Chapter 5

Zinc deficiency

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Summary

Research conducted during the past 10–15 years suggests that zinc deficiency is widespread and affects the health and well-being of populations worldwide. The objective of this chapter is to quantify the regional and global magnitude, distribution and disease burden implications of zinc deficiency.

We conducted a systematic literature search to identify relevant studies investigating the role of zinc in human health. This search indicated that evidence on the burden of disease related to zinc deficiency would be limited to the results of randomized controlled trials (RCTs) conducted among paediatric populations in developing countries, and would provide information on whether zinc deficiency affects the incidence of diarrhoea, pneumonia and malaria illness among children aged 0–4 years. There are no global estimates of zinc deficiency in paediatric or other populations; however, the International Zinc Nutrition Consultative Group (IZiNCG) has developed a method for estimating the prevalence of inadequate zinc intakes based on the presence and bioavailability of zinc in each country's food supply.

A systematic review of relevant epidemiological research involved meta-analysis from 11 intervention trials. Results of our review indicate that zinc deficiency in children aged <5 years increases the risk of incidence for diarrhoeal disease by 1.28 (95% CI 1.10–1.50), pneumonia by 1.52 (95% CI 1.20–1.89) and malaria by 1.56 (95% CI 1.29–1.89). We extended those results as best estimates of the risk of mortality from these causes as a result of zinc deficiency. Following the IZiNCG technique, the global prevalence of zinc deficiency was estimated at 31%, ranging from 4–73% across subregions.[1] Based on these estimates, zinc deficiency was estimated to cause 176 000 diarrhoea deaths, 406 000 pneumonia deaths and 207 000 malaria deaths. The associated loss of disability-adjusted life years (DALYs) attributable to zinc deficiency amounts to more than 28 million. The burden of disease due to zinc

deficiency is borne most heavily by countries in Africa, the Eastern Mediterranean and South-East Asia. The burden was approximately equally shared between males and females.

The results of this review suggest that zinc deficiency contributes substantially to the morbidity and mortality of young children throughout the world. Available evidence from RCTs on the strength of the association between zinc deficiency and morbidity from diarrhoea, pneumonia and malaria, combined with the high estimated prevalences of inadequate zinc diets, translates into a significant burden of disease attributable to deficiency of this micronutrient. Evidence relating zinc deficiency to health outcomes in children aged >5 years and adult men and women was not available. Given the likely high prevalence of inadequate zinc intakes in these other groups, research is needed to determine the magnitude of the potential health effects.

1. Introduction

Zinc is a trace mineral essential to all forms of life because of its fundamental role in gene expression, cell development and replication (Hambridge 2000). Severe or clinical zinc deficiency was defined last century, as a condition characterized by short stature, hypogonadism, impaired immune function, skin disorders, cognitive dysfunction and anorexia (Prasad 1991). Although severe zinc deficiency is considered rare, mild-to-moderate zinc deficiency is likely prevalent throughout the world today (Sandstead 1991). Lack of consensus on indicators of zinc deficiency has hampered efforts to document prevalences of zinc deficiency. Despite this, RCTs of zinc supplementation in areas with habitual low zinc intakes have begun to demonstrate how low dietary intakes of zinc adversely affect child health (Brown et al. 1998a; Zinc Investigators' Collaborative Group 1999, 2000). For this reason, it is important to attempt to quantify the prevalence of zinc deficiency and its contribution to the global burden of disease. The goal of this chapter is to describe the methods used to quantify the magnitude, distribution and disease burden implications of zinc deficiency.

2. Nature and definition of the risk factor

Millions of people throughout the world may have inadequate levels of zinc in the diet due to limited access to zinc-rich foods (animal products, oysters and shellfish) and the abundance of zinc inhibitors, such as phytates, common in plant-based diets (Sandstead 1991). Our understanding of the public health importance of inadequate zinc intakes has been hampered by a lack of indicators of zinc status for identifying individuals with zinc deficiency (Wood 2000).

