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Micronutrient deficiency in children

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Malnutrition increases morbidity and mortality and affects physical growth and development, some of these effects resulting from specific micronutrient deficiencies. While public health efforts must be targeted to improve dietary intakes in children through breast feeding and appropriate complementary feeding, there is a need for additional measures to increase the intake of certain micronutrients. Food-based approaches are regarded as the long-term strategy for improving nutrition, but for certain micronutrients, supplementation, be it to the general population or to high risk groups or as an adjunct to treatment must also be considered. Our understanding of the prevalence and consequences of iron, vitamin A and iodine deficiency in children and pregnant women has advanced considerably while there is still a need to generate more knowledge pertaining to many other micronutrients, including zinc, selenium and many of the B-vitamins. For iron and vitamin A, the challenge is to improve the delivery to target populations. For disease prevention and growth promotion, the need to deliver safe but effective amounts of micronutrients such as zinc to children and women of fertile age can be determined only after data on deficiency prevalence becomes available and the studies on mortality reduction following supplementation are completed. Individual or multiple micronutrients must be used as an adjunct to treatment of common infectious diseases and malnutrition only if the gains are substantial and the safety window sufficiently wide. The available data for zinc are promising with regard to the prevention of diarrhea and pneumonia. It should be emphasized that there must be no displacement of important treatment such as ORS in acute diarrhea by adjunct therapy such as zinc. Credible policy making requires description of not only the clinical effects but also the underlying biological mechanisms. As findings of experimental studies are not always feasible to extrapolate to humans, the biology of deficiency as well as excess of micronutrients in humans must continue to be investigated with vigour.

Micronutrients: Childhood infections: Diarrhoea: Acute respiratory infections: Child development

Malnutrition increases morbidity and mortality and affects physical growth and development. It is becoming increasingly clear that some of these effects are the result of specific nutrient deficiencies. While public health efforts must be targeted to improve dietary intakes in children through breast feeding and appropriate complementary feeding, there is scope and need for additional measures to increase intake of specific nutrients, when their deficiency is shown to cause unacceptable adverse effects in a large segment of the population (WHO, 1998*a*).

Countries are able and willing to launch interventions only if they perceive the disease burden to be large (ACC/SCN, 2000*a*). Systematically collected prevalence data in populations, using reliable tools, that closely correlate with functional effects is an essential first step. Obtaining such data is not always an easy task for several reasons. Micronutrient deficiencies, at a functionally important level may not result in a readily identifiable clinical condition. As an example, for each case of anaemia there are at least two cases of iron deficiency. Except in rare hereditary disorders, clinical diagnosis of the commonly occurring zinc deficiency is not feasible. Moreover, there may be causes other than low intakes, such as malaria and hookworm infection, that increase the severity and/or consequences of the deficiency.

Simple serum or plasma level assessment is what is usually feasible as a biochemical indicator in population-based assessment of micronutriture. For many micronutrients, these levels are significantly affected by commonly occurring acute infections, although recent studies indicate that at least for zinc, this may be more of a concern when assessing individuals than populations (Brown, 1998). Cut-off values for deficiency are often arbitrary, vary from study to study and may accordingly, when applied to

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observational studies, increase or reduce the magnitude of association between deficiency and impaired function. Substantial differences from laboratory to laboratory is another problem. Age, sex, and pregnancy are other factors that influence micronutrient status. Developing practical and reliable measures of micronutrient deficiency is for these reasons a continuing and important challenge.

Iodine, iron and vitamin deficiencies are major public health problems (WHO, 1998*a*). The prevalence of and disease burden associated with deficiency of several other micronutrients, including zinc, B vitamins, calcium and selenium, are still not well documented (FAO, 1988; Allen *et al.* 1995; McCullough *et al.* 1990). Measuring the prevalence of multiple micronutrient deficiency is also important. Micronutrient deficiencies often coexist and there are important nutrient interactions, not only at the site of absorption, such as for zinc and iron, but also in functional terms.

