Achievements, challenges, and promising new approaches in vitamin and mineral deficiency control

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Micronutrient deficiencies (MNDs) contribute significantly to the world's disease and mortality burden. Global efforts addressing MNDs have achieved significant yet heterogeneous progress across and within regions and countries. For vitamin A and iodine interventions, enhancing achievements in coverage require further political and financial commitment and targeting of hard-to-reach populations. Anemia control must focus on prevention among preschoolers and adolescent women and on integrated public health programs. Current international guidelines on iron supplementation and cut-off values for anemia need revision. For zinc, advocacy to accelerate the application of revised diarrhea management guidelines is critical, as are efficacy studies on food-based interventions and preventive supplementation.

INTRODUCTION

The lack of essential vitamins and minerals affects more than one-third of the world's population, particularly women and children in resource-poor households, with devastating consequences for public health and social development. It is estimated that as many as 2 billion people are at risk of zinc deficiency; 1.6 billion suffer from iron deficiency; and approximately 2 billion have insufficient iodine intake. Vitamin A deficiency affects more than 125 million children under 5 years of age, of whom roughly one-half will become blind and die within 12 months of losing their sight. These vitamin and mineral deficiencies contribute considerably to the burden of disease linked to adverse functional outcomes such as stunting, increased susceptibility to infections, birth defects, cognitive losses, blindness, and premature mortality. This review will focus on these four nutrients because deficiencies in these four constitute a public health challenge of considerable magnitude; in addition, it will highlight the important lessons learned so far in the global efforts to control and prevent these deficiencies safely and sustainably.

GLOBAL ACHIEVEMENTS AND CHALLENGES IN ADDRESSING MICRONUTRIENT DEFICIENCIES

Vitamin A

Vitamin A deficiency (VAD) is a major public health problem in more than half of all countries. Most of the populations affected live around the equatorial plane, typically in poor rural and periurban settings where dietary vitamin A intake is inadequate, infections are frequent, and child mortality typically exceeds 70 per 1,000 live births. Definite progress in reducing VAD has been achieved in the last decade.[1] In general, eye lesions declined throughout the 1990s. The principal message is that we have proven and affordable solutions available

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that can be combined and integrated with existing delivery mechanisms within and outside the health sector to optimize impact. Basically, such interventions can be divided into food-based approaches (dietary diversification and food fortification) and periodic supplementation.

Food-based approaches. Dietary diversification through nutrition education and horticultural approaches has been achieved in many settings. Moreover, community-based interventions yield other kinds of outcomes that are critical for development, namely empowerment of the poor and gender equity, among others. Pilot studies in Mozambique have shown new varieties of carotene-rich sweet potatoes to be effective in reducing the prevalence of low serum retinol in young children.[2] Fortification of sugar with vitamin A has been effectively applied on a national scale through private-public arrangements in four Central American countries in which mandatory fortification has contributed significantly to the reduction of VAD, particularly when complemented with programs providing vitamin A supplementation for children younger than 2 years of age.

Vitamin A supplementation. Globally, there has been a threefold increase in effective coverage with vitamin A supplementation (VAS) since 1999.[3] On average, approximately 70% of all children aged 6–59 months in eligible countries receive at least one megadose of vitamin A and 58% are fully protected with the recommended two doses. Of the 78 countries with recognized VAD, 46 have policies for postpartum VAS as well. However, there are specific challenges that need to be addressed and opportunities for improvement that must be seized in order to achieve optimal program performance and for virtual elimination of VAD to become a reality.

Securing funding and solving strategic bottlenecks constitute the key challenges in achieving sustainable universal VAS coverage. The Global Alliance for Vitamin A (GAVA) has calculated that of the estimated 800 million vitamin A doses required annually to achieve universal coverage of children under the age of 5 years who are at risk of VAD, approximately 50% are at risk of not being delivered due to policy and access constraints (shortfall) and to management gaps in planning, funding, training, demand generation, and supply (slippage). Sustainability is also of concern because only ~50% of VAD priority countries earmark financial resources towards vitamin A programs. On the positive side, around a dozen countries already procure their own vitamin A supplies, and VAS programs are being included in poverty-reduction strategies or sector-wide plans in 26 countries. However, there is still a need to advocate for policies that warrant effective and universal coverage as well as a need to sustain VAS as a key child survival intervention.