Estimating the prevalence of zinc deficiency is difficult because plasma or serum zinc concentrations, the most widely used indicators of zinc

deficiency at the population level, have not been assessed in national or regional surveys in developing countries. Even in developed countries, such indicators are not used for methodological and cost reasons.

Zinc deficiency is largely related to inadequate intake or absorption of zinc from the diet, although excess losses of zinc during diarrhoea may also contribute (Gibson 1994; WHO 1996). The distinction between intake and absorption is important, because although some intakes of zinc may be acceptable, the levels of inhibitors (e.g. fibre and phytates) in the diet may mean that inadequate amounts of zinc are absorbed. For this reason, zinc requirements for dietary intake are adjusted upward for populations in which animal products, the best sources of zinc, are limited, and in which plant sources of zinc are similarly high in phytates. Because zinc is not well conserved in the body and because zinc deficiency is directly related to dietary zinc intake, an indirect approach to quantify the prevalence of zinc deficiency would be to examine the adequacy of zinc in the diet in various regions throughout the world.

Dietary surveys are conducted in many countries, but few such surveys exist in developing countries (Gibson 1994; Parr 1992; WHO 1996). Even when dietary intake data are available, incomplete information on the content of zinc and its bioavailability in local foods has made calculation of zinc bioavailability problematic.

2.1 Prevalence of zinc deficiency

Several alternative approaches have been taken to estimate the adequacy of the diet in various regions of the world. For example, the World Health Organization (WHO) (1996) used a factorial approach to estimate the average basal and normative zinc requirements (i.e. minimum amount of zinc to cover losses in individuals adapted or not adapted to low usual dietary intakes of zinc) for population subgroups, and then considered issues of zinc bioavailability from the typical diet in various regions of the world to derive estimates of the minimal dietary intake of zinc that would meet these requirements. They then compared the estimated dietary intakes of zinc from 210 dietary surveys conducted throughout the world as a percentage of the minimal dietary intake of zinc, and identified surveys in which the mean intake of zinc did not meet the minimal basal or normative level of intake. Overall, this method led to the conclusion that populations with inadequate intakes of zinc were likely widespread throughout the world, but concentrated in areas of the world consuming plant-based diets in which zinc was only of low to moderate bioavailability. For example, of 148 surveys conducted in populations with presumed highly bioavailable zinc (mostly western Europe and the United States of America), only one dietary survey indicated a mean intake lower than the minimal zinc intake to meet average normative requirements for zinc. In contrast, among 47 surveys conducted in populations with moderate zinc bioavailability, 40 indicated average

intakes lower than the minimal normative zinc intake, and of 15 surveys conducted in populations with low zinc bioavailability, none reported mean intakes greater than the minimal normative zinc intake. Based on this approach, it was concluded that zinc nutrition in developing countries should be a priority area for research, and emphasized the need for studies of dietary intakes and dietary constituents. Although carefully constructed, this analysis could not provide us with the required data on estimated regional prevalences of zinc deficiency.

In 2001, Brown et al. published an approach that used available data on per capita food availability from 172 countries to estimate the prevalence of inadequate zinc intakes worldwide. Subsequently IZiNCG (forthcoming) revised this approach, improving on the method for assessing the bioavailability of zinc in the food supply. We used this second approach because of the improved methodology and more conservative estimates of deficiency, and were provided with estimated prevalences of inadequate intakes of zinc in the diet in each of the 14 subregions (K. Brown, personal communication). The technique is described briefly below.

