Multiple Micronutrient Interventions Are Efficacious, but Research on Adequacy, Plausibility, and Implementation Needs Attention

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Abstract

Evidence for the efficacy of multiple micronutrient (MMN) supplementation has been established by state-of-the-art randomized controlled trials (RCT). These efficacy trials have also provided strong evidence of the widespread occurrence of deficiencies. Trials intended to demonstrate a public health benefit must show that the magnitude of benefit is adequate for policy considerations. In the MMN efficacy studies the magnitude of impact was generally inadequate. The extent to which this was due to various factors that affect individuals’ potential to respond to MMN supplementation has not been examined, and trials have not been designed to provide insights into why impact is below expectation. For instance, when birth weight was the outcome of concern, impact was not related to presumed need, judged by baseline birth-weight values. Also, contrary to expectations, the impacts were greater among the heavier mothers. Our inability to examine issues of adequacy, plausibility, and implementation with efficacy trial approaches as they are currently conducted, calls into question the present standards for designing and interpreting community RCT in nutrition. Improving the capacity of efficacy studies to yield more meaningful data requires a number of modifications to current practices, such as including measures of the intermediary behavioral and biological steps between intervention and biological outcomes to assess the adequacy and plausibility of the findings. The progression from RCT to program interventions must also extend research to program delivery and uptake to ascertain the full program impact pathway. This in turn requires novel organizations of relationships between research and program development and implementation.

logically precedes external validity (generalizability), for which RCT are not well suited (2). There are, however, serious weaknesses in RCT studies in nutrition (8), and the recent methodology, Grading of Recommendations Assessment, Development and Evaluation GRADE for establishing evidence-based interventions presented at this meeting (9) does not remedy these weaknesses. The problems relate to issues of adequacy of impact and the plausibility of findings. In addition, it is important to consider the need for research to improve trial design, to discuss the relationship of research plausibility and impact to future implementation, and to integrate basic epidemiological and implementation research by means of better organization, as recommended by Ross (10).

Do the MMN efficacy trials demonstrate benefit? The purpose of efficacy trials is to provide evidence of impact. The scientific requirements for efficacy trials are clear and well accepted. MMN efficacy trials require a comparison of an intervention group that receives the MMN intervention with a control group that does not. The two groups must be statistically and epidemiologically comparable, a condition attained through randomization. Randomization assures that the statistical results (e.g., $P < 0.05$) indicate a probability of causal impact (11).

All the RCT trials reviewed at the workshop randomized the two groups correctly. Overall they were shown to be efficacious in that the meta-analyses showed a significant impact of MMN interventions on the outcomes of interest ($P < 0.05$). In contrast to iron supplementation trials (12), where the comparison groups did not receive a biological intervention, all the control groups in these trials received interventions that included some micronutrients, such as iron and folate, that have previously been shown to be efficacious. Therefore, the impact reported in these efficacy trials is the effect of the addition of other MMN to those of the comparison groups. Without information on changes over the intervention period among a group that did not receive intervention, one does not know the full impact of the MMN. One might suppose incorrectly that the full impact would be at least as large as the added impact.

The fact that the trials only measured added impact is particularly relevant when the added impact is negative. A negative impact indicates that there are antagonisms among the nutrients in the intervention that diminish the impact. As an example, Ayoya et al. (13) recently reported results from a small randomized trial in which the MMN intervention, which included iron and folate, raised hemoglobin levels by 3.4 g/L, whereas an intervention of iron-folate without the other micronutrients raised hemoglobin by 6 g/L relative to a control group without micronutrients. Thus, the added MMN decreased the impact of the iron folate by almost half, but the MMN impact was nevertheless positive and beneficial. Without the control group, one would have inferred incorrectly that the overall effect was $-2.6$ g/L and therefore detrimental.

The impression that MMN does not decrease, and may even increase, neonatal mortality (14) is based on the comparison of a group taking MMN supplement including iron and folate with a control group taking iron and folate without other micronutrients. There was no control group that did not receive any micronutrients. Both the iron-folate and MMN supplements improved neonatal mortality in a 2003 study (15), but MMN supplements were not more effective than iron-folate, which is what Ronsmans et al. (14) also found. Similarly, ignoring the significant effect of iron on birth weight (16) may underestimate the total impact of MMN.

