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Zinc: the missing link in combating micronutrient malnutrition in developing countries

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The first cases of human Zn deficiency were described in the 1960s in the Middle East. Nevertheless, it was not until 2002 that Zn deficiency was included as a major risk factor in the global burden of disease, and only in 2004 did WHO/UNICEF include Zn supplements in the treatment of acute diarrhoea. Despite this recognition Zn is still not included in the UN micronutrient priority list, an omission that will continue to hinder efforts to reduce child and maternal mortality, combat HIV/AIDS, malaria and other diseases and achieve the UN Millennium Development Goals for improved nutrition in developing countries. Reasons for this omission include a lack of awareness of the importance of Zn in human nutrition, paucity of Zn and phytate food composition values and difficulties in identifying Zn deficiency. Major factors associated with the aetiology of Zn deficiency include dietary inadequacies, disease states inducing excessive losses or impairing utilization and physiological states increasing Zn requirements. To categorize countries according to likely risk of Zn deficiency the International Zinc Nutrition Consultative Group has developed indirect indicators based on the adequacy of Zn in the national food supplies and/or prevalence of childhood growth stunting. For countries identified as at risk confirmation is required through direct measurements of dietary Zn intake and/or serum Zn in a representative sample. Finally, in at risk countries either national or targeted Zn interventions such as supplementation, fortification, dietary diversification or modification, or biofortification should be implemented, where appropriate, by incorporating them into pre-existing micronutrient intervention programmes.

Zinc: Deficiency: Micronutrient: Malnutrition: Developing countries

Cases of human Zn deficiency were first described as early as the 1960s in male adolescent dwarfs from the Middle East consuming plant-based diets containing high levels of phytate, known to inhibit Zn absorption, and low levels of animal foods, rich sources of readily-available Zn (Prasad *et al*. 1963). Since that time Zn deficiency has been identified in many other regions of the world. Nevertheless, its numerous adverse consequences on human health have only recently been recognized. Indeed, it was not until 2002 that Zn deficiency was included as a major risk factor to the global and regional burden of disease, along with Fe, vitamin A and I deficiency (Ezzati *et al*. 2002), and in 2004, World Health Organization/UNICEF (2004) included Zn supplements in their recommended treatment regimen for acute diarrhoea. Despite this recognition, however, Zn is still not included in the United Nations (1991) micronutrient priority list, an omission that continues to hinder efforts to reduce childhood stunting, morbidity and mortality in developing countries (Hambidge, 1997).

There are several reasons for the omission of Zn from the United Nations (1991) priority list; they include the continued lack of awareness of the importance of Zn in human nutrition and the lack of food composition values for Zn and its anti-nutrients for local staple foods from developing countries. The lack of such values leads, in turn, to a lack of quantitative data on Zn intakes. In addition, because Zn is a type 2 nutrient assessment of Zn deficiency is especially difficult. In type 2 nutrient

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deficiencies (e.g. Zn, N, essential amino acids, P, Mg and K) the body limits growth and/or reduces excretion in an effort to conserve the limiting nutrient. As a result, even in severe Zn deficiency, tissue Zn concentrations may not be low because the body conserves Zn. Moreover, the signs and symptoms associated with type 2 nutrient deficiencies are normally non-specific, and for Zn they may include stunting, wasting and loss of function in tissues with rapid turnovers (e.g. immune function and skin; Golden, 1988).

Importance of zinc for human health

Zn is required for the activity of >100 enzymes involved in most major metabolic pathways and, consequently, is necessary for a wide range of biochemical, immunological and clinical functions (Hotz & Brown, 2004). As a result, multiple functions in the body are affected by Zn deficiency, including physical growth, immune competence, reproductive function and neuro-behavioural development. These adverse health consequences of Zn deficiency vary with age; low weight gain, diarrhoea, anorexia and neuro-behavioural disturbances are common during infancy, whereas skin changes, blepharo-conjunctivitis and impairments in linear growth are more frequent among toddlers and schoolchildren (Hambidge, 1989). Manifestations among the elderly include hypoguesia (reduced ability to taste sweet, sour, bitter, salty and umami), chronic non-healing leg ulcers and recurrent infections (Kohn *et al.* 2000).

