Evidence in Multiple Micronutrient Nutrition: From History to Science to Effective Programs

Klaus Kraemer, Saskia de Pee, and Jane Badham

Abstract

The workshop involved key researchers from academic and development organizations reviewing what we have learned about multiple micronutrients and applying that knowledge to providing guidance to public health policy and program design. The participants highlighted the importance of evidence-based interventions, not to restrict evidence slanted toward one single origin but to appreciate the totality of evidence from history, epidemiology, basic science, randomized-controlled studies, and meta-analyses to inform policy and guideline development for the implementation of effective programs. It has to be understood and accepted that although the need for an evidence-based approach to nutritional recommendations is fundamental and cannot be disputed, there are distinct differences between evidence-based medicine and evidence-based nutrition practice. The level of confidence and certainty needed to launch programs to reduce micronutrient deficiencies can be different from what is required to treat a disease. An effective approach would be to ensure that both research and programs at scale are running in parallel and that both receive adequate attention and funding to fine tune the program or stop it when it is no longer required. There was much valuable discussion on the topic of what types of research methodologies are suitable for what type of intervention and, importantly, what is required before public health policy can be set. This paper is an introduction to a series of articles in this supplement that discuss the evidence on multiple micronutrients and what is required to establish policies and launch effective multiple micronutrient programs. J. Nutr. doi: 10.3945/jn.111.142414.

Introduction

The Roman author, orator, and politician Cicero said, “History is the witness that testifies to the passing of time; it illuminates reality, vitalize memory, provides guidance in daily life and brings us tidings of antiquity.” This is as true now as when it was written around 43 B.C. And it is also true when it comes to the field of micronutrients and public health.

During the Second World Congress of Public Health Nutrition in Porto, 23–25 September 2010, the Swiss-based humanitarian initiative Sight and Life convened a workshop involving key researchers from academic and development organizations to review what we have learned about multiple micronutrients, to apply that knowledge to the reality of health, both optimal and diseased, and to provide guidance to public health policy. The participants highlighted the importance of evidence-based interventions, not to restrict evidence slanted toward one single origin but to appreciate the totality of evidence from history, epidemiology, basic science, RCT6, and meta-analyses to inform policy and guideline development for the implementation of effective programs.

The challenge we face going forward, however, is the need to balance the evidence, critical to forming and growing the knowledge and for continued monitoring, evaluation, and fine-tuning of programs. This is the witness that testifies to the passing of time; it illuminates reality, vitalize memory, provides guidance in daily life and brings us tidings of antiquity.” This is as true now as when it was written around 43 B.C. And it is also true when it comes to the field of micronutrients and public health.

6 Abbreviations used: MNP, micronutrient powder; RCT, randomized-controlled trial; SUN, Scaling Up Nutrition.
tuning of the policies that guide public health nutrition, turning the evidence into scaled-up programs at a community level. The latter is of some urgency. The latest Millennium Development Goals report (1) shows that some regions are far from reaching the 2015 targets and the SUN roadmap (2) stresses that “Proven solutions are available and nations want to act on this knowledge. Investments in SUN will yield immediate returns. They will save lives, enable children and their mothers to have a better future, contribute to livelihoods, reduce poverty and contribute to the economic growth of nations” (Table 1). At the same time, in her acceptance speech on receiving the 2010 World Food Programme Leadership Award for fighting global hunger, U.S. Secretary of State Hillary Clinton (3) said, “It’s important that we focus on science and research again . . . to look for ways to bring about the widespread distribution of micronutrients and develop hardier, micronutrient-rich crops.” The dilemma is to decide whether more research is still needed to sharpen our knowledge of what to do and how to do it or to turn immediately to scaling-up of interventions at a country level to achieve the Millennium Development Goals. Bjørn Lomborg (4), Director of the Copenhagen Consensus Centre, recently wrote that “Billions of dollars are given and spent on aid and development by individuals and companies each year. Despite this generosity, we simply do not allocate enough resources to solve all of the world’s biggest problems. In a world fraught with competing claims on human solidarity, we have a moral obligation to direct additional resources to where they can achieve the most good.” Perhaps it is a case of ensuring that both research and programs at scale are running in parallel and that both receive adequate attention and funding, for if we neglect one for the other, in the future we could find that we have missed an important opportunity to improve health, save lives, and improve knowledge related to effective interventions.

The Concept of Evidence-Based Nutrition

The concept of the iterative nutritional paradigm explained by Semba (5) in this volume links how, over time and in different parts of the world, major ideas and events have shaped the evolution of thinking toward micronutrient nutrition. It also highlights the importance of an integrated approach and how we must never stop learning, because, as new research comes to light, so our understanding grows and evolves, allowing us to reshape, revise, and refine the advice we give and the policies we make toward ultimately improving the health and lives of our world’s 7-billion-and-growing population.