Furthermore, iodine and selenium are involved in the normal function of the thyroid gland and inadequate intake of both micronutrients causes hypothyroid cretinism. Research in Tibet suggests that this co-deficiency causes Kashin-Beck's disease, a condition associated with short stature caused by multifocal necrosis of the growth plates in the long bones and osteoarthritis (Moreno-Reyes *et al.* 1998).

Our understanding of the consequences of iron, vitamin A and iodine deficiency in children has advanced considerably (ACC/SCN, 2000*a*; WHO, 2000). Iron deficiency anaemia affects physical growth. Whether iron deficiency *per se* significantly increases the incidence and/or the severity of infections is not well established and there is even concern that administration of iron during latent or uncontrolled infections may be unsafe (Weinberg, 1996), as was shown during bacterial infections in neonates (Farmer & Becroft, 1976; Barry & Reeve, 1977; Becroft *et al.* 1977). It was recently concluded that reasonable oral doses do not cause increase in malaria (INACG, 1999; Menendez *et al.* 1997). Parenteral administration of iron however, increases malarial morbidity in non-immune individuals and possibly morbidity of other infections as well (Oppenheimer *et al.* 1986*a*; Oppenheimer *et al.* 1986*b*). The dominant adverse effect of iron deficiency is on cognition in children (Edgerton *et al.* 1979; Fairweather-Tait, 1992; Walter, 1993; Gillespie, 1997; Gillespie, 1998). There is clinical evidence for reduced immuno-competence in individuals with iron deficiency but it is less clear whether this leads to increased severity of infection. A recent analysis of the economic consequences of iron deficiency has estimated the median value of productivity losses due to iron deficiency to be about EURO 4 per capita or 0–9 % of the Gross National Product for a range of developing countries (Edgerton *et al.* 1979).

Vitamin A is an essential micronutrient for the normal function of the visual system, for growth, development, and maintenance of epithelial cellular integrity as well as for immune function and reproduction (Bhan & Bhandari, 1998; WHO, UNICEF & IVACG, 1997; WHO, 1998*b*; WHO & UNICEF, 1998). Effects on epithelial barriers and on the immune system occur even with subclinical deficiency, leading to increased severity of some infections and an increased risk of death among children. Vitamin A supplementation was reported to reduce mortality by 23 % in children 6 months to 5 years of age in vitamin A deficient areas (Beaton *et al.* 1993). This indicates that low body vitamin A, even without overt clinical manifestations, has important health consequences, particularly on the outcome of important infections (Beaton *et al.* 1993). Vitamin A supplementation at appropriate levels has been found to improve vitamin A as well as iron status. A vitamin A sugar fortification programme in Guatemala resulted in improved iron status of the population (Mejia & Arroyave, 1982; Mejia & Chew, 1988; Suharno & Muhilal, 1996; Gillespie, 1997).

Iodine is required for the synthesis of thyroid hormones and plays a key role in cell replication. Gestational iodine deficiency leads to abortions, still births, congenital anomalies, low birth weight, cretinism, psychomotor defects and increased neonatal mortality. Goitre, hypothyroidism, impaired mental function, retarded mental and physical development and diminished school performance is seen during childhood and adolescence. Severe iodine deficiency causes substantial linear growth retardation which can be partly reversed by iodine supplementation (Delange, 1985; WHO, 1998*a*; Delange, 1999; WHO, UNICEF & ICCIDD, 1999). In adults, complications of goitre such as hypothyroidism and impaired mental function persist.

Zinc deficiency has long been suspected to be prevalent in children in developing countries where diets are low in animal products and high in phytates. Diarrhea exacerbates zinc deficiency due to intestinal loss. Observational studies are of limited value in identifying functional effects of its deficiency since reliable indicators of zinc status that are suitable for field studies are not available and the possible confounding effect of coexisting nutrient deficiencies is difficult to eliminate. Several recent studies in preschool children of developing countries have shown that zinc supplementation does not only result in enhanced linear growth, but also leads to substantial reductions in the incidence and severity of acute and persistent diarrhea, and possibly of lower respiratory tract infections (Child Health Research Project, 1997; Black, 1998*a*; Sazawal *et al.* 1998; Brown *et al.* 1998; Zinc Investigators' Collaborative Group, 1999; Roy *et al.* 1999). In this issue, Black & Sazawal have reviewed available zinc trials in children. The fact that the effects of zinc supplementation in developing country children seems to be more pronounced in severe diarrheal and acute respiratory illnesses raises the possibility of mortality reduction if the zinc intake in deficient populations can be increased. Clinical trials addressing this issue are underway in Tanzania, Nepal and India.