Multiple delivery strategies are required for universal coverage with VAS. Twice-yearly campaigns, routine health service delivery, community-based distribution schemes, and outreach services are all needed to ensure high-level coverage that includes hard-to-reach populations. When VAS is included with other child survival services, such services become more meaningful for the community as well as for the health delivery system itself, and coverage increases (Figure 1). Delivering packaged services also makes good economic sense.

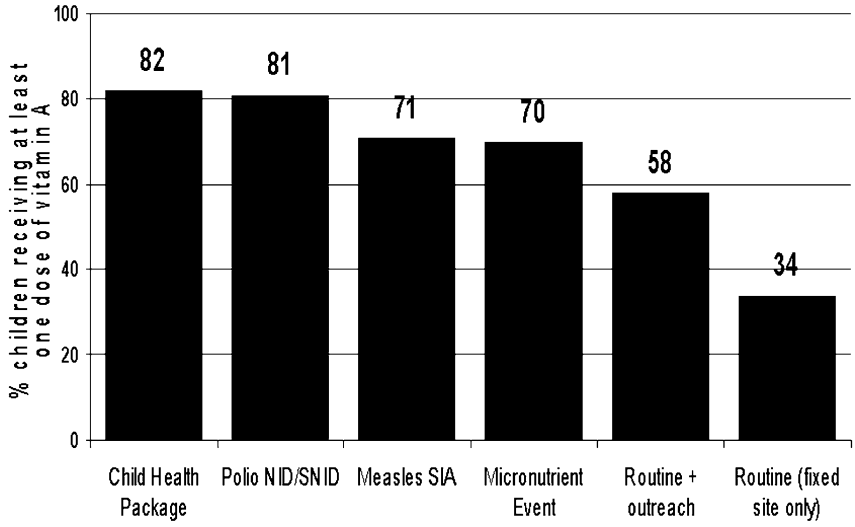

Figure 1 **Packaged delivery yields highest coverage: Mean one-dose coverage by distribution strategy (1999–2004).** Data from *UNICEF State of the World's Children, 2006.*[4]

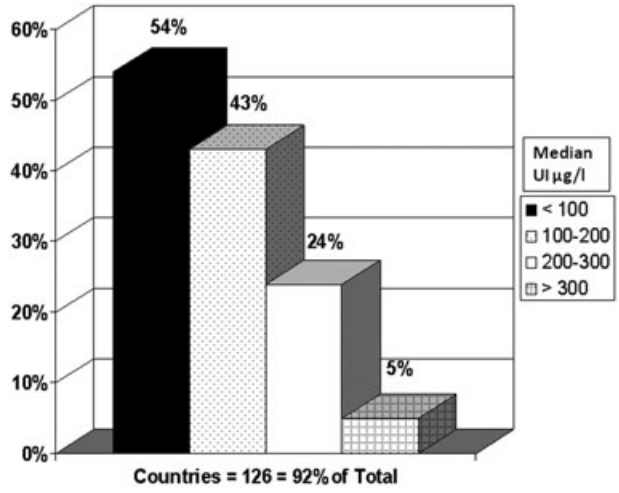

Figure 2 **Iodized salt consumption (≥15 ppm) by region: 1998–2004.** Based on latest available estimates for consumption of adequately iodized salt from 97 developing countries with data from 1998–2004, covering 95% of the developing world's population.
Data from *UNICEF State of the World's Children, 2006*.[4]

Iodine

Iodine deficiency disorders (IDDs) encompass a wide spectrum of early ontogenetic alterations caused by impaired thyroid function between week 15 of gestation and year 3 of postnatal life. The reproductive and cognitive impact translates into limited social and economic growth. Notwithstanding the gravity of the problem, we have already missed the mark twice by having failed to achieve the IDD elimination goals, both in 1995 and in 2000.

