Evidence for Multiple Micronutrient Effects Based on Randomized Controlled Trials and Meta-Analyses in Developing Countries

Parul Christian* and James M. Tielsch

Center for Human Nutrition, Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD

Abstract

Providing multiple micronutrients via supplements, powders, or fortified ready-to-use foods is increasingly becoming a strategy for simultaneously addressing multiple nutrient deficiencies in developing countries. The pros and cons of the “gold standard” randomized controlled trial (RCT) design and meta-analyses of trials for establishing efficacy of nutritional interventions are discussed. Over the past decade, numerous RCT have been undertaken to test the efficacy of multiple micronutrient supplementation in both pregnant women and young children. Outcomes of interest have ranged from birth weight to child growth, and infant morbidity and mortality to nutrient status and cognitive function. These RCT have also been submitted to meta-analyses for estimating pooled effect sizes for various outcomes. Meta-analyses of antenatal multiple micronutrient supplementation reveal a modest but significant increase in birth weight of 22.4 g (95% CI: 8.3, 36.4 g) and an 11% (95% CI: 3, 19) reduction in low birth weight but no impact on preterm birth or perinatal mortality. In children, small effect sizes of 0.13 (95% CI: 0.06, 0.21) for length/height and 0.14 (95% CI: 0.03, 0.25) for weight have been shown with 3 or more micronutrients compared to fewer micronutrients, but there is limited evidence for an impact on outcomes such as morbidity and cognitive function. Gaps in research and future challenges for programmatic application of this strategy for both pregnant women and young children are discussed. J. Nutr. 142: 173S–177S, 2012.

Introduction

It is now well recognized that micronutrient deficiencies occur not singly but in combination in many low- and middle-income countries. They may be caused by a range of shared factors, including diets lacking in adequate nutritional quality in part related to poverty, seasonal variation in food availability, and cultural food practices. Low bioavailability of nutrients, especially from plant sources, or factors such as illness or infection, further exacerbate deficiency due to poor nutrient utilization. Periods of rapid growth such as the intrauterine period or early preschool age are especially vulnerable, because nutritional requirements during these are high.

Despite the high likelihood of the existence of a large burden of micronutrient deficiencies in developing countries, the extent across a range of micronutrients has not been well described. This is largely due to the lack of assessment of biochemical indicators, which requires invasive blood drawing, maintaining a cold chain, and adequate laboratory facilities, equipment, and trained technicians. And yet there now exists an increasing number of randomized control trials (RCT) that have begun to elucidate the impact of multiple micronutrient supplementation, especially in pregnant women and young children, on a range of health and functional outcomes (1–4).

In this paper, we review for the symposium and for readers of the symposium proceedings basic facts and principles about RCT and systematic reviews that are important to understanding the issues and the comments in other papers from the symposium. We also provide a limited review of the existing evidence regarding the impact of multiple micronutrient supplementation.
among pregnant women and children on outcomes including status, birth size, gestational duration, and growth in developing countries. These have been recently summarized in a few meta-analyses and systematic reviews of existing trials. Thus, the purpose of this short review is 2-fold: first, to discuss the role of RCT, meta-analyses, and systematic reviews in demonstrating the evidence on the efficacy of nutritional interventions in the developing world that ultimately aid in moving policies and programs forward and, second, to examine, based on the recent few RCT and systematic reviews, the existing evidence for the beneficial impact of multiple micronutrient supplementation in pregnant women and young children on a range of outcomes. This short review is not a systematic review; rather, its scope is limited to summarizing the existing major recent meta-analyses and systematic reviews related to multiple micronutrient interventions.

**RCT as the Gold Standard for Evaluating Efficacy of Nutritional Interventions**

**Key advantages.** A RCT or an experimental design is largely considered the gold standard for evaluating the efficacy of a nutritional intervention in the same way as other public health or medical interventions (5,6). The guiding principle underlying the RCT design is the concept of causation. Use of this design allows an association of cause and effect to be made between the tested drug or intervention and the health outcome being assessed. A key characteristic of the RCT is the concept of comparing like with like; that is, comparing the outcomes of randomized “treatments” between groups of participants who are otherwise similar in all respects, especially their underlying baseline risk. Thus, advantages of random assignment include solving the key problems with nonexperimental or quasi-experimental designs, including reverse causation, confounding, and selection bias.

