared with doing nothing from a health system perspective.
II. To estimate the effect of supplementation and fortification strategies in terms of improvements in DALYs compared with doing nothing.
III. To estimate the ICER and the associated uncertainty for supplementation vs doing nothing and for fortification vs doing nothing.
IV. To provide policy recommendations regarding optimal strategies for population-level control of anaemia in young children.

2. METHODS

2.1. Overview

This study is a cost-effectiveness analysis using data from the BRISC randomised controlled trial. It was conducted from a healthcare system perspective using a time horizon of 12 months (trial follow-up period). The one-year time horizon meant discounting was not necessary. The report of this study follows the Consolidated Health Economic Evaluation Reporting Standards (32), and a checklist is presented in Appendix A.1.3.

2.2. BRISC trial design

The BRISC trial, a double blinded placebo controlled study, evaluated the impact of supplementation with iron syrups or home fortification with iron-containing MNPs in children below 2 years old (31). Children were randomized to iron syrup with placebo powder, MNPs with placebo syrup, or placebo syrup and placebo powder for 3 months (intervention period) and followed-up for another 9 months (follow-up period). Iron syrups used in the trial contained 12.5 mg of iron as ferrous sulphate. MNPs contained 12.5 mg of iron as ferrous fumarate, and in addition included 0.3 mg of vitamin A, 30 mg of vitamin C, 0.16 mg of folic acid, and 5 mg of zinc. These formulations met the WHO recommendations for daily iron supplementation (15) and MNPs for food fortification (16).

The trial took place in three administrative units (unions) of Rupganj, a rural non-malaria-endemic subdistrict (*Upazila*) in Narayangaj District, Bangladesh.

Children eight months of age were screened for potential eligibility (31). Those with marked anaemia (Hb<8.0g/dL), current febrile illness, severe malnutrition, history of blood transfusion, any inherited red cell disorder, or currently receiving iron-containing supplements were excluded.

The primary outcome was cognitive development measured using Bayley III Cognitive Composite Score (31). No difference in cognitive composite score on the Bayley Scales of Infant and Toddler Development was observed after 3-months of intervention or at 9 months after completion. Therefore, cognitive development was not used in assessment of outcome for cost-effectiveness study. Secondary outcomes included developmental and growth indices, anaemia, iron deficiency, and infection risks. Anaemia was assessed using capillary haemoglobin (Hb) levels measured by HemoCue-301®. Haemoglobin levels were measured at baseline, post-intervention, and post-follow-up.

2.3. Ethical approval

BRISC trial was prospectively registered at Australian and New Zealand Clinical Trials Registry (identifier ACTRN1261700066038 (33)) and WHO International Clinical Trials Registry Platform (identifier U1111-1196-1125 (34)). The clinical trial study protocol and informed consent forms were reviewed and approved by Melbourne Health Human Research Ethics Committee, Australia (HREC/16/MH/353; 2016.269) and Ethical Review Committee of International Centre for Diarrhoeal Disease Research, Bangladesh (ICCDR,B). For this project, an amendment to a Melbourne Academic Centre for Health (MACH) research collaboration agreement was obtained to enable student and supervisors to be included in BRISC trial ethics

documentation. To have access to trial dataset, we obtained the trial data dictionary and questionnaires from the study statistician and used them to complete a data request form. In this form, we specified the study objectives, detailed the planned analyses, and listed the variables required.

2.4. Health outcomes

The outcome for the cost-effectiveness analyses was DALYs due to anaemia. DALYs were calculated as sum of the years of life lost (YLL) due to premature mortality and the years lost due to disability (YLD), i.e., $DALY = YLL + YLD$ (35, 36). Using DALYs allows the comparison of interventions across different health conditions. There was no difference in mortality between the treatment groups in the BRISC trial (31), therefore $\Delta YLL = 0$ and $YLLs$ were not used in DALY estimation. $YLDs$ were calculated by weighting the average disability weights due to anaemia between study visits by the duration between the visits (more details and formula can be found in Appendix A.1.2). Thresholds for haemoglobin concentrations to diagnose anaemia according to WHO guidelines (6) are given in Table 1. The table also includes the corresponding disability weights for the severity levels of anaemia, which were obtained from Global Burden of Disease 2019 (37).

TABLE 1. HAEMOGLOBIN LEVELS TO ASSESS SEVERITY OF ANAEMIA

Haemoglobin (grams/Litre)	Diagnosis*	Disability weight†
110 or higher	None	0.000
100 to 109	Mild anaemia	0.004 (95% CI, 0.001 - 0.008)
70 to 99	Moderate anaemia	0.052 (95% CI, 0.034 - 0.076)
70 or lower	Severe anaemia	0.149 (95% CI, 0.101 - 0.209)

* WHO cut-offs Haemoglobin concentrations for diagnosing and assessing severity of anaemia (6)
† Magnitude of health loss associated with various severity of anaemia from GBD 2019 (37)

2.5. Resource use and costs

2.5.1. Costing perspective

Costs of implementing population-level iron interventions in children were estimated from a health system perspective. The costing perspective determines the scope of the costs to be analysed. While a societal perspective is ideal in that it includes all related costs regardless of who pays for them, a health system perspective is often used for decision making and was therefore chosen for this analysis. Thus, expenses incurred by households and indirect costs due to lost productivity were excluded.

2.5.2. Identifying resource use

The main categories of health system resource use include intervention resources and healthcare utilization. Intervention resources include active iron agents (iron syrups or MNP sachets) and programme resources (start-up and implementation) required to deliver iron to children (38). Healthcare utilization comprises resource use related to unplanned outpatient visits/hospitalizations and treatment of acute watery diarrhoea (AWD). Only unplanned visits were used because we assume that any differential number of visits between those who received iron interventions and children that did not may be related to the intervention. Therefore, routine visits like vaccination appointments were excluded.

2.5.3. Measuring resource use

Quantities of intervention resources were estimated using amounts of MNPs or iron syrup required by a child over the intervention period of the trial. Each child randomized to MNPs fortification needs a total of 90 sachets and 195mL of iron

syrups (15mL every week). (39). In Bangladesh, iron syrups are available in 200mL bottles, therefore one such bottle would suffice. Resource use for programme delivery were obtained from literature due to difficulties in disentangling trial protocol-driven costs.

TABLE 2. UNIT COSTS

Component	Unit	Cost per unit ($)	Notes and sources
Intervention			
Iron syrups	bottle	$ 0.63	15ml per child per week (total 200ml) Unit costs from ACME Laboratories Ltd available from local sources (MedEx)*
Micronutrient powders	sachet	$ 1.60	1 sachet per child per day (total 90 sachets) Unit costs from BRISC study as procured from Renata Ltd
Programme delivery†	child	5.33 $	$4.5 yearly cost per child estimates from the HFTAG based on pilot programmes
Treatment of infectious morbidity			
Hospital visits	visit	1.79 $	Mean consultation cost per visit to health centre (WHO-CHOICE)
Hospital stays	bed day	5.34 $	Mean bed-days cost per stay in primary hospital (WHO-CHOICE)
Treatment of diarrhoea with “some dehydration”	case	0.09 $	Cost for treatment using WHO pocketbook
Treatment of diarrhoea with “severe dehydration”	case	1.74 $	Cost for treatment using WHO pocketbook

HFTAG – Home-Fortification Technical Advisory Group; CHOICE – Choosing Interventions that are Cost Effective; BRISC – Benefits and Risks of Iron Supplementation in Children
* Sources include personal communication on Ferroglobin prescribing information (40), confirmed by MedEx, an online database of pharmaceutical prices (41), and ranges of unit cost of iron syrups in Directorate General of Drug Administration [Bangladesh] Allopathic Drug Database (42).
† includes start-up costs and implementation costs. Components of implementation costs include personnel training and time, supplies, media, transport, equipment, maintenance, utilities.

