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Effect of Multiple Biofortified Food Crops-based Meals on Micronutrient Status and Immune Function in The First 1000 Days of Life in India: Study Protocol for a Randomized Controlled Feeding Trial v2.0 V.2

Saurabh Mehta[1,2], Bryan Gannon[1,2], Camille E. Jones[1], Laura S. Hackl[1], Shoba A. Udipi[3,4], Varsha Thakker[3,4], Aparna Thorat[3,4], Wesley Bonam[5], Jere D. Haas[1], Julia L Finkelstein[1,2]

[1]Division of Nutritional Sciences, Cornell University, Ithaca NY 14853;

[2]Institute for Nutritional Sciences, Global Health, and Technology, Cornell University, Ithaca NY 14853;

[3]Shreemati Nathibai Damodar Thackersey (SNDT) Women's University, Mumbai, India;

[4]Kasturba Health Society, Medical Research Centre, Mumbai, India;

[5]Arogyavaram Medical Centre, Madanapalle, Andhra Pradesh, India

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Mehta Research Group @ Cornell

Saurabh Mehta

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Effect of Multiple Biofortified Food Crops-based Meals on Micronutrient Status and Immune Function in The First 1000 Days of Life in India: Study Protocol for a Randomized Controlled Feeding Trial

Saurabh Mehta[1,2], MBBS ScD, Bryan M. Gannon[1,2], PhD, Camille E. Jones[1], MPH, Laura S. Hackl[1], PhD, Mag.pharm., Shoba A. Udipi[3,4], PhD, Varsha Thakker[3,4], BHSc, Aparna Thorat[3,4] Wesley Bonam[5], MBBS, Jere D. Haas[1], PhD, Julia L. Finkelstein[1,2], MPH, ScD

[1]Cornell University, Ithaca, NY, United States of America.[2]Institute for Nutritional Sciences, Global Health, and Technology (INSiGHT), Cornell University, Ithaca, NY, United States of America.[3]Shreemati Nathibai Damodar Thackersey (SNDT) Women's

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University, Mumbai, India.[4]Kasturba Health Society, Medical Research Centre, Mumbai, India.[5]Arogyavaram Medical Centre, Madanapalle, Andhra Pradesh, India.
*Correspondence should be addressed to smehta@cornell.edu. Division of Nutritional Sciences, Cornell University, 314 Savage Hall, Ithaca, NY 14850, Tel. 607-255-2640; Fax. 607-255-1033.

Key Points:

- Deficiencies of iron, zinc, and vitamin A remain major public health concerns particularly in low- and middle-income populations of people who largely consume limited, cereal-based diets.
- We aimto evaluate the potential of regular consumption of biofortified crops on growth, nutritional status, and immune function among children. Mothers receive the same intervention, and we are collecting data and biological specimens from them; however, only the analyses of child data and outcomes is currently funded.

Abbreviations used: CIP, International Potato Center; DSMB, Data and Safety Monitoring Board; ICARDA,International Center for Agricultural Research in the Dry Areas;ICRISAT,International Crops Research Institute for the Semi-Arid Tropics;LAZ, length-for-age Z-score;NFHS, National Family Health Survey; SNDT, Shreemati Nathibai Damodar Thackersey; SPIRIT, Standardized Protocol Items: Recommendations for Intervention Trials; WLZ, weight-for-length Z-score.

Disclosures: SM has an equity interest in VitaMe Technologies (DBA VitaScan), which is commercializing point-of-care assays for nutritional status informed by his research as a faculty member at Cornell University. CEJ is supported by the National Institutes of Health under award 5 T32 HD087137. The content of this protocol is solely the responsibility of the authors and does not necessarily represent the official views of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, or the National Institutes of Health. All other authors: no conflicts of interest.