TABLE 1 SUN recommended nutrition interventions (2) 1

<table>
<thead>
<tr>
<th>Intervention</th>
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<tbody>
<tr>
<td>Adequate intake of vitamins and minerals for the most in need through</td>
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<tr>
<td>dietary diversification, supplementation, and fortification.</td>
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<tr>
<td>Improved complementary feeding for infants and young children using</td>
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<tr>
<td>locally available and affordable food.</td>
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<tr>
<td>Increased production of food that will enhance the diversity and nutritional</td>
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<td>quality of local diets.</td>
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<td>Social marketing of practices that will lead to better nutrition.</td>
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<tr>
<td>Improving the nutritional content of processed food.</td>
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<tr>
<td>Empowering women to achieve optimal nutrition during pregnancy and</td>
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<tr>
<td>when children are born (breastfeeding, antenatal supplementation,</td>
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<tr>
<td>appropriate complementary feeding from 6 mo, food-related hygiene).</td>
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<tr>
<td>Therapeutic feeding for malnourished children with special foods.</td>
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</table>

1 SUN, scaling up nutrition.
Management of Adequate Micronutrient Intakes and Guidelines

The field of micronutrients carries some inherent risks, as there can be a relatively narrow range of safe intakes, which is challenging when setting safe levels for supplementation and fortification. Vitamin A is a case in point (12). On the one hand, there are significant numbers of people at risk of insufficient micronutrient intake; on the other, there is a potential risk that some consumers may exceed the upper limit of tolerable intake over a longer period due to the consumption of certain foods (e.g., liver and liver products). Therefore, both low and high intakes need to be balanced to create a maximal public health impact for the target population. The identification of nutritional need should not only provide the means to permit the implementation of programs when need exists but also should provide those that would permit the appropriate modification or even suspension of programs when that need ceases to exist.

Neufeld and Cameron (13) in this issue point out that, although the estimation of need compared to risk can be determined through detailed research studies, such information is rarely available or affordable at a population level, especially in the countries with the highest vulnerability to micronutrient deficiencies. In addition, deficiency prevalence has the disadvantage of identifying only those who have reached a state of nutrient insufficiency so as to alter biochemical or biological processes; it does not provide information on whether, in general, uptake is optimized, therefore limiting us to the interpretation of biomarkers, with their inherent limitations, and to identifying the risk of deficiency rather than optimal nutrition.

To ensure that the outcome of a fortification, supplementation, or dietary modification program is adequate and does not lead to harmful intakes, it is important to collect food intake data on all foods and supplements consumed. This needs to be supported by findings on nutritional status, including biochemical or clinical data. In assessing the scientific evidence, it is critical to take into account the complexity of diet as the exposure from all sources. Even in developing countries where deficiency is more likely to happen than exceeding of the upper intake level, research to ensure the safety of the selected model has to go hand in hand with the interventions themselves. Public health interventions need to accommodate potential benefits and risks and these can only be established by scientific research and continued re-evaluation of micronutrient gaps and the risk compared to benefit ratio. Ultimately, there needs to be a delicate balance between political wisdom and judgment of the best available, systematically assembled evidence.

In 2009 the WHO adopted a new process by which recommendations for safe and effective micronutrient interventions are developed in order to ensure the use of best practices and available evidence. Guideline development for interventions pertaining to vitamin A supplementation and home fortification with multiple micronutrient powders (MNP) has just been completed. A useful resource will be the WHO eLibrary of Evidence for Nutrition Actions. This will provide the evidence and tools for scaling-up micronutrient interventions and will contain information about the evidence on both health systems and effective delivery systems reported by Pena-Rosas et al. in this issue (14).

Emerging Evidence

Effective assessment of nutritional status and its determinants is critical in public health interventions and there is a need for biomarkers that are accurate and reliable and that reflect nutrient exposure, status, and function. This encompasses the development of specific biomarkers that can both be used across a range of applications and then a process for harmonizing decisions regarding their use under specific conditions, especially in developing country program settings. Wasantwisut and Neufeld’s (15) article in this issue, on the use of biomarkers in program evaluation, outlines the Biomarkers of Nutrition for Development initiative that aims to provide guidance for the selection and interpretation of biomarkers that meet a range of interests among food and nutrition stakeholders. The paper specifically looks at the commonly deficient vitamin A, iron, zinc, folate, and vitamin B12 but also stresses the need to consider excess and, ultimately, optimal health.