With regard to health effects of zinc deficiency, there are several unresolved issues. Are the effects of zinc supplementation on morbidity only the result of correction of deficiency, and as such restricted to zinc deficient children, or does zinc also have a pharmacological effect? Can anthropometry be used to identify children likely to be zinc deficient? The effect of zinc supplementation in children below 6 months of age, particularly in those born with low birth weight, is of particular interest as they carry

a high risk of severe systemic infections and death. Early findings from an Indian trial showed a 67 % mortality reduction in small for gestational age infants 1–8 months old who were supplemented daily for the first year of life (Black, 1999, personal communication). Routine zinc supplementation improves physical activity but the effects on cognition are still uncertain (Black, 1998*b*).

Selenium deficiency has been identified in China, Tibet, New Zealand and the Russian Federation. It can result in thyroid injury and decreased thyroid hormone production. Moreover, it may cause Keshan's disease, which is an endemic cardiomyopathy mainly affecting children and women of childbearing age. Epidemiological evidence linking selenium deficiency to Keshan's disease (Ge & Yang, 1993) led to large scale selenium supplementation programmes which together with changes in the diet has virtually eliminated the disease from China. However, more work is required to define acceptable norms for selenium intake, the prevalence of its deficiency and its public health significance.

Acute infections such as diarrhea and pneumonia, last longer and are more severe in the malnourished host. There is now evidence that therapeutic use of specific nutrients early in some acute illnesses may reduce episode severity and duration and even case fatality. This has been established for all these outcomes with vitamin A in measles and for episode severity and duration with zinc in acute and persistent diarrhea (Sazawal *et al.* 1995; WHO, UNICEF & IVACG, 1997; WHO, UNICEF & ICCID, 1999; Penny *et al.* 1999). On the other hand, overzealous administration of large doses of zinc to severely malnourished children was shown to actually increase mortality, highlighting the need for attention to safety issues (Faruque *et al.* 1998). In this issue, Mahalanabis & Bhan discuss the policy implications of therapeutic use of single or multiple micronutrients during acute illness in children. Overall, individual micronutrients must be used only if the gains are substantial and the safety window between therapeutic and toxic dose is sufficiently wide.

The need to deliver safe but effective amounts of zinc to children in developing countries can be determined only after data on deficiency becomes available and the studies on mortality reduction following supplementation are completed. In countries where iron–folic acid supplementation is recommended up to 3 years of age, such as in India, the possibility of adding zinc to this formulation is an option if constituted in a way that does not significantly affect the bioavailability of either of the three micronutrients nor reduce the compliance in the target group. This may be feasible if the relative dosage and salts are compatible and appropriate. Food fortification and plant breeding are clearly more practical options for increasing the intake of micronutrients for which body stores are not built, as in the case of zinc.

In the Goa conference, data presented from Pune, India, indicated that, among adults, vitamin B_{12} deficiency may be more prevalent than folate deficiency. This observation is supported by recent findings among pregnant Nepali women and among children in Delhi (Bondevik *et al.* 2000; Gomber *et al.* 1998). In the current issue, Refsum points out that folate supplementation to individuals with latent or overt vitamin B_{12} deficiency may, in fact, worsen the metabolic consequences of such deficiency. Moreover, Sandstrøm points out that the intake of aqueous solutions of iron, i.e. as in iron supplements, may impinge on zinc uptake. Accordingly, studies to evaluate the clinical and metabolic consequences of iron–folate supplementation and, over a longer time perspective, to examine the relevance and feasibility of broadening the supplement to include other micronutrients, such as vitamin B_{12} and zinc, should be considered.

