Title
Micronutrient Research, Programs, and Policy: From Meta-analyses to Metabolomics

Journal
Advances in Nutrition, 5(3)

ISSN
2161-8313

Author
Allen, Lindsay H

Publication Date
2014-05-01

DOI
10.3945/an.113.005421

Peer reviewed

SUPPLEMENT
Proceedings of the IUNS 20th Congress of Nutrition

Micronutrient Research, Programs, and Policy: From Meta-analyses to Metabolomics[1–3]

Lindsay H. Allen*
USDA, Agricultural Research Service Western Human Nutrition Research Center, University of California, Davis, Davis, CA

ABSTRACT

Micronutrient deficiencies are widespread among women and children in undernourished populations. Research has identified effective approaches to their prevention, including supplementation, fortification, and dietary and other public health interventions. These interventions have made tremendous improvements in the quality of life, health, and survival of populations around the world, yet the impact varies by nutrient, population, and the outcomes chosen that reflect nutritionally driven change. The WHO guides governments and agencies toward effective strategies to prevent micronutrient deficiencies in women and children, but these are often informed by imperfect studies with limited measures of impact and the inadequate program evaluations and survey databases produced by the nutrition community. The resulting knowledge gaps limit our ability to discern what interventions are effective, under what conditions, among whom, and perhaps most important, why. However, we are moving into an era of opportunity to apply the tools of modern nutrition science, including improved methods of assessing nutritional status, "omics," bioarchival access, systems biology thinking, and interdisciplinary collaborations, that can deepen and broaden our understanding of how micronutrients affect health, how their deficiencies diminish human capacity, and how interventions can improve the well-being of those in need. Relevant training and greater cross-disciplinary efforts will be required to ensure a cell-to-society approach that can systematically address where, to whom, and how to provide micronutrients in the future. *Adv. Nutr. 5: 344S–351S, 2014.*

Introduction

There is no doubt that micronutrient interventions have a very significant, positive impact on morbidity, mortality, and health, especially for women, infants, and children. However, substantial gaps in our knowledge remain such that current intervention policies are probably not optimal. This article provides an overview of those knowledge gaps and the research and actions still needed to inform current policies and programs about delivering micronutrients. We need to take advantage of more modern technologies and approaches in nutrition science to expand our knowledge about the effects of micronutrient interventions on biology and health.

[1] Published in a supplement to *Advances in Nutrition*. Presented at the International Union of Nutritional Sciences (IUNS) 20th International Congress of Nutrition (ICN) held in Granada, Spain, September 15–20, 2013. The IUNS and the 20th ICN wish to thank the California Walnut Commission and Mead Johnson Nutrition for generously providing educational grants to support the publication and distribution of proceedings from the 20th ICN. The contents of this supplement are solely the responsibility of the authors and do not necessarily represent the official views of the IUNS. The supplement coordinators were Angel Gil, Ibrahim Elmadfa, and Alfredo Martinez. The supplement coordinators had no conflicts of interest to disclose.
[2] Presented in author's role as E.V. McCollum International Lecturer in Nutrition, American Society for Nutrition.
[3] Author disclosure: L. H. Allen, no conflict of interest.
* To whom correspondence should be addressed. E-mail: lindsay.allen@ars.usda.gov.

Current Status of Knowledge

To provide a logical structure to this review, it starts by addressing current micronutrient policies and programs recommended for women and children in developing countries (**Table 1**). These recommendations are taken primarily from those of WHO reports, many of which are supported by evidence laid out in their e-Library of Evidence for Nutrition-Based Actions (eLENA) (1). We should recognize that the WHO has very limited ability to guide most of the research that produces this evidence and is dependent on a wide community of academic experts and stakeholders to conduct the studies and translate the available data into policy. Thus, basing this critique on WHO guidelines is in no way intended to criticize the WHO's excellent efforts to turn existing data into policy recommendations.

Pregnancy. From a public health perspective, adequate maternal nutritional status during pregnancy is one of the most critical concerns. Nearly one-quarter of all newborns are of low birth weight, which increases the risk of mortality, morbidity, and functional impairments in infancy and childhood and is a recognized risk factor for chronic disease in later life. Approximately 10% of births are preterm, most of which are

  Adv. Nutr. 5: 344S–351S, 2014; doi:10.3945/an.113.005421.

TABLE 1 Current WHO recommendations for micronutrient interventions in pregnancy, lactation, infants, children, and nonpregnant/nonlactating women[1]

Stage of the life span				
Pregnancy	**Lactation**	**Age 0–6 mo**	**Age 6 mo–5 y**	**Women and children**
Iron + folic acid	No recommendations	Breast milk	Vitamin A capsules Iron Multiple micronutrient (powders, lipid-based supplements, and/or fortified complementary food) Nutrient-dense household foods	Iron if anemic Staples fortified with iron, vitamin A, zinc, folic acid, vitamin B-12

[1] Data primarily from WHO's eLENA Web site (http://www.who.int/elena/en/). Universal salt iodization is recommended at all ages.

in Africa and Asia. Because a high proportion of women giving birth to preterm or low-birth-weight infants are deficient in ≥1 micronutrients, there has been a substantial amount of investment in understanding the extent to which maternal micronutrient interventions can improve pregnancy outcome, which has been evaluated in the eLENA reports.

