Impact of Iron Fortification on Anaemia and Iron Deficiency among Pre-school Children Living in Rural Ghana

Samuel Kofi Tchum[1,2*], Fareed Arthur[2], Bright Adu[3], Samuel Asamoah Sakyi[4], Latifatu Alhassan Abubakar[1], Dorcas Atibilla[1], Seeba Amenga-Etego[1], Felix Boakye Oppong[1], Francis Dzabeng[1], Benjamin Amoani[5], Thomas Gyan[1] and Kwaku Poku-Asante[1]

[1]Department of Biochemistry and Biotechnology, College of Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; [2]Kintampo Health Research Centre, Kintampo-North, Ghana; [3]Department of Immunology, College of Health Sciences, Noguchi Memorial Institute for Medical Research, University of Ghana, Legon, Accra, Ghana; [4]Department of Molecular Medicine, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; [5]Department of Biomedical Sciences, School of Allied Health Sciences, University of Cape Coast, Cape Coast, Ghana.

***Corresponding Author:** Samuel Kofi Tchum, Kintampo Health Research Centre, Kintampo-North, Bono East, Ghana.

Email: kofi.tchum@kintampo-hrc.org. Phone: +233 244923774

Abstract

Background

Micronutrient interventions, principally vitamin A and zinc supplementation for children, and fortification of foods with iron and iodine, are considered the most cost-effective global development efforts. Multiple micronutrient powder is a mixture of at least iron, zinc and vitamin A used to prevent malnutrition in children and during health emergencies. Micronutrient deficiencies are a universal health burden among young children in developing countries. However, the use of this low cost but sustainable micronutrient powder as an innovative home-fortification approach to control a common nutritional disorder like iron deficiency anaemia among pre-school children living in malaria endemic sub-Saharan Africa is unclear. The aim of our study was to determine the effect of providing long-term continued prophylactic micronutrient powder with iron on the risk of iron deficiency and anaemia among pre-school children living in rural Ghana.

Methods

This population-based randomized-cluster trial was conducted in the Bono region of Ghana from 3rd April to 6th July 2010. 1958 children were recruited, and 967 randomly assigned to receive prophylactic micronutrient powder with iron and 991 assigned to receive placebo. The trial participants were children aged between 6 to 35 months, identified at home and able to eat semi-solid foods (with or without breast milk). Structured questionnaires were administered, their blood samples were also taken for biochemical analysis. They were randomly assigned to receive daily micronutrient powder without or with iron (12·5 mg) added to complementary meals immediately after enrollment for five months. Each participant also received anti-malaria treated bednet and chemotherapy. Weekly follow up visits were conducted at home or health facility where data on

malaria using rapid diagnostic test and hospital admissions were collected. The primary outcome was post supplementation of prophylactic micronutrient powder with iron to mitigate the effects of iron deficiency and anaemia.

Results

1958 children were recruited and 967 randomly assigned to receive prophylactic micronutrient powder with iron and 991 assigned to receive placebo. Loss to follow up was 7 % (143), with vital status at 35 months of age reported for 1904 (97.2 %). Anthropometry, anaemia, iron status, demographic characteristics and dietary intakes were similar between the groups at baseline. Baseline haemoglobin level was significantly higher compared to haemoglobin level at endline ($p < 0.0001$). Though, we recorded an increase in haemoglobin ($p = 0.0001$) and ferritin ($p = 0.0002$) levels in the iron group than in the placebo group at the end of the intervention. Soluble transferrin receptor levels were more saturated among children from the iron group compared to placebo group ($p = 0.012$). Anaemic status in the iron group improved compared to the non-iron group ($p = 0.03$).

Conclusion

The risk of childhood morbidity and mortality in rural Ghana is high, mainly due to iron deficiency anaemia. National nutritional policy coupled with the current WHO recommendations are required to support the provision of prophylactic micronutrient powder with iron in order to improve anaemic and iron status among pre-school children in rural Ghana.