The first randomized controlled trial (RCT) of Zn and growth was conducted in 1976 among US infants fed a cow's-milk-based Fe-fortified formula with (4 mg/l) or without Zn (Walravens & Hambidge, 1976). Since that time there have been approximately 100 RCT investigating the effects of Zn supplementation on the growth of children of all ages and four meta-analyses. In a meta-analysis by Brown *et al.* (2002) of thirty-three RCT (twenty-seven in developing countries) conducted between 1976 and 2000 on prepubertal children it was found that Zn supplementation results in a positive response in linear growth and weight gain (but not weight-for-height). The response is especially marked in those children who are stunted or underweight at baseline, emphasizing that a positive growth response to Zn supplementation is more likely to be apparent among children with pre-existing growth failure (Brown *et al.* 2002). In some of these Zn-supplementation trials the males have shown a greater response to Zn supplementation than the females (Hambidge *et al.* 1972, 1985; Ruz *et al.* 1997).

In the last decade several RCT among high-risk groups such as infants, young children and pregnant women have investigated the preventive effects of Zn supplements on several other important health outcomes. For example, results of a pooled analysis of Zn supplementation trials in infants and young children in several developing countries have confirmed a preventative effect of Zn in reducing the incidence of diarrhoeal infection (based on nine RCT and irrespective of age, gender, baseline wasting or serum Zn; Bhutta *et al.* 1999) and acute lower respiratory infections (based on five RCT; Bhutta *et al.* 1999), with reductions in

the incidence of diarrhoea and pneumonia of 18% and 41% respectively. Zn may also be involved in reducing the severity of malaria attributable to *Plasmodium falciparum* parasitaemia (Bates *et al.* 1993; Shankar *et al.* 2000), although probably not to the number of episodes (Muller *et al.* 2001). Although only a few RCT have investigated Zn supplementation in relation to mortality, results for term small-for-gestational-age infants in north India (Sazawal *et al.* 2001) and older children in Burkina Faso (Muller *et al.* 2001) have been promising. Reductions in mortality of 67% and 50% respectively compared with the control groups have been reported for these two trials, although in the Burkina Faso trial the difference was not found to be significant. In a more recent report (Baqui *et al.* 2002) deaths resulting from non-injury were found to be reduced by 51% among infants and preschool children in Bangladesh provided with supplemental Zn (20 mg) for 14 d as an additional component of a community-based diarrhoea treatment programme. On-going large-scale preventive Zn-supplementation trials involving children aged 1–35 months in Zanzibar, Nepal and India will provide more definitive estimates of the effect of Zn on childhood mortality.

The therapeutic effects of Zn supplements on children with acute and persistent diarrhoea, pneumonia, measles and malaria have also been investigated in a series of efficacy trials in several developing countries. Again, dramatic reductions in the duration of acute and persistent diarrhoea and severe acute lower respiratory infection have been observed (Baqui *et al.* 2002; Brooks *et al.* 2004; Mahalanabis *et al.* 2004), but so far no therapeutic effect has been noted with daily Zn supplements for measles (Mahalanabis *et al.* 2002) or malaria therapy (Zinc Against Plasmodium Study Group, 2002).

Unlike the effects on growth and morbidity, results of the RCT on maternal health and pregnancy outcome have been inconsistent (Osendarp *et al.* 2003). These discrepancies may be related, in part, to differences in the outcomes assessed, as well as the study location and design. Only a few of these studies have been conducted in developing countries, and they have differed in relation to dose, duration, gestational period of Zn supplementation, number of subjects studied and the baseline Zn nutriture, as well as the confounding factors that have been taken into account. The most common outcomes investigated have been birth weight and gestational age, each of which has shown positive responses to supplemental Zn in some (Garg & Arshad, 1993; Goldenberg *et al.* 1995), but not all (Osendarp *et al.* 2000, 2003), studies. Indeed, in RCT in Latin America and Asia no positive effects on birth weight or the duration of pregnancy have been observed in those subjects receiving Zn supplements (Osendarp *et al.* 2003). Beneficial effects on fetal neuro-behavioural development, such as lower fetal heart rates and greater fetal movements, have been reported after supplementing Peruvian mothers with Zn, Fe and folate compared with those receiving only Fe and folate alone (Merialdi *et al.* 1998, 2004). In one of the supplementation studies a reduced incidence of diarrhoea, dysentery and impetigo was also noted at 6 months among low-birth-weight infants whose mothers had received Zn supplements during pregnancy (Osendarp