Declining prevalence worldwide. Success in IDD prevention rests on the effectiveness of universal salt iodization (USI). Approximately 80% of the 130 countries with a significant IDD problem have implemented legislation on salt iodization since the late 1990s. At an estimated annual per capita cost of less than US$0.05, two-thirds of households consume adequate quantities of iodine, based on the latest estimates for iodized salt consumption from 97 developing countries with data for 1998–2004 (Figure 2). Still, roughly one-third of the world's population consumes insufficient dietary iodine and is thus at risk of IDD (urinary iodine <100 µg/L) (Figure 3).[5] Seventy-two percent of the populations at risk live in China, Pakistan, India, Indonesia, and Ethiopia.

The way forward. Sustained elimination of IDD requires the constant vigilance of a range of professional and public interests. It is particularly important to understand this as the target of USI has been crossed. Sustaining the achievements just described will entail the following: 1) Focused effort to obtain critical political and financial commitments at country and global levels, from the private, public, and civil sectors. The long-term impact of this endeavor results in ownership, commitment, and financial pledges by decision-makers. 2) Building a new public and political awareness of the scale and consequences of the problem. Community participation must be promoted and enhanced by focusing on nongovernmental organizations, schools, consumer forums, etc. IDD must be presented to all relevant audiences as an assault on the mental and physical development of the nation's population – not as an obscure nutritional problem. 3) Forming national alliances that represent consumers and decision-makers. This assures sharing of information and

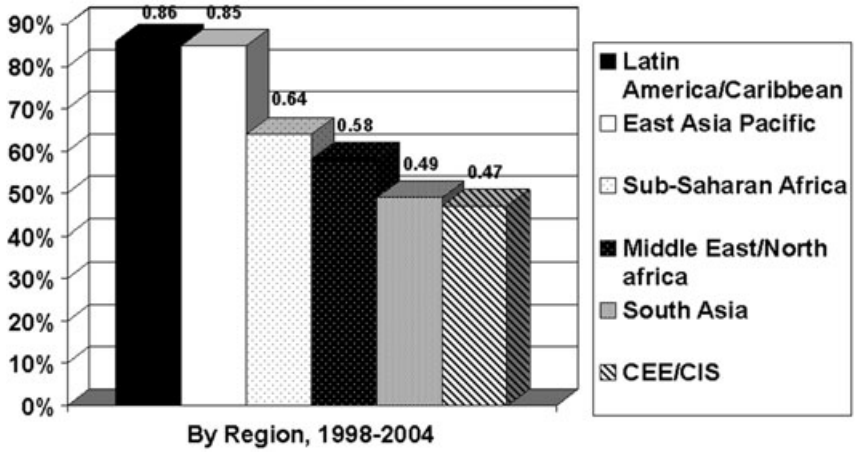

Figure 3 **Countries with IDD as a significant public health problem.** One-third (36.5%) of the world's school-age children have IU < 100 µg/l (based on median IU in school-age children).
Data from the *WHO Global Database on IDD*.[6]

implementation of required action and greatly enhances sustained salt iodization. For partnerships with the food industry to be fully participatory, the legal and financial conditions that will allow the private sector to play its central role in eliminating IDD must be created. 4) Transfer of scientific knowledge into program actions. The International Council for the Control of Iodine Deficiency Disorders (ICCIDD) and the Network for Sustained Elimination of Iodine Deficiency websites, which have links to an extensive bibliography that includes UNICEF's monograph series and the ICCIDD Newsletter, are only a couple of examples of available resources for prompt transformation of scientific findings into programs. 5) At the global and national levels, dynamic and efficient monitoring systems that are inherently connected to an advocacy and communications machinery. Without these, IDD control will not progress at the speed allowed by currently available technical solutions to the problem.

Iron

Iron deficiency (ID) is the most frequent nutritional disorder and one of the leading factors for disability and mortality worldwide. The World Health Organization (WHO) estimates that anemia affects 47.4% of children under the age of 5 years, 25.4% of school-age children, 30.2% of nonpregnant women, 41.8% of pregnant women, 12.7% of men, and 23.9% of the elderly.[7] Approximately 50% of anemia cases in developing countries are associated with ID, and for each case of ID anemia there are 1–2.5 cases of ID without anemia.