During pregnancy, the WHO recommends that nonanemic adolescents and women take a once-weekly supplement containing 120 mg iron and 2800 μg folic acid throughout their pregnancy (2). The rationale for this policy is to reduce maternal anemia, iron deficiency, and low birth weight. The WHO judged this recommendation to be strong for prevention of anemia and improvement in gestational outcomes, but the quality of the evidence for preventing low birth weight was judged to be very low. Anemic women, including those diagnosed with anemia during pregnancy, should be given daily iron supplements throughout pregnancy (3). For such women, taking iron + folic acid reduces the risk of low birth weight (RR: 0.81), anemia, and iron deficiency but has only a small effect on birth weight (+31 g) and no effect on preterm delivery or neonatal deaths. One limitation of the evidence supporting both weekly and daily recommendations is that there have been few randomized controlled trials with a true placebo group, because providing iron and folic acid is the standard of care in most countries where the studies were conducted.

Folic acid supplementation (and fortification) in the periconceptional period definitely lowers the risk of neural tube defects in susceptible women, but the rationale for continuing supplementation after 30 d postconception (after the neural tube is closed) is less clear. As stated in the WHO guidelines "folic acid supplementation after the first month of pregnancy may not prevent neural tube defects. However it will contribute to other aspects of maternal and fetal health" (2). These benefits were not stated. In addition, the very high dose of folic acid in weekly supplements was chosen by investigators simply because it was 7 times the daily dose, but there is limited evidence about what is the most effective and safe dose for weekly supplementation.

Rather than taking iron plus folic acid alone, evidence has accumulated to show that pregnant women would benefit more from taking supplements containing multiple micronutrients. A meta-analysis of 12 trials that evaluated the efficacy of the UNICEF "UNIMAP" multiple micronutrient supplement, which contains 14 micronutrients in levels approximating the recommended daily intake for pregnant women, concluded that several outcomes were significantly better than the comparison intervention, which was usually iron + folic acid; birth weight increased by 22 g, low birth weight decreased by 11%, and small-for-gestational-age deliveries decreased by 10% (4). Although the overall effect on birth weight was small, an important observation was that the improvement in birth weight increased, on average, by 7.6 g for each unit higher maternal BMI, across the BMI range of ~16 to 30, and in almost all of the trials. Why this occurs is not known and warrants further research. The observation raises the question of "capacity to respond" to micronutrient interventions (5). Clearly, mothers and their offspring respond in different ways and to different extents.

The UNIMAP trials and meta-analysis included a study in Nepal in which term infants in the multiple micronutrient–supplemented group had a higher RR (1.74) of mortality in the first 3 mo of life compared with those born to women supplemented with 2–4 micronutrients (6). The same team recently replicated the earlier trial in 44,657 pregnant women in Bangladesh (7). Comparing the effects of multiple micronutrients to the iron + folic acid control group, the RRs of preterm birth, low birth weight, and still births were 0.87, 0.88, and 0.89, respectively. Birth weight was 55 g greater and head circumference was 0.21 cm larger due to the 0.3-wk increase in gestational age; infant mortality was lower (in females). There was no effect of multiple micronutrients on prevalence of small-for-gestational age. The benefits of multiple micronutrients vs. iron + folic acid are also becoming apparent in studies of the international lipid-based nutrient supplement trial in Ghana (Kathryn G. Dewey, University of California, Davis, personal communication).

Importantly, there have been major differences in the pregnancy outcome responses to micronutrient interventions, both within and across randomized controlled trials (8). Examples of these response modifiers include the following: the positive relation between maternal BMI and birth weight in the UNIMAP trials (4); the fact that maternal anemia at baseline in Guinea-Bissau (9) and both anemia and malaria in Malawi predicted a greater increase in birth weight response; that, in the United States, iron supplements alone increased birth weight by 225 g (10), an amount rarely incurred by interventions in developing countries; and giving food with multiple micronutrients had a greater effect on birth weight than did the micronutrients alone for women with lower BMIs in Burkina Faso (11). The underlying mechanisms that caused this heterogeneity of response are not understood, so it is not yet possible to optimize pregnancy micronutrient interventions. Systematic evaluation protocols are needed.

