TECHNICAL BRIEF

Information Gaps for Scaling-up Programs to Improve Zinc Nutrition

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BACKGROUND

This document focuses on the existing gaps in information needed to design large-scale programs to enhance zinc nutrition.

A recent publication of the International Zinc Nutrition Consultative Group (IZiNCG) discusses how adequate zinc nutrition is necessary for optimal child health, physical growth, and normal pregnancy outcomes (IZiNCG, 2004). Recent community-based intervention trials have found that zinc supplementation decreases rates of diarrhea and acute lower respiratory infections among young children (Zinc Investigators Group, 1999), two of the most important causes of child mortality in lower income countries. Several studies have detected significantly reduced death rates among children who receive supplemental zinc (Sazawal et al, 2001; Baqui et al, 2002; Brooks et al, 2005). Notably, a recent Lancet series on child mortality estimated that universal (>90 percent) coverage with intervention programs to prevent zinc deficiency would reduce child mortality by approximately five percent globally. This places zinc programs among the top five suggested approaches for ensuring improved child survival (Jones et al, 2003). In addition to the effects of zinc on morbidity and mortality from common childhood infections, a number of studies indicate that preventive zinc supplements increase the linear growth and weight gain of stunted or underweight children (Brown et al, 2002).

Despite the remarkable effects of zinc supplementation, public health planners have been slow to embrace zinc-related interventions. Reasons for the lack of large-scale programs to prevent zinc deficiency may include the limited information available on the prevalence of zinc deficiency and the need for practical intervention strategies that can be linked to ongoing health and nutrition programs. The following sections will review the current state of knowledge and information gaps in each of these areas.

ASSESSMENT OF POPULATION ZINC STATUS

Current Situation

There is no ideal biomarker of individual zinc status that is sufficiently sensitive to small changes in zinc nutriture. However, the World Health Organization (WHO), UNICEF, the International Atomic Energy Agency (IAEA), and IZiNCG, recently developed guidelines for assessing population zinc status (WHO, in press). These experts recommend using serum zinc concentration as an appropriate biomarker for population-wide zinc status, and they proposed tentative cut-offs to identify low serum zinc concentrations and the prevalence of low serum zinc levels. These latter thresholds can be used to indicate a public health concern due to zinc deficiency. The guidelines further suggest using quantitative information on dietary zinc (and phytate) intake not only to detect populations at risk of zinc deficiency but also to identify potential food vehicles for zinc fortification. Finally, the guidelines suggest that the rate of stunting or underweight among children less than five years of age can be used as a proxy indicator of zinc deficiency in situations where it is not possible to collect data on serum zinc concentration or dietary zinc intake. The latter recommendation is based on the fact that previous studies have found that children who are moderately or severely stunted or underweight (height-for-age or weight-for-age Z-scores<-1.5) respond to zinc supplementation, whereas less severely growth restricted children do not (Brown, 2002).

To date, very few countries have systematically collected information on population zinc status, so the global prevalence of zinc deficiency remains unknown. To address this issue on an interim basis, IZiNCG has proposed using suggestive evidence of zinc deficiency, based on the rates of stunting of under-five children (as justified above) and information on the absorbable zinc content of the national food supply using FAO's food balance sheets (Wuehler, 2005). According to these two sets of suggestive evidence, IZiNCG reports that approximately one-third of the global population live in countries with a high risk of zinc deficiency (IZiNCG, 2004).

Information Gaps

Because of the limited amount of information available on the true prevalence of zinc deficiency, national surveys of representative samples of the population are needed in high risk areas. To carry out these assessments, the range of factors that affect serum zinc concentration should be examined as well to permit the development of simple, efficient methods for collecting blood samples that yield the most accurate and valid results. Studies are also needed to validate the suggested cut-offs of zinc status indicators in relation to the functional effects of zinc deficiency. Additional field-applicable biomarkers of zinc status need to be developed. Finally, the suggestive evidence for classifying the population risk of zinc deficiency needs to be validated against objective biomarkers of zinc status.

ZINC INTERVENTION STRATEGIES

Three major nutrition-related strategies have been proposed to control zinc deficiency: supplementation, fortification, and dietary diversification/modification. Supplementation can be further divided into preventive supplementation and therapeutic supplementation for treatment of diarrhea and possibly other infections. The current state of knowledge and major information gaps will be described below in relation to each of these intervention strategies.

PREVENTIVE SUPPLEMENTATION

Current Situation

The current evidence on the functional benefits of zinc on morbidity and mortality and physical growth, as described above, is based mainly on findings from preventive zinc supplementation trials (Zinc Investigators Group, 1999; Sazawal et al, 2001; Baqui et al, 2002; Brown et al, 2002; Brooks et al, 2005). Almost all preventive zinc intervention trials to date used a randomized, placebo-controlled efficacy trial design, and little is known about the effectiveness of preventive zinc supplementation when it is delivered under realistic program conditions. Moreover, the published information on zinc intervention trials completed among children 6–35 months of age was derived from studies that used a single daily dose of zinc, ranging from 3 to 20 mg/d in individual studies, and most failed to monitor for possible adverse effects. Only one study compared daily versus weekly zinc supplementation and hardly any results are available from dose-response studies. Thus, more information is needed on optimal dosing regimens and duration of zinc supplementation. IZiNCG currently recommends dietary zinc intakes of 3–5 mg/d for children ages 6–47 months (depending on age and type of usual diet), and an upper limit of intake (based on the level at which no adverse effects are detected) of 6–8 mg/d (IZiNCG, 2004). However, empirical evidence is needed from dose-response studies to confirm the efficacy and safety of these recommendations.