Table 1. Intakes of zinc and phytate (mg/d) and phytate:zinc molar ratios of children's diets in developing countries (from Gibson, 1998)
(Values are means with their standard deviations unless otherwise indicated)

Country	n	Zn	SD	Phytate	SD	Phytate:Zn	SD
North East Thailand*	229	4·4 (3·5, 5·4)		77 (66, 109)		2 (1, 2)	
Guatemala	136	9·0	2·7	962 (576, 1427)		11	
Papua New Guinea	67	4·4	1·2	570	555	13	3
Ghana	76	5·1	1·1	393	134	8	2
Egypt**	96	5·2	1·6	796	248	16	3
Malawi*	81	6·0 (4·5, 7·3)		1242 (874, 1617)		21 (18, 25)	
Kenya	100	3·7	0·9	1066	324	28	4
Mexico	59	5·4	1·3	1666	650	30	7

n, number of children
*Median (inter-quartile range).
**Includes yeast-leavened bread.

et al. 2001). Clearly, more studies in developing countries are needed, preferably involving follow-up investigations of growth, mental and psychomotor development, as well as morbidity and mortality of the infants.

Increasingly, Zn-supplementation trials are now focusing on neuro-behavioural function in infants and early childhood, and results have been mixed. There are some indications that Zn supplementation may result in higher activity levels (Sazawal et al. 1996; Bentley et al. 1997) and improvements in developmental scores among infants (Friel et al. 1993) and young children (when given together with psycho-social stimulation; Meeks Gardner et al. 2005), as well as improved neuropsychological test performance among schoolchildren (Sandstead et al. 1998), but more studies are needed to confirm these findings.

Aetiology of zinc deficiency in developing countries

Three major factors are responsible for the development of Zn deficiency in developing countries: dietary inadequacies; disease states that induce excessive losses or impair utilization of Zn; physiological states that increase Zn requirements.

Inadequate intakes of dietary zinc

Rural diets in developing countries are predominantly plant-based; consumption of cellular animal-protein foods such as meat, poultry and fish is often small because of economic, cultural and/or religious constraints. As a result, the content and/or the amount of Zn available for absorption from such diets is low, and is probably the primary cause of Zn deficiency.

Information on Zn intakes in developing countries is limited because of the paucity of data on the Zn content of local staple foods. Substitution of Zn values for staple foods grown in Western countries is not advisable because the Zn content of plant-based foods tends to reflect the Zn levels of the local soil (Sunanda et al. 1995; Alloway, 2004). Table 1 presents available data on Zn intakes of children in selected developing countries. It should be noted that children from Malawi, Egypt, Mexico and Guatemala tend to have higher Zn intakes because their diets are predominantly cereal-based compared with those of children from Papua New Guinea and Ghana; nevertheless, the Zn is poorly absorbed (see following discussion). Children from Papua New Guinea and the forest regions of Ghana have diets based on starchy roots and tubers that have a lower Zn content (Gibson, 1993). In north-east Thailand low Zn intakes are linked in part to the low levels of Zn in the soil (Alloway, 2004), and thus the low Zn content of rice grown in this region.