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Abstract

Introduction. Deficiencies of iron, zinc, and vitamin A remain major public health concerns particularly in low- and middle-income countries that largely consume cereal-based diets that are limited in nutrients. Biofortification of staple crops with micronutrients has demonstrated efficacy in single-crop, single-micronutrient evaluations. A trial including biofortified pearl millet, wheat, and sweet potato with higher concentrations of iron, zinc, and vitamin A is planned in infants and young children and their mothers in India.
Methods and analysis. A two-arm parallel randomized controlled feeding trial will be conducted among mother-child pairs (target *N*= 200) in rural villages in Andhra Pradesh, India. Participants will be randomized as mother-child pairs to receive meals containing either biofortified or conventional crops. Meals will be centrally prepared and delivered to local feeding centers. Threemeals (breakfast, lunch and snack) will be provided daily, 6 days per week, for 9 months. Anthropometry and morbidity will be assessed monthly, and micronutrient status, immune function, and developmental assessments will be evaluated at baseline, mid-, and endpoint. Biological samples, including blood and stool, will be collected and stored for batch analyses.
Ethics and dissemination. Clearance has been obtained from the Health Ministry Screening Committee of the Indian Council of Medical Research. Ethical approval has been obtained from the Cornell University Institutional Review Board and the Arogyavaram Medical Centre Institutional Ethics Committee. Study results will be disseminated at research conferences and articles in peer-reviewed scientific journals.
Trial registration number. Clinical trial registration number NCT02648893. CTRI registration number CTRI/2019/04/018589.
Keywords: Biofortification, iron deficiency, maternal and child nutrition, staple crops, vitamin A deficiency, zinc deficiency

Introduction

The burden of malnutrition resulting from inadequate intakes of key micronutrients, particularly iron, zinc, and vitamin A, contributes to a substantial loss of health and resources globally.[1-3] Biofortification is a promising strategy to address inadequate micronutrient intakes by enhancing the nutrient content or bioavailability in commonly consumed food crops,[4] which has received considerable research interest[5] and international attention.[6] Numerous crops have been biofortified with various nutrients, such as iron, zinc, and provitamin A.

Previous studies have demonstrated efficacy of these crops in different populations with regards to biochemical and functional outcomes, but have thus far typically focused on single-crop, single-micronutrient interventions, including high-iron beans and pearl millet,[7,8] high-zinc maize,[9] high-provitamin A maize,[10] and high-iron rice.[11] To date, the impact of a regular consumption of meals prepared from multiple biofortified crops by mother-child pairs during the complementary feeding period has not been assessed.

A multiple biofortified food crops trial will be conducted in rural South India (Clinicaltrials.gov NCT02648893) with the objective to

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evaluate the effect of regular consumption of biofortified crops on growth, nutritional status, immune function and cognitive function among children in the complementary feeding period. Primary outcomes of child growth and indicators of malnutrition, including stunting, wasting, and biomarkers for micronutrient deficiency, as well as immune function will be compared between two intervention arms (biofortified vs. conventional meal provision). Recipes included in the treatmentwere previously tested for suitability and acceptability.[12]

Materials and Methods

Study setting

This study will be conducted in rural areas near Madanapalle, Andhra Pradesh. A central clinical facility and kitchen will be located at Arogyavaram Medical Centre. Feeding centers will be established close to participants' homes to minimize their travel time and burden.

Study design

A two-arm, parallel, randomized controlled feeding trial will be conducted among mother-child pairs. The intervention arms will consume recipes prepared from either biofortified or conventional sweet potato, wheat and pearl millet three times daily, 6 days/week, for nine months, excluding holidays, with monthly follow-up during the intervention period (**Figure 1**). A census will be conducted before the start of the trial to identify potential participants living near the proposed feeding centers. Screening and baseline visits will be conducted to determine participant eligibility, establish informed consent, and enroll participants into the trial.

Sample size considerations

Based on our earlier studies, if the mean serum ferritin concentration is 15 ng/mL in the control group with a standard deviation of 15 ng/mL,[8]we will be able to detect a mean difference of 6.9 ng/mL in the intervention group with 80% power, using a two-sided test with 75 subjects in each arm. Assuming equal allocation and 25% attrition, we will target a sample size of N=200 pairs. This is within biological plausibility and aligns with the effect size observed in our earlier trial with pearl millet alone.[8]We expect to achieve adequate participant enrollment and retention by conducting sustained recruitment activities, including door-to-door visits, community sensitization meetings, and visits with community stakeholders.