Data are available on the per capita food availability in each country based on country-level information on food production, imports and exports, as reported on food balance sheets (FBS) by the Food and Agriculture Organization of the United Nations (FAO) on an annual basis. Per capita availability of energy was estimated from this information, and population estimates for each country in 1998 (FAO 1999). Per capita zinc availability was estimated based on the zinc : energy ratio, which was derived using FAO values for energy for each food and values of the World Food Program (World Food Dietary Assessment System 1997) for the estimated zinc content of each food. To examine the bioavailability of zinc in the diet, IZiNCG gathered published information from studies of zinc absorption from test meals, and conducted a pooled analysis to derive a prediction equation for the percentage absorbable zinc based on information on the zinc, phytate, calcium and total protein content of the diet. This equation and information on the levels of zinc, phytate, calcium and total protein available per capita per meal (assuming three meals per day) calculated from the FBS database were then applied to estimate the percentage absorbable zinc for each of the 172 countries with available FBS data. The proportion of absorbable zinc ranged from 11% to 22%. Countries were then categorized as having low (<14%), moderate (15–16%) or high (>17%) mean percentage absorbable zinc in the food supply, based on their main staple food (wheat, rice, maize and other cereals, and tubers) and the contribution of animal protein to the energy available in the food supply.

The average daily zinc requirement for each country was estimated by calculating the mean of the recommended zinc intakes for low, average and high bioavailability diets for the various sexes and ages (WHO 1996), weighted by the sex and age distribution of the country's popu-

lation, as obtained from the WISTAT database (WISTAT 1994). To calculate the estimated percentage of the population with inadequate zinc intake, they assumed that the mean intake of food was equal to mean availability of food, and that the standard deviation of intake is 25% of the mean—i.e. coefficient of variation (CV) = 0.25 (WHO 1996). Under assumptions of normality, they calculated the proportion of individuals with intakes below the country-level daily zinc requirement, and thus at risk of zinc deficiency due to inadequate zinc intake (IZiNCG forthcoming). Again, this method is conservative when compared to the previously published method using bioavailability estimates, which considered only the phytate:zinc molar ratio in the food supply (Brown et al. 2001).

The method does not account for zinc intake from breast milk or from drinking water. However, breast milk is only an adequate source of zinc in the diets of infants aged less than six months, and zinc intakes from drinking water typically increase total zinc intakes by only 2% provided a usual water intake of 2 l/day.

A secondary consideration for our calculations was the selection of the appropriate counterfactual (i.e. theoretical minimum exposure) for zinc deficiency. Unlike some other exposures, zero prevalence of zinc deficiency is in theory possible, and would likely result in complete eradication of the zinc disease burden due to this risk factor. Thus, for purposes of the analysis, we designated the theoretical minimum exposure to be as "no inadequate intakes of zinc" or zero prevalence of inadequate intakes of zinc.

Using the method described above, the estimated global prevalence of zinc deficiency is 31%, and ranges from 4% to 73% (Table 5.1). The prevalences of zinc deficiency are low (4–7%) in AMR-A, EUR-A, EUR-C and WPR-A. Intermediate prevalences of 9–26% are found in AMR-B, EUR-B and WPR-B. High prevalences are found in AMR-D (68%), throughout South and Central Africa (37–62%), North Africa and the Eastern Mediterranean region (25–52%), and South and South-East Asia (34–73%).

3. Health outcomes considered

To proceed with a systematic investigation of the evidence regarding the role of zinc in human health, we disaggregated and then linked both specific health outcomes and target populations. The considered health outcomes included risk and/or severity of diarrhoea, pneumonia, malaria, measles, cognitive dysfunction, physical impairment, visual impairment or blindness and mortality. The target populations consisted of the following age–sex groups: children aged 0–4 years; children 5–14 years; women 15–44 years; men 15–44 years; all adults ≥45 years. Despite this disaggregated approach to defining risk groups, upon review of the literature described below, we concluded that there were few pub-

Table 5.1 Estimated prevalence of inadequate zinc intakes by subregion[a]