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Introduction

The global occurrence of anaemia for pre-school children is 43 % of which about 42 % is attributable to iron deficiency [1]. Early childhood anaemia diminishes cognitive ability and causes developmental delays and disability [1, 2]. Zinc deficiency is alleged to be as prevalent as iron deficiency affecting about 293 million children below five and is accountable for 13 % of lower respiratory tract infections [3]. Multiple micronutrient powder (MNP) is a mixture of at least iron, zinc, and vitamin A used to prevent malnutrition in children and during health emergencies [4]. Micronutrient deficiencies are a universal health burden, particularly for young children in developing countries [5]. Micronutrient interventions, principally vitamin A and zinc supplementation for children, and fortification of foods with iron and iodine, are considered the most cost-effective global development efforts [6]. MNP with iron given to children improve motor and cognitive performance and mitigate severe anaemia prevalence [7, 8] but has no effect on malaria morbidity and mortality if anti-malarial interventions were available [9, 10].

Little data exist on whether given long-term continued prophylactic MNP with iron to children aged 6 to 35 months living in malaria endemic sub-Saharan African countries will reduce iron deficiency anaemia (IDA). Moreover, the risk of iron deficiency (ID) and anaemia among pre-school children living in these countries remain a major public health threat [11]. Data obtained from 1993 to 2005 indicated that iron deficiency was prevalence in more than 24 % of the global pre-school children population [1, 12]. In sub-Saharan Africa, the problem was worsened by the coexistence of preventable anaemia and malaria resulting in increased childhood morbidity and mortality [13, 14]. Previous studies involving motor and mental (social and cognitive) development among pre-school children have indicated the need for early prevention of childhood

anaemia through innovative but sustainable iron intervention programmes because such poor motor and cognitive skills have been associated with moderate anaemia (haemoglobin < 100 g / L) and might be irreversible [15-17].

In 2003, a randomized placebo-controlled trial conducted in Pemba, Zanzibar involving 32,000 pre-school Tanzanian children was stopped promptly on the advice from the trial's Data Safety Monitoring Board (DSMB) due to higher hospitalizations or mortality rate in the iron groups [10]. However, a further secondary subgroup analysis involving a recruited iron-replete children at baseline (BL) discovered a limitation on the risk of adverse events, which led to ethical difficulties and complicated study designs in malaria endemic areas [10]. The UNICEF and WHO joint statement was uncertain about MNP use, since the absorption characteristics differ considerably from iron syrups or tablets if given to children aged between 6 and 36 months [18]. In 2006, the joint statement was amended to specifically recommend home fortification of foods plus MNP with iron to children at risk of iron deficiency and anaemia [19]. Finally, based on substantive findings, the WHO in 2016 recommended that in heavily malaria transmission areas, pre-school children at risk of iron deficiency and anaemia should be provided with oral iron intervention if they have access to anti-malaria intervention strategies (insecticide-treated bednets, anti-malarial drug therapy and vector-control programmes [3]. Further studies are therefore needed to answer the question of whether continued long-term prophylactic iron fortification might improve intrinsic iron and anaemic status among pre-school children living in malaria endemic regions. Thus, the overall aim of this study was to determine the effect of providing long-term continued prophylactic MNP with iron on the risk of iron deficiency and anaemia among pre-school children living in rural Ghana.

Subjects and Methods

Study Area

Our trial was conducted in Wenchi Municipality and Tain District in the Bono Region of Ghana. In 2010, the combined population for the two contiguous areas was 198,125. A total of 11,215 pre-school-aged children, representing nearly 0.3 % of total children under five in Ghana were living in the two districts [20]. A total of 8,548 compounds in 99 smaller communities existed in Wenchi Municipality (n = 89,739) and Tain District (n = 108,386) [20]. Rains in the trial areas start from April to November with a mean rainfall per annum of 1250 mm plus an average temperature range from 18 – 38 °C [21]. This period is characterized by high malaria transmission. In Ghana, malaria is mostly caused by *P. falciparum* with an estimated 2·3 million cases in 2017, thus making it holoendemic [22]. In 2003, anaemia prevalence among pre-school-aged children was 76·1 % (95 % C.I. 73·9 -78·2 %) [23, 24].

Study Design

This study was a population-based randomized-cluster trial conducted in the Bono region of Ghana. The trial participants were young children, identified at home and able to eat semi-solid foods (with or without breast milk). For five months, all participants received daily micronutrient powder without or with iron (12·5 mg) added to complementary meals. However, children who had severe anaemia (haemoglobin < 70·0 g / L), severe malnutrition (weight-for-length z-score < -3·0), receipt of iron in supplements within the past 6 months or chronic disease were excluded. In order to maximize the opportunity for optimum anaemia and iron status assessment, the study occurred in the rainy season during high malaria transmission.