However, at this point there is insufficient evidence to support the use of multiple micronutrient formulations in infants and young children and, indeed, because of interactions or of opposing effects on the immune or other systems, the benefits as compared to single or a limited number of micronutrients may be reduced. Multiple micronutrients are currently recommended in severely malnourished children or in those who, for some reason, are unable to achieve adequate dietary intakes for extended periods of time, such as children with chronic gastrointestinal or other disorders (WHO & UNICEF, 2000).

Substantial progress has been made in recent years towards the elimination of iodine deficiency and in reducing the prevalence of vitamin A deficiency (WHO, UNICEF & IVACG, 1997; UNICEF, MI, WHO, CIDA & USAID, 1998; ICCIDD, 1998; WHO, UNICEF & ICCIDD, 1999). On the other hand, the effectiveness of the programmes for the control of iron deficiency has been poor. Despite available tools, iron supplementation programmes have been limited by insufficient supplies, inadequate commitment of health care providers and their supervisors, and poor compliance in the target populations who often are unaware of mild to moderate anaemia and its consequences. Recent analyses show that neither daily nor intermittent supplementation is likely to prove effective in developing countries and other strategies are required for improving utilizable iron intakes (Beaton & McGable, 1999). Apart from supplementation, progress has been made in iron fortification of staple and complementary foods and this approach needs to be pursued with vigour. Recent reviews suggest that the concern regarding iron overload in iron deficient populations may be exaggerated, although the safety issues must of course be continuously evaluated.

Plant breeding to increase the content and bioavailability of iron and other micronutrients holds great promise (Graham & Welch, 1996; Ruel & Bouis, 1998). The goals are to increase the concentration of micronutrients and/or the efficiency of their utilization in the crop, decrease the concentration of absorption inhibitors such as phytates and increase the amount of promoter compounds (for iron and zinc in particular) such as sulphur containing amino acids (ACC/SCN, 2000*b*). The technologies span from the selection of naturally occurring genetic variants with relatively high metabolic efficiency in the use of elements such as zinc, genetic modification of plants, and the creation of new foods using biotechnology to micronutrient fortification of fertilizers. Although extensive use of phosphorous-containing fertilizers is necessary for high yields of cereals it can also induce zinc deficiency in crops, especially in many of the new high yielding

varieties, and may also increase the phytate content of the grain used for human consumption. Adding zinc sulphate to zinc deficient soils can increase crop yields substantially and also, to some extent, increase the zinc content of the edible portions of the plants. This is an example of an agricultural intervention where producers benefit while consumers may experience a substantial health benefit. However, there are many challenges. Will farmers be interested in crop cultivars that have higher micronutrient concentrations or utilization efficiency but little or no yield advantage? Will the target population have access to or accept these new foods? Moreover, strategies that increase the concentrations of some micronutrients may have a negative impact on the bioavailability of others, such antagonism may be observed between copper, zinc and manganese.

There are still problems related to the delivery of vitamin A (WHO, UNICEF & IVACG, 1997; HKI, 1997; WHO, 1998*b*; WHO & UNICEF, 1998; UNICEF, MI, WHO, CIDA & USAID, 1998; WHO, UNICEF, MI, World Bank, CIDA & USAID, 1997). The intention is to deliver at least two doses per year to deficient child populations. Measles immunization is often the only effective opportunity to deliver vitamin A. Addition of vitamin A to national immunization days has been proposed and even adopted in some places (WHO, UNICEF, MI, World Bank, CIDA & USAID, 1997; WHO & UNICEF, 1998; WHO, 1998*b*). One important concern is that this may tend to destabilise the delivery of vitamin A through routine health care and nutritional services. The sustainability and safety of such an approach must be carefully evaluated.

There is wide agreement in support of food-based approaches as the long-term strategy for improving nutrition in general and micronutriture in particular (Muhilal *et al.* 1988). Fortification of maize and sugar with vitamin A are currently being explored in some countries. Other innovations include egg promotion in Indonesia and genetic modification of staple foods to enhance vitamin A bioavailability, as has been attempted with iron.

Credible policy making requires a detailed description of not only the clinical effects but also the underlying biological mechanisms. As findings of experimental studies are not always feasible to extrapolate to humans, the biology of deficiency as well as excess of micronutrient in humans must continue to be investigated with vigour using a multidisciplinary approach.

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