Differences in the major food sources of Zn also have an important impact on the amount of dietary Zn absorbed. Unrefined cereals and legumes contain high levels of phytic acid (myo-inositol hexaphosphate), known to be a potent inhibitor of Zn absorption in both adults (Turnlund et al. 1984; Egli et al. 2004) and children (Davidsson et al. 2004). Phytic acid forms insoluble Zn–phytic acid complexes in the intestine (Lönnerdal, 2000). The negative effect of phytic acid on Zn absorption follows a dose-dependent response, and the Phy:Zn molar ratio of a diet can be used to predict the proportion of absorbable dietary Zn. Diets with molar ratios >15 have been associated with biochemical Zn deficiency in human subjects (Oberleas & Harland, 1981; Bindra et al. 1986; Ferguson et al. 1993; Huddle et al. 1998). It should be noted that the phytate:Zn molar ratios in the diets of children from Malawi, Kenya, Mexico and Guatemala who consume maize-based diets are very high. Lower molar ratios are observed in Egyptian children whose diets are based on wheat leavened bread, Ghanaian children who consume tubers and/or fermented maize products and in children of north-east Thailand who consume glutinous rice. Leavening with yeast and microbial fermentation both hydrolyse phytic acid to lower inositol phosphates (i.e. inositol monophosphate to inositol tetraphosphate) that do not inhibit Zn absorption (Lönnerdal et al. 1989), whereas when glutinous rice is soaked overnight before cooking and the water is discarded, as practised in north-east Thailand, water-soluble sodium, potassium or magnesium phytates in rice are lost by diffusion into the soaking water (Perlas & Gibson, 2002).

Several other dietary components may inhibit the bioavailability of Zn (Lönnerdal, 2000), including high amounts of Ca in the presence of high phytate, and possibly polyphenols (Ganji & Kies, 1994; Coudray et al. 1998). Most plant-based diets, however, have a Ca content that is too low to inhibit Zn absorption, although

notable exceptions are diets in Latin America based on lime-soaked maize (Fitzgerald *et al.* 1993) and regions in which betal (*Areca catechu*) nut is chewed with lime (Gibson, 1993) or soils are calcareous and geophagia (soil eating) is practised (World Health Organization, 1996). In Asian diets some types of fermented soyabean protein may have a negative impact on Zn absorption, depending on the processing method (Erdman & Pneros-Schneier, 1994; Davidsson *et al.* 1996).

Some dietary components enhance Zn absorption. For example, increasing the amount of protein in the diet enhances Zn absorption, and if the protein is from animal sources (e.g. meat or fish) the enhancing effect is even greater (Lönnerdal, 2000). Organic acids (citric, lactic, acetic, butyric, propionic and formic acids) produced during fermentation also have the potential to form soluble ligands with Zn in the gastrointestinal tract, and thus facilitate Zn absorption (Pabon & Lönnerdal, 1992; Lönnerdal, 2000), although the magnitude of this effect has not been extensively investigated.

Excessive losses

Additional factors that may exacerbate suboptimal Zn status, especially among population groups living in developing countries in which Zn intakes are inadequate, include increased faecal and/or endogenous losses of Zn through diarrhoea (Castillo-Duran *et al.* 1988) and geophagia (Hooda *et al.* 2004). Malabsorption of Zn resulting from alterations in permeability and absorptive capacity of the intestine may also occur in tropical areas of developing countries. Such changes in the intestinal tract appear to be induced, at least in part, by exposure to a variety of viral, bacterial and protozoal pathogens and/or changes in gut microbial flora (Menzies *et al.* 1999), and may have been responsible for the large endogenous faecal losses of Zn that have been reported to perturb Zn homeostasis in Malawian children (Manary *et al.* 2000, 2002). The presence of hypochlorhydria may also impair Zn absorption because the formation of soluble chelates of Zn is dependent on the acid pH of the stomach (Sturniolo *et al.* 1991). Malabsorption syndromes, including sprue, Crohn's disease and inflammatory bowel diseases, may also result in poor absorption of Zn and increased losses of Zn from the body (Prasad *et al.* 1963; Aggett & Harries, 1979).

High physiological requirements

Physiological requirements for Zn are increased during periods of rapid growth because of the critical role of Zn in DNA replication, RNA transcription and endocrine function. Hence, infants and young children are vulnerable to Zn deficiency, especially if they have a smaller content of hepatic Zn metallothionein at birth as a consequence of low birth weight (Zlotkin & Cherian, 1988; Castillo-Duran *et al.* 1995) and/or poor maternal Zn status (Osendarp *et al.* 2001). In such cases their subsequent dietary requirements for Zn for catch-up growth will be very high (Hambidge, 1997). Males probably have higher requirements for Zn than females, because of their higher growth rates and greater proportion of muscle per kg body weight; muscle contains a higher content of Zn than fat (Hotz & Brown, 2004).