Ethical Issues and Trial Monitoring

The ethics committees of the Ghana Health Service (GHS), Food and Drugs Authority (FDA) of Ghana, Kintampo Health Research Centre (KHRC) and Hospital for Sick Children (SickKids) Canada approved our trial. Registered ClinicalTrials.gov number was NCT01001871. The trial was overseen by a Data and Safety Monitoring Board, which was constituted in October 2009 and held three meetings during the course of the trial. Members of the board included international and local health policy makers expertized in randomized controlled trials, nutrition, paediatrics, statistics and social sciences. The board's statistician summarized the compiled outcome data at the end of the recruitment phase and half-way via the intervention stage. The children's primary caregivers consented to participate in the study. For the interim analysis, if there were any serious adverse events (i.e. hospital admissions or deaths) in the iron group than the non-iron group, the agreement *a priori* was that the study would be terminated.

Recruitment of Subjects

Participants aged between 6 to 35 months were enrolled from early April 2010 through to July 2010 and randomly assigned (ratio 1:1) to receive either iron or no iron at the compound level with the aid of computer-generated model. A cluster represents a compound which comprise of one or more households living in the same residence with the resident families having at least one child eligible for inclusion into the trial. In order to prevent cross contamination between the groups via food sharing, a cluster randomization design was employed. Upon enrolment, each child was provided with an insecticide treated net (ITN) and the caregiver was educated on its appropriate usage. Sachets containing the powdered fortificant (MNP-Sprinkles® Mumbai, India) without or

with iron were similar except a subtle 'A' or 'B' labelled markings and double-blinded to the caregivers and study team.

The children from the iron group were provided a daily MNP dose containing elemental iron (12·5 mg) in microencapsulated ferrous fumarate, vitamin A (400 μg), ascorbic acid (30 mg) and zinc (5 mg) [25, 26]. Similar fortificant without iron (Placebo) was provided to the children in the non-iron group. Caregivers were all provided with MNP and instructed to mix the package's contents with a small bit of semi-solid meals on daily basis. This dosing MNP regimen continued for 5 months and then the participants were further monitored an extra month without the powdered fortificant. During the duration of the study, routine weekly household visits were conducted by field researchers (FRS) to assess participants' health (including axillary temperature) and collected data on MNP adherence, ITN use and morbidity. Caregivers were also advised to take their sick or febrile children to the nearest health facilities for assessment and prompt treatment between the routine visits.

Specimen and Data Collection

The participants' health was assessed at baseline (BL) and endline (EL) of MNP intervention including body temperature. At BL and EL, 500 μL blood sample was taken from the finger or heel into 0.5 mL ethylenediaminetetraacetic acid (EDTA) tube. The HemoCue Hb 201^{+} analyzer (HemoCue AB, Angelholm, Sweden) was used to measure the haemoglobin (Hb) levels and severely anaemics were referred immediately. Preliminary rapid diagnostic test (RDT) (Paracheck *Pf* ® Device, Orchid Biomedical Systems, Verna, Goa, India) for malaria was quickly done and those confirmed positive for the test were treated for malaria. After recovery, participants were enrolled if

all other inclusion criteria were met. At the laboratory, haematological, malaria microscopy, acute protein phase and iron biomarkers were tested on the remaining blood. If a child is febrile (i.e. axillary temperature > 37.5 ºC) or febrile 48 hours ago, 100 µL capillary blood sample was collected into 0.5 mL EDTA tube for full blood count, malaria rapid and blood smear test (for parasitaemia and speciation) during the study as described in the following procedures [26].