Inclusion and exclusion criteria

Inclusion criteria:

Signed or thumb-printed, informed consent of the biological mother of children 6-24 months old, regardless of sex. Participating pairs must be willing to attend the feeding center daily, have no plan to leave the study area > 4 weeks during the intervention period, and consent to standard-of-care deworming schedules for participating children.

Exclusion criteria for children:

Presence of any known food allergies, current diagnosis of malaria, dengue fever, or severe malnourishment, ever diagnosed with tuberculosis or HIV, presence of severe wasting [weight-for-length Z score (WLZ) < -3],[13]moderate anemia (hemoglobin < 9 g/dL).

Exclusion criteria for mothers:

Severe anemia according to WHO cutoffs (hemoglobin < 8 g/dL).

Randomization, allocation concealment, and blinding

A Cornell Statistical Consulting Unit (CSCU) statistician will generate a random allocation list using a random permuted block design for treatment assignment (coded as four colors) and random-midpoint sampling using a statistical software package (SAS v9.4). This list will only be known to the statistician and database developer until study completion, and neither will be present at the field site. To improve blinding, treatment arms will be coded as four colors (e.g. green, pink, yellow, blue), with two colors corresponding to one treatment arm and the remaining two to the other treatment arm. Colors will automatically be assigned to mother-child pairs upon randomization and will appear as a letter next to their personal study identification numbers. The color code will be made known only to a minimal set of personnel required to ensure optimal intervention delivery. Staff monitoring food preparation, delivering food and measuring intake to participants at feeding centers, and assessing outcome were blinded form the color code. Meals made with biofortified or conventional crops will be prepared in separate areas of a central kitchen, then packaged for transport in color-coded containers, which will be delivered to feeding centers and served by trained research personnel who are blinded to the color coding. Outcome assessors will be blinded regarding the treatment groups. Treatment arms will be coded for blinding during primary data analysis.

Intervention and comparator delivery

Selection of crops for this study was based on local consumption and/or production patterns as well as the availability of biofortified varieties containing higher concentrations of micronutrients compared to their conventional counterparts. The identified

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varieties included high-iron and zinc pearl millet, high-zinc wheat, and high-provitamin A sweet potato. Wheat and pearl millet planting and harvest will be coordinated by the International Crops Research Institute for the Semi-Arid Tropics (ICRISAT) and milled into whole grain flour. Wheat varieties include biofortified: BHU-6, and conventional: HD2967. Pearl millet varieties include biofortified: Dhanashakti, and conventional: DG9444. Sweet potato planting and harvest will be coordinated by the International Potato Center (CIP). Sweet potato varieties include biofortified: Kamalasundrai, and conventional: white local variety. Sweet potato will be washed, steamed until soft (20–30 minutes), peeled, pureed, and frozen at -18°C until use. Wheat and pearl millet will be stored in a commercial climate-controlled storage facility (approximately 50-55% humidity, 6–14°C).

Recipes were developed in collaboration with Shreemati Nathibai Damodar Thackersey(SNDT) Women's University in Mumbai in consultation with local study staff to ensure local acceptability. A 12-day rotating cyclic menu has been generated using identified culturally acceptable recipes to ensure adequate crop intakes. Experimental and control-group recipes differed only in the crop varieties used. Recipes, including biofortified and conventional varieties, were previously shown to be highly acceptable with no difference in child's intake or mother's hedonic scale ratings.[12]

Feeding centers will be staffed with trained research personnel to ensure appropriate delivery of intervention arms and recording of recipe intakes.Mother-child pairs will attend the feeding center daily for meals. Breakfast and lunch will be consumed at the feeding center; snacks may be consumed either at the feeding center or at participants' homes. Recipes consumed at feeding centers will be recorded by weighing administered food before and leftover food after consumption. Snacks consumed at participants' homes will be quantified via self-report the next day. Crop and food sampling will occur throughout the intervention period to verify expected micronutrient concentrations by study arm.

