Provision of Multiple Rather Than Two or Fewer Micronutrients More Effectively Improves Growth and Other Outcomes in Micronutrient-Deficient Children and Adults¹–³

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Abstract
Deficiencies of multiple micronutrients (MMN) usually coexist in developing countries, but supplements have usually provided only 1 or 2 micronutrients (MN). To inform policy, in this article we compared the relative benefits of supplying MMN vs. a placebo or 1 or 2 MN on the following: children’s growth, health, and development; pregnancy outcome; nutritional status; and HIV/AIDS mortality and morbidity in adults. Sufficient data were available to perform random-effects meta-analyses of randomized controlled trials (RCT) for the effects of MMN on child growth and nutritional status. Results for other outcomes are presented as effect sizes (ES) when available. In children, MMN interventions resulted in small but significantly greater improvements in length or height (ES = 0.13; 95% CI: 0.055, 0.21) and weight (ES = 0.14; 95% CI: 0.029, 0.25), hemoglobin (ES = 0.39; 95% CI: 0.25, 0.53), serum zinc (ES = 0.23; 95% CI: 0.18, 0.43), serum retinol (ES = 0.33; 95% CI: 0.050, 0.61), and motor development. A Cochrane review reported that compared with no supplementation or a placebo, MMN supplementation during pregnancy reduced the relative risk of low birth weight (0.83), small-for-gestational age (0.92), and anemia (0.61); however, MMN were not more effective than iron folic acid alone. There is some evidence that MMN supplementation improves CD4 counts and HIV-related morbidity and mortality in adults. The efficacy of MMN varies across trials, but overall there is evidence that outcomes are better than when providing ≤2 MN. The policy implications of these studies are discussed. J. Nutr. 139: 1022–1030, 2009.

Introduction
Multiple micronutrient (MMN)⁶ deficiencies are very common, usually resulting from poor-quality diets. The most prevalent micronutrient (MN) deficiencies, iron, vitamin A, zinc, vitamin B-12, riboflavin, vitamin D, and vitamin E, usually occur together due to a low intake of animal source foods (1,2).

During the last few decades there has been strong interest in the adverse effects of MN deficiencies on health, growth, and development, although much of the research has focused on the effects of single MN. Interventions to improve the status of MMN simultaneously makes sense from both a biological and a programmatic perspective, and the cost of adding additional MN to supplements or fortificants is relatively low. Thus, in the last 5–10 y, the effects of MMN interventions on health and development have been evaluated in pregnant women, infants, preschool and school-aged children, and persons with HIV/AIDS in efficacy trials primarily as well as in a few complementary feeding programs.

To date there has been no comprehensive review of the effects of MMN on multiple outcomes, to our knowledge. A few meta-analyses have been conducted on selected outcomes, including child growth (3), HIV/AIDS (4), and pregnancy (5). The purpose of this paper is to review the efficacy of interventions with MMN supplements or fortified foods on growth, nutrient status, morbidity, and cognitive and motor development in children, and on HIV/AIDS and pregnancy outcomes in adults. Meta-analyses were conducted for outcomes with sufficient data and effect sizes (ES) calculated for other outcomes where appropriate.
Methods

Search strategy. We identified published articles using PubMed and the ISI Web of Science, with no language or date restriction. Key words used to search the literature were: MN(s), vitamins, minerals, pregnancy, growth, morbidity, mortality, child development, cognitive development, motor development, HIV, and AIDS. Additional studies were identified from review articles and personal communications.