Another feature of the trials is that they demonstrate that the populations in which they were conducted were deficient in at least some of the MMN in addition to iron and folate. This is an important contribution because indicators of deficiency are inadequate for many micronutrients, as reviewed in this workshop (17,18). In fact, efficacy trials are fundamental tools for demonstrating remediable deficiencies, and, when they are well designed (6), they can also identify those who benefited from the supplementation.

In conclusion, the RCT reviewed in the workshop showed that MMN supplementation is efficacious relative to iron and folate control groups, but the total benefits relative to no micronutrients are likely to be underestimated, given that the comparison groups also received some micronutrient intervention. The fact that the trials document improvement in MN status also confirms the presence of deficiencies in the populations studied.

Is the benefit adequate to justify implementing and sustaining a program? Trials to demonstrate public health benefit must show that the magnitude of benefit is adequate for policy considerations. As stated above, in the case of MMN trials the magnitude that was studied is the added benefit of the MMN intervention to that of iron-folate supplementation. This added magnitude should be compared to the magnitude of the benefit of iron-folate supplement relative to no iron-folate. Without estimating the benefits of the iron folate compared to no supplementation, one cannot judge the relative advantages of adding MMN. An example of how this can be done for another type of nutritional intervention is the study reported by Ruel and Donegan (3,4). This type of comparison is required for policy decisions to determine if the MMN interventions are worth the added costs and potential side-effects.

The most common trade-off for decisions about public health actions are between the costs of planning, implementing, and sustaining programs compared to the positive returns in health and well-being. The costs include opportunity costs, as well as direct costs. They also include harm. In the studies mentioned in this workshop, an example of harm is the increase in neonatal deaths in the MMN groups suggested by Ronsman's analysis (14). Assessing the positive returns requires information on the magnitude or “adequacy” of the response. Unfortunately, at present there is no commonly accepted measure for determining adequacy unless one has in hand all the benefits and costs, in which case cost-benefit analyses can be used (19). Regimen and delivery efficacy trials cannot provide information for cost-benefit analysis. This information must come from program efficacy trials or other program information.

In the absence of cost-benefit information, a common approach is to measure the adequacy of desirable effect in public health by ascertaining the proportion of the population that achieves some norm of survival, health, nutrition, or performance. This is the approach that is used for the millennium development goals. This “all or none” (binomial) approach is straightforward and widely understood. Unfortunately, it hides the dynamics of change. In contrast, continuous measures permit one to examine the dynamics of change [e.g., see Figure 4 in (6)]. The field of nutrition is blessed by having many continuous measures. Consequently, one often presents impact data with continuous variables, as was the case in this workshop for birth weight (6). The impact can be expressed in absolute values, such as grams and centimeters, or effect sizes. However, neither the absolute impact nor the effect size can be used to ascertain the impact considered.
in relation to the potential to respond to the intervention. Therefore, the assessment of adequacy requires knowledge about potential to respond.

Potential to respond is a major source of biological heterogeneity of response across and within RCT (2,20). The potential to respond in nutrition RCT is the difference between what is and what could be or the difference between the baseline and normative standards. Multiple factors affect the potential to respond to micronutrient interventions. Individuals in the population who are already replete do not respond to additional micronutrients. In a population with endemic under-nutrition there will always be some individuals who are not deficient and others whose deficiencies are so moderate that they will have only a marginal response at best. Clearly, these individuals dilute the impact of the intervention, but it may not be easy to identify them because measures for MMN deficiencies are inadequate (17). Others may not respond because of genetic influences on absorption and utilization [e.g., (21)]. Also, individuals whose diets lack an essential component required for absorption or utilization do not have the potential to respond [e.g., fat is needed to absorb carotene to improve vitamin A nutrition (22)].

Maternal height has a major influence on birth weight everywhere, in both well-nourished and poorly nourished populations. In poor countries, where the majority of short stature in women reflects their own prenatal and postnatal malnutrition, MMN cannot be expected to override the association of stature and birth weight. Finally, it may be the case that the distribution of intake in an RCT was insufficient to attain the full adequacy of response, even though the dose-response between intake and response was good (23).