Another growing field of research with potential public health implications is research into micronutrient-related genetic variation. Considering that vitamin A deficiency remains a leading public health problem, the identification of low responder
phenotypes that negatively affect the conversion of β-carotene to vitamin A could be important. The research of Lietz et al. in this issue (16) and others working in genomics might unlock some of the current puzzles and also highlights the need to explore new avenues in the field of micronutrient research.

And, just as we look to the future and new areas of research, so too must we look back and see how the early research methodologies, which resulted in many major micronutrient advances and predominantly used laboratory and animal studies, could perhaps play a more integrated role in public health nutrition in the future. In this issue, Ross (17) aptly suggests that they could serve as a first line of interrogation for study designs and thereby play a role in refining the designs of human studies so that large, expensive, and logistically difficult human trials yield the best possible information. Regrettably, the approach of linking large human studies and programs to supporting basic research has largely been neglected by funding agencies who have not yet understood that this might ultimately be more cost effective than funding individual approaches independently. This is indeed food for thought and reminds us of the need to keep a broad perspective and consider all the options as we move forward.

**Moving Forward and Delivery Platforms**

As with the research, policies aimed at improving poor nutrition need to take a wide view. It is vital to balance responsibility between the individual and society. It is increasingly well accepted that, for policy to be effective, it is essential to identify and intervene at the most critical rate-limiting level and for programs to be complementary, supportive, and coordinated.

The International Food Policy Research Institute (IFPRI) has investigated the potential for using four broad types of delivery platforms—health, agriculture, market-based, and social protection programs, to deliver multiple micronutrient interventions (supplementation, fortification, and dietary modification) using seven criteria, namely that programs are well targeted, include the right interventions for the problem, are used as expected by targeted beneficiaries, are implemented as planned, have an impact on expected outcomes, achieve high coverage, and are sustainable. In the paper “Selecting Programs and Delivery Systems for Multiple Micronutrient Interventions” by Olney et al. (18) in this issue, the authors illustrate each delivery platform’s strengths and weaknesses as well as identifying critical knowledge gaps and highlighting what needs to be done to make more effective use of the different platforms, noting that each has a role to play. Cross-cutting issues that need to be addressed going forward when interventions are taken to scale include: ensuring a strong behavior change component, addressing the supply chain (including human resources), efficacy and impact assessment are critical, and greater advocacy at the key program decision-maker level.

A concern is that, although MNP have been shown to be effective in the treatment of anemia in moderately anemic children aged 6–24 mo, the effectiveness of MNP in large-scale program settings is scarce. Rah et al. (19) describe in this volume the experiences and findings of MNP distribution programs undertaken in refugee camps and emergency settings in Bangladesh, Nepal, and Kenya. Studies in these settings showed some improvements in anemia prevalence in certain subgroups, yet no significant improvements were seen in others. In addition, stunting significantly decreased in some settings. This paper shows that anemia may not be appropriate as a stand-alone indicator to assess the effectiveness of MNP. In addition, it highlights, importantly, that a key challenge in scaling up MNP programs is to ensure a high level of acceptance and adherence to the regime by the beneficiaries. This involves the need for extensive planning and monitoring around broader issues such as packaging design, formative research, social marketing, and staff training. It is also important to highlight that the same standards regarding ethics need to be applied in MNP evaluations, as are common practice in human studies with the Helsinki Declaration as the minimum. Implementation of MNP programs in complex and evolving environments is challenging.

Assessment of program implementation and impact is increasingly important. To receive the proposed donor funding for the Scaling-Up Nutrition initiatives for example, it is critical to determine whether strategies and programs reach the desired outcomes. As stated by Olney et al. (18), good program implementation and achieving the desired acceptance and behavior change is a prerequisite for having an impact. Assessing impact of a large-scale program requires a very different approach from a RCT, because programs can rarely withhold an efficacious intervention from a randomly selected group of individuals. The plausibility approach described by Habicht et al. (20) is the most suitable approach for evaluating program impact, as it assesses whether the observed change is likely to be due to the intervention, by also examining all other possible causes of change. The plausibility design can use different comparison groups to determine with greater certainty what change is likely to have occurred due to the program. The comparison group could be from the targeted group itself, for example, by monitoring change longitudinally in a cohort or through repeated cross-sectional surveys and at the same time assessing intervention exposure and adherence. A second option is to choose a comparison group from a nontargeted group of the same population and collect the same data from them as from the target group (e.g., adolescent girls who are not targeted and those under five who are targeted) whether through following cohorts or repeated cross-sectional surveys. In this scenario, the data from the nontargeted group show that the treatments, as are common practice in human studies with the Helsinki Declaration as the minimum. Implementation of MNP programs in complex and evolving environments is challenging.

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