Inclusion criteria. Studies varied in many aspects of the MMN interventions (Supplemental Table 1). These included: duration and frequency of supplementation, number and type of MN supplemented, control group (e.g., for pregnancy studies, the control group was usually given iron or iron + folic acid), age of subjects, and delivery system (supplement or fortified food). Only randomized controlled trials (RCT) lasting at least 4 wk were included in the analysis. The control group could be a placebo (including unfortified control food or beverage), riboflavin, iron alone, zinc alone, riboflavin + iron, riboflavin + zinc, or iron + folic acid (the latter most often in pregnancy), and the intervention could be a supplement or a fortified food. “Supplements” are defined here as tablets, powders, or beverages that contain ≤419 kJ/d (100 kcal/d) of cereal or milk, whereas the term “fortified foods” refers to MMN preparations containing more energy and macronutrients, which could theoretically affect MN (MN) absorption and other outcomes. “Multiple” MN were defined as those providing >3 MN, because studies containing less than this were usually designed to explore the individual effects of 1 or 2 MN.

Outcomes. Some studies measured multiple outcomes, but to compare data across studies, the effects of MMN interventions on specific outcomes were examined separately. Outcomes included growth of children (change in length or height, and weight), morbidity of infants and children, child development, pregnancy outcome, effects on HIV/AIDS, and anemia and nutritional status. For each outcome, previous reviews and meta-analyses are referred to when available, followed by the presentation of the current meta-analysis for each outcome (except pregnancy) using data from studies meeting the inclusion criteria. For outcomes with insufficient data to conduct a meta-analysis, the results of individual studies are described and presented in table format.

Analytical approach. The ES of all interventions meeting the inclusion criteria were calculated in the current meta-analysis and are shown in Figure 1 for length and height and in Figure 2 for weight. The values are presented in order of the age of the children, from youngest on the left to oldest on the right. Most of the studies were on infants and preschoolers, with only 5 on school children (7,8,19,21,22). Overall, MMN improved length or height, and weight compared with a control group, with an ES of 0.13 (95% CI: 0.055, 0.21; P = 0.0015) for length and 0.14 (95% CI: 0.029, 0.25; P = 0.015) for weight. Study type, baseline HAZ, WAZ, and age did not influence the ES for changes in growth.

Five individual studies showed a significant effect of MMN on increases in height, for all children in 3 studies (8,14,23) and only in subgroup analyses in 2 studies (10,11); in Mexico, MMN increased linear growth only in the children aged <12 mo (10) and in Vietnam, only children who were stunted at baseline had a greater increase in linear growth with a daily or weekly MMN supplement compared with a placebo (11). The 2 largest ES were in a subgroup analysis on stunted children (HAZ < −2) in Vietnam (11) (data not shown). None of the other studies investigated whether the response was greater in stunted children. Our metaregression analysis did not show that children with lower initial HAZ scores would benefit more than those with higher scores.

Morbidity and mortality of children

MMN interventions were effective in reducing morbidity in some studies (28,29), but not others (13,17,18,27,30), and data were unsuitable for use in a meta-analysis. There was a small, 15% increase in diarrhea in Bangladesh when MMN were compared with a placebo and (not shown) a 29% increase in severe diarrhea in Peru when MMN were compared with a zinc control (18). Two studies, in India (28) and Pakistan (29), reported a significant reduction in diarrhea (18 and 11%, respectively). The study in India also found a significant reduction in fever (7%) and respiratory infections (26%). There were no studies, to our knowledge, of the effect of MMN on child mortality.

Mental and motor development of children

A series of papers recently published in The Lancet (31–33) identified stunting, iodine, and iron deficiency as risk factors for
poor child development and cognitive stimulation as a protective factor. The impact of MMN interventions was suggested as an area that needed further research (33).

Although investigators have studied the effects of single nutrient interventions on the mental and motor development of children, very few RCT have evaluated the effects of MMN on these outcomes. The 4 studies all show a positive effect of MMN on motor development (15,34–36) (Table 1). The interventions differed in each study, including weekly supplements to young children (34), a fortified complementary food (15), a MN powder or a fortified spread (36), or supplementation of HIV-positive pregnant women followed by assessment of the effects on development of their children (35). In contrast, neither of the studies that reported effects on mental development demonstrated a significant effect of the intervention (34,35).