Subregion	*Number of countries*	*Population (millions)*	*Energy (kcal/d)*	*Zinc (mg/d)*	*Phytate:zinc ratio*	*Available zinc (mg)*	*Mean % of adjusted requirement*	*% inadequate intakes (95% CI)*
AFR-D	25	278.7	2453 (327)	10.0 (2.1)	25.8 (2.6)	1.14 (0.20)	57.3 (10.8)	36.5 (26.4–46.6)
AFR-E	20	322.6	2075 (370)	8.6 (1.6)	27.9 (3.7)	0.94 (0.20)	46.7 (12.4)	61.6 (49.3–73.9)
AMR-A	3	315.7	3514 (234)	12.1 (1.0)	12.6 (0.8)	2.85 (0.37)	85.3 (7.4)	6.3 (0–16.1)
AMR-B	26	418.6	2828 (244)	10.4 (1.8)	20.6 (5.7)	1.66 (1.15)	65.4 (14.8)	26.0 (17.9–34.1)
AMR-D	6	68.5	2241 (223)	7.5 (1.0)	24.7 (6.6)	0.91 (0.15)	44.5 (5.6)	68.4 (54.7–82.1)
EMR-B	10	130.4	2946 (195)	8.5 (1.1)	22.0 (2.7)	1.12 (0.40)	60.9 (6.1)	25.2 (21.1–29.3)
EMR-D	9	339.7	2544 (460)	7.8 (1.9)	25.0 (3.4)	0.91 (0.19)	52.2 (11.7)	51.8 (33.8–69.8)

EUR-A	22	409.4	3378 (154)	12.6 (1.1)	11.5 (1.8)	3.53 (0.93)	92.0 (8.4)	3.9 (2.8–5.0)
EUR-B	16	213.6	3073 (433)	10.2 (1.5)	18.4 (4.6)	1.63 (0.62)	73.2 (10.1)	12.7 (8.9–16.5)
EUR-C	6	247.0	3020 (109)	11.2 (0.7)	13.8 (1.1)	2.18 (0.37)	83.5 (4.7)	5.7 (4.4–7.0)
SEAR-B	3	285.1	2616 (203)	9.1 (1.1)	26.9 (3.4)	1.00 (0.06)	56.9 (6.0)	33.5 (14.7–52.3)
SEAR-D	6	1198.0	2356 (127)	7.9 (0.7)	27.5 (0.4)	0.85 (0.07)	43.5 (4.8)	72.5 (62.3–82.7)
WPR-A	4	148.9	2954 (122)	11.8 (0.9)	16.6 (3.4)	2.13 (1.27)	91.2 (2.9)	3.6 (3.2–4.0)
WPR-B	13	1498.3	2705 (159)	10.7 0.9)	19.0 (1.3)	1.47 (0.23)	80.5 (8.7)	8.5 (3.6–13.4)
World	172	5874.3	2706 (434)	9.9 (2.0)	21.3 (6.0)	1.51 (0.90)	66.5 (19.4)	31.3 (26.7–35.9)

[a] Presented as means (standard deviations).

Source: IZiNCG (forthcoming).

lished studies regarding the contribution of zinc deficiency to morbidity or mortality in any age group other than children aged 0–4 years. For this reason, the chapter focuses on the contribution of zinc deficiency to the global burden of disease among children aged 0–4 years.

4. Risk factor–disease relationship

4.1 Search strategy

Evidence for the relationship between zinc deficiency and various diseases was gathered through literature searches of published studies. Articles related to zinc deficiency in human populations were identified for review based upon a Medline database search of literature published 1966–2001 in English or with an English abstract. The search was conducted using combinations of the following keywords: zinc, deficiency, mortality, death, morbidity, acute respiratory infection, pneumonia, diarrhoea, measles, malaria, child, pregnancy, infant, neonatal, fetal, premature, congenital, abortion, stillbirth, miscarriage, birth weight, retardation, development, intelligence, cognitive, psychomotor and neurological. Further searches on Medline were conducted using author names and the "related articles" option.