Yet another issue is the optimal content and dose of micronutrients in supplements for pregnant women, which may vary by region. Most of the trials have been conducted with UNICEF's UNIMAP supplement, which contains 14 micronutrients, in amounts approximately equal to the RDAs for pregnancy (WHO/United Nations University). However, supplementation with twice the RDA increased mean birth weight by 177 g more than the RDA in anemic Guinea-Bissau women (9), whereas in Tanzania providing twice the RDA to HIV-positive pregnant women had no additional effect on risk of low birth weight or small for gestational age or on birth weight (12). Notably, giving the RDA often is insufficient to increase the plasma concentrations of most micronutrients to concentrations generally accepted as indicating adequate status, as exemplified in a Nepal study in which the prevalence of deficiency across nutrients ranged from 22% to 88% in late pregnancy (13). It remains to be seen if lipid-based micronutrient supplements are more effective than giving them as powders. It is also not clear to what extent improvements in infant micronutrient status in the first 6 mo of life can result from maternal supplementation in pregnancy and early lactation, but a Bangladeshi study suggests that these are limited (14).

Lactation. At present, there are no specific recommendations for micronutrient supplementation of lactating women, even though micronutrient requirements are highest during lactation. Exclusive breastfeeding is recommended for the first 6 mo of life, supported by evidence that this practice lowers the risk of infant morbidity and mortality and has a number of other positive effects. When the 6-mo recommendation was made by WHO in 2001, it was accompanied by the statement that "available data are insufficient to exclude…potential risks with exclusive breastfeeding for 6 mo, including growth faltering and iron and other micronutrient deficiencies in some infants" (15). When the WHO revised its growth standards in 2006, they revealed a much greater problem of weight and length faltering during the first 6 mo than had been recognized previously (16). Without doubt, potential contributors to this growth faltering include small maternal size, low birth weight, infections, and prenatal programming. Nevertheless, we need to ensure that the quality of breast milk, and especially its micronutrient content, is adequate when the mother's micronutrient status and/or intake are poor. There is little information concerning this question, and the quality of milk composition data is questionable even in wealthy countries. Few samples have been analyzed, collection and sampling procedures are often unknown, some mothers may have been taking supplements, and some older analytical methods were inaccurate (17). Moreover, there is evidence that the concentrations of most B vitamins (except for folate); vitamins A, C, and D; and iodine and selenium can be very low (18). Milk composition values are used as the basis to set recommended intakes for infants and young children and lactating women. If actual intakes from breast milk are lower than usually assumed, this means that estimates of micronutrient needs from complementary foods may be underestimated. More efficient and accurate methods for measuring micronutrients in human milk are now available and are being applied to obtain more information on these important questions, including whether supplementation of pregnant and/or lactating mothers can increase micronutrients in their milk and improve infant status.

Infancy through age 5 y. Recommendations for developing-country children in this age group include universal high-dose vitamin A supplementation (50,000 IU once during the first 6 mo, then 100,000 IU from 6 to 11 mo of age and 200,000 IU every 6 mo after 12 mo of age), which reduces the risk of mortality and blindness. The Global Alliance for Vitamin A recognizes that vitamin A intake from other sources has gradually increased over the past decade, especially where fortified oil and other foods are now available. The Global Alliance for Vitamin A is in the process of developing a framework that will enable decision makers to evaluate whether and where high-dose supplementation needs to be continued (19). The WHO does not currently recommend high-dose vitamin A supplementation in the first days of life because of the inconsistent effects on morbidity and mortality prevention in trials to date. Four ongoing trials, some of which include measures of immune function, will soon provide further clarification about this issue. Iron supplements are still recommended for children between 6 and 23 mo of age where the prevalence of anemia is >40% or where the diet does not include fortified foods, but because of concerns about the safety of iron supplements especially where malaria and other infections are common, this question is being studied in the NIH's Iron and Malaria Project. The eventual goal is to describe best practices for preventing and treating iron deficiency, through improving understanding of the mechanisms by which iron can interact with immune function, identifying useful biomarkers, and testing different iron preparations and interventions.

There was considerable optimism that supplementation or fortification of complementary foods with multiple micronutrients would prevent the growth stunting that is so common between 6 mo and ~3 y of age. However, several meta-analyses have revealed the effects on growth to be small: the effect size for weight and length is ~0.2 (20,21). The benefit is small regardless of the age of the child at baseline or the initial prevalence of stunting, and effects on anemia are not greater than those of iron alone. More information is needed on how micronutrients affect motor and mental development. In our meta-analysis there were improvements in motor development in all 4 studies in which it was examined and improvements in mental development in 1 of 2 studies (20). Improved methods for evaluating the effects of nutrition on child development should lead to further clarification of this question. Thus, micronutrient interventions are still necessary to prevent deficiencies during the period of complementary feeding and may have benefits that are as yet only partially recognized, but they still provide only a small part of the solution for the prevention of stunting. As in the case of pregnancy outcomes, we also need to better understand the modifiers of children's response to improved micronutrient status.