Quantities of medications used in treating dehydration due to diarrhoea were estimated using WHO (43) and ICCDR,B guidelines (44). Briefly, children having diarrhoea with “some dehydration” are managed with oral rehydration therapy (ORT) with zinc (2 packets or oral salts and 1 blister of zinc tablets) in

an outpatient setting. Those who have diarrhoea with “severe dehydration” are admitted in a hospital and given intravenous rehydration followed by ORT with zinc as described above. Outpatient visits for children with episodes of diarrhoea with “some dehydration” were measured as number of consultations. Inpatient stays (hospitalizations) by children having diarrhoea with “severe dehydration” were measured as using number of bed days. The number of consultations and hospital visits were obtained from BRISC trial data.

2.5.4. Valuing costs

Costs were estimated by multiplying resource quantities with unit costs in Table 2. These unit costs were mainly taken from the BRISC study and local sources. Hospital bed day and outpatient visit unit costs were obtained from WHO-CHOICE database (45). Estimates of programme delivery costs were obtained from the Home-Fortification Technical Advisory Group which were based on MNP pilot programmes (29, 46). Costs related to the trial were excluded. All costs were gathered in original currency and converted to 2020 US dollars. Inputs reported in other currencies were converted to Bangladeshi Taka using World Bank reported exchange rates (47), adjusted to 2020 value using gross domestic product (GDP) deflators reported by World Bank (48), and converted to US dollars using period average exchange rates in 2020 (47). Costs were not discounted due to the one-year time horizon during which the trial follow-up occurred.

2.6. Statistical and cost-effectiveness analyses

Means of costs and DALYs were estimated for Iron supplementation, MNP fortification and doing nothing. ICERs were calculated for supplementation vs

doing nothing and for fortification vs doing nothing. The ICER for supplementation vs fortification was not calculated because neither of these is the standard of care. Cost-effectiveness was evaluated by dividing the difference in costs of different options by their differential effectiveness. For instance, in comparing fortification (MNP) vs doing nothing (DN), we have

$$ICER = \frac{Costs_{MNP} - Costs_{DN}}{-(DALY_{MNP} - DALY_{DN})}.$$

A negative sign is used in the denominator because we want to estimate averted DALYs. An intervention (fortification or supplementation) was defined as more cost-effective than doing nothing if it is (i) dominant – less costly and at least as effective; (ii) more costly and more effective and a decision maker is willing to pay the additional cost to avert a DALY (iii) less costly and less effective and a decision maker is willing to accept additional DALYs to save costs.

For the base case analysis, missing haemoglobin data were filled using multiple imputation by chained equations (MICE), stratified by treatment group, with separate model at each study visit (49). 40 imputations were performed – this number was at least equal to the percentage of missing data in the available cases as recommended by White *et al* (50). More details and justification for the imputation process are provided in Appendix A.1.3. After multiple imputation, passive imputation was performed to fill missing values of functions of imputed variable haemoglobin (that is, to convert haemoglobin values to anaemia categories, and then to DALYs using disability weights). The overall mean difference in DALYs between treatments was estimated using Rubin's rules (51), as the average of estimates from each of the imputed data. Mean

costs and DALYs were reported for a cohort of 1,000 children to facilitate interpretation of results.

Bootstrapping is a non-parametric method which uses large number of resamples to construct an empirical distribution for a statistic such as ICER (52). Using this approach, 2,000 random samples of the same size as our cost and DALY data are drawn with replacement. Since DALYs were a function of imputed haemoglobin data, these resamples were taken from each of the 40 multiply imputed datasets and a mean calculated for each set of 40 imputations (53, 54). The bootstrapped data was used construct a 95% confidence interval. The bootstrapped differences in mean cost between supplementation or fortification and doing nothing were plotted against the associated bootstrapped differences in mean DALYs on an incremental cost-effectiveness plane. In this plane, doing nothing was anchored at the origin.

2.6.1 Uncertainty analyses

A Cost Effectiveness Acceptability Curve (CEAC) was constructed to compare all three strategies and to assess decision uncertainty. For each bootstrap resample, the net monetary benefit (NMB) was calculated using the formula $NMB = (-DALY \times WTP) - Cost$. Within each replicate and maximum willingness to pay (WTP), the strategy with the highest NMB was selected. Over all replications, the probability that a strategy has the highest NMB is the proportion of bootstrap replicates that it yields the highest NMB. For example, the probability that iron supplementation is optimal at a particular WTP is the fraction that $NMB_{iron} > NMB_{DN}$ and $NMB_{iron} > NMB_{MNP}$. The CEAC was constructed by plotting the probability of cost-effectiveness against ranges of maximum WTP per DALY averted. Two WTP thresholds were used as

reference in interpreting the CEAC. These were $200 (about average of estimated health opportunity costs in Bangladesh) (55, 56) and $985 (0.5 times GDP per capita of Bangladesh in 2020) (57). Half GDP per capita has been suggested as health opportunity costs in LMICs (58). Further justification of the choice of these thresholds are provided in the Discussion.

2.6.2. Sensitivity analyses

A two-way sensitivity analysis explored the impact of simultaneously varying costs of active iron agents (iron syrups or MNPs) and costs of programme delivery on the probability of cost-effectiveness. These two parameters were chosen because there were very different between the groups, and they are potentially modifiable when planning for an iron intervention programme. Cost of healthcare utilization was not considered for sensitivity analysis because the recourse use in the three treatment groups were similar. To implement the sensitivity analysis, one of the imputation datasets were extracted using the Stata command `mi extract #.` Then, for each small unit change in costs of active iron agents and programme delivery, the probability that the intervention will be cost-effective at a given WTP thresholds (defined as $NMB > 0$ where $NMB = \lambda \times \Delta DALYs - \Delta Costs$) was calculated. Separate sensitivity analyses were conducted separately using two thresholds ($200 and $985) on two comparisons (fortification vs doing nothing and supplementation vs doing nothing).

All analyses were performed using Stata version 16.1 SE (59).

3. RESULTS

3.1. Participant Characteristics

Table 3 shows the baseline characteristics of children by treatment group. Among children with complete haemoglobin data at all three study visits, baseline characteristics appeared similar across the treatment groups. There were only slight differences in the proportion of children of female sex (placebo – 52.7%, MNPs – 48.8%, iron syrups – 54.1%) and anaemic at baseline (placebo – 44.1%, MNPs – 40.7%, iron syrups – 46.3%). Proportion of children who consumed up to 70% of their assigned intervention was higher in the placebo group (66.0%), compared to MNP group (61.0%) and iron syrup (60.1%). Since the placebo group did not receive active iron, no adjustment was considered necessary.

There were notable differences in baseline characteristics when comparing those with complete data and children with missing data for the variables female sex in supplementation group, union in all groups, and baseline anaemia status in MNP fortification group. Children with complete haemoglobin measurements were more likely to adhere to the intervention and consume at least 70% of their assigned active iron agent compared to those with incomplete data (82.2% vs 61.0% in MNP group and 82.2% vs 60.1% in iron supplementation group). These baseline characteristics and adherence were included in the imputation model for missing data.