Requirements for Zn are also greater during pregnancy as a result of the accrual of Zn in fetal and maternal tissues and during lactation for the secretion of Zn in breast milk, especially during the early months (Institute of Medicine, 2001). There is some evidence that Zn absorption tends to increase during pregnancy and lactation (Fung *et al.* 1997) to meet the increased needs for Zn, although mobilization of Zn from bone or renal conservation does not occur (King, 2001). Despite this adaptation, women who experience frequent reproductive cycling appear to be particularly at risk of Zn deficiency (Gibson & Huddle, 1998).

Identifying the risk of zinc deficiency in populations

Currently, few developing countries have information on Zn status at the national level, with the notable exception of Mexico and Pakistan. In view of the paucity of such national data the International Zinc Nutrition Consultative Group (IZiNCG) have derived estimates of the global risk of Zn deficiency based on two indirect indicators: (a) the amount of absorbable Zn in national food supplies from food balance sheet data in 176 countries (for details, see Hotz & Brown, 2004); (b) the prevalence of growth stunting in preschool children from the World Health Organization (1997) global database. The cut-off values indicative of high, moderate or low risk of Zn deficiency, based on the percentage of the population at risk of an inadequate intake of bioavailable Zn, are shown in Table 2.

Alternatively, the World Health Organization (1997) cut-off value that indicates when childhood growth stunting is a problem of public health concern can be used to indicate a high risk of Zn deficiency at a national level. Use of this indicator has been adopted by IZiNCG because stunted (but not non-stunted) children show a positive linear growth response to Zn supplementation (Brown *et al.* 2002). In addition, IZiNCG has developed a

Table 2. Use of suggestive evidence to estimate the national risk of zinc deficiency (from Hotz & Brown, 2004)

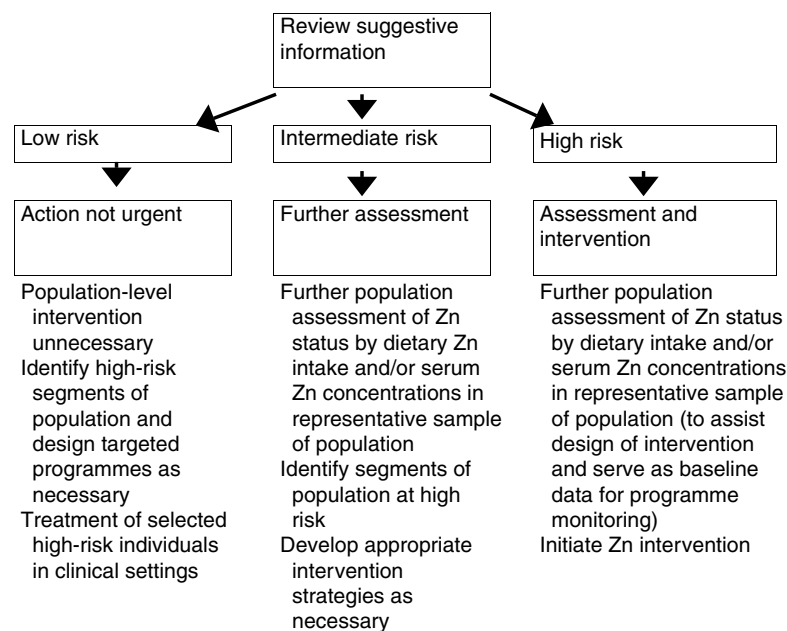|	National level data		
Level of risk of Zn deficiency	Percentage of population at risk of inadequate bioavailable Zn intake		Prevalence (%) of stunting (low height-for-age) among children <5 years of age
Low	<15	and	<10
Moderate	10–<25	or	10–<20
High	≥ 25	and	≥ 20

Fig. 1. Steps in the assessment of population zinc status and suggested programmatic responses, according to the likely risk of zinc deficiency. (From Hotz & Brown, 2004.)

composite index of the national risk of Zn deficiency, based on combined information on stunting rates and the adequacy of Zn in the national food supply (Table 2). This index is based on the significant correlation between the national prevalence of stunting among children <5 years of age and the percentage at risk of inadequate Zn intakes (r 0·60, $P<0·0001$; Hotz & Brown, 2004).