Paradoxically, for a public health problem of this magnitude, there has been very little progress in its control in the developing world, mostly because of low compliance with iron supplementation, poorly designed food fortification programs, insufficient targeted interventions for infants and young children, and lack of integration of nutritional interventions with other public health and development programs. Most recently, the safety of certain iron interventions and of some of the principles behind them has been questioned in light of findings related to the interaction between malaria and iron metabolism, as well as those pertaining to the role of iron as a promoter and an amplifier of oxidative chemistry, which leads to DNA, protein, and lipid damage. This section reviews the safety of iron supplementation from two different evidence-based perspectives: the current position of the WHO on iron supplementation for infants and young children living in malaria-endemic conditions, and, more briefly, the scientific soundness and safety of iron interventions for women of reproductive age, based on a recent series of findings.

Prevention and control of iron deficiency in infants and young children in malaria-endemic areas.[8] For the reasons listed above, the provision of additional iron to infants and young children should be a public health priority. However, there is concern that universal supplementation of children with iron and folic acid in areas of high malaria transmission might be harmful. The two largest clinical trials conducted to date to evaluate the impact of zinc and/or iron-folic acid supplementation on the mortality and severe morbidity of preschool children were conducted, first, in a location with stable, perennial, and intense transmission of *Plasmodium falciparum* malaria in Tanzania[9], and second, in a similarly poor but nonendemic rural site in Nepal.[10] Iron and folic acid supplements resulted in an increased rate of severe adverse (morbidity and mortality) events in children in the Zanzibar site only, particularly among those who were not iron deficient. In both sites, iron supplementation was highly efficacious and safe when given to iron-deficient children. The results from Zanzibar, however, raised the issue of safety and efficacy for supplemental iron administration to infants and young children in areas of high malaria endemnicity. An expert consultation to examine this issue was convened by the WHO in Lyon, France, 12–14 June 2006. As seen in Table 1, the Lyon Consultation reached consensus on several important issues related to providing additional iron to infants and young children.[11] In nonmalaria areas, current WHO recommendations for the control of ID and ID anemia are still valid for infants and young children.[12]

Preventing iron deficiency and excess in women of childbearing age. In summary, iron supplementation improves iron status during pregnancy and the postpartum period,[13,14,15] and infants born to mothers who take iron-containing supplements seem to derive protection from ID anemia.[16] Low-dose iron supplements (30 mg/day) during pregnancy have been shown to improve birth weight,[17] even in the offspring of nonanemic iron-replete pregnant women from industrialized countries. However, there is a considerable body of evidence that points to the potential for iron supplements to be harmful. Doses ranging from 36 to 100 mg per day may exacerbate oxidative stress,[18,19] while supplementation with 38–65 mg of iron can reduce zinc absorption.[20] The lower dose of iron recommended by international guidelines (60 mg) can also increase hemoglobin above 13.0 g/dL, which has been associated with negative effects.[21,22] Several studies have found that the risk of hemoconcentration increases significantly when prenatal iron is administered in excess of physiological demand for several months, as proposed by current international guidelines (e.g., 60–120 mg/day), which have been based largely on hemoglobin regeneration efficacy trials. Such

Table 1 **Lyon Consultation recommendations on iron interventions for children under 2 years of age in malaria-endemic regions (paraphrased).**

Region/age group	Recommendation
Non-malarial regions	Current WHO recommendations for the control of ID and IDA are still valid for infants and young children: INACG, WHO, UNICEF (1988)[12] WHO (2007)[11]. Delayed cord clamping, exclusive breastfeeding for the first 6 months of life, and complementary foods high in bioavailable iron are also recommended.
Malaria-endemic regions	
Children under 6 months	• Ensure optimal iron status during pregnancy • Delayed cord clamping • Exclusive breastfeeding • Coordination with malaria prevention and treatment programs • Premature and low-birth-weight infants: iron supplements for 3 months, starting at 2 months (due to very high likelihood of iron deficiency) • Full-term, normal-birth-weight infants: screening for iron deficiency; iron for 3 months, starting as early as 2 months in iron-deficient infants • No folic acid should be added to supplements for this age group
Children 6 to 2 months	• Coordination with malaria prevention and treatment programs: Prevention and control of malaria is paramount, as malaria is especially dangerous at this age (treated bed nets and antimalarial treatment when required) • Provision of general healthcare, apart from control of parasitic and infectious diseases • Control of infections and other parasitic diseases • Breastfeeding, provision of nutritionally adequate complementary foods fortified with iron of high bioavailability • Where fortified complementary foods are not available, supplemental iron given with food for 3 months only to iron-deficient children (laboratory screening where possible, for clinical anemia) • No folic acid supplementation