Specimen Processing and Analysis

Thick and thin blood films were prepared and the thin films fixed with methanol. Both smears were then geisma-stained. Each sample slide was read by two independent microscopists and if discrepancy between the two readers was over 50 %, a third microscopist was consulted [26]. The confirmed malaria cases (RDT assay) were treated with artemisinin-based combination therapy (ACT), a combination of Artesunate-Amodiaquine or Artemether-Lumefantrine administered as the current first-line national antimalarial chemotherapy treatment [27]. To verify if treatment was successful, the participants were monitored for 14 days after the first dose and on the 7^{th} and 14^{th} day, malaria status was assessed using both RDT and microscopy. The haematology auto-analyzer (Horiba ABX Micros 60-OT-CT-OS-CS, Montpellier, France) measured the full blood counts (FBC). The QuikRead 101 analyzer (Orion Diagnostica, Espoo, Finland) immunoturbidimetrically measured plasma C-reactive protein (CRP). Red blood cell zinc protoporphyrin (ZPP) was measured using a haematofluormeter (Model 206D, Aviv Biomedical Inc., Lakewood, NJ, USA). Indirect enzyme-linked immunosorbent assay (ELISA) measured plasma ferritin (Fn) (Spectro Ferritin S-22, Ramco Laboratories Inc. USA) and transferrin receptor (TfR) (TFC-94, Ramco Laboratories Inc. USA) levels as described in the following procedures [26].

Outcomes

Our primary outcomes were anaemia (Hb < 100 g / L) and iron deficiency (Fn < 30 µg / L, ZPP > 52 µmol / mol heme). Acknowledging that Fn and ZZP interpretation will be confounded by acute phase response, we excluded these indicators for those children who had an elevated CRP (> 8 mg / L) [28, 29]. Secondary outcomes included clinical malaria, expressed as any parasitaemia level including reported febrile or axillary temperature > 37·5 ºC within 48 hours [30]. Certain medical episodes such as malaria parasitaemia levels exceeding 5000 / µL, hospitalization as a result of diarrhoea (three or more watery or loose stools within 24 hours), other pneumonia symptoms (such as cough, tachypnea, lower chest wall indrawing and either pleural effusion or consolidation on a chest X-ray) and finally, cerebral malaria or meningitis based on clinical judgement were considered severe.

Statistical Analysis

Our hypothesis indicated that anaemia and iron deficiency prevalence rates would significantly improve among the children from the Fe group than their non-Fe counterparts. Using a 67 % reduction in anaemia prevalence as baseline rate [31], with power of 90 % and 5 % type I error, if all exposed participants had the same level of risk at start of the trial, then we can assumed a 30 % prevalence of anaemia among the placebo group at the end of MNP intervention. However, after accounting for a loss of 15 % to follow-up, a calculated sample size of 1940 participants (970 per group) was used. Visual Fox Pro version 9.0 data management programme was used to double-enter all clinical and epidemiological data for discrepancies, typographical errors and extreme observations. Errors from the database were regularly verified with field staff and discrepancies resolved prior to decoding the randomization and analyzing the data using STATA (Stata

Statistical Software: Release 11. College Station, TX: StataCorp LP, 2015). Descriptive statistics were used to summarize the study variables. The prevalence of anaemia, iron deficiency and iron anaemia at the end of the study was reported with their 95% confidence intervals. Using logistic regression, the risk of anaemia, iron deficiency and iron deficient anaemia were compared between the Fe and non-Fe group. Generalized estimating equation with robust standard errors was used to obtain population-averaged estimates and to account for the household level clustering. Parameter estimates were reported as odds ratio with their 95 % confidence intervals Separate models were considered for anaemia, iron deficiency and iron deficient anaemia. In all the models, we adjusted for child's age (≤ 12 months, 13 - 24 months and > 24 months) and sex. Also, we adjusted for baseline anaemia, baseline iron deficiency and baseline iron deficient anaemia in the model for anaemia, iron deficiency and iron deficient anaemia respectively. All analysis were carried out on an intention-to-treat (ITT) basis.

Results

A total of 2220 children aged 6 - 35 months from 22 communities were screened for eligibility from 3rd April to 6th July 2010 (Figure 1). Of these, 262 (11.8 %) were excluded according to pre-specified criteria. A total of 1958 children were randomly assigned to receive either prophylactic micronutrient powder (n = 967) or placebo (n = 991) (Figure 1). Characteristics of the children were similar between the groups (Table 1). By the end of the study (24 weeks), about 3.0 % of the participants were lost to follow-up (Fe = 67 versus non-Fe = 76) for 863·8 child years of total observation time. The lost to follow-up in both groups was as a result of moved-outs from the trial area. Adherence was similar between the groups (90·7 % for Fe versus 93·0 % for non-Fe children) and ITN use also did not differ (mean 91·9 %) (Table 1).