Pregnancy outcome
A review of RCT of MN efficacy concluded that the only supplements that affected birthweight were magnesium (which reduced small-for-gestational age births by 30%) and calcium (which reduced the risk of low birthweight) (37). No MMN interventions were included. A Cochrane analysis conducted in 2005 (5) reviewed 9 trials that provided MMN (defined as $>3$ MN) in pregnancy with a total $n$ of 15,378. The review concluded that MMN significantly reduce risk of low birthweight [relative risk (RR) = 0.83], small-for-gestational age (RR = 0.92), and anemia (RR = 0.61) compared with no supplementation or a placebo. However, these benefits were not significantly better than those obtained with iron + folic acid alone.

An updated meta-analysis of pregnancy intervention trials was not conducted here, because the Systematic Review Team of Multiple Micronutrient Supplements During Pregnancy, under the Micronutrient Working Group of the Standing Committee on Nutrition of the United Nations, is currently completing a pooled analysis of data from trials that used the UNICEF/UNU/WHO international MMN preparation “UNIMMAP” supplement designed for pregnant and lactating women. They are expected to provide further information about whether MMN increase perinatal and neonatal death, a concern raised by an analysis that combined the outcomes of 2 separate MMN trials in Nepalese pregnant women (38).

Few investigators have assessed adequately the effects of MMN supplements on the MN status of pregnant women. The most thorough study in this regard revealed that MMN reduced the prevalence of deficiencies of folate, riboflavin, and vitamins B-12, B-6, D, and K, but a remarkably high prevalence of deficiency persisted after supplementation (39). This suggests that higher doses should be considered and tested.
HIV/AIDS

Five published articles on RCT of the effects of MN supplementation on morbidity and mortality from HIV infection were reviewed and published online by the Cochrane Collaboration in 2005 (4). None of these trials tested the effects of MMN in adults and only 2 included MMN. Since then there have been 3 new trials of MMN efficacy in persons with HIV (35,40–45).

Morbidity, mortality, indicators of disease, and transmission in the absence of highly active antiretroviral therapy.

Three RCT have evaluated the effect of MMN on mortality from HIV and AIDS (Table 2). One conducted in pregnant HIV-positive Tanzanian women reported an overall reduction in mortality (46,47). In that study, pregnant women were supplemented with MMN, with or without vitamin A, or a placebo from 14 to 27 wk of gestation and for many years following, although the inclusion of vitamin A in the supplement was eventually stopped due to evidence of increased risk of mother-to-child transmission (MTCT) of HIV in the vitamin A arms of the trial (47). In the other 2 studies, the benefit was limited to subgroups. In Thailand, for participants with a baseline CD4 count <200, there was a reduced risk of mortality in those who received the MMN supplement compared with those receiving a placebo (48). Participants in Tanzania had tuberculosis (of whom one-half were also HIV positive) and received zinc alone, MMN alone (no zinc), zinc + MMN, or a placebo daily for 8 wk. There was no overall reduction in mortality due to type of supplement. However, HIV coinfected patients who received MMN + zinc had a 71% reduction in mortality compared with those who received a placebo (45).

The 1 RCT that examined the effects of MMN on morbidity in nonpregnant adults found significant reductions in 13 of 15 HIV-related complications (46).

MMN supplementation increased CD4 counts in 3 of the 4 studies in which they were measured (42,46,48,49) and reduced viral load in the Tanzanian study compared with a placebo (47), but not in the other 3 studies (42,45,48). MTCT, either apparent or apparent, was reduced in Tanzania in the women at greatest risk of transmission during delivery or through breast-feeding, was reduced in Tanzania in the women at greatest nutritional risk. Additionally, the effects of MMN on viral loads in cervicovaginal secretions or semen have been measured in 3 studies (42,50,51). One reported an increase in cervicovaginal shedding of HIV in the MMN vs. placebo group, which was not significant in women who were selenium deficient at baseline (42). Neither of the other 2 studies found a significant effect of MMN on this outcome (50,51).