Meeting children's micronutrient needs through food. From ages 6 to 24 mo and beyond, recommendations include advice that young children should consume nutrient-dense household foods. The WHO's Principles of Complementary Feeding include the following: vegetarian diets do not meet needs; eat a varied diet with meat, poultry, fish, or eggs daily; eat vitamin A–rich fruits and vegetables daily; and ensure adequate fat content. The WHO guidelines also recognize that dairy products are a good source of nutrients but that they are low in iron. Yogurt, cheese, and dried milk mixed into foods are recommended rather than fresh milk, which carries a higher risk of contamination. The question arises of how often it is feasible for children to meet their micronutrient needs if complementary foods are not fortified or if they are not given supplements. It has long been recognized that, without fortification, the densities (amount per kcal) of iron, zinc, calcium, and B vitamins in the usual complementary foods do not meet recommended intakes in most developing-country populations. In Guatemala, even the best (top 13%) rural and urban household diets had iron, zinc, and calcium densities far lower than are required to meet the needs of young children (22).

How is it possible, from a teleologic perspective, that it appears to be practically impossible for infants and young children to obtain their micronutrient requirements from unfortified foods? To some extent, the difficulty of filling this apparent micronutrient gap could be caused by problems with the values for recommended nutrient intakes for young children. Many of these recommendations are extrapolated up or down between Adequate Intake values for infants (based on reports of the composition of human milk, not all of which are correct, as discussed above) and older children or even adults. This leads to large inconsistencies between values recommended at ages 7 to 12 mo and 12 to 23 mo. For example, across these 2 periods, Institute of Medicine recommendations for vitamin A, vitamin C, iodine, and iron decrease by 40%, 31%, 70%, and 64%, respectively, and those for folate, calcium, and phosphorus increase by 90%, 85%, and 70%. Not only are these large changes in recommended intakes biologically implausible but they make it very difficult to integrate feeding recommendations and formulate products that bridge late infancy into early childhood. Although the WHO/FAO recommendations transition more smoothly across this period, they represent Recommended Nutrient Intakes and there are no Estimated Average Requirements; the latter values are needed to estimate the prevalence of inadequate intakes in a population. In summary, there is a need to revisit the question of micronutrient intake recommendations for infants and young children, including the establishment of Estimated Average Requirements and "harmonization" across the period from infancy to early childhood. This will support the global efforts to improve micronutrient intake across this period and enable evaluations to be more accurate.

In general, dietary patterns are more strongly associated with maternal, infant, and young child nutritional status and outcomes than are intakes of nutrients. There are several ways of categorizing such patterns. One useful approach is the indicator of dietary quality "percent of energy from animal source foods." This dietary indicator was developed in the Nutrition Collaborative Research Support Program in the 1980s and predicted many functional outcomes in concurrent research projects in Mexico, Egypt, and Kenya (23), including infant and child growth (24). To express animal source food (ASF) intake as a percentage of total energy requires quantitative data on intake and adequate food composition tables, but this level of accuracy may not always be required because more qualitative measures such as the usual intake of ASFs and dietary diversity are also positively associated with growth in many studies (25).

Arguably, lack of sufficient ASFs in diets is the main cause of many micronutrient deficiencies including iron, zinc, vitamin A, riboflavin, and vitamins B-6 and B-12 (23). However, there exists no global indicator for ASF adequacy; on the basis of the prevalence of vitamin B-12 deficiency alone, it appears that at least 10–15% of energy intake should be consumed as ASFs (26). Further efforts to produce a global indicator would be useful for dietary planning and evaluation purposes.

The main categories of ASFs are dairy products; meat, fish, and poultry; and eggs. These have substantially different micronutrient composition and ideally need all to be consumed in adequate amounts (23). Meat intake is correlated with child growth in many studies, but recent research reveals the surprising finding that including meat supplements during the period of complementary feeding has no effect on growth or iron, zinc, or vitamin B-12 status. This generalization holds across 5 studies, in which from 30 to 75 g of meat was provided in interventions lasting from 5 to 9 mo (27). Possible explanations include a too-short period of supplementation and inappropriate control groups (such as fortified cereals); however, several of the trials did provide toward the upper limit of the amount of meat a child can consume. In contrast, supplementation with ASFs improved many outcomes for Kenyan children ages 7 to 10 y (28). For 2 y, children were evaluated in 4 intervention groups: those who received ~85 g meat/d, those who received 250 mL milk/d, those who received an equicaloric serving of the local meal *githeri* (maize and vegetables with added oil), or those who received a control diet and whose family received a goat at the end of the project. In general terms, the meat supplement improved children's cognitive performance, school test scores, physical activity, initiative, leadership, arm muscle mass, and vitamin B-12 status. Milk improved the linear growth of stunted children and their vitamin B-12 status.