Abbreviations: ID, iron deficiency; IDA, iron deficiency anemia.

an approach would have missed the negative effects of excessive iron supplementation, such as low birth weight and exposure to reactive oxygen species. This risk may be avoided, ideally, by starting weekly supplementation several months prior to pregnancy. Alternatively, a lower daily dose of iron (30 mg) diminishes gastrointestinal side effects but does not address the logistic problems that have hitherto constrained daily supplementation programs.[23,24]

Finally, there are at least two crucially important and basic questions that remain unanswered in this area: "Are the currently proposed hemoglobin reference levels during gestation appropriate?" and "How do we accelerate the mainstreaming of delayed cord clamping?". The first of these topics is fully addressed elsewhere in this issue.

Zinc

Magnitude of zinc deficiency, consequences, and alternatives for action. Zinc deficiency is an important factor contributing to increased morbidity, mortality, and impaired development of children in underprivileged settings. Evidence from randomized controlled trials of zinc supplementation provides a strong basis for the importance of zinc in reducing growth stunting and the prevalence of diarrhea, pneumonia, and childhood mortality.[25,26,27,28] Estimates suggest that 20% of the world's population may be at risk of inadequate dietary intake of zinc and the populations at highest risk are concentrated in South and Southeast Asia, Sub-Saharan Africa, Central America, and the Andean region. The most vulnerable groups are premature and small-for-gestational-age infants, and preschool children, particularly those 6–23 months of age.

Zinc intervention strategies. Potential program options for improving population zinc status include delivery of supplemental zinc, fortification of staple foods at the national level or of special foods targeted at specific subpopulations, and strategies to modify diets to increase the amount of bioavailable zinc based on nutrition education or agricultural interventions.

Zinc supplementation. Zinc supplementation to young children in at-risk populations on a routine basis and/or for the treatment of diarrhea is expected to have a high impact on zinc and health status, particularly among populations with high rates of low-birth-weight or small-for-gestational-age infants, stunting, diarrhea, or lower respiratory tract infections. The use of a 10–14-day

course of supplemental zinc in conjunction with oral rehydration solution is currently recommended by WHO/UNICEF[29] for the treatment of acute diarrhea. For preventive supplementation, both clinical and operational research is needed to determine optimal doses and dosing schedules as determined by potential delivery mechanisms (e.g., daily versus weekly supplementation). Despite the well-documented benefits of supplemental zinc in at-risk populations, there are currently no formal recommendations for preventive programs. A recent WHO consultation (Geneva, Switzerland, September 15–16, 2006) on the impact of preventive zinc supplementation on infant and child mortality concluded that daily zinc supplementation taken during 6 months by children younger than 36 months of age is associated with a significant (9%) reduction in mortality.[30]

Food fortification. Zinc fortification of complementary foods is expected to have a moderate to high impact on zinc status and health in young children. While the impact of universal fortification of staple foods is not expected to be high, it is considered an important action for improving the adequacy of zinc intake in the overall populations in which intake is presently low. While there are no obvious technical barriers to including zinc in new or existing food fortification programs, there is still a need for well-designed trials to help determine rates of zinc fortification that are efficacious in affecting zinc status.

Dietary diversification/modification. Evidence for the impact of such food-based strategies on zinc status (e.g., increased intake of animal-source food, reduced dietary content of phytate, zinc biofortification of staple foods) is still limited, and well-designed and controlled intervention studies are needed to move these strategies forward.

CONCLUSION

In summary, continued research and advocacy are needed to promote greater awareness among key decision-makers in public health of the importance of micronutrient nutrition for health, and to encourage governments, international agencies, and private organizations to take appropriate actions to ensure the sustainability of proven interventions. For certain micronutrients, specific fortification and dietary diversification and behavior modification interventions warrant further controlled studies of efficacy to provide information on adequate design of these strategies. As for preventive supplementation, some research is still needed to optimize doses and determine its safety and effectiveness, as is the case with iron and zinc.

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Declaration of interest. The authors have no interests to declare.

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