A partial solution to the problem of determining the potential to respond when other non-nutritional negative factors such as malaria are known to be important, is to include nutritionally replete individuals in the study who are not expected to benefit (24). These individuals, who are facing the same environmental circumstances, comprise the response level for a “repleted norm.” Another method is to extrapolate the deficit caused by other factors to correct official norms (24). Alternatively, one can estimate the asymptote of dose-response as the asymptote establishes the norm in that population (24).

In summary, the foregoing discussion reveals that although it is challenging to develop metrics for adequacy of impact (or of benefit), which could be used for comparing outcomes, they can and should be developed. Without such metrics one falls back on comparing the magnitude of impact to that of other interventions aimed at the same outcomes. For example, the 22-g impact on birth weight estimated in the meta-analysis (6) can be compared to the impact of food supplementation interventions (25). They are of similar magnitude, and therefore could be considered adequate, but both are small compared to the hundreds of grams of potential impact in some of the populations studied.

Are the results plausible?

When the results of efficacy trials include findings that are counterintuitive or do not fit with expectations, such events typically lead to further research to identify the factors that explain them. In fact, this is a primary process in scientific work. When the results of meta-analyses of RCT are used to derive policy implications, there should be a similar investigative process in the form of plausibility analysis. Thus, in the case of MMN supplementation and birth weight, the finding by Fall et al. (6), of no positive dose-response relationship to the population deficiency in birth weight, and the counterintuitive finding that birth weight response was only found among heavier women (higher BMI), should trigger further investigation before the overall findings of a positive impact are used to support policy decisions.

We suggest that the absence of a positive dose-response in relation to baseline deficiency and an absence of response among thin mothers may occur because the MMN supplementation could not be used because of macronutrient deficiencies. Protein and energy deficiencies were present in almost all of the populations in the studies. The fundamental nutritional concept of a “limiting nutrient” does not appear to have been taken into consideration in these MMN trials nor in the document that derived the policy implications from the findings (25). The likelihood that protein and energy malnutrition dampened the potential to respond is high and needs to be investigated in future trials. The fact that one sees >100% adequacy in some trials may be because protein-energy requirements were already met, and the limiting nutrients really were MMN; “hidden hunger” is actually hidden in these apparently well-nourished populations—in contrast to “overt” hunger in others.

From the perspective of using research results to inform policy, a follow-up on the implausible meta-analysis results illustrates the importance of incorporating plausibility analysis as a routine aspect of the sequence of research from initial bench research through research for policy and program development to evaluation. Plausibility analyses include assessing the biological intervention impact pathways by measuring the biological intermediary changes between the intervention at the level of the individual and the outcome. This assessment ascertains which of the plausible mechanisms explained the impact or lack of impact (26). This type of analysis forces one to consider more mechanisms of biological action than are implicit in the design of most RCT.

Are the trials implemented as planned?

Another source of heterogeneity within and across RCT is behavioral heterogeneity in aspects of the implementation. Behavioral heterogeneity is as important as biological heterogeneity. Behavioral heterogeneity in implementation occurs in two sectors: intervention delivery and household utilization. To date there has been little examination of behavioral heterogeneity in MMN trials. Looking ahead to policy decisions, it is essential to use efficacy trials to examine behavioral intervention pathways and the extent to which the results may have been attenuated by problems in the pathway from introduction of the supplement in the intervention group to actual consumption (e.g., in the right amount, right frequency, for the right duration) by the intended subjects.

Linking efficacy research to implementation research

A major risk associated with the generally limited impact documented from MMN efficacy trials is that interest in the potential of MMN approaches to address endemic deficiencies will fade. There is already some evidence that donors are losing interest in MMN interventions. The efficacy trial findings must be put into the context of what is already well known about the essentiality of micronutrients for performance, health, and survival, and about their widespread deficiencies, as demonstrated by the efficacy of the supplementation trials reviewed in the workshop. The issue is not whether anything should be done, but what should be done and how it should be done. Basic research into issues of the potential to respond, antagonisms, and side-effects is urgently needed. Efficacy research must also be expanded and better linked to program development and
implementation and include a systematic investigation of implementation issues, but ultimately it must investigate the full program impact pathway (27) from implementation design through delivery of the intervention, to intervention reception and understanding of associated information, to household transmission of the intervention to the recipient, and finally, through the biological pathways of ingestion, absorption, and metabolism to the final outcome of improved nutritional status. The Program Impact Pathway includes not only the behavioral and biological intervention pathways but also the contributions of synergistic and antagonistic effects of other influences on the outcomes. The construct of "program impact pathways" derives from work on "program theory" (27). Of particular importance will be knowledge about the implementation steps from bureaucratic behaviors within programs (28,29), which affect service delivery; through behaviors between the interface of programs and households (30), which affect program utilization and compliance with recommended use of services and products; and finally to intra-household behaviors (30). A recent review of large-scale RCT of the effects of conditional cash transfer programs on nutrition found that almost none of these studies had sufficient information to permit examination of their program impact pathways (31). Our review of various other RCT in nutrition (8) came to the same conclusion.