Dairy products may be more effective in supporting child growth than micronutrient supplements or fortified foods. A meta-analysis of 12 studies that examined dairy product intake and physical stature revealed that height was 0.4 cm greater per every 750 mL milk/d consumed (29). Although 7 countries were included in the analysis, several were wealthier and most children were 7–13 y old. We have reported that most complementary feeding interventions that included milk resulted in greater growth (30). Although more work needs to be done to confirm the value and feasibility of using milk for improving growth in various settings, it seems inappropriate to ignore the potential impact of this food in the face of the relative failure of multiple micronutrient supplementation or fortification to serve as a "magic bullet" for preventing stunting. Moreover, milk lends itself well as a vehicle for fortificants.

Older children and adult women: food fortification and biofortification. For many good reasons, most attention to micronutrient interventions has focused on "the thousand days," which include pregnancy and the infant and young child during the first 2 y postpartum. Recommendations for nonpregnant women and older children are not well developed. They include universal salt iodization, and iron in the event of anemia. Two other major micronutrient strategies are fortification and biofortification, which attempt to improve the micronutrient status of the entire household. The WHO/FAO published their *Guidelines on Food Fortification with Micronutrients* in 2006 (31). An important directive in these guidelines was "the decision to implement a fortification program requires documented evidence that the micronutrient content of the diet is insufficient or that fortification will provide a health benefit." Experience has shown patchy attention to these guidelines. The main strategy has been flour fortification, with the effective support and implementation by the Flour Fortification Initiative.

At least 79 countries have legislation in place to fortify at least 1 major cereal grain. Of these, 78 fortify wheat and some fortify maize and/or rice. Flour is now fortified with folic acid in all of these countries except for Venezuela, the Philippines, and the United Kingdom for the purpose of reducing risk of folic acid–preventable spina bifida and anencephaly. A recent update of the program's success estimated that 25% of these defects are being prevented based on a new model that assumes 200 μg folic acid/d is required for prevention, and that additional resources and political will are required to increase this effort (32). Arguments against this viewpoint include indications, still to be substantiated adequately, that high intakes of folic acid could have adverse health effects, especially in the elderly or where vitamin B-12 status is poor (as is the case in most populations in whom ASF consumption is low) (33).

Interestingly, however, folate status is usually better than that of most or all other micronutrients because poorer households rely more on legumes and vegetables as staples in their diets (34). There has been limited effort to follow the WHO/FAO 2006 recommendation that there is need to document that usual dietary intake or status is insufficient before starting a fortification program. It is hoped that this effort will be encouraged and supported by ongoing efforts to identify a cutoff for erythrocyte folate below which folic acid fortification will provide benefit. An additional issue that needs to be resolved is whether pregnant women should continue to receive routine folic acid supplementation with iron in regions where foods are fortified with the vitamin, especially where vitamin B-12 status is poor. It appears to be the combination of fortification with supplementation that causes high folic acid intakes (35), increasing serum or erythrocyte folate to concentrations that might cause concern.

In addition to folic acid, the WHO recommends the individual or combined addition of iron, vitamin A, zinc, and vitamin B-12 to wheat and maize flours (1,31). They point out that nutritional need, and technical issues including knowledge of the appropriate amount of nutrients to add, interactions with the food constituents and with other nutrients, the type of flour and consumer acceptability, should be considered before the initiation of a fortification program. In the case of iron, fortification has often been ineffective in the past due to the use of poorly absorbable or bioavailable compounds to prevent undesirable sensory changes in the food, leading to revised fortification recommendations in 2010. It has been difficult to demonstrate that zinc fortification of flour improves zinc status or growth (36). Suitable food vehicles for vitamin A fortification include oils and fats, in which it is most stable; sugar; cereals and flours; and milk. Finally, although it is now recommended that vitamin B-12 be added to flour because of the high prevalence of this deficiency in developing countries, there was little evidence of efficacy of the recommended fortification amount when the guideline was made. Our recent evaluations in Cameroon have now demonstrated effectiveness for improving breast milk and plasma vitamin B-12 (S. Shahab-Ferdows, USDA-Agricultural Research Service Western Human Nutrition Research Center, unpublished data).

In the extensive efforts to fortify flours with micronutrients, it should be recognized that data on intake and biomarkers of status provide complementary information. This is exemplified by a recent survey to establish appropriate fortification vehicles and amounts in Uganda (37). In our opinion, investment in obtaining this information is critical and the time and labor costs are minimal compared with those incurred in implementing the eventual program. Standard protocols to facilitate and standardize this process, and more demonstrations of their importance, are needed.

Comments on the progress of biofortification are beyond the scope of this review. Progress is indeed substantial, although biofortification efforts currently are focused on improving vitamin A, iron, and zinc status such that other micronutrients will continue to be needed from other sources.