Countries can apply this composite index to establish the likely risk of Zn deficiency, and respond accordingly, as shown in Fig. 1. Countries with a moderate or severe risk of Zn deficiency should undertake a more precise assessment of the magnitude of risk of Zn deficiency in the population by using direct measures of Zn status such as dietary Zn intake (Gibson & Ferguson, 1999), serum or plasma Zn and/or indicators based on a functional response to Zn supplementation (for details, see Hotz & Brown, 2004).

In the 1999 National Nutrition Survey in Mexico both serum and dietary intakes of Zn (based on a single 24 h recall) were measured in children <2 years of age and women aged 12–49 years (Villalpando *et al*. 2003; S Rodriguez-Ramirez, A Garcia-Guerra, J Rivera-Dommarco and C Hotz, unpublished results). In general, more rural children were found to be at risk of low serum Zn concentrations and inadequate Zn intakes than urban children, with those aged 1–4 years at highest risk. Further, both children and women with a low socio-economic status had a greater risk of low serum Zn concentrations than their counterparts with a high socio-economic status. In the 2002 National Nutrition Survey in Pakistan (Z Bhutta, unpublished results) a similar trend for serum Zn concentrations indicative of Zn deficiency was observed among rural preschool children compared with urban preschool children.

Intervention strategies to combat zinc deficiency in developing countries

Ideally, Zn should be incorporated into pre-existing intervention programmes designed to combat vitamin A, Fe and I deficiencies, and the appropriate precautions taken, where necessary, to eliminate risk of any competitive antagonistic interactions between these micronutrients. Both short-term measures (supplementation and fortification) and long-term solutions (i.e. dietary diversification or modification and biofortification) can be used to alleviate Zn deficiency in developing countries.

Zinc supplementation

Zn supplementation is a short-term strategy that relies heavily on individual compliance. It requires a consistent supply, delivery and consumption of the supplement to targeted high-risk groups that need a quick improvement in Zn status (e.g. pregnant women, low-birth-weight infants and malnourished infants; Hotz & Brown, 2004). When given alone Zn supplements should be taken, preferably daily, with subjects in the fasting state to maximize absorption, but when given in combination with other micronutrients the supplement should be taken with meals to avoid possible antagonistic micronutrient interactions (Sandström *et al*. 1985; Sandström, 2001; Lönnerdal, 2004). The cost of adding Zn (as $ZnSO_4$) to a pre-existing micronutrient supplement will range from about US $0·05–0·19 *per capita* per year, depending on the age-group. To date, no routine large-scale targeted Zn-supplementation programmes exist, although World Health Organization/UNICEF (2004) now recommend giving Zn together with oral rehydration salts for the clinical

management of acute diarrhoea. The cost-effectiveness of this strategy has been analysed by Robberstad *et al.* (2004). Efforts are also underway in Bangladesh to make dissolvable Zn tablets available throughout the country as a treatment for diarrhoea (LB Blum, unpublished results).

Fortification

Fortification is a cost-effective method that can be used at the national level to prevent deficiency of both Zn and other micronutrients without any change in existing dietary patterns or any personal contact with the recipients (Hotz & Brown, 2004). Currently, the two chemical forms of Zn generally recognized as safe by the US Food and Drug Administration that are commonly used are ZnO and $ZnSO_4$, each of which is well accepted by consumers (Lopez de Romaña *et al.* 2002), with no difference in relative bioavailability when added as a fortificant to wheat flour or pasta at the level of 60 or 100 mg Zn/kg wheat flour (Lopez de Romaña *et al.* 2003) or when added as a fortificant to maize tortillas (Hotz *et al.* 2005). However, $ZnSO_4$ may be preferable for malnourished children with hypochlorhydria (Sturniolo *et al.* 1991). The additional cost of adding Zn to a national Fe fortification programme at a level ranging from 30 mg Zn/kg flour to 70 mg Zn/kg flour is US $0·03–0·04 *per capita* per year, an estimate that takes into account the expenses involved in Zn analyses for monitoring both quality and programmes.