Some of the other key elements of this study design include investigator control over the assignment of the intervention using randomization to create comparable intervention groups, one of which is a control group, usually a placebo or standard of care intervention. Masking, generally double, that is, both the investigators and participants are unaware of who is receiving the treatment or the placebo, is also a common characteristic of a RCT. The community/cluster-randomized trial is a special class of RCT commonly employed when an intervention is to be distributed to a large number of individuals, with a village or community (called a cluster) instead of an individual being used as a unit of randomization (7). This method of randomization can result in more efficient distribution of the intervention and reduces the chances of crossover.

**Problems with RCT and overcoming them.** Disadvantages of RCT include higher cost, impaired external validity under certain conditions, and differential attrition from the experimental and control groups, which can lead to the problem of selection bias. A partially offsetting disadvantage of cluster randomization is reduced power (or reduced effective sample size) if there is within-cluster correlation, but this can be taken into account when estimating the number of clusters needed in the study and methods for statistical analyses that are employed to adjust for the within-cluster correlation.

A well-executed RCT will ensure: 1) wide eligibility criteria to enhance generalizability; 2) high comparability between intervention and control groups to minimize confounding and maximize internal validity; 3) appropriate masking to exclude selection and investigator bias; 4) an adherence rate that is as close to 100% as possible; and 5) a high follow-up rate that does not differ in the intervention and control groups. The Consolidated Standards of Reporting Trials Statement provides guidelines for reporting on RCT, which in turn allows the evaluation of its conduct during peer review (8). In addition, one or more ethical review boards and a Data Safety Monitoring Board provide the needed oversight for appropriate conduct of the trial and adherence to the protocol while the trial is ongoing in addition to ensuring protection of human participants, consent procedures, and monitoring of adverse events. More recently, required registration of RCT with specially established registers such as Clinicaltrials.gov (9) ensures that the full body of RCT addressing a particular topic is known thus reducing the potential for publication bias.

For public health and nutrition policy and decision-making, alternate nonexperimental study designs allowing plausibility and adequacy statements, especially in the evaluation of performance and impact of public health interventions, have been recommended (10,11). However, for new, previously untested interventions, a standard RCT must provide the evidence for its efficacy under a controlled setting.

**Relevance of context.** In nutrition, as in other areas of public health, contextual factors are extremely relevant both in the design of RCT and in the interpretation of the results, revealing either a positive or no impact of the intervention being tested. Understanding the existing levels of micronutrient deficiencies and how they co-vary and co-occur, for example, will help determine which nutrients are lacking in the diet and need to be replenished through supplementation, fortification, dietary counseling, and other strategies. Populations may differ with respect to key limiting deficiencies and assuming homogeneity in their prevalence across different settings or a consistent impact on outcomes of correcting those deficiencies would be a mistake. Additionally, other contextual factors, including existing levels of infections in the population (e.g., malaria), environmental exposures (e.g., arsenic, aflatoxins), and genetic conditions (e.g., thalassemia), can modify the impact of micronutrient interventions being tested. It is because contextual factors vary that there arises a need to replicate RCT under differing settings. This raises the question of whether global policies and guidelines for some interventions are appropriate. The recent example of the harmful effect of providing iron supplements to children in areas with endemic malaria demonstrates that a regional policy may be needed (12).

**Meta-Analyses and Systematic Reviews for Informing Policies and Guidelines**

Some basic concepts in systematic reviews and meta-analysis that are frequently used for policy-making in evidence-based public health are provided below.