Abstracts were reviewed to select English-language articles that examined the effect of zinc deficiency (as defined by clinical, epidemiological or biochemical assessment) or supplementation/fortification on several health outcomes of interest in human populations. These health outcomes included infant or neonatal, child or adult mortality; incidence or severity of malaria, diarrhoea, measles or acute respiratory infection; prevalence of mental retardation or cognitive dysfunction; and risk prevalence of physical impairment such as hearing or neurological dysfunction. Once copies of articles were obtained, additional publications were identified from the reference lists of those articles. The only studies excluded from review were animal studies and case reports.

4.2 Methods for combining risk estimates from individual studies

The most appropriate study design to assess prospective risk for our purposes would be a prospective cohort study. Unfortunately, no such studies were identified despite an exhaustive search. Certainly this relates in part to the fundamental problem of characterizing the zinc status of individuals discussed above. There have been, however, a significant number of RCTs of zinc supplementation examining morbidity outcomes in young children living in developing countries with presumably low intakes of zinc. The studies that were identified and included in our calculations are summarized in Table 5.2.

The studies included were RCTs of zinc supplementation for the prevention of one of three health outcomes: diarrhoea, pneumonia or

Table 5.2 Studies contributing data on the effect of zinc deficiency on morbidity among children, aged 0–4 years

Country (reference)	*Study design*	*Supplement*	*Age (months)*	*Sample size*		*Enrolment criteria*	*Outcomes measured*		
				Zinc group	*Control group*		*Diarrhoea*	*Pneumonia*	*Malaria*
Burkina Faso (Müller et al. 2001)	Continuous supplementation (6 days/ week) over a 6-month period. Malaria defined based on community-based active case detection	12.5 mg zinc as sulfate	6–31	356	353	Community-based (included for diarrhoea only)	✓	—	✓
Ethiopia (Umeta et al. 2000)	Continuous supplementation (6 days/ week) for 6 months	10 mg zinc as sulfate	6–12	92	92	Stratified based on length-for-age <–2 SD	✓	—	—
Gambia (Bates et al. 1993)	Twice weekly supplementation over a 1.25-year period. Supplement provided in a fruit-flavoured drink; malaria defined as clinic visit with confirmation by microscopic evaluation	70 mg zinc as zinc acetate	6–28	55	54	Matched on age and sex	—	—	✓
Guatemala (Ruel et al. 1997)	Daily supplementation for 28 weeks	10 mg zinc as sulfate	6–9	45	44	Community-based	✓	—	—
India (Bhandari et al. 2002)	Daily supplementation for 16 weeks	10 mg zinc to infants; 20 mg zinc to older children; as gluconate	6–35	1241	1241	Community-based	—	✓	—

continued

Table 5.2 Studies contributing data on the effect of zinc deficiency on morbidity among children, aged 0–4 years (*continued*)

Country (reference)	*Study design*	*Supplement*	*Age (months)*	*Sample size*		*Enrolment criteria*	*Outcomes measured*		
				Zinc group	*Control group*		*Diarrhoea*	*Pneumonia*	*Malaria*
India (Sazawal et al. 1997, forthcoming)	Daily supplementation for 26 weeks	10 mg zinc as gluconate, vitamin A, B, D, E	6–35	286	293	Recovered from acute diarrhoea	✓	✓	—
Jamaica (Meeks-Gardner et al. 1998)	Daily supplementation for 12 weeks	5 mg zinc as sulfate, vitamin A, B, C, D	6–24	31	30	Weight-for-height <–2 SD	✓	✓	—
Mexico (Rosado et al. 1997)	Continuous supplementation (5 days/ week) for 54 weeks	20 mg zinc as methionate, half with iron	18–36	97	97	Community-based	✓	—	—
Papua New Guinea (Shankar et al. 1997, 2000)	Continuous supplementation (6 days/week) over a 46–7 week period. Malaria defined based on active case detection as well as clinic visits, confirmed by microscopic evaluation	10 mg zinc as gluconate	6–60	136	138	Community-based	✓	—	✓
Peru (Penny et al. 1999)	Daily supplementation for 26 weeks	10 mg zinc as gluconate	6–35	80	79	Recovered from persistent diarrhoea	✓	✓	—
Viet Nam (Ninh et al. 1996)	Daily supplementation for 22 weeks	10 mg zinc as sulfate	4–36	73	73	Weight-for-age and height-for-age <–2 SD	✓	✓	—