National fortification of maize and/or wheat flour with Zn and other micronutrients has already been implemented in Mexico, Indonesia and South Africa, but so far no evaluation of these programmes has been published. For high-risk groups such as infants and young children a few targeted fortification programmes have been introduced, including milk powder fortified with Zn plus other micronutrients in Mexico (JA Rivera, S Villalpando, C Hotz, R Robledo, T Shamah, E Monterrubio, RJ Ciysins and R Blancard, unpublished results), Chile (Torrejon *et al.* 2004) and Brazil, but to date no clear improvements in Zn status have been noted.

Complementary food supplements have also been developed to supply minerals (including Zn) and vitamins at the level of 1 or $2 \times RDA$ to infants (>6 months) and young children, irrespective of the amount of complementary food consumed (for review, see Nestel *et al.* 2003). The complementary food supplements have been designed so that their use does not necessitate any changes in existing feeding practices. At present, three types of complementary food supplements are available: crushable or water-soluble tablets (foodlets); sprinkles; fortified spreads. Ideally, the foodlets and sprinkles should be added to the complementary food after cooking and consumed soon after to avoid destruction of both heat-labile vitamins (e.g. vitamin C) and the encapsulation system used to stabilize micro- and macronutrients.

Several efficacy trials of the complementary food supplements have recently been completed, although only a few of these trials have measured biochemical Zn status (Zlotkin *et al.* 2003; Smuts *et al.* 2005). In the International Research on Infant Supplementation study (Smuts *et al.* 2005) both a reduction in the biochemical prevalence

of Zn deficiency and a small improvement in weight gain were reported among children consuming a foodlet-based multiple micronutrient supplement compared with those receiving a placebo. More recently, results of an effectiveness trial (Ciliberto *et al.* 2005) have been reported in which both improvements in weight gain and reductions in morbidity were found in malnourished children receiving a home-based therapeutic food (i.e. a micronutrient-fortified spread) compared with those given the standard inpatient therapy based on the World Health Organization (1999) guidelines. The first phase of the standard inpatient therapy consists of a milk-based liquid food containing modest amounts of energy and protein, which is replaced by a specially-formulated high-energy high-protein liquid-based food once the children's appetite and clinical conditions have improved.

Some efficacy trials have been conducted in which Zn has also been included in multi-micronutrient-fortified beverages for schoolchildren (Ash *et al.* 2003; Abrams *et al.* 2003), and pregnant women (Makola *et al.* 2003), and in a multi-micronutrient-fortified seasoning powder incorporated into a school lunch for primary schoolchildren in north-east Thailand (P Winichagoon, J McKenzie, V Chavasit, T Pongcharoen, S Go Wachirapant, A Boonpraderm, MS Manger, KB Bailey, E Wasanturisut and RS Gibson, unpublished results).

Dietary modification or diversification

Both supplementation and fortification rely on a stable infrastructure and require financial support on a long-standing sound economic basis. However, the third strategy, dietary modification or diversification, is a more sustainable long-term, economically-feasible and culturally-acceptable strategy that can be used to alleviate several micronutrient deficiencies simultaneously without any risk of antagonistic interactions. A variety of approaches can be incorporated into a dietary modification or diversification programme, with the aim of increasing the total amount of dietary Zn and enhancing its absorption, and they will be summarized briefly (for details, see Ferguson *et al.* 1995; Gibson *et al.* 1998; Gibson & Hotz, 2001).

The best strategy for enhancing the Zn content of household diets is to promote the consumption of meat, poultry or fish, all good sources of readily-available Zn. Dried small whole soft-boned fish, in the form of a flour, can be used to enrich cereal-based porridges for feeding to infants and young children (Temple *et al.* 2002). This Zn source has the added advantage of not requiring refrigeration and can be consumed in countries in which religious and/or cultural factors prevent the consumption of meat and poultry. Cellular animal protein also promotes the absorption of Zn (and non-haem-Fe) from plant-based foods by forming soluble ligands with Zn, even in the presence of phytic acid (Sandström *et al.* 1989; Lönnerdal, 2000).