Making policy decisions on the basis of micronutrient intervention studies. As the number of published intervention studies has increased over time, it has become the preferred strategy to base policy decisions on evidence-based reviews and meta-analyses such as those performed by the Cochrane Collaboration and WHO. Additional analyses of this type were used to support the updated *Lancet* series on Maternal and Child Nutrition (38). Such analyses summarize the results of many studies and add power to detect effects. There are limitations to this process, however. The outcomes included are generally quite limited, such as pregnancy outcome, child growth, anemia, and, in larger studies, morbidity and mortality. Although these may be the most important outcomes from a public health perspective, other outcomes (e.g., cognitive function, health, metabolism, epigenetic effects, bone growth, and immunocompetence) may also be important but are rarely measured, leading the reviewers to conclude that insufficient data are available to advise policy. We now tend to ignore results that have been replicated in only a few studies. Another issue is that the responses to micronutrient interventions within and across studies are often very heterogeneous, as discussed above. Unfortunately, there is often a lack of information on the variables needed to understand the causes of this heterogeneity. It would be useful to identify these potential variables and guide investigators in the importance of collecting this information to the greatest extent possible. Until this is done it remains difficult to predict the efficacy and effectiveness of micronutrient interventions in specific locations and population groups.

The opportunity to improve outcome measures using modern approaches. In wealthier countries "nutritional systems biology" has become a more frequently used approach to measuring the impact of food and nutrient interventions (39). Systems biology uses a multidisciplinary approach to measure changes in, and interactions between, cells, tissues, and organs. Although micronutrient intervention studies have typically restricted outcomes to anthropometry, biomarkers of nutritional status, limited neurobehavioral measures, and morbidity/mortality, modern analytical techniques used in systems biology can measure the function of specific organs; signaling among cells; detailed metabolic, genomic, proteomic, and epigenetic changes; response of the inflammasome; and the role of and changes in the gut microbiome. These measures rely on "omics" technologies, which can have many applications for assessing the impact of micronutrient interventions. For example, omics methodology could detect new and unanticipated metabolic responses, some of which could affect later chronic disease risk, and changes in gene expression and epigenetic responses, especially to interventions in pregnancy and early life; explain heterogeneity in growth and other responses; and identify new metabolic and functional biomarkers. Currently, there are relatively few examples of the application of systems biology to issues in international micronutrient nutrition. Preliminary data from our own laboratory include metabolomic (lipomic) evidence of changes in serum lipids, suggesting reduced hepatic lipogenesis, in Botswanian schoolchildren given a drink for 2 mo that provided the RDA for 12 micronutrients and changes in multiple pathways in vitamin B-12–deficient elderly Chileans when supplemented with the vitamin. In The Gambia, the season of conception has been shown to affect DNA methylation at putative metastable epialleles, possibly due to seasonal changes in the consumption of one-carbon methyl donors such as folate, choline, and vitamin B-12 (40).

How can we apply systems biology methods to improve the evidence concerning true impacts of micronutrient interventions? Examples are beginning to appear in the literature (41,42). Clearly it is important to teach systems biology, laboratory methods, and statistical approaches for analyzing "big data" as part of training curricula. Millions of existing samples have been or are being banked from interventions that, to date, have only included more traditional outcomes; collaborations should be established to enable these to be analyzed by using systems biology methods. The ongoing MAL-ED Project (43), which studies enteric infections in children, provides an example of a team that "conducts epidemiological, microbiological, physiological, immunological and psychological tests, integrates the data and develops models and tools for other researchers to use." Substantial effort is still needed to form the interdisciplinary teams and analyze the resulting big data sets that challenge conventional approaches to analysis and interpretation.

In conclusion, it is evident from the above discussions that current guidelines for micronutrient interventions are patchy in that they omit important periods of life such as lactation; neglect some population groups such as schoolchildren, men and nonpregnant women, and the elderly; may be difficult or infeasible to meet, such as adequate micronutrient intakes from the household diet; or are of limited efficacy for an intended purpose, such as prevention of stunting.

Nevertheless, it is critically important to protect the current momentum in micronutrient programs, while paying attention to filling the information gaps in a systematic way. When many expensive trials continue to provide conflicting conclusions about the efficacy of interventions, clearly more attention needs to be paid to the underlying factors that affect response. This includes study of the biologic mechanisms that may be involved, such as in the ongoing trials on perinatal vitamin A supplementation and the safety of iron for young children. There is a tremendous opportunity to apply nutritional systems biology methods to identify the true impacts of interventions, the potential for harm as well as benefit, underlying mechanisms, and new biomarkers and to explain inconsistent results. Many banked samples are already available for this purpose, and their analysis can lead us into a better-informed, more efficient, and more interesting era of micronutrient research.

Acknowledgments

The author thanks Dr. Kathryn Dewey, University of California, Davis, for sharing the information from the international lipid-based nutrient supplement trail in Ghana. The sole author has responsibility for all parts of the manuscript.