TABLE 3. CHARACTERISTICS OF PARTICIPANTS BY AVAILABILITY OF HAEMOGLOBIN DATA

Variable	Placebo		Fortification with MNPs		Supplementation with iron syrups	
	Missing (N=609)	Complete (N=491)	Missing (N=593)	Complete (N=506)	Missing (N=589)	Complete (N=512)
Female sex	291 (47.8%)	259 (52.7%)	301 (50.8%)	247 (48.8%)	273 (46.3%)	277 (54.1%)
Wealth index	-0.0 (2.4)	-0.1 (2.5)	0.1 (2.4)	-0.1 (2.4)	0.1 (2.4)	-0.2 (2.5)
Family care indicator*	13.6 (7.2)	13.7 (6.9)	13.3 (7.2)	13.3 (7.1)	13.2 (6.9)	13.3 (7.3)
Maternal education						
No education	29 (4.8%)	20 (4.1%)	27 (4.6%)	16 (3.2%)	21 (3.6%)	32 (6.3%)
1-8 years	306 (50.2%)	261 (53.2%)	316 (53.3%)	287 (56.7%)	324 (55.0%)	267 (52.1%)
9-12 years	254 (41.7%)	193 (39.3%)	227 (38.3%)	193 (38.1%)	223 (37.9%)	198 (38.7%)
>12 years	20 (3.3%)	17 (3.5%)	23 (3.9%)	10 (2.0%)	21 (3.6%)	15 (2.9%)
Union						
Bhulta	174 (28.6%)	185 (37.7%)	179 (30.2%)	181 (35.8%)	190 (32.3%)	170 (33.2%)
Golakandail	244 (40.1%)	143 (29.1%)	234 (39.5%)	153 (30.2%)	240 (40.7%)	150 (29.3%)
Rupganj	191 (31.4%)	163 (33.2%)	180 (30.4%)	172 (34.0%)	159 (27.0%)	192 (37.5%)
Baseline anaemia†	254/576 (44.1%)	219/491 (44.6%)	224/551 (40.7%)	239/506 (47.2%)	260/561 (46.3%)	236/512 (46.1%)
Baseline iron deficiency‡	152/548 (27.7%)	120/482 (24.9%)	144/531 (27.1%)	130/494 (26.3%)	167/536 (31.2%)	140/498 (28.1%)
Iron deficiency anaemia§	104/548 (19.0%)	84/482 (17.4%)	92/531 (17.3%)	90/494 (18.2%)	122/536 (22.8%)	103/498 (20.7%)
70% Adherence¶	402 (66.0%)	410 (83.5%)	362 (61.0%)	416 (82.2%)	354 (60.1%)	421 (82.2%)

Notes: Data are presented as mean (SD) for continuous measures, and n (%) or n/total (%) for categorical measures.

* Scores on family care indicator total score range from 0 to 42, with higher scores indicating more activities

† Anaemia was defined as defined as a haemoglobin level of <11 g per decilitre)

‡ Iron deficiency was defined as a ferritin level of <12 μg per litre or <30 μg per litre if the C-reactive protein level was >5 mg per litre),

§ Iron deficiency anaemia was defined as concurrent anaemia and iron deficiency

¶ Proportion of children that consumed at least 70% of their assigned active iron agents or placebo

3.2. Health Outcomes

The main results of the clinical trial demonstrated that supplementation with iron or MNPs reduced prevalence of anaemia compared with placebo (31). The prevalence of anaemia was lowest in the iron group (28.9%) as compared to the MNP (34.1%) and placebo (40.8%) (prevalence ratio comparing iron vs. placebo, 0.71 [95% CI, 0.61 – 0.82]; MNPs vs. placebo, 0.83 [95% CI, 0.72 – 0.95]). In this study, haemoglobin levels were converted to anaemia severity levels and used to estimate DALYs using disability weights and time spent in the anaemic state. This generated a mean DALY of 0.0089 (95% CI, 0.0087 – 0.0091) per child in the placebo group, which was greater than that in a child receiving MNPs (0.0049, 95% CI, 0.0047 – 0.0050) or iron syrups (0.0037, 95% CI, 0.0036 – 0.0038).

3.3. Resource use and costs

Table 4 presents a summary of the key resource use of children during the 12-month period of the trial. Overall, the number of unplanned visits to outpatient departments due to diarrhoea with “some dehydration” were similar in the three groups (placebo – 167 visits; MNP – 170 visits; iron – 163 visits). The number of children who were taken to the hospital for cases of diarrhoea with “severe dehydration” were also similar. Those in MNP group spent slightly higher number of nights in the hospital (51 nights) compared to those receiving placebo (41 nights) or iron syrups (43 nights). However, this may be due to chance considering the low number of hospital visits in our data.

TABLE 4. MEAN QUANTITIES OF RESOURCE USE OVER ONE YEAR FOR IRON INTERVENTIONS COMPARED TO PLACEBO

Component	Placebo (N=1100)		Fortification with MNPs (N=1099)		Supplement with iron syrup (N=1011)	
	Mean (SD)	No. of children	Mean (SD)	No. of children	Mean (SD)	No. of children
Intervention-related						
Units of iron or MNP intervention	NA	1100	90 (0.00)	1099	1 (0.00)	1011
Programme delivery resources	NA	1100	1 (0.00)	1099	1 (0.00)	1011
Healthcare visits						
Cases of diarrhoea with "some dehydration" *	0.152 (0.62)	167	0.154 (0.60)	170	0.148 (0.54)	163
Number of outpatient hospital visits	0.151 (0.62)	167	0.154 (0.60)	170	0.148 (0.54)	163
Cases of diarrhoea with "severe dehydration" *	0.027 (0.17)	30	0.029 (0.18)	32	0.024 (0.16)	26
Number of inpatient hospital stays	0.037 (0.27)	41	0.046 (0.32)	51	0.039 (0.29)	43

MNP – micronutrient powders; SD – standard deviation; NA – not applicable

* Diarrhoea cases that did not result in hospitalization were classified as diarrhoea with "some dehydration" while those requiring overnight hospital stay were deemed classed as diarrhoea with "severe dehydration"

Table 5 details the estimated costs for the three strategies – doing nothing (placebo), fortification (with iron-containing MNPs), and supplementation (using iron syrups). The mean healthcare cost (SD) per child was $0.6 (2.3) for doing nothing, $8.1 (2.5) for supplementation, and $7.0 (2.2) for fortification. The programme delivery costs for fortification and supplementation intervention programmes were assumed to be the same ($5.8 per child). Accordingly, the difference in costs between fortification and supplementation is mostly driven by the cost of the active iron agents ($1.6 for MNPs and $0.6 for iron syrups).

TABLE 5. COSTS OVER ONE YEAR FOR IRON INTERVENTIONS COMPARED TO DOING NOTHING

	Doing nothing Mean (SD)	**Fortification with MNPs** Mean (SD)	**Supplement with syrups** Mean (SD)	**MNP vs doing nothing***	**Iron vs doing nothing***
Intervention					
Cost of active iron agents (syrups or MNPs)	0.00 (0.00)	1.60 (0.00)	0.63 (0.00)	1.60 (1.60 – 1.60)	0.63 (0.63 – 0.63)
Cost of programme delivery	0.00 (0.00)	5.80 (0.00)	5.80 (0.00)	5.80 (5.80 – 5.80)	5.80 (5.80 – 5.80)
Healthcare use					
Cost of outpatient visits	0.29 (1.18)	0.29 (1.14)	0.28 (1.03)	0.00 (-0.09 – 0.10)	-0.01 (-0.10 – 0.08)
Cost of non-severe diarrhoea treatment*	0.032 (0.12)	0.033 (0.12)	0.033 (1.11)	0.00 (-0.01 – 0.01)	0.00 (-0.01 – 0.01)
Cost of inpatient hospital stays	0.21 (1.55)	0.26 (1.81)	0.22 (1.66)	0.05 (-0.09 – 0.19)	0.01 (-0.12 – 0.14)
Cost of severe diarrhoea treatment	0.056 (0.34)	0.060 (0.38)	0.048 (0.32)	0.01 (-0.03 – 0.03)	0.01 (-0.04 – 0.02)
Total costs	0.59 (2.28)	8.06 (2.53)	7.02 (2.22)	7.47 (7.27 – 7.67)	6.43 (6.24 – 6.61)