Funding for research to elucidate implementation pathways is presently low. For example, when one examines the distribution of research funding to improve or develop new technologies to address the causes of childhood mortality versus funding for research on the use of current technologies, the ratio is 97:3% (32). This ratio is particularly disturbing in view of the fact that more than two-thirds of child deaths in poor countries are due to inadequate delivery of interventions with proven efficacy (33). Understanding program impact pathways will become over-ridingly important when a variety of programs and platforms (e.g., health, agriculture, market-based, social protection) are tested as potential delivery systems for MMN interventions, as outlined by Ruel (33) in this workshop.

The relationship of research on biological aspects of micronutrients and social research on interventions to improve micronutrient status in populations is complex and, at present, inadequately conceptualized. Making progress in the translation of basic scientific knowledge to effective policies and programs requires the development of models to achieve coordination between biological and social research on micronutrients and between research and program implementation.

Using community-based efficacy trials to investigate social responses of participants and program delivery issues offers an important opportunity for developing integrated models. For example, postintervention analysis of the social characteristics of responders and nonresponders in an RCT that tested the efficacy of iron-fortified soy sauce in China produced important insights for policy and program delivery (34). Clearly, micronutrient efficacy trials are not uniform in their potential to yield insights about all of the social aspects of concern as some of them use delivery systems that differ so substantially from feasible program delivery models that they are of limited use for that purpose. Other research is required to address these issues, either incorporated into RCT (11) or building on RCT (2) so that the plausibility and adequacy results can be interpreted.

In addition to strong conceptual models, achieving coordination between research and programs involves more than goodwill, it requires institutional structures that facilitate coordination by means of appropriate funding and incentive structures. An early example of a structure that encompassed the breadth from biological research to practical solutions is the work of the INCAP under the direction of Nevin Scrimshaw (1949–1962), in which biological research was prioritized to address the nutritional needs of the region (35). In addition to major scientific insights into the extent and causes of malnutrition, and into basic biological solutions to the problems they identified, INCAP went on to develop products (e.g., iodized and vitamin A salt and Incaparina, a cereal-based complementary food for young infants) that were economically feasible and even attractive to private industry. Their next step was to investigate conditions for the long-term sustainability of mechanisms of distribution for the products and to implement them through legislation and long-term binding contracts for quality control. The findings from this integrated research approach had global significance because many of Central America’s nutritional problems were prevalent worldwide. The significance of the integrated INCAP approach was not recognized at that time as a legitimate objective for scientific research, a misperception that still hampers the institutionalization of research to achieve evidence-based programs.

A current model (36) that illustrates a structural integration of research and program implementation for micronutrients is the nutrition research unit of the Mexican National Institute for Public Health (INSF). This unit has contractual links to nutrition intervention implementing agencies, and it has the infrastructure for basic and applied research. INSF undertakes research to assess not only impact, but also the adequacy, of large-scale interventions (37) and conducts both biological (38) and behavioral (30) research to improve impact when inadequacies are identified. Other similar models can be designed by building strong partnerships between different institutions that focus on one or two of these complementary areas (39).

In conclusion, a review of the current situation with respect to improving micronutrient status of populations shows that, in addition to addressing important biological questions, research on this critical health issue needs to include studies on how to establish and maintain effective research-programmatic coordination, beginning with specification of the basic principles about conducting research for policy decisions and program implementation (40), and designing and testing models of coordination (17,37). The methodology for designing and testing these models is now a dream. It must be made a reality.

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