Literature Cited

1. WHO. e-Library of Evidence for Nutrition Actions (eLENA). Geneva: World Health Organization; 2013.
2. WHO. Guideline: intermittent iron and folic acid supplementation in non-anemic pregnant women. Geneva: World Health Organization; 2012.
3. WHO. Daily iron and folic acid supplementation in pregnant women. Geneva: World Health Organization; 2012.
4. Fall CH, Fisher DJ, Osmond C, Margetts BM. Multiple micronutrient supplementation during pregnancy in low-income countries: a meta-analysis of effects on birth size and length of gestation. Food Nutr Bull. 2009;30:S533–46.
5. Habicht JP, Pelto GH. Multiple micronutrient interventions are efficacious, but research on adequacy, plausibility, and implementation needs attention. J Nutr. 2012;142 Suppl:205S–9S.
6. Christian P, West KP, Khatry SK, Leclerq SC, Pradhan EK, Katz J, Shrestha SR, Sommer A. Effects of maternal micronutrient supplementation on fetal loss and infant mortality: a cluster-randomized trial in Nepal. Am J Clin Nutr. 2003;78:1194–202.
7. West KP Jr, Shamim A, Labrique A, Ali H, Shaikh S, Mehra S, Schulze K, Klemm R, Wu L, Merrill RD, et al. Efficacy of antenatal multiple micronutrient (MM) vs iron-folic acid (IFA) supplementation in improving gestational and postnatal viability in rural Bangladesh. FASEB J. 2013;27:385.6.
8. Kawai K, Spiegelman D, Shankar AH, Fawzi WW. Maternal multiple micronutrient supplementation and pregnancy outcomes in developing countries: meta-analysis and meta-regression. Bull World Health Organ. 2011;89:402–11B.
9. Kaestel P, Michaelsen KF, Aaby P, Friis H. Effects of prenatal multimicronutrient supplements on birth weight and perinatal mortality: a randomised, controlled trial in Guinea-Bissau. Eur J Clin Nutr. 2005; 59:1081–9.
10. Cogswell ME, Parvanta I, Ickes L, Yip R, Brittenham GM. Iron supplementation during pregnancy, anemia, and birth weight: a randomized controlled trial. Am J Clin Nutr. 2003;78:773–81.
11. Huybregts L, Roberfroid D, Lanou H, Menten J, Meda N, Van Camp J, Kolsteren P. Prenatal food supplementation fortified with multiple micronutrients increases birth length: a randomized controlled trial in rural Burkina Faso. Am J Clin Nutr. 2009;90:1593–600.
12. Kawai K, Kupka R, Mugusi F, Aboud S, Okuma J, Villamor E, Spiegelman D, Fawzi WW. A randomized trial to determine the optimal dosage of multivitamin supplements to reduce adverse pregnancy outcomes among HIV-infected women in Tanzania. Am J Clin Nutr. 2010;91:391–7.
13. Christian P, Jiang T, Khatry SK, LeClerq SC, Shrestha SR, West KP Jr. Antenatal supplementation with micronutrients and biochemical indicators of status and subclinical infection in rural Nepal. Am J Clin Nutr. 2006;83:788–94.
14. Eneroth H, El Arifeen S, Persson LA, Lonnerdal B, Hossain MB, Stephensen CB, Ekstrom EC. Maternal multiple micronutrient supplementation has limited impact on micronutrient status of Bangladeshi infants compared with standard iron and folic acid supplementation. J Nutr. 2010;140:618–24.
15. WHO. The optimal duration of exclusive breastfeeding: report of an expert consultation. Geneva: World Health Organization; 2001.
16. Victora CG, de Onis M, Hallal PC, Blossner M, Shrimpton R. Worldwide timing of growth faltering: revisiting implications for interventions. Pediatrics. 2010;125:e473–80.
17. Allen LH. B vitamins in breast milk: relative importance of maternal status and intake, and effects on infant status and function. Adv Nutr. 2012;3:362–9.
18. Allen L, Graham J. Assuring micronutrient adequacy in the diets of young infants. In: Delange FM, West KP Jr, editors. Micronutrient deficiencies in the first months of life. Basel (Switzerland): Karger AG; 2003. p. 55–88.
19. Greig A, Neufeld L. A framework for shifting from universal vitamin A supplementation. Ottawa (Canada): The Micronutrient Initiative; 2012.
20. Allen LH, Peerson JM, Olney DK. Provision of multiple rather than two or fewer micronutrients more effectively improves growth and other outcomes in micronutrient-deficient children and adults. J Nutr. 2009;139:1022–30.
21. Ramakrishnan U, Goldenberg T, Allen LH. Do multiple micronutrient interventions improve child health, growth, and development? J Nutr. 2011;141:2066–75.