MNP – fortification with iron-containing micronutrient powders; Iron – supplementation with iron syrup; SD – standard deviation; CI – confidence interval

* Comparison from two-sample t-test with equal variances with 95% confidence interval in parentheses

3.4. Cost-effectiveness analysis

As shown in Table 6, fortification with iron-containing MNPs was estimated to cost, on average, $7,355 (95% CI 7,301–7,403) higher per 1,000 children compared to doing nothing. MNPs were estimated to avert 4.0 (3.7–4.3) DALYs per 1,000 children. This yields an incremental cost-effectiveness ratio (ICER) of $1,852 (95% CI 1,728–1982) per DALY averted for fortification strategy compared to doing nothing. Supplementation with iron syrups was estimated to cost, on average, $6,350 (95% CI 6,299–6,397) higher per 1,000 children compared to doing nothing. Iron syrups were estimated to avert 5.2 (4.9–5.4)

DALYs per 1,000 children. This yields an incremental cost-effectiveness ratio (ICER) of $1,229 (95% CI 1,172–1,293) per DALY averted for supplementation strategy compared to doing nothing. Supplementation dominated fortification (that is, supplementation with cost less and averted more DALYs compared to fortification).

TABLE 6. COSTS AND COST-EFFECTIVENESS RESULTS FOR IRON INTERVENTION STRATEGIES

	Doing nothing Mean (SE)	**Fortification with MNPs** Mean (SE)	**Supplement with syrup** Mean (SE)	**MNP vs doing nothing***	**Iron vs doing nothing***
Imputed data	*N=1100*	*N=1099*	*N=1101*		
Costs ($)†	663 (626–702)	8,018 (7,981–8,054)	7,013 (6,980–7,046)	7,355 (7,301–7,403)	6,350 (6,299–6,397)
DALYs/DALYs averted†	8.9 (8.7–9.1)	4.9 (4.7–5.0)	3.7 (3.6–3.8)	4.0 (3.7–4.3)	5.2 (4.9–5.4)
ICER				1,852 (1,728–1,982)	1,229 (1,172–1,293)
Complete cases	*N=491*	*N=506*	*N=512*		
Costs ($)†	638 (426 - 849)	7,817 (7,673 – 7,960)	7,047 (6,848 - 7246)	7,179 (6,922 - 7436)	6,409 (6,120 – 6,699)
DALYs/DALYs averted†	10.5 (9.1 – 12.0)	5.9 (4.9 – 6.9)	4.1 (3.4 - 4.9)	4.6 (2.8 – 6.4)	6.4 (4.8 – 8.0)
ICER				1,558 (817 – 2,299)	998 (718 – 1,278)

* Bootstrapped standard errors (SE) and 95% confidence interval (CI) in parentheses
† Results presented per 1,000 children

When restricting the analysis to only participants with complete haemoglobin data at all study visits, ICER for fortification strategy compared with doing nothing ($1,560 [95% CI 1,136–1,983]) was slightly lower than that when missing haemoglobin data were replaced by imputed values. The same was observed when comparing supplementation strategy with doing nothing ($996

[95% CI 842–1,151]). This difference could be due to better adherence for complete cases as compared to cases with two haemoglobin measurements.

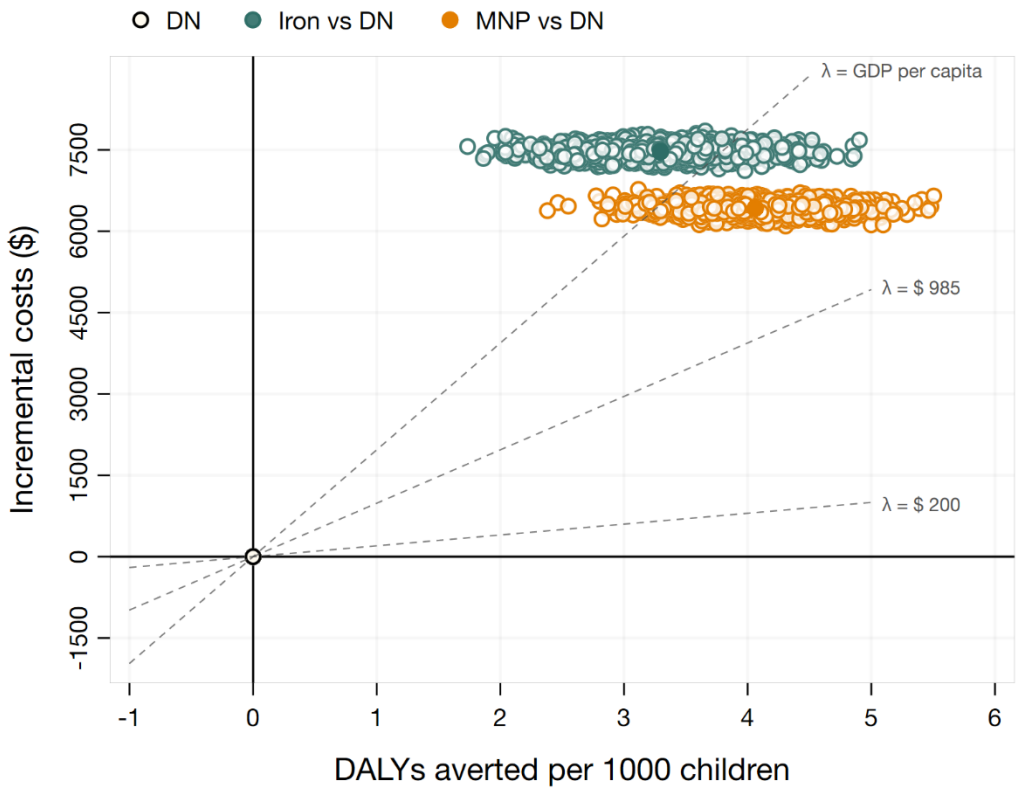

FIGURE 1. INCREMENTAL COST-EFFECTIVENESS PLANE SHOWING JOINT DISTRIBUTION OF INCREMENTAL COSTS AND DALYS FROM 2000 BOOTSTRAPPED REPLICATIONS.

Closed circles represent the point estimate of ICER estimate. Open circles are bootstrap replications. DN – doing nothing; GDP – gross domestic product.

Figure 1 provides the incremental cost-effectiveness plane showing a scatter plot of the incremental mean costs and DALYs from 2000 bootstrapped replications. Each replication represents the pooled mean from 40 imputations. The plane is split into four quadrants with doing nothing at the origin. The spread of the points in relation to the axes indicates the level of the uncertainty regarding incremental costs and DALYs. The incremental costs in are plotted closely together, indicating that the incremental costs were not very different

between bootstrap replications. This is because programme delivery costs were applied at a fixed rate for both interventions and healthcare use were similar between the groups.

For both fortification and supplementation strategies, all data points fell in the north-eastern quadrant (i.e., positive differences in mean costs while averting DALYs). This implies that whether these interventions are cost-effective will depend on the amount a decision maker is willing to pay to avert a DALY. At our predefined thresholds of $200 and $985 per DALY averted, it is unlikely that either fortification or supplementation would be cost-effective. If the threshold is increase to GDP per capita of Bangladesh ($1970), supplementation becomes very cost-effective. However, this threshold is very high and may be unrealistic for many LMICs (58). The plane for fortification vs supplementation is provided in Appendix A.2.1. The corresponding plane for analysis using complete cases is provided in Appendix A.2.2.