A number of studies have examined the effects of zinc on iron absorption and vice versa, using both tracer methods and biochemical and functional responses to longer term supplementation. Longer term studies suggest that each mineral reduces the magnitude of the biochemical response observed with single nutrient supplementation (Dijkhuizen et al, 2001; Lind et al, 2003; Berger et al, 2006), although nutritional status is still enhanced to a considerable extent despite the nutrient-nutrient interactions. Findings regarding the impact of zinc supplementation with or without iron on functional outcomes are less consistent. Simultaneous delivery of iron and zinc may undermine the growth-enhancing effect of zinc (Lind et al, 2004) and possibly the benefits of zinc for reducing morbidity and the benefits of iron for psychomotor development. In contrast, positive effects on the incidence and duration of diarrhea in infants and young children have been found with concomitant iron and zinc supplementation compared with iron supplementation alone (Rosado et al, 1997; Baqui et al, 2003). However, studies of combined multiple micronutrient supplementation (including iron and zinc as well as other micronutrients) in Peru (Penny et al, 2004) and Bangladesh (Baqui et al, 2003) failed to detect the morbidity reduction that was observed when zinc alone was provided.

Information Gaps

Information is needed on the optimal safe and effective dose of preventive zinc supplements for children of different ages and the appropriate frequency and duration of supplementation, with and without other micronutrients. Information is also needed on the operational effectiveness and efficiency of combining zinc supplementation with other routine health/nutrition contacts, such as growth monitoring, EPI, or periodic vitamin A supplementation activities. Finally, information is needed on the best way of integrating preventive and therapeutic supplementation programs.

THERAPEUTIC SUPPLEMENTATION FOR TREATMENT OF DIARRHEA AND OTHER INFECTIONS

Current Situation

A set of treatment studies has been completed to examine the impact of zinc supplementation during episodes of diarrhea on the severity and duration of these illnesses. The vast majority of these treatment trials have concluded that therapeutic zinc supplementation decreases the duration of diarrhea among children greater than six months of age (Zinc Investigators Group, 2000), although it has no demonstrable benefit among younger infants (Fischer-Walker, in press). Notably, some studies of therapeutic zinc supplementation found a reduced incidence of subsequent episodes of illness for as long as two months following the initial period of treatment and greater weight gain during that interval among the supplemented children.

In response to these findings, the WHO and UNICEF released a joint statement regarding the appropriate clinical management of acute diarrhea, which urges the provision of oral rehydration solution (ORS) and home-available fluids, breastfeeding, continued feeding of other foods, selective use of antibiotics, and the administration of zinc supplements (20 mg/d for children >12 months of age and 10 mg/d for infants) for 10 to 14 days with each episode of diarrhea (WHO & UNICEF, 2004). Following the publication of these recommendations by WHO and UNICEF, several lower-income countries have begun incorporating zinc supplementation in their therapeutic regimen for diarrhea.

Therapeutic zinc supplementation also has been evaluated for the treatment of respiratory infections and malaria. There is insufficient and inconsistent information on the effect of zinc supplementation on the severity and duration of acute lower respiratory tract infections, and the data are inconsistent with regard to upper respiratory tract infections (Hulicz, 2004). There is little information on zinc as a component of the therapeutic regimen for tuberculosis, and there is no apparent benefit of zinc supplementation for the treatment of malaria (ZAPSG, 2002).

Information Gaps

The optimal dose of zinc supplements for therapeutic purposes remains untested. Moreover, it is conceivable that a separate therapeutic program might be unnecessary if a successful preventive program has been implemented, so this issue should be examined. Therapeutic supplementation for other illnesses, such as pneumonia and tuberculosis, require further study; and treatment of other illnesses, such as skin infections, viral infections (including HIV), and enteric parasitic infections, have received remarkably little attention.

FORTIFICATION

Current Situation

Most of the available information on the impact of food fortification with zinc was collected during controlled efficacy trials. In some cases, zinc was the only nutrient that differed between the intervention and control groups, so it was possible to attribute differences in functional outcomes to zinc. In other cases, zinc was included in a mix of multiple micronutrient fortificants. The results of controlled fortification trials in which only zinc was added are inconsistent. A few studies found a significant increase in serum zinc concentration in the group that received the zinc-fortified product (Hambidge et al, 1979; Matsuda et al, 1984; Kilic et al, 1998), but none of the available studies identified a positive impact of zinc fortification on children's growth. The one study that systematically collected information on rates of morbidity found no beneficial impact of zinc fortification (Brown, in press). Thus, the results of these trials are generally disappointing, although the methodological limitations of some of these studies must be recognized.