**Meta-analyses.** A commonly applied methodology to consolidate evidence regarding the impact of an intervention from RCT is called meta-analysis. In a meta-analysis, results of the individual studies are combined to produce an overall statistic (13). Originally developed to combine a number of clinical trials that were too small to provide precise and definitive results, the key concept of meta-analysis is to maintain the core principle of clinical trials: to compare like with like. Strict inclusion and
exclusion criteria for patients enrolled in the trials are used, and the averaged effects are generalized to the population from which the original trials data are derived. Strict definitions of outcomes and maintenance of randomization is critical for drawing appropriate inference and special care is taken to generate bias-free average effect estimates (14). Increasingly, consistency in results across studies, but also systematic variations in estimates across studies, has become of interest to examine. Special regression methods are available that allow combining results from different trials to estimate the “common” average effect of treatment as well as to allow for the y-intercept to vary across studies.

**Systematic reviews.** A systematic review, on the other hand, attempts to identify, appraise, and synthesize all the empirical evidence that meets prespecified eligibility criteria to answer a given research question. Systematic reviews are also commonly used for decision-making related to policy and programs. Specifically relevant for nutrition and public health are the Cochrane Reviews that are systematic reviews of research in health care and health policy. The application of systematic reviews and meta-analyses to nutrition has been extensively covered recently (15–18), but these were largely related to nutritional issues applicable to high-income countries. Systematic reviews use a highly structured process that includes appropriate literature searches and its documentation, defined procedures for data abstraction, specific rating of quality of studies, inclusion only of studies that meet the defined criteria, a priori statements of analytic methods and comparisons, and subgroup and sensitivity analyses.

**Antenatal Multiple Micronutrient Supplementation Effects**

The foundation for the research in this area is the global interest in establishing the efficacy of a universal multiple micronutrient supplement formulation for use among pregnant women in developing countries, an effort led and actively pursued for the last decade by UNICEF/WHO/UNU. This supplement formulation, containing 15 micronutrients, all at an approximate RDA for pregnancy, is called United Nations International Multiple Micronutrient Preparation and was developed by a coordinated technical group (19). The multiple micronutrient intervention strategy is modeled after the common practice of women in developing countries using prenatal supplements but in whom the individual or combined effects of supplemental micronutrients on birth outcomes is less clear, because micronutrient deficiencies are not as common. In developing countries, on the other hand, multiple micronutrient deficiencies commonly coexist and may be severe, rendering women more likely to benefit from the provision of multiple micronutrients during pregnancy. Thus, the UNIMAPP supplement was tested in 9 of 12 RCT of antenatal multiple micronutrient supplements in sub-Saharan Africa, South Asia, Southeast Asia, and Latin America (20). These RCT were largely conducted using the standard of care of iron-folic acid, which is recommended for antenatal use in most developing countries, as the control group. These trials, with the exception of two, had birth weight as the primary outcome and were powered to see improvements only in birth weight.

The 12 completed trials were subjected to meta-analyses to examine impact on birth weight, low birth weight, and perinatal mortality (2,3). Mean birth weights varied widely across settings. The primary findings were that multiple micronutrient supplementation enhanced birth weight by a modest 22.4 g (95% CI: 8.3, 36.4) and reduced low birth weight by 11% (95% CI: 3.19) but did not have any impact on preterm delivery (<37 wk of gestation) and perinatal mortality [RR: 1.00 (95% CI: 0.93, 1.09) and 1.11 (95% CI: 0.93, 1.33), respectively]. The impact on birth weight was larger in women with higher BMI and there was also an increase in large-for-gestational age birth (2).

Of note is that despite the reduction in low birth weight seen with this intervention, this did not seem to afford any survival benefit to the offspring. One large trial in Lombok, Indonesia involving ~30,000 pregnant women, however, showed a significant impact on 3-mo infant mortality, although perinatal or neonatal mortality were not reduced (21). In contrast to this, in China, antenatal iron-folic acid [RR: 0.53 (95% CI: 0.29, 0.97)] but not multiple micronutrient supplementation significantly reduced neonatal mortality compared with the control group of folic acid alone (22). Similarly, in Nepal, in a long-term follow-up study of offspring whose mothers participated in a micronutrient supplementation trial during pregnancy, iron-folic acid compared to the control reduced the mortality rate from birth to 7 y of age by 31% [RR: 0.69 (95% CI: 0.49, 0.99)], but this reduction was not observed with the multiple micronutrient supplement (23).