The cost-effectiveness plane assessed the iron interventions *individually* compared to doing nothing. To reflect uncertainty in the decision between more than two alternatives, we require the incremental cost and effect pairs of the strategies to be compared *jointly*. Figure 2 presents the cost-effectiveness acceptability curves (CEACs) for the two iron intervention strategies and doing nothing. When the decision maker is unwilling to pay anything to avert a DALY, the probability that iron interventions are optimal is 0%, in which case doing nothing is preferred. Regardless of the WTP threshold, it is almost certain that MNP fortification strategy is not a preferred strategy (doing nothing is preferred at $\lambda < 1560$ and supplementation is preferred at $\lambda > 1560$).

The CEAC in Figure 2 also contains cut-offs at two cost-effectiveness thresholds of $200 and 0.5 times GDP per capita ($985). At these thresholds, the probability that interventions using iron syrups is optimal is 0%. At a higher, more optimistic threshold of $1970 (GDP per capita of Bangladesh in 2020), the probability of the cost per DALY averted of iron supplementation strategy for children falling below this threshold ceiling value was over 95%.

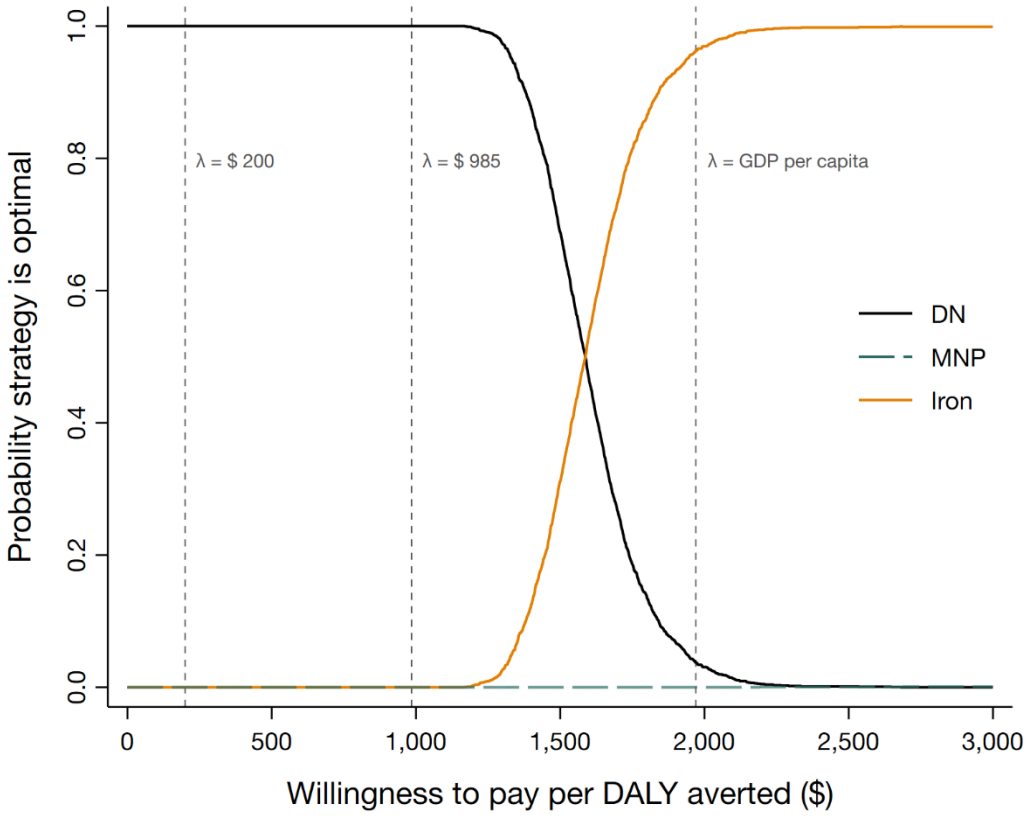

FIGURE 2. COST-EFFECTIVENESS ACCEPTABILITY CURVES

Cost-effectiveness acceptability curve showing the probability that fortification with iron-containing MNPs or supplementation with iron syrups is optimal, compared to doing nothing for a range of given WTP threshold per DALY averted

3.5. Sensitivity analyses

Sensitivity analysis explored the impact of variation in cost parameters (that is, cost of active iron agents and cost of programme delivery). Figure 3 shows a

series of contour plots illustrating the impact of changes in costs of active iron agents (iron syrups or MNP sachets) and programme delivery costs on the probability of cost-effectiveness (defined as $NMB > 0$) at a threshold (λ) of US$200 and US$985 (0.5 times the GDP per capita of Bangladesh in 2020) where $NMB = \lambda \times \Delta DALYs - \Delta Costs$.

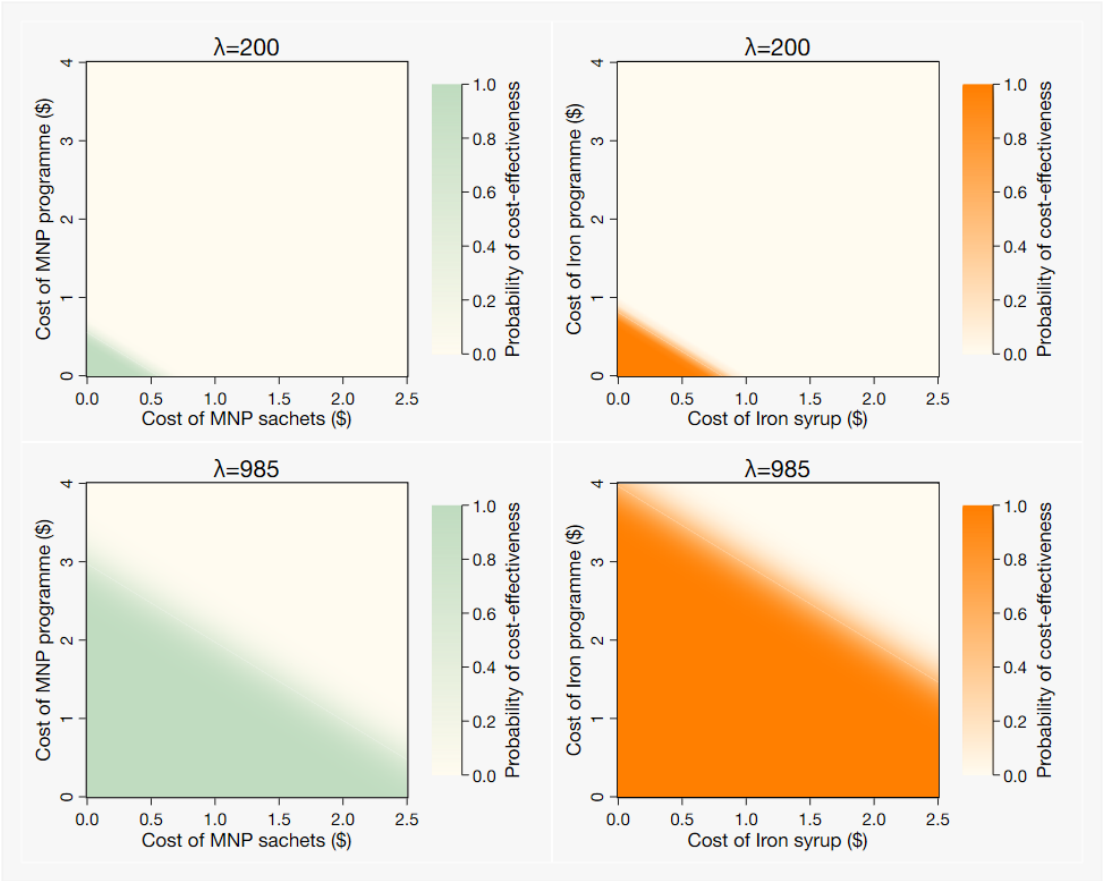

FIGURE 3. TWO-WAY SENSITIVITY ANALYSIS

Contour plots showing impact of changes in intervention and programme delivery costs on the probability of cost-effectiveness. λ – cost-effectiveness threshold.