22. Vossenaar M, Solomons NW. The concept of "critical nutrient density" in complementary feeding: the demands on the "family foods" for the nutrient adequacy of young Guatemalan children with continued breastfeeding. Am J Clin Nutr. 2012;95:859–66.
23. Murphy SP, Allen LH. Nutritional importance of animal source foods. J Nutr. 2003;133 Suppl:3932S–5S.
24. Allen LH, Backstrand JR, Stanek EJ, Pelto GH, Chavez A, Molina E, Castillo JB, Mata A. The interactive effects of dietary quality on the growth and attained size of young Mexican children. Am J Clin Nutr. 1992;56:353–64.
25. Arimond M, Ruel MT. Dietary diversity is associated with child nutritional status: evidence from 11 demographic and health surveys. J Nutr. 2004;134:2579–85.
26. Allen LH, Rosenberg IH, Oakley GP, Omenn GS. Considering the case for vitamin B12 fortification of flour. Food Nutr Bull. 2010;31: S36–46.
27. Krebs NF, Mazariegos M, Chomba E, Sami N, Pasha O, Tshefu A, Carlo WA, Goldenberg RL, Bose CL, Wright LL, et al. Randomized controlled trial of meat compared with multimicronutrient-fortified cereal in infants and toddlers with high stunting rates in diverse settings. Am J Clin Nutr. 2012;96:840–7.
28. Neumann CG, Murphy SP, Gewa C, Grillenberger M, Bwibo NO. Meat supplementation improves growth, cognitive, and behavioral outcomes in Kenyan children. J Nutr. 2007;137:1119–23.
29. de Beer H. Dairy products and physical stature: a systematic review and meta-analysis of controlled trials. Econ Hum Biol. 2012;10:299–309.
30. Dror DK, Allen LH. The importance of milk and other animal-source foods for children in low-income countries. Food Nutr Bull. 2011;32: 227–43.
31. WHO/FAO. Guidelines on food fortification with micronutrients. Geneva: World Health Organization; 2006.
32. Youngblood ME, Williamson R, Bell KN, Johnson Q, Kancherla V, Oakley GP Jr. 2012 Update on global prevention of folic acid-preventable spina bifida and anencephaly. Birth Defects Res A Clin Mol Teratol. 2013;97:658–63.
33. Smith AD, Kim YI, Refsum H. Is folic acid good for everyone? Am J Clin Nutr. 2008;87:517–33.
34. Allen LH. Causes of vitamin B12 and folate deficiency. Food Nutr Bull. 2008;29:S20–34; discussion S5–7.
35. Tinker SC, Cogswell ME, Hamner HC, Berry RJ. Usual folic acid intakes: a modelling exercise assessing changes in the amount of folic acid in foods and supplements, National Health and Nutrition Examination Survey, 2003–2008. Public Health Nutr. 2012;15:1216–27.
36. Das JK, Kumar R, Salam RA, Bhutta ZA. Systematic review of zinc fortification trials. Ann Nutr Metab. 2013;62 Suppl 1:44–56.
37. Kyamuhangire W, Lubowa A, Kaaya A, Kikafunda J, Harvey PW, Rambeloson Z, Dary O, Dror DK, Allen LH. The importance of using food and nutrient intake data to identify appropriate vehicles and estimate potential benefits of food fortification in Uganda. Food Nutr Bull. 2013;34:131–42.
38. Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S, Webb P, Lartey A, Black RE. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? Lancet. 2013;382:452–77.
39. van Ommen B, Cavallieri D, Roche HM, Klein UI, Daniel H. The challenges for molecular nutrition research 4: the "nutritional systems biology level". Genes Nutr. 2008;3:107–13.

40. Waterland RA, Kellermayer R, Laritsky E, Rayco-Solon P, Harris RA, Travisano M, Zhang W, Torskaya MS, Zhang J, Torskaya MS, et al. Season of conception in rural Gambia affects DNA methylation at putative human metastable epialleles. PLoS Genet. 2010;6:e1001252.
41. Kaput J, van Ommen B, Kremer B, Priami C, Pontes Monteiro J, Morine M, Pepping F, Diaz Z, Fenech M, He Y, et al. Consensus statement understanding health and malnutrition through a systems approach: the ENOUGH program for early life. Genes Nutr. 2014;9:378.
42. Cole RN, Ruczinski I, Schulze K, Christian P, Herbrich S, Wu L, DeVine LR, O'Meally RN, Shrestha S, Boronina TN, et al. The plasma proteome identifies expected and novel proteins associated with micronutrient status in undernourished Nepalese children. J Nutr. 2013;143: 1540–8.
43. The MAL-ED Project. Interactions of Malnutrition and Enteric Infections: Consequences for Child Health and Development. [cited 2013 Dec 5]. Available from http://mal-ed.fnih.org.