At baseline, the mean Hb concentration was similar in both the Fe and non-Fe group (10.3 g / L in both groups, p-value = 0.69) (Table 2). Out of the 1958 children enrolled, 1806 (92.2 %) were blood-sampled after the MNP intervention (Table 2). We also observed that, the mean Hb level in both groups was significantly higher at baseline compared to endline ($p < 0.0001$). However, the mean Hb level after the intervention was significantly lower in the non-Fe group compared to the Fe group (9.3 ± 1.5 g / L versus 9.7 ± 1·7 g / L respectively, p = 0·0001) (Table 2).

Baseline prevalence of anaemia, iron deficiency and iron deficiency anaemia were similar in the Fe and non-Fe group ($p > 0.05$) but the endline prevalence of these iron indicators were significantly improved in the Fe compared to the non-Fe children ($p < 0.05$). Moreover, in Fe and non-Fe groups, the endline prevalence rates of anaemia, iron deficiency and iron deficiency anaemia were significantly improved compared to the baseline prevalence rates of these iron indicators ($p < 0.05$) (Table 2). Similarly, among children who were iron deficient at baseline (n = 818), their mean ZPP concentration differences were greater in the non-Fe group (indicating greater risk of iron deficiency) compared to the Fe group (11·9 ± 162·0 for Fe versus 9·6 ± 139·3 μmol / mol of heme for non-Fe versus Fe children) ($p < 0·0001$). Paradoxically, almost all subjects in both groups who provided blood samples at endline were iron deficient (mean 99·1 %), thereby, rather grossly overestimating the prevalence of ID when compared with the conventional criteria (> 52 μmol / mol haem) (Table 2). Of the children who had blood-sampled at endline, 52.7 % were moderately anaemic (47.8 % for Fe versus 52.2 % for non-Fe children) and overall prevalence of severe anaemia (Hb < 70 g / L) was 6.0 % (4.2 % for Fe versus 7.7 % for non-Fe children). At endline, the prevalence of anaemia was 58.6 % (N = 1059, 95 % CI: 56.3 % - 60.9 %).

The prevalence of moderate and severe anaemia were 52.7 % (N = 951, 95 % CI: 50.3 % – 55.0 %) and 6.0 % (N = 108, 95 % CI: 5.0 % - 7.2 %) respectively (Table 2). Iron deficiency was prevalent in 24.5 % (N = 443, 95 % CI: 22.6 % - 26.6 %), while the prevalence of iron deficiency anaemia was 13.5 % (N = 243, 95 %: 12.0 % - 15.1 %) (Table 2). The prevalence of anaemia, iron deficiency and iron deficiency anaemia by Fe and non-Fe group was presented in Table 3. From the results of the risk adjusted logistic regression analysis, the odds of anaemia, iron deficiency and iron deficiency anaemia was significantly higher in the children from the non-Fe group compared to those in the Fe group (Table 3).

Discussion

The results of our study indicated that daily prophylactic micronutrient powder plus iron mixed with a small bit of semi-solid meals to children aged 6 - 35 month increased haemoglobin levels, improved anaemic and iron status in rural Ghana. These findings were consistent with studies that reported improvement in iron deficiency and anaemia after prophylactic micronutrient powder supplementation [7, 32, 33]. Our results were also similar to other MNP trials in Ghana [7, 26], Gambia [34], Turkey [35] and Kyrgyzstan [36] that also observed improved haemoglobin levels and iron status among young children on MNP supplements. The improved Hb levels and iron status may be due to iron response to the hormone erythropoietin, that accelerated the production of new erythrocytes via erythropoietic processes in the bone marrow [36]. In our study, we also observed that the transferrin receptor levels were more saturated after the intervention among the Fe-containing fortificant children than the placebo and this finding was consistent with other Fe-supplementation studies that evidenced the benefit of daily Fe fortificants among pre-school children [35, 37].