Several studies have evaluated the effects of fortifying different food products with multiple micronutrients, including zinc. Serum zinc concentrations of older infants did not respond to zinc-containing, multi-micronutrient fortified, cereal-based complementary foods in the four studies that measured this outcome (Lartey et al, 1999; Oloefse et al, 2003; Faber et al, 2005; Lutter at al, 2006; Brown et al, in press). Moreover, there were no effects of the interventions on the infants' growth, although this non-response may have been due to the fact that they were not sufficiently growth-restricted to benefit from zinc. In contrast with the results from cereal-based products, serum zinc concentrations increased significantly among two different sets of school children who received a multi-micronutrient fortified beverage between meals (Abrams et al, 2003) or a multi-micronutrient fortified seasoning powder with meals (Winichagoon et al, 2006). The reason for the different results of these two studies is uncertain but may be related to the age of the subjects or to the nature of the fortification vehicles. Regrettably, very little information is available from large-scale, programmatic interventions.

Studies investigating the impact of home-based fortification using a mixture of vitamins and minerals packaged in small sachets containing a daily dose of micronutrients have focused mainly on the prevention of anemia and iron deficiency (Zlotkin et al., 2003; Giovannini et al., 2006). Little is known about the impact of other micronutrients included in the multi-micronutrients mixture. In particular, there is limited information regarding their impact on zinc status. One study assessed the impact of a proprietary formulation "Sprinkles" with and without zinc on zinc-related outcomes and found no difference in serum zinc concentration or growth between the two groups (Zlotkin et al., 2003). However, the study duration of only two months might have been too short to show such effects. Moreover, the Sprinkles provided in this study contained very high doses of iron (80 mg/d), which might have interfered with zinc absorption. A recent study in Cambodia compared growth increments during a 12 month period among children who received either Sprinkles containing multiple micronutrients (including 5 mg zinc) or iron and folic acid only vs. placebo (Giovannini et al., 2006). The supplements had no impact on the children's growth, but the sample size was just marginally adequate (n=68 per group) to be able to detect any changes. In summary, the health benefits of zinc included in "Sprinkles" have not yet been proven.

Information Gaps

Information is needed on the efficacy of zinc fortification programs (with and without other micronutrients), including their impact on biochemical indicators of zinc status and related functional outcomes. Similar information is needed for home fortification programs with zinc-containing micronutrient mixtures, such as Sprinkles.

DIETARY DIVERSIFICATION/MODIFICATION

Current Situation

Diets in low income countries are predominantly plant-based and consumption of animal-source foods, such as meat, poultry, and fish, is often limited because of economic, cultural, and/or religious constraints. As a result, the zinc content of such diets is low and the efficiency of absorption is limited. Dietary inadequacy is probably the primary cause of zinc deficiency. To increase the zinc content in the diets, small-livestock husbandry, aquaculture, and production of other indigenous zinc-rich food can be promoted. At the household level, reduction of phytate content of the diet can be achieved by using simple techniques to activate phytase, which is present naturally in cereals and legumes. Several recent in vivo studies using stable isotopes in adults (Adams et al, 2002; Egli et al, 2004) and infants (Davidsson et al, 2004) have reported improved zinc 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 zinc in the diets of rural households in low income countries (Gibson, 2006). Such strategies have the added advantage of simultaneously improving the content and bioavailability of iron, vitamin B_{12}, vitamin A, and calcium while enhancing protein quality and digestibility (Gibson et al, 2003). However, programmatic experience with the promotion of home processing techniques to increase absorbable zinc in the diet is surprisingly limited, considering the large amount of literature showing their effectiveness in reducing phytate and increasing zinc absorption in clinical studies.

Several strategies can be used to increase the zinc content of plant-based staples. These include the use of zinc fertilizers, plant breeding to select for high-zinc cultivars, and genetic modification techniques. Although these methods appear promising, research is needed to evaluate their economic, environmental, and health effects before these strategies can be recommended for implementation.

It is important to recognize that programs designed to promote exclusive breast feeding during the first six months of life can also be construed as zinc intervention programs, because human milk is an adequate source of zinc during this period. However, the concentration of zinc in milk decreases substantially with increasing infant age, so additional food sources of zinc are generally required by six months (and possibly earlier in low birth weight infants). Thus, complementary feeding programs also should be designed with consideration of their likely impact on young children's zinc intakes and zinc status.

Information Gaps

There is little experience from large-scale programs to promote increased intake of zinc-rich foods. Practical information is needed on how best to identify locally available, low-cost, culturally acceptable zinc-rich foods and promote their consumption by those at risk of zinc deficiency. Likewise, information is needed on the best ways of implementing both large-scale and home-based food processing interventions to enhance zinc absorption from the usual diet. Agricultural interventions to increase dietary zinc content through improved agronomic practices and/or plant breeding need to be implemented and assessed. Finally, interventions to improve infant feeding practices (exclusive breast feeding and appropriate complementary feeding) should be evaluated with regard to their impacts on zinc status.

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