✓ Measured.
— Not measured.

malaria. In addition, there are numerous RCTs in which zinc supplements are evaluated as therapeutic agents (Zinc Investigators' Collaborative Group 2000), but these are not included. In all, nine studies contributed findings on zinc deficiency and risk of diarrhoea (Meeks-Gardner et al. 1998; Müller et al. 2001; Ninh et al. 1996; Penny et al. 1999; Rosado et al. 1997; Ruel et al. 1997; Sazawal et al. 1997; Shankar et al. 1997; Umeta et al. 2000), five contributed findings on risk of pneumonia (Bhandari et al. 2002; Meeks-Gardner et al. 1998; Ninh et al. 1996; Ruel et al. 1997; Sazawal et al. 1998), and three contributed findings on risk of malaria (Bates et al. 1993; Müller et al. 2001; Shankar et al. 2000).

The data required for this work are the risk of each health outcome associated with zinc deficiency. This was calculated as the inverse of the odds ratio or relative risk estimated from RCTs given two assumptions: subjects in the study population have some level of zinc deficiency, and supplementation with zinc eliminated zinc deficiency. Because the first of these assumptions is likely to be generally but not universally true, and the second assumption is *not* likely to be true, we view our results as conservative.

4.3 Diarrhoea

The results of the nine RCTs with findings on zinc deficiency and diarrhoea incidence are presented in Table 5.3. The results are presented for each individual study as well as a pooled estimate of all nine studies. The pooled estimate was derived using random effects models as described

Table 5.3 Zinc deficiency and risk of diarrhoea incidence

	Zinc group		*Control group*		*Relative risk*
Country (reference)	*Episode*[a]	*Follow-up*[b]	*Episode*[a]	*Follow-up*[b]	*(95% CI)*
Burkina Faso (Müller et al. 2001)	322	49126	374	47844	1.19 (1.03–1.39)
Ethiopia (Shankar et al. 1997)	27	16790	59	16790	2.22 (1.39–3.45)
Guatemala (Ruel et al. 1997)	387	8482	467	8361	1.22 (1.08–1.41)
India (Sazawal et al. 1997)	934	44866	1033	45555	1.09 (1.00–1.31)
Jamaica (Meeks-Gardner et al. 1998)	39	2604	37	2265	1.09 (0.69–1.72)
Mexico (Rosado et al. 1997)	82	42322	132	42751	1.59 (1.20–2.13)
Papua New Guinea (Umeta et al. 2000)	63	27490	77	29465	1.14 (0.82–1.59)
Peru (Penny et al. 1999)	564	13178	661	13648	1.14 (1.01–1.27)
Viet Nam (Ninh et al. 1996)	56	11242	100	11242	1.79 (1.28–2.50)
All					1.28 (1.10–1.49)

[a] Episode refers to an episode of diarrhoea as per the case definition in the individual study.

[b] Follow-up refers to the total number of child-days of follow-up or disease surveillance in each study.

in a previous pooled analysis (Zinc Investigators' Collaborative Group 1999). Although each study reported the effects of zinc supplementation on the incidence of diarrhoeal illness, we have presented estimates of the relative risk of diarrhoeal disease incidence due to zinc deficiency. As shown, the pooled estimate indicates that the relative risk of diarrhoea in young children due to zinc deficiency is 1.28 (95% CI 1.10–1.49).

In 1999, a pooled analysis was conducted of published RCTs of zinc supplementation to reduce diarrhoea and pneumonia morbidity in young children (Zinc Investigators' Collaborative Group 1999); at that time, seven of these studies had been published (Meeks-Gardner et al. 1998; Ninh et al. 1996; Penny et al. 1999; Rosado et al. 1997; Ruel et al. 1997; Sazawal et al. 1997; Umeta et al. 2000). The pooled estimate based on these studies indicated that zinc deficiency increases the risk of diarrhoea in young children by 1.33 (95% CI 1.14–1.59).