Iron deficiency and IDA prevalence rates improved at the end of the intervention among the children in the Fe group than those from the non-Fe group (Table 2). Moreover, the children who were iron-deficient (AOR = 1.68) and iron-deficient anaemics (AOR = 2.12) in the Fe group were more likely to recover from ID and IDA respectively compared to their counterparts in the non-Fe group after the intervention. These findings were consistent with other Fe-MNP trials [38, 39]. Even though, some other studies associated ID and IDA prevalence rates equivocally with the effect of MNP intervention [37, 40, 41]. Reasons for our observation, though poorly understood, maybe attributed to the fact that Fe is the only micronutrient, homeostatically regulated via absorption and the mechanism behind the iron-regulatory hormone, hepcidin is currently incomprehensible. However, some others investigators have suggested that in the presence of malaria and Fe fortificant, hepcidin may be upregulated to prompt dyserythropoiesis [42]. This then deprived the malaria pathogens of circulating Fe, a source of nutrient for their survival in the host [42]. The resultant increased Fe stored within ferritin in the hepatocytes via the transferrin receptors may lead to the replacement of Fe, a substrate for the enzyme ferrochelatase with zinc and may elevate ZPP levels [43]. The directionality of these findings suggested a risk-lowering effect of MNP [i.e. since the confidence interval favoured a lower risk ratio (RR)]. However, an exploratory sub-group analysis of baseline haemoglobin and ZPP concentrations indicated that children from the Fe group who were iron replete (ZPP $\leq$ 52 μmol / mol of heme) with moderate anaemia (Hb 70 - 100 g / L) had a 25 % lower risk of symptomatic malaria (RR 0·85, 95 % C.I. 0·53 - 1·36) and a 28 % lower risk of severe malaria (RR 0·82, 95 % C.I. 0·48 - 1·39) compared to non-Fe children who were iron replete and moderately anaemic at baseline (data not shown). Moreover, baseline moderate anaemia and iron deficiency were strongly associated with a 36 %

reduced risk of clinical (RR 0·73, 95 % C.I. 0·56 - 0·94) and a 39 % for severe malaria (RR 0·70, 95 % C.I 0·52 - 0·95) than being iron replete and anaemics at baseline. These findings were consistent with systematic reviews of 39 studies among 32,759 children on daily Fe supplement living in malaria hyper-endemic areas [3]. Paradoxically, whole blood ZPP levels were limited in discriminating between the participants with and without iron deficiency (Table 2). Even when combined with haemoglobin levels, no added diagnostic value was observed but rather grossly overestimated ID prevalence rate when compared to the conventional cut off points (> 52 μmol / mol haem). These findings from our study were consistent with other MNP studies that used ZPP as additional iron indicator [44-46], but contrary to other MNP intervention findings too [46, 47]. This may have been attributed to the differences in ZPP cut-offs used to define iron deficiency, which was lower in our study (> 52 μmol / mol of heme) compared to Zanzibar (> 80 μmol / mol of heme) [10]. Several ZPP cut-offs for defining iron deficiency have been proposed on the basis of the population group being studied and the specimen processing method (e.g. washed versus unwashed red blood cells). The blood samples in our study were washed before being analyzed. To our knowledge, this was not done in the Zanzibar trial and so a higher ZPP cut-off was observed [48]. Despite this adjustment, however, differences in iron status classification between trials may have affected the comparability of statistical outcomes. One main common finding between our study and that of Zanzibar was the significant protective effect of iron to mitigate the risk of iron deficiency and anaemia among the young children. In contrast, however, we did not find a significant risk lowering MNP effect associated with baseline iron deficiency alone without concurrent anaemia.

We did not increased the risk to hospital admission at 35 months between the intervention group and control arm. This differs from a similar trial in Zanzibar which reported an increase risk to malaria related admissions among study children who received iron [10]. Other suggestions may be that the lower risk to hospitalization in our study was due to anti-malaria ITNs and drug chemotherapy interventions that were provided to the study children. In our study, hospitalization rates were the same between the groups during or after the intervention (OR = 1·20, 95 % C.I. 0·91 - 1·58; $p > 0.05$). Moreover, the incidence of other clinical diagnoses (pneumonia, diarrhoea or meningitis) among the hospitalized children were also similar between groups with or without a concurrent malaria diagnosis ($p > 0.05$). In 2009, a systematic review of 14 studies reported that the provision of iron mitigated the risk of clinical malaria but the effect was reversed when routine malaria management and surveillance were absent [49]. However, none of the studies included iron fortification intervention trials. It was also unclear whether the data on malaria morbidities were obtained by parental report or whether the children were examined by trained fieldworkers. Our study used powdered iron fortificant (ferrous fumarate) with different absorption characteristics from the iron supplements (provided in the form of iron and folic acid tablets) used in the Zanzibar trial. Furthermore, the microencapsulation of the iron (ferrous fumarate) protected the iron in the food matrix from oxidation, which likely reduced and delayed peak plasma iron concentrations [50-52]. This may have reduced the level of freely accessible iron in circulation and mitigated the risk of malaria.