At threshold ceiling of $200, the combination of mean value of MNP sachets ($1.6) and any cost of programme delivery does not yield any scenario that is cost-effective. Iron interventions will be cost-effective if the programme delivery costs were completely taken away ($0), leaving the health system to incur only the cost of providing iron syrups ($0.6 per child).

At threshold ceiling of 0.5 times GDP per capita ($985), fortification with MNPs will have at least 50% probability of cost-effective compared doing nothing if the programme delivery costs were $1.5 per child per year or below. At the same ceiling, supplementing with iron syrups will have at least 50% probability of cost-effective compared doing nothing if the programme delivery costs were as high as $3.5 per child per year or below. These cost scenarios are well below the mean cost of program delivery of $5.80 used in the base case analysis.

4. DISCUSSION

4.1. Summary of results

This analysis was carried out to determine whether iron supplementation or food fortification was preferred to doing nothing for population control of anaemia among children younger than 2 years in Bangladesh. Fortification with MNPs strategy cost more, when compared to supplementing with iron syrups strategy or to doing nothing. The health outcomes were comparable between iron and MNPs, with slightly higher DALYs averted by iron strategy. When comparing all three strategies at the same time, MNP were never optimal at any cost-effectiveness threshold $0 and $3000 per DALY averted.

The decision whether to adopt iron supplementation as a strategy for population control of anaemia depends on the value that the decision maker is willing to pay to avert a DALY. In Bangladesh and many LMICs, this threshold value is not explicitly stated but could be inferred from previous decisions and estimates of opportunity costs. This study used $200 and $985, the latter equivalent to half GDP per capita of Bangladesh in 2020 (55, 56) . A 2017 ranking of publicly-funded health interventions in LMICs (60) found more than half of the interventions had an ICER of $200 per DALY averted. Previous studies have estimated the threshold in Bangladesh to be either $150 per DALY averted (56) and $230 per QALY gained (55). Half GDP per capita was used because it has been suggested as health opportunity costs in LMICs (58). Additionally, 90% of interventions in LMICs for children cost less than $1000 per DALY averted (60) which is roughly half GDP per capita in Bangladesh in 2020 (57). Our results

indicate the ICER of $1,852 per DALY averted for fortification and $1,229 per DALY averted for supplementation was well above these WTP thresholds.

4.2. Generalizability, Strengths and Limitations

The results of this study are only applicable to non-malaria endemic settings and where the prevalence of severe anaemia is low. In non-endemic settings, estimates suggest that between 38-62% (average 50%) of anaemia is responsive to iron interventions (17). In malaria endemic settings, the proportion amenable to iron is only 6–32% (17), and malaria control strategies could have more impact (61, 62).

The WHO guidelines on iron supplementation are based on the prevalence of anaemia without considering its severity. Mild anaemia has a disability weight of 0.004, compared with 0.052 for moderate anaemia and 0.149 for severe anaemia (37). Therefore, in areas where the prevalence of mild anaemia is very high (or the prevalence of severe anaemia is very low), providing iron interventions may not avert many DALYs while increasing the public health costs. In the BRISC study, children with “marked” anaemia (defined as haemoglobin level below 80 grams per litre) were excluded. This exclusion criteria could underestimate the DALYs averted by both interventions if more severely anaemic children appear to benefit more from iron interventions. However, only 52/4400 (1.2%) of screened children fell in this category (31), so results are not expected to change enough to affect decision making.

All cost components relevant to estimating total costs of iron interventions were included. The BRISC trial had data on healthcare utilization, so it was possible to incorporate provider costs. However, this study used a limited health system

perspective for this study, so direct non-medical costs (such as transportation) borne by households and indirect costs due to lost productivity were not incorporated. This is not likely to impact on results given there was no meaningful difference in unplanned medical visits between the groups.

A moderate to large sample size and using appropriate methods to capture uncertainty are a strength of this study. The sample size was large enough to detect small differences in DALYs between the groups. Though there was a high proportion of missing data, these were handled using multiple imputation. The proportion of children with 70% adherence to assigned intervention was very different among children with haemoglobin data at all timepoints and children with any missing haemoglobin data at any timepoint (see Table 3). There was complete adherence data enabled this variable to be used in the imputation model, and for values to be filled with higher accuracy. By combining imputation with non-parametric bootstrapping, the analysis captured the uncertainty surrounding the ICER in the presence of missing data.

A limitation in this study is that results are only valid for a one-year time horizon. Extrapolating beyond this horizon could reduce the ICER because, at the end of the follow-up period of the trial, children who had received an iron intervention still had at least 20% reduction in anaemia prevalence (31). However, it is unclear how long these benefits will last so estimating years of life lived with disability (YLDs) would be problematic.

4.3. Comparison with previous studies

Seven studies examining the economic evaluation of population-level iron interventions have been published (23-29). The results in these studies differed

remarkably because of differences in intervention design, study population, choice of outcomes, and the conditions (malaria, diarrhoea, anaemia) used in estimating health outcomes. Most studies reported that iron interventions were of good value for money. The ICER of $1,852 for MNPs in this study was over 10 times higher than $159 per DALY averted reported in Ahmed *et al* (28). This could be because, in that study, costs were an underestimate (explained below) and MNPs were purchased by households. The ICER of $1,852 in this study is close to were similar to $1,557 per DALY averted reported in Pasricha *et al* (29).

Studies that used averted productivity losses from improved cognition as health outcome (25-27), reported that MNPs were of good value for money. However, the effects of MNPs on cognition were not confirmed in the BRISC trial (31) or in systematic reviews of MNPs in children (19, 20). When productivity losses averted were not considered, the costs per DALY averted in these studies ranged from $ 354 to $ 1,254 in Pakistan (26) and from $ 843 to $ 3,341 in India (27). By comparison, this study found that MNPs would cost $1,852 per DALY averted. In those studies, the programme delivery resource use was not included in estimation of costs. If programme costs were added, then these ICERs would be much higher.

It was not feasible to disentangling trial protocol-driven costs and get an accurate estimate of programme delivery costs. Therefore, this study used programme costs at $4·50 per child reported by Home Fortification Technical Advisory Group (46). This unit cost has been used in a previous study on cost-effectiveness of micronutrient powders (29). In comparison, the BRAC micronutrient sales intervention in Bangladesh had an estimated total program

cost of US $14 million over 5 years (28), equivalent to an annual cost of about $0.5 per child based on over 5 million children living in the communities reportedly reached. When caregivers in these communities were surveyed, about 50% of them had been visited by community health workers who were responsible for improving the distribution of MNPs (63). Therefore, the costs per child in the BRAC programme is likely an underestimate. A recent MNP pilot programme in Uganda estimated the cost of programme delivery to be $53 per child using a community distribution platform, and to exceed $60 when this intervention is scaled up (64).

This study obtained costs of iron interventions from local manufacturers and then explored the impact of varying cost parameters on overall cost-effectiveness. The price per 90 sachets of MNPs used was $1.60. In comparison, United Nations Children's Fund (UNICEF) supplied the same quantity of MNPs at $ 1.65 for 90 sachets per child between 2015 and 2020 (22). Therefore, the costs of MNPs used in the BRISC trial were like global prices. Nevertheless, we varied the cost of active iron agents (syrups or MNPs) and programme delivery in a two-way sensitivity analysis. Our results show that in very optimistic scenarios (for instance, a threshold of 0.5 times GDP per capita and cost of iron syrups not exceeding $0.6 per child), programme delivery costs will need to be as low as $3.5 per child per year in 2020 prices for supplementation to be cost effective. Comparing with costs reported in pilot programmes (46, 64), keeping programme delivery costs below $3.5 appears unrealistic.