In summary, there is some evidence that supplementation with MMN reduces mortality, and possibly morbidity, in adults with HIV/AIDS, although additional studies are needed in other populations.

Morbidity, mortality, and disease indicators in patients provided highly active antiretroviral therapy.

An area that needs further investigation is whether MMN are a beneficial adjunct therapy for people receiving highly active antiretroviral therapy (HAART). Only 2 RCT (duration > 4 wk) have examined this question, but both demonstrated a benefit and no adverse effects (41,49). In Poland, adults receiving MMN compared with a placebo for 6 mo had greater increases in serum vitamin A, C, and E, less DNA modification, and improved immune function, but no change in CD4 counts (49). In the US, there were no negative effects of adding MMN to HAART on fasting serum glucose, insulin, or lipids or on kidney or liver function. In addition, people receiving MMN had 24% higher CD4 counts after 12 wk of supplementation than those who received a placebo (41). However, both of these trials were small and included only a few outcomes.

Hb, anemia, and nutritional status

Most (17/19) studies that included child growth as an outcome had data on the effects of MMN on Hb concentration, and in addition, 9 trials reported effects on Hb and anemia but did not measure other outcomes such as growth (29,30,52–58). Most studies used a placebo control, some studies included both iron and placebo controls (23–26,30), and 2 (53) included an iron + folic acid control. MMN were given daily, several times a week, or weekly, with some trials comparing different dosing frequencies. The iron content of the MMN ranged from 5 to 22 mg/d, but most commonly was 5 to 10 mg.

### TABLE 1  Efficacy of MMN for improving motor and mental development in children

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Control group</th>
<th>n</th>
<th>Child development measure</th>
<th>Motor outcome</th>
<th>Mental outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>(15)</td>
<td>South Africa</td>
<td>Unfortified food</td>
<td>266</td>
<td>Gross motor milestones (25 items)</td>
<td>ES = 0.29*</td>
<td>—</td>
</tr>
<tr>
<td>(34)</td>
<td>Bangladesh</td>
<td>Riboflavin</td>
<td>80</td>
<td>Bayley Scales of Infant Development II</td>
<td>ES = 0.39*</td>
<td>ES = 0.045</td>
</tr>
<tr>
<td>(35)</td>
<td>Tanzania</td>
<td>Placebo</td>
<td>327</td>
<td>Bayley Scales of Infant Development</td>
<td>RR = 0.4*</td>
<td>RR = 1.3</td>
</tr>
<tr>
<td>(36)</td>
<td>Ghana</td>
<td>Nonintervention group</td>
<td>276</td>
<td>% of children able to walk independently at 12 mo</td>
<td>24%*</td>
<td>—</td>
</tr>
</tbody>
</table>

1 Probability of having a score <70 on the Bayley Scales of Infant Development Psychomotor Index.
2 Difference in prevalence of attained walking alone at 12 mo old between the nonintervention group and the Nutributter group.
3 *P < 0.05.

### TABLE 2  Efficacy of MMN for improving HIV/AIDS indicators and associated outcomes in adults

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Population</th>
<th>n</th>
<th>Mortality (RR)</th>
<th>Viral load (ES)</th>
<th>Other significant effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>(48,51)</td>
<td>Thailand</td>
<td>Adults</td>
<td>481</td>
<td>0.53*</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(42)</td>
<td>Kenya</td>
<td>Nonpregnant women</td>
<td>400</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(46,47)</td>
<td>Tanzania</td>
<td>Pregnant and lactating women</td>
<td>1083</td>
<td>0.72*</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(43,44)</td>
<td>Tanzania</td>
<td>Pregnant and lactating women</td>
<td>1083</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(41)</td>
<td>USA</td>
<td>Adults taking HAART</td>
<td>40</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