Our study was conducted in the rainy season when malaria transmission was high, resulting in very dense malaria parasitaemia in both groups (Table 1) though, the Fe intervention had no influence on the level of malaria parasitaemia [26]. Per-protocol analysis, (49 % of the Fe group,

n = 1023) similar findings to the intent to treat (ITT) analysis in terms of the overall incidence of clinical and severe malaria was observed. Contrary to the ITT analysis, however, the risk of clinical malaria on the impact of the fortificant powder with iron was not modified by baseline iron deficiency or anaemia status. Normally, as maternal passively-acquired immunity wanes in infants and young children, malaria becomes a major contributor to anaemia due to direct haemolysis of both parasitized and uninfected erythrocytes by the body's immune system and also temporary bone marrow malfunction [3, 53]. Other contributors of anaemia are consumption of semi-solid weaning diet low in Fe that mostly contains non-bioavailable iron [54]. The high demand for more dietary Fe during childhood development may be a limiting factor among infants and young children from low income or poor homes [54]. After the study, a total of five deaths were recorded, malaria and septicaemia accounted for three deaths (1 for Fe versus 2 for non-Fe children) and both malnutrition with severe dehydration and road traffic accident (both Fe children) claimed one life each according to reports from conducted medical and verbal autopsy. But these child mortalities were not related to MNP intervention in our study. Yet these findings were not influenced by the MNP intervention.

Conclusion

Our findings did not only addressed a research gap in knowledge but advocated an important nutritional policy that will mitigate childhood iron deficiency and anaemia if implemented in iron supplementation programme as a preventive strategy based on recommendations from WHO and UNICEF [3, 18]. However, for ethical reasons, the provision of ITNs and prompt / appropriate malaria treatment (whenever indicated) ensured that all the children benefited from the prevailing malaria control activities. Therefore, we are confident that our results and the current WHO

guidelines [3] recommending the use of MNP to treat and prevent iron deficiency and anaemia among preschool children should rekindled the interest and advocacy to implement MNP use as a national nutrition policy in malaria endemic country like Ghana.

Declarations

Ethical Approval and Consent to participate

Ethics approval for the original clinical trial was obtained from the Ghana Health Service (GHS) Ethical Review Committee, Food and Drugs Authority (FDA) of Ghana, Kintampo Health Research Centre (KHRC) Institutional Ethics Committee Institutional Ethics Committee and Hospital for Sick Children (SickKids) Research Ethics Board, Canada. The secondary analysis of trial data, as well as the primary analysis of immunogenetic data, were approved by the SickKids Research Ethics Board and KHRC Institutional Ethics Committee Institutional Ethics Committee. Informed consent was obtained from each participant's primary caregiver before screening and enrolment in the trial.

Consent for publication

Not applicable.

Availability of data and Materials

The datasets supporting the conclusions of this article are available upon request.

Competing Interest

The authors declare that they have no competing interests.

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Contributors

KT, FA, BA, SS, BA, TG and KP made primary contributions to overall trial development, design and manuscript writing. KT coordinated the trial under the supervision of FA and KP. KT, LA and DA conducted and managed the laboratory analyses. SA designed the database and data management system. FO and FD conducted the statistical analyses. All the authors reviewed and approved the final paper.

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Authors' Information

[1]Department of Biochemistry and Biotechnology, College of Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; [2]Kintampo Health Research Centre, Kintampo-North, Ghana; [3]Department of Immunology, College of Health Sciences, Noguchi Memorial Institute for Medical Research, University of Ghana, Legon, Accra, Ghana; [4]Department of Molecular Medicine, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; [5]Department of Biomedical Sciences, School of Allied Health Sciences, University of Cape Coast, Cape Coast, Ghana.

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