Several household food preparation and processing methods can be used to reduce the phytate content of foods based on cereals and legumes. These methods are based on the enzymic hydrolysis of phytic acid to lower inositol

phosphates that is induced by germination and fermentation (Gibson *et al*. 1998). Soaking, followed by decanting of the soaking water, can also be used to reduce the phytate content of cereal and legume flours by passive diffusion of the water-soluble sodium, potassium and magnesium phytates (Hotz & Gibson, 2001; Perlas & Gibson, 2002; Temple *et al*. 2002). Soaking also removes other anti-nutrients such as saponins and polyphenols. Several recent *in vivo* isotope studies in adults (Adams *et al*. 2002; Egli *et al*. 2004; Hambidge *et al*. 2004) and infants (Davidsson *et al*. 2004) have reported improvements in Zn absorption in cereal-based foods prepared with a reduced phytate content.

A combination of dietary strategies involving increased consumption of animal-source foods and phytate reduction is the preferred approach to enhance both the content and bioavailability of Zn in the diets of rural households in developing countries. Such strategies have the added advantage of simultaneously improving the content and bioavailability of Fe, vitamin B_{12}, vitamin A and Ca while enhancing protein quality and digestibility (Gibson *et al*. 2003), and at the same time lowering the levels of toxins such as haemagglutinins and cyanide. When fermentation is also used, microbiological safety and the keeping quality of the food is increased. To be effective, such strategies must be integrated with ongoing national agriculture, food, nutrition and health education programmes and implemented using a participatory approach to ensure their acceptability, adoption and sustainability (Gibson *et al*. 1998).

Biofortification

Future intervention strategies at the crop production level include biofortification to increase the content and/or bioavailability of Zn in staple food crops. Strategies may include the application of foliar or soil Zn fertilizers to improve the content of Zn in staple food crops (e.g. wheat, maize, sorghum, beans) grown in Zn-deficient soils, as practised in Turkey (Yilmaz *et al*. 1997), although care is needed because amounts that are too high can have negative effects on plant growth and soil micro-organisms (Frossard *et al*. 2000). Plant breeding also has the potential to increase Zn concentrations in the seeds of common beans (*Phaseolus vulgaris* L.), rice (especially aromatic varieties), wheat and, to a lesser extent, maize (Welch & Graham, 2004) with no negative correlations between grain yield and Zn density in the seeds. Nevertheless, the effect of processing on the content and bioavailability of Zn in these seeds has not yet been established.

Molecular biological and genetic modification approaches can also be used to alter the amounts of Zn absorption modifiers in plant foods, the levels of which are influenced by both genetic and environmental factors. Possible approaches include new varieties of cereal grains with (a) an increased content of methionine and cystine to promote Zn absorption in human subjects or (b) an enhanced ability to extract Zn from the soil (Hirsch & Sussman, 1999) and/or (c) a reduced phytic acid content (Raboy *et al*. 1989). *In vivo* stable-isotope studies have demonstrated increases in Zn absorption when adults are fed polenta or tortillas prepared from low-phytate hybrids of maize compared with a wild-type hybrid of 'normal' phytate content (Adams *et al*. 2002; Hambidge *et al*. 2004). Genetic engineering is also being used to introduce phytases from moulds such as *Aspergillus niger* into cereal grains, although currently such phytases are almost completely deactivated during normal cooking procedures. Studies using the thermo-stable *Aspergillus fumigatus* phytase are in progress (Brinch-Pedersen *et al*. 2002).

Moving from science to programmes

Ultimately, the success of any approach for combating Zn deficiency depends on political and policy leadership in the country and a strong commitment to developing an acceptable, equitable and sustainable solution. To date, only two developing countries have included Zn in their national surveys. Hence, on-going efforts are needed to ensure that the assessment of Zn status is included as a component of all micronutrient surveys in countries categorized as being at moderate or high risk of Zn deficiency, and that high-risk countries implement programmes to combat Zn deficiency with strategies that are appropriate for the target group and the setting.

In an effort to raise the profile and importance of adequate Zn nutriture for optimal health, physical and mental function and survival in developing countries, the IZiNCG has been established. So far, IZiNCG has held two symposia in conjunction with meetings of the International Vitamin A Consultative Group and the International Nutritional Anaemia Consultative Group, and it has published a detailed technical document (Hotz & Brown, 2004). The next step for IZiNCG will be to provide recommendations for Zn programmes.

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