1 *P < 0.05.
2 Significant (P < 0.05) decrease in mortality and MTCT in women with low baseline nutritional and immunological status.
The overall ES across the trials show that MMN are certainly effective at increasing Hb compared with a control group, with a mean ES of 0.39 (95% CI: 0.25, 0.53; \( P = 0.001 \)) (Fig. 3). Studies that used a fortified food were significantly more effective in improving Hb (ES = 0.60, 95% CI: 0.32, 0.88, \( P \)-value for fortified compared with other study types = 0.001). Younger children had a larger increase in Hb due to MMN than did older children (\( P = 0.006 \)). Baseline Hb, HAZ, and WAZ were unrelated to the ES.

Fewer studies reported change in the prevalence of anemia. The mean reduction in the point prevalence of anemia with MMN vs. a noniron placebo ranged from 10 to 40%. There was a greater reduction in anemia with a higher amount of iron in the MMN (Fig. 4A), and in populations with a higher prevalence of anemia at baseline (Fig. 4B).

In the MMN interventions that reported changes in serum (or plasma) zinc and retinol, the control contained neither of these nutrients. MMN had a significant effect on serum zinc in 8 of the 12 studies where MMN were given daily. The mean ES was 0.23 overall (95% CI: 0.18, 0.43; \( P = 0.034 \)) (Fig. 5). There was a difference in the change in serum zinc by type of study (\( P = 0.006 \)). Daily supplementation compared with either placebo or iron was significantly better at improving serum zinc compared with the other study types (ES = 0.45, 95% CI: 0.18, 0.43, \( P \) for difference = 0.001 and ES = 0.42, 95% CI: −0.70, 1.54, \( P \) for difference = 0.013, respectively). In the meta-regression model, lower HAZ and higher serum zinc at baseline predicted a larger response to MMN (\( P = 0.0059 \) and \( P = 0.024 \), respectively). One paper only reported the effects of MMN on changes in serum retinol (59); the overall ES was 0.33 (95% CI: 0.05, 0.61; \( P = 0.023 \)) (Fig. 6), with no significant difference due to the type of study. However, children with lower baseline HAZ, WAZ, and serum retinol had a larger retinol response (\( P < 0.001 \), \( P = 0.002 \) and \( P < 0.007 \), respectively).

**Discussion**

This review shows that the efficacy of MMN varies across trials and outcomes, but that overall there is substantial evidence that outcomes are improved compared with 0–2 MN.

Providing MMN vs. 0–2 MN improves growth (in length and weight) and young child motor development. In addition MMN reduce anemia, and improve the zinc and vitamin A status of infants, children and school children. However, the ES of MMN on Hb and serum zinc differ depending on the type of study. Somewhat surprisingly fortified food (compared with unfortified food) had a significantly larger effect on Hb compared with other interventions, including daily or weekly MMN vs. placebo and daily MMN vs. iron. For improving serum zinc, daily MMN supplements were more effective than fortified food or weekly supplements. Few studies have been conducted on the effects of MMN on morbidity, and none on mortality. Given our overall conclusion that MMN interventions support better child growth, nutritional status and motor development than a placebo, with no reported adverse effects, it may, however be unnecessary to conduct more large mortality trials.
There is some evidence of benefits of MMN supplements for reducing adult morbidity and mortality, improving birth outcomes, and increasing CD4 counts. These results need to be confirmed in other populations. To date, no studies of MMN have been conducted, to our knowledge, in children with HIV/AIDS. More studies are needed to examine patients receiving HAART and also the effects on MTCT.

For pregnant women, the published meta-analysis shows a reduction in low birthweight, small-for-gestational age, and anemia when MMN were compared with no supplementation or a placebo, but no greater response to MMN when compared with iron + folic acid alone. The important issue of possibly increased perinatal and neonatal mortality due to maternal MMN supplementation during pregnancy in some populations will be addressed in the forthcoming publication of the pooled analysis of the UNIMMAP supplements.