Participant follow-up and sample collection

Health check-ups, anthropometric measurements, and stool collection for all participants will be conducted monthly. Blood sampling from all participants will be conducted at baseline, mid- (one random serial sample between months 2–7), and endpoint (**Figure 1**). For a subset of participants, sample collection at these timepoints will also include mothers' breast milk and both mothers' and children's saliva. Socioeconomic and demographic information and vaccination history will be collected at base- and end-line. Monthly data collection will include a clinical exam, child's and mother's anthropometry, morbidity history, and an infant and young child feeding module. Baseline, mid- and endpoint data collection will additionally include dietary intake via food frequency questionnaires and 24-hour recalls, and childcognitive developmental assessment. Complete blood counts will be performed immediately after blood collection, and remaining blood and all other biological samples will be processed and stored at -80°C until batch analysis. Between follow-up appointments, a trained participant retention team will conduct regular community meetings at each feeding center and will initiate home visits with the families of participants who repeatedly miss attending the feeding center without prior notice or who have any questions about the study.

Study outcomes

Primary outcomes include physical growth, biomarkers of nutritional status and immune function, anddevelopment assessment from baseline through endpoint. Child's anthropometry (weight, length/height,mid-upper arm and head circumference, triceps and subscapular skinfolds) will be assessed monthly throughout the trial. Weight-for-age, weight-for-length, and length-for-age Z-scores will be calculated, as well as growth rates (kg/month and cm/month), controlling for age.[14]Nutritional biomarkers, including iron (hemoglobin, serum ferritin, and serum soluble transferrin receptor); zinc (plasma zinc); and vitamin A (serum retinol and retinol binding protein) will be adjusted for inflammation.[15,16]Immune function will be assessed by cytokine measurements and morbidity data collected throughout the trial, including changes and frequency of morbidities such as diarrhea, fever, and any other acute or chronic diseases throughout follow-up. Participants will be encouraged to visit the central clinic at any time for health-related reasons and visit information will be recorded. The Development Assessment Scale in Indian Infants (DASII) test will be performed to assess specific aspects of memory and attention.

Data collection, storage, and analysis

Field staff will be trained on data collection procedures and responsible conduct of research. The majority of data will be collected on iPads or laptops using a mobile electronic data capture system, ConnEDCt, on the iOS platform customized for this trial.[17]This platform ensures data quality by necessitating multiple data entry for anthropometric measurements, alerts for values entered which are outside defined thresholds, and password-protected, time-stamped electronic signatures for each submitted form. Data will be uploaded, stored, and accessed with use of a secure server to facilitate real-time feedback and error checking as well as to expedite data analysis and dissemination. Confidentiality of participants will be maintained; participants' names will be removed from data for analyses and identifying codes will be stored on password-protected computers. Biological specimens will be collected and processed by trained professionals and analyzed at certified laboratories in India. Intention-to-treat analysis will be used to determine the effect of a biofortified food basket on the described outcomes. Advanced analyses will use mixed models to account for covariates of interest (e.g. recipe intake, age, sex, feeding center). We will use restricted cubic splines to plot dose-response

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curves to detect any non-linearity associations or threshold effects. Non-parametric tests will be conducted as required in the case of non-normally distributed data. Statistical analysis will be done in SAS v9.4 (University Edition, SAS institute, Cary, NC).

Data and safety monitoring board and reporting of adverse events
A Data and Safety Monitoring Board (DSMB) will be established for this study and will include content experts who are not involved in the conduct of the trial and a statistician. The DSMB will monitor the study and periodically evaluate the progress and outcomes of the intervention.Endpoints considered to define safety and efficacy to establish unblinding and stopping guidelines, as per the DSMB, include: 1) diagnosis of development of severe acute malnutrition; 2) occurrence of all-cause death; 3) demonstration of efficacy by a significant beneficial effect on child's growth (height-for-age and weight-for-length Z-scores) or hemoglobin concentrations. All (serious) adverse events will be reported via (serious) adverse event forms. When a (serious) adverse event occurs, study personnel will undertake all necessary precautions to ensure safety and well-being of study participants.