Only the effects of iron interventions on anaemia were used in estimating health outcomes – effects on cognitive development and diarrhoea were excluded.

Previous economic analyses of the benefits of iron interventions using cognitive development in estimation of outcomes have derived the effect sizes from assumptions or observational studies (25-27). The BRISC trial was the first randomized controlled trial with long enough follow-up to show a real difference, if there was any, in cognitive development outcomes. This study excluded this measure because the BRISC trial did not find any meaningful difference in cognitive scores or reports of symptoms of diarrhea and other infections between the treatment groups (31). Moreover, systematic reviews of RCTs have not found convincing evidence that iron interventions improve cognitive development or that they increase the incidence or prevalence of diarrhoea (18-20).

4.4. Future research priorities

Epidemiological research is needed to determine the contribution of various risk factors (micronutrient deficiency, infections, and infestations) to the burden of anaemia. Knowing the specific contribution of a risk factor will inform the choice of intervention for control of anaemia. Where MNP is the chosen intervention, it could also inform the appropriate composition of micronutrients in the sachets that will maximize health benefits while keeping costs at a minimum. Comparing daily versus intermittent frequencies of intake of iron and micronutrient powders can inform appropriate dosing for higher DALYs averted. Also important is the evidence on long-term effects of iron interventions on functional outcomes (65). If these were to show that iron syrups or MNPs substantially improves cognitive and motor development at a later age, then they may be more cost-effective.

Cost-effectiveness research on comparing universal provision with targeted interventions (screening and treating only children with greater severity of anaemia) is required. This could substantially reduce costs in settings where the proportion of mild anaemia out of all anaemia is very low. There are a few considerations for this kind of research. First, what haematological indices to screen for. *Iron deficiency anaemia* could be a more sensitive measure to inform amenability of anaemia to an iron intervention than screening for *anaemia.* However, to measure iron indices, sufficient blood specimens need to be centrifuged, frozen, and transported to standard laboratories (65). In resource constrained settings, this is simply not feasible. Also, incorporating costs of screening will increase costs and reduce probability of cost-effectiveness. The levels of severity of anaemia to treat (moderate or severe) is another consideration – this will depend on prevalence in a particular setting. One final consideration is the type setting for screening – whether in a health facility or home visits in the community.

Implementation research is needed on strategies to reduce costs of iron interventions and especially programme delivery. If the contribution of deficiency in micronutrients contained in MNPs is known, low impact micronutrients could be removed from MNPs which could reduce costs. Appropriate design and implementation of programme activities could also reduce costs. One option would be to fully integrate iron interventions with existing programmes, so it shares existing resources and is therefore cheaper. This is the same strategy employed with vitamin A and immunization programmes. However, the vitamin A model may not work because iron interventions require more frequent dosing. Because of more frequent dosing,

effective behaviour-change strategies are required to sustain adherence. Home visits to deliver intervention material and improve adherence may not be scalable because they require human resources per child visited. Finally, costs could rise as coverage extends beyond willing caregivers in accessible areas to hard-to-reach populations or children residing in more remote areas. Therefore, estimating the appropriate population coverage that incurs the least average costs while reducing anaemia prevalence substantially would be required.

5. CONCLUSION

Public health interventions must be justified on grounds of both epidemiological evidence and value for money from economic evaluation. This is even more important in interventions for anaemia, because many children are affected, and any funding decision will have huge budget impact. Previous research has shown that universal provision of iron interventions reduces prevalence of anaemia in children under 2 years. However, with ICERs above $1000, this study suggests that universal supplementation is not cost-effective even in optimistic scenarios based on reasonable cost-effective thresholds. MNPs are more costly than iron syrups, and both have comparable effectiveness, therefore iron supplementation dominates MNP fortification.

The result of this study supports funding organizations and policy makers in Bangladesh and other LMICs that are considering whether iron interventions should be funded. It will help decide on funding decisions based on characteristics of the setting in which these interventions are to be delivered. It will also inform prioritization of interventions to yield the greatest health benefit. For instance, if a policy maker is not willing to pay between $1,000 and $2,000 per DALY averted from these interventions, then iron interventions should not be funded. Instead, other cost-effective interventions should receive the funding.

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APPENDIX

A.1. Supplementary information

A.1.1. Search Terms for Literature Review

CABDirect Global Health (1973 to April 25, 2021) searched on 27th April 2021

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((anaemia OR anemia) AND (iron OR ("micronutrient powder*")) AND (child* OR infant*) AND (("economic evaluation") OR ("cost effective*") OR DALY*)) AND ( ((sc:(( "HE" ) )) ))
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Ovid MEDLINE (1946 to April 23, 2021) searched on 27th April 2021

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((anaemia or anemia) and (iron or "micronutrient powder*") and (child* or infant*) and ("economic evaluation" or "cost effective*" or DALY*)).af.
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A.1.2. CHEERS[1] Checklist

Section/Item	Item No.	Recommendation	Reported on
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared	Title page
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Abstract
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	Pages 7 to 9 Page 12, para 3 Page 13, para 4
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Pages 15 to 16
Setting and location	5	State relevant aspects of the system(s) in which the decision(s)need(s) to be made.	Page 15
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 18
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 22, para 2
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 15, para 1 Page 22, para 1
Discount rate	9	Report the choice of discount rate(s) used for costs and	Page 22, para 1

[1] Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013; 16:231-50.

Section/Item	Item No.	Recommendation	Reported on
		outcomes and say why appropriate.	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 17, para 2
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	Pages 15 to 16
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Not applicable
Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Page 18, para 1
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Pages 19 to 20
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Not applicable
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 21
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Not applicable
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Not applicable

Section/Item	Item No.	Recommendation	Reported on
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty	Pages 22 to 24 Page 22, para 4 (missing data) Page 23, para 3 (uncertainty) Page 24, para 2 (sensitivity)
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Reported in methods (Table 2)
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios	Pages 29 to 30 (resource use and costs) Page 31 (Incremental cost-effectiveness ratios)
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective)	Pages 32 to 33
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Not applicable
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Not applicable
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 37 (summary) Page 38 (generalizability) Page 38 (limitations) Page 40 (current knowledge)

Section/Item	Item No.	Recommendation	Reported on
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Not applicable
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Not applicable

A.1.3. Disability Weights for estimating DALYs.

The disability weights used for this study are a weighted average of respective disability weights for the appropriate severity of anaemia weighted by the duration of time a child was in the particular (non) anaemic state. The time-weighted DW is given as.

$$DW = t_{int} * \frac{DW_0 + DW_3}{2} + t_{post} * \frac{DW_3 + DW_{12}}{2}$$

Where DW_0 refers to disability weight for anaemia status at randomization. DW_3 refers to disability weight for anaemia status at 3 months from randomization (end of intervention). DW_{12} refers to disability weight for anaemia status at 12 months from randomization (9 months of post-intervention follow-up). t_{int} refers to proportion of time spent in intervention phase. $t_{int} = \left(\frac{3\ months}{12\ months}\right) = 0.25$. t_{post} refers to proportion of time spent in intervention phase. $t_{post} = \left(\frac{9\ months}{12\ months}\right) = 0.75$.