It is undoubtedly necessary to increase the dose of at least some MMN delivered, both in pregnancy and in other population groups, to reduce the remaining high prevalence of deficiency and possibly improve the impact. Only 1 RCT has compared the effect of supplementing pregnant women with twice the Recommended Daily Allowance (2RDA) (except for iron) or 1RDA of 15 MN compared with iron + folic acid (60). The 2RDA supplement caused a significant reduction in birthweights < 3000 g and in low birthweight infants of women who were anemic (and presumably more deficient in several MN) at baseline, whereas the 1RDA supplement was no more effective than the control. Different doses should be tested systematically in future trials with MMN supplements, fortified foods, and lipid-based nutrient spreads. More data are needed on the effects of MMN on other nutritional status outcomes and cognitive development. In addition, more attention should be given to the issues of targeting (e.g. whether we should target stunted children), optimal delivery vehicles (including supplements, fortified foods, dry MMN powders, and fortified spreads), and program efficacy and effectiveness. The benefits from maternal supplementation in lactation should also be investigated.

Implications for policy. Only 2 current policies on the use of MMN were identified. WHO’s “Guiding Principles on Feeding Non-Breastfed Children 2 to 24 Months of Age” states: “as needed, use fortified foods or vitamin-mineral supplements (preferably mixed with or fed with food) that contain iron.” Also, “if adequate amounts of animal-source foods are not consumed, these fortified foods or supplements should also contain other MN, particularly zinc, calcium and vitamin B-12” (61). More recently, UNICEF/WHO recommended the use of MMN supplements in populations affected by an emergency (62). In addition to these specific recommendations, WHO/FAO recommends the fortifi-
cation of food staples with MMN. The selection of MMN and amounts to add should be based on knowledge of the prevalence of inadequate intakes in a population group (63).

The limited recommendations on MMN use by policy-making agencies is in part the result of uncertainty about their efficacy and safety, an information gap that the current review and analysis attempts to improve. Ideally, a major policy decision such as universal or targeted interventions with MMN compared with ≤2 MN needs to be supported by evidence to convince agencies, governments, and individuals that this will produce substantial improvements in public health, such as reduced mortality or morbidity, or the prevention of serious mental deficit. Although WHO recommends iron + folic acid supplements for pregnant women and young children, it is well known that coverage and compliance is very poor, especially for children. Fortified complementary foods for children, as well as the newer lipid-based nutrient spreads and powders that can be added to foods, are potentially more attractive.

Do the results of the efficacy trials to date provide sufficient evidence to support an international recommendation to use MMN rather than 0–2 MN? In total, they provide considerable evidence for relatively small benefits for child growth and development, pregnancy outcome, reduced mortality, and CD4 counts in HIV/AIDS (but with few studies conducted); a substantial reduction in anemia (but not compared with iron + folic acid alone), and improvements in vitamin A and zinc status. These may be the greatest benefits it is reasonable to expect and MMN are relatively cheap and feasible to supply. On the other hand, we are still lacking evidence of major impacts on child mortality and morbidity and the important question of whether MMN provided during pregnancy increase perinatal mortality needs to be resolved. If it is still necessary to obtain such evidence, perhaps by testing different formulations and amounts of MN, this needs to be decided and research focused on this question. Agencies and scientists need to develop a coordinated, systematic plan that prioritizes research and optimizes and assesses program efficacy and effectiveness. A huge investment has already been made in testing MMN interventions, but we still need to answer important questions such as: when is supplementation or fortification with only 1 or 2 MN justified or should MMN always be supplied; what doses should be delivered; and how do we prioritize, integrate, and monitor the many available approaches for delivering MMN? In addition, those responsible for the delivery of MN should establish a coordinated, systematic plan for providing and delivering them to relevant population groups in ways that are effective, cost-effective, feasible, and safe.

Literature Cited