4.4 Pneumonia

The results of the five RCTs with findings on zinc deficiency and pneumonia incidence are presented in Table 5.4. The results are presented for each individual study as well as a pooled estimate across all five studies. As shown, it is estimated that zinc deficiency increased the risk of pneumonia in young children by 1.52 (95% CI 1.20–1.89).

With the exception of the study by Bhandari et al. (2002), the studies had been included in a published pooled analysis of the effects of zinc supplementation on pneumonia (Zinc Investigators' Collaborative Group 1999). The summary estimate from that analysis was of similar magnitude: the relative risk of pneumonia due to zinc deficiency in young children was 1.69 (95% CI 1.20–2.45).

Table 5.4 Zinc deficiency and risk of pneumonia incidence

	Zinc group		*Control group*		*Relative risk*
Country (reference)	*Episode*[a]	*Follow-up*[b]	*Episode*[a]	*Follow-up*[b]	*(95% CI)*
India (Bhandari et al. 2002)	88	132 000	118	134 400	1.32 (1.01–1.72)
India (Sazawal et al. 1998)	24	44 866	43	45 555	1.76 (1.08–2.94)
Jamaica (Meeks-Gardner 1998)	0	2 604	1	2 265	3.13 (0.16–100.0)
Peru (Penny et al. 1999)	9	13 178	11	13 648	1.22 (0.51–2.86)
Viet Nam (Ninh et al. 1996)	45	11 242	81	11 242	1.79 (1.25–2.56)
All					1.52 (1.20–1.89)

[a] Episode refers to an episode of pneumonia as per the case definition in the individual study.

[b] Follow-up refers to the total number of child-days of follow-up or disease surveillance in each study.

4.5 Malaria

Three RCTs of zinc supplementation to prevent malaria morbidity were identified. In Papua New Guinea, Shankar et al. (2000) found a 38% (95% CI 3–60%) reduction in malarial attacks based on clinic visits for malaria or fever with confirmed parasitaemia above a predefined threshold. Using an analogous definition, Bates et al. (1993) also found an approximately one-third reduction in malarial attacks, but it was not statistically significant ($P = 0.09$), and the authors concluded there was no effect of zinc deficiency on malarial attack rates. However, Shankar et al. (2000) obtained the original data from the study (Bates et al. 1993) and utilized random effects models to derive a pooled estimate of a 36% (95% CI 9–55%) reduction in clinic-based malarial attacks with parasitaemia with zinc supplementation. The paper by Müller et al. (2001) utilized a different methodology to detect malarial illness—community-based daily surveillance—and thus, examined a different aspect of malarial illness. They found no significant reduction in malarial incidence by treatment, with a zinc treatment odds ratio of 0.98 (95% CI 0.86–1.11). Studies with community-based malaria surveillance largely detect associations with early manifestations of a malaria episode, and on episodes tending to be less severe, whereas studies focusing on clinical malaria episodes detect effects on the progression of a malaria episode, and on cases perceived to be severe enough to warrant a visit to the health centre (Cox et al. 1994). Because of the heterogeneity of outcomes studied, and our desire to focus on malarial morbidity that contributes to the global disease burden estimates (Snow et al. 1999), we excluded the study by Müller et al. (2001) from further analysis. Instead we used Shankar's pooled analysis to derive a relative risk for malaria morbidity associated with zinc deficiency in young children of 1.56 (95% CI 1.29–1.89).