Ethics and dissemination
This study is approved by Arogyavaram Medical Centre Institutional Ethics Committee (IR800009889), the Cornell Institutional Review Board for Human Participants (Protocol 1508005782), and the Indian Council of Medical Research (5/9/37/Indo/FRC/2017-Nut) in accordance with the Declaration of Helsinki. The nature of the study will be explained to potential participants, and all mothers will provide signed, written and video-recorded informed consent prior to any study procedures. Participation will be voluntary, and refusal to participate will not impact access to care for mothers or their children. Participants excluded for low hemoglobin, malnourishment, or other health reasons will be referred for appropriate medical care.

Study results will be disseminated at research conferences and in peer-reviewed journals. This protocol has been prepared in accordance with the Standardized Protocol Items: Recommendations for Intervention Trials (SPIRIT) statement.[18]This trial is registered at clinicaltrials.gov (NCT02648893) and the Clinical Trials Registry of India (CTRI; registration numberCTRI/2019/04/018589).

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Protocol Addendum
Summary
This document is an addendum to the protocol for the study 'Effect of Multiple Biofortified Food Crops-based Meals on Micronutrient Status and Immune Function in The First 1000 Days of Life in India' in response to the COVID-19 pandemic with the following changes to the study protocol:
1. Pausing of all study activities in accordance with institution and national guidelines
2. Ongoing remote participant follow-up and retention
3. Resumption of participant follow-up
4. Protocol modifications to minimize COVID-19 transmission risk

Pausing of study activities
Intervention delivery and outcome assessment were paused in March, 2020 in alignment with the Government of India nationwide lockdown in response to the COVID-19 pandemic. Subsequent lockdown phases and restrictions have followed, and national and institutional policies were followed to guide resumption of study activities.

Ongoing remote participant follow-up and retention
Study staff maintain remote contact with participants remaining in the trial using mobile devices following study protocols. Staff share information related to COVID-19 safety, government guidelines, safety information, and ongoing planning of study logistics.

Resumption of participant follow-up
Endline appointments for participants remaining in the study will resume following research safety guidelines from governments and institutional research ethics boards. No intervention delivery will be resumed. In order to complete endline assessments of study participants, we will complete the research questions through the following procedures and protocol modifications.

Protocol modifications to minimize COVID-19 transmission risk
Study activities will be resumed complyingwith government and institutional research ethics board guidelines and includingthe following modifications:

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Intervention and outcomes

- Study activities will be limited to conducting endpoint assessments of participants remaining in study, including questionnaires and biological sample collection. Intervention delivery will remain suspended while endpoint appointments are conducted.
- Study procedures will be conducted outside as much as possible to minimize time participants and staff spend indoors.
- Some originally planned outcome assessments (e.g., DASII, clinical exam if not indicated) will not be continued due to logistical considerations of ensuring proper sanitation and distancing.

Logistics

- Policies will be put in place to prevent staff and/or participant interactions if symptoms are present in themselves, household members, or community members(e.g., routine screening questions and temperature checks).
- Study visits will be scheduled in a way that minimizes contact between participants in general areas.
- Participants may only bring one additional person to take care of the child during study visits.

Personal protective equipment, behavior, and sanitation

- Enhanced implementation of respiratory hygiene/cough etiquette including education of participants and staff, posted signs using pictures and local language, use of masks, hand hygiene, and spatial separation.
- Use of personal protective equipment to minimize transmission including mask use for staff and participants. Gloves will continue to be used for biological sampling.
- Enhanced cleaning and sanitation of study transportation and research areas.
- Enhanced handwashing procedures for staff and participants.

Figure 1: Study design

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