For example, if a child was healthy (not anaemic) at baseline, had mild anaemia after 3 months and severe anaemia (need to change this to moderate anaemia as only one child had this outcome at the end of the 12 months trial follow up period) at 12 months, then $t_{int} = 0.25$; $t_{int} = 0.75$; DW_0 = 0.004; DW_3 = 0.149; DW_{12} = 0.000, and the disability weight is

$$DW_{none.mild.seve} = 0.25 * \frac{0.000 + 0.004}{2} + 0.75 * \frac{0.004 + 0.149}{2} = 0.058$$

A.1.4. Multiple Imputation method

For the base case analysis, missing haemoglobin data were calculated using multiple imputation by chained equations (MICE), stratified by treatment group, with separate model at each study visit.[2] Data were assumed to be missing at random (MAR). The number of imputed data sets was greater than the percentage of missing haemoglobin data within any treatment group.[3] The highest proportion of missing data was observed among placebo group at the post-intervention visit (39.8% missing values); therefore 40 imputations were performed. The imputation model included union, sex of the child, family care indicator (FCI) score, maternal education, and 70% adherence as covariates. Missing data in these covariates were mean imputed before including in the multiple imputation model. This was done by replacing missing values using the pooled mean of non-missing data from all treatment groups.[4]

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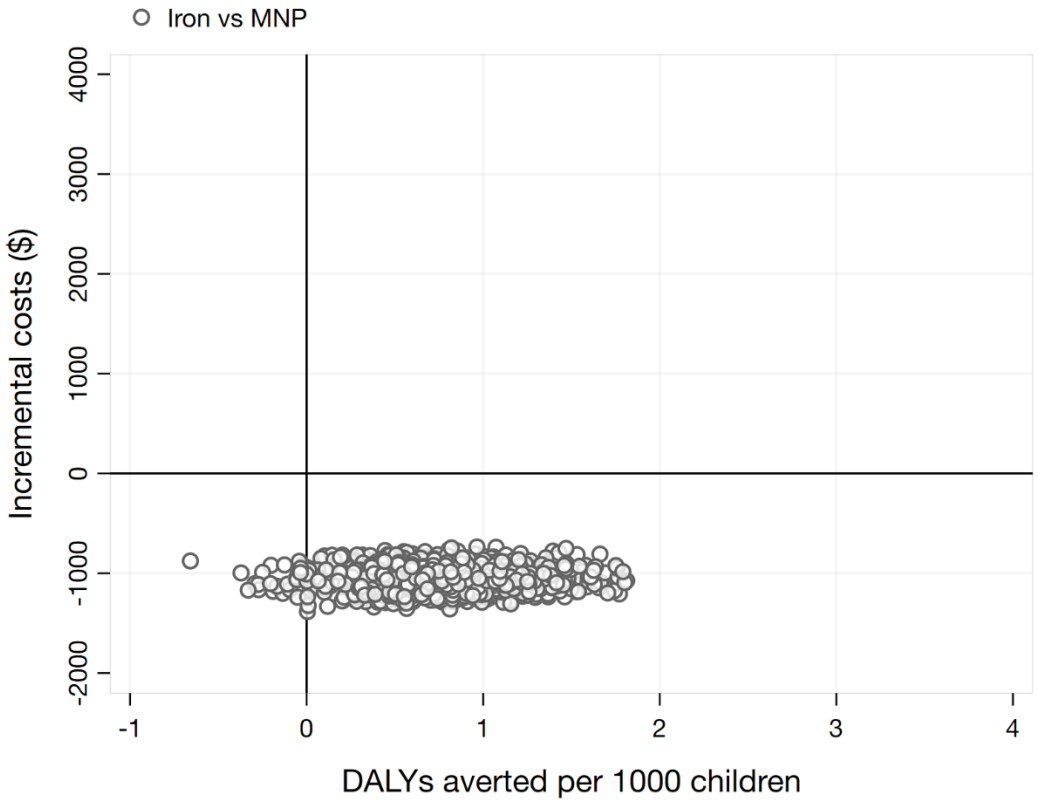
[2] Braat S, Larson L, Simpson J, Hasan MI, Hamadani JD, Hossain SJ, et al. The Benefits and Risks of Iron interventionS in Children (BRISC) trial: Statistical analysis plan. F1000Research; 2020.

[3] White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Statistics in Medicine. 2011;30(4):377-99.

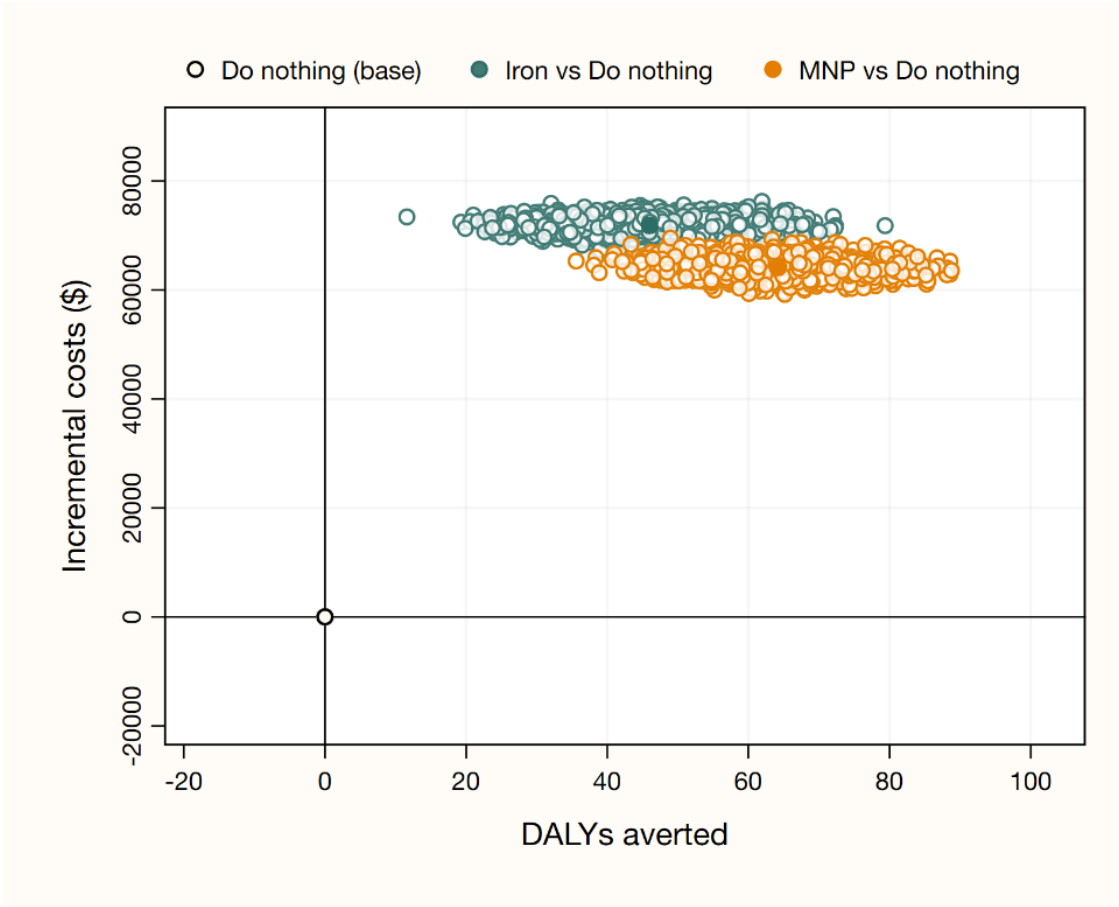
[4] Faria R, Gomes M, Epstein D, White IR. A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials. PharmacoEconomics. 2014;32(12):1157-70.

A.2. Supplementary results

A.2.1. Incremental cost-effectiveness plane for Supplementation vs Fortification



A.2.2. Incremental cost-effectiveness plane using complete cases



A.2.3. Cost-effectiveness acceptability curves using complete cases