Despite some remaining questions of its efficacy or at least its lack of clear evidence for a health benefit to the infant, the systematic review has prompted a call for replacing iron-folic acid supplements with multiple micronutrients for antenatal use in developing countries (24).

**Multiple Micronutrient Supplementation in Children and Effects on Growth and Cognition**

Unlike in pregnancy, there are few systematic evaluations of the impact of multiple micronutrient supplementation among children. A comprehensive review of the effects of multiple micronutrients compared with two or fewer micronutrient showed small effect sizes on outcomes of growth, including improved length/height [effect size: 0.13 (95% CI: 0.06, 0.21)] and weight [effect size: 0.14 (95% CI: 0.03, 0.25)] (1). The composition of supplements varied between studies and it is not easy to discern one or two specific formulations for future use from this evaluation. A previous meta-analysis has demonstrated that iron alone or vitamin A alone does not significantly affect either linear or ponderal growth (25). In contrast, five trials of multiple micronutrient supplementation in which the intervention was more uniform containing vitamin A, iron, zinc, B vitamins, and folic acid had a somewhat higher effect size for height and weight [0.28 (95% CI: 0.16, 0.41)], but this was not significant [0.28 (95% CI: −0.07, 0.63)] (24). However, in four collaborative parallel trials conducted using the same multiple micronutrient formulation in a food-let, a pooled analysis found higher (P < 0.05) weight gain/month (0.21 ± 0.09 g) compared to the control (0.21 ± 0.09 g) but not for height (26).

Meta-analyses of studies have also shown significant improvements in biochemical indicators of micronutrient status, including hemoglobin, serum zinc, and retinol (1). Although not submitted to a meta-analysis, four studies showed positive effects of multiple micronutrients on motor development but not mental outcomes; however, the evidence for impact on morbid-
ity was equivocal (1). In a systematic review of RCT comparing the effect of three or more micronutrients with placebo among children 6–16 y of age, pooled random effect estimates across 17 studies were not significant for fluid or crystallized intelligence (27). However, four trials revealed an effect of 0.30 SD ($P = 0.044$) for academic performance, but no significant effects were found for other cognitive domains. At present, there are few policies or programs for daily multiple micronutrient supplementation of children under 2 or 3 y of age. Vehicles for delivery, being most commonly tested include point-of-use fortification of complementary foods using micronutrient powders and Micro-nutrient Sprinkles, food-jets, and milk or milk powder or fortified lipid-based supplements.

Summary

It is commendable that a systematic evaluation of multiple micronutrient supplementation in pregnancy was undertaken in low-income country settings not commonly seen for other nutritional strategies. This evaluation found evidence for modest benefits on outcomes such as birth weight and small for gestational age, but not perinatal mortality. One major lacunae in this research is related to the lack of adequate understanding of underlying biological mechanisms in humans for the demonstrated impact on some outcomes but not others, especially potential nutrient-nutrient interactions, both synergistic and antagonistic, that may partly explain the inconsistency in results (28). This is of particular relevance for trials involving children in which nutrient composition of supplement formulations varied widely. Although multiple micronutrient intervention as a strategy is being considered for wide-scale implementation, current programs of antenatal iron-folic acid supplementation are failing to achieve high coverage; supplies and logistics of delivery of supplements, not to mention the lack of an enhanced antenatal care system, are major hurdles that need to be overcome before either iron-folic acid or multiple micronutrients can be expected to have broad reach (29). Additionally, in many settings, data on the burden of deficiencies across a range of micronutrients is limited, which would make any future evaluation of intervention impact and change in nutrient status a challenge both among women and young children. Future work should focus on enhancing existing antenatal iron-folic acid and perhaps multiple micronutrient supplementation programs to improve coverage and reach. Among children, universal supplementation may not be an immediate priority, but enhancing complementary foods with micronutrient-rich foods or micronutrient powders may be a strategy to consider for improving status and growth.

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Literature Cited