4.6 Mortality

Clearly, zinc deficiency contributes to increased risk of incidence for important childhood diseases that are predominant causes of death among children. Direct estimation of the risk of cause-specific mortality among children due to zinc deficiency is not available from the literature. Unless there were an expectation that zinc deficiency reduced case-fatality or severity of these diseases, the risk of mortality due to zinc deficiency should be at least equivalent to the risk of disease occurrence due to zinc deficiency. For this reason, we have proposed that the relative risk of mortality related to diarrhoea, pneumonia and malaria associated with zinc deficiency, are 1.28, 1.52 and 1.56, respectively (Table 5.5). These might well be conservative estimates, given the high likelihood that zinc deficiency increases the risk of severity and death during illness with diarrhoea or pneumonia (Zinc Investigators' Collaborative Group 1999, 2000). There are three pieces of direct evidence that zinc deficiency increases mortality in young children. First, Indian infants

Table 5.5 Estimated effect of zinc deficiency on morbidity and mortality due to diarrhoea, pneumonia and malaria in children aged 0–4 years

	Morbidity	*Mortality*
Illness	*Relative risk (95% CI)*	*Relative risk (95% CI)*
Diarrhoea	1.28 (1.10–1.49)	1.28 (1.10–1.49)
Pneumonia	1.52 (1.20–1.89)	1.52 (1.20–1.89)
Malaria	1.56 (1.29–1.89)	1.56 (1.29–1.89)

born small for gestation who received zinc supplements six days a week were 0.32 (95% CI 0.12–0.89) less likely to die during infancy than those receiving the control supplement (Sazawal et al. 2001). Second, Bangladeshi children who received supplements of 20 mg/d zinc as adjuvant to oral rehydration solution (ORS) during diarrhoea, were half as likely to die than those receiving ORS alone (Baqui et al. unpublished data). Third, zinc supplementation was associated with a marginally significant reduction in all-cause mortality (5 deaths vs 12 deaths, $P = 0.10$) in the study by Müller et al. (2001). With respect to malarial deaths, it should be reiterated that the reduction in malaria attacks attributable to zinc supplementation was based on clinic attack rates, that is, more severe malaria morbidity rather than less severe illness that would be detected through community-based surveillance, as conducted in the study by Müller et al. (2001). Finally, it should be noted that infections themselves cause secondary zinc deficiency because zinc is sequestered by the liver as part of the acute phase response and is thus less available for many cellular functions (Keen et al. 1993). This point provides additional rationale as to why zinc deficiency may be more strongly related to deaths than to illness incidence. This may also partially explain findings that zinc supplementation reduces the duration of diarrhoeal episodes in prospective trials, as well as in trials in which zinc supplements are provided therapeutically (Zinc Investigators' Collaborative Group 1999, 2000).

4.7 Disease causation mechanisms

The results of this body of research do not define the explicit biological mechanisms through which zinc deficiency increases disease risk in young children. There is no doubt, however, that zinc is a critical nutrient for cell replication and function and thus, critical for normal functioning of all body systems. The first system known to be compromised with even mild deficiencies of zinc is the immune system, reflecting the profound and ubiquitous role zinc plays in immune function. As recently reviewed by Shankar and Prasad (1998), zinc deficiency impairs multiple aspects of immune function, including barrier and non-specific immunity, spe-

cific immune components (lymphyocytes, monocytes and macrophages, neutrophils, natural killer cells), and mediators of immune function such as glucocorticoid and thymulin activity, and cytokine function. Given the multiple roles of zinc in the immune function, it is not surprising that zinc deficiency should confer increased risk of morbidity and mortality due to infectious diseases.

Zinc deficiency also results in reduced growth rates in animals, and there is ample evidence from RCTs that the provision of supplemental zinc to young children can reduce growth faltering in preschool-aged children. Recently, Brown et al. (1998a) published a meta-analysis of more than 52 RCTs investigating the effect of supplemental zinc on anthropometric status or growth in children. The results of their analysis indicate that improvements in zinc intakes achieved with supplemental zinc (at dosages similar to those reported here) improve the weight-for-age and height-for-age *z*-scores by 0.26 SD and 0.22 SD, respectively. It is heuristic to conclude that some of the improved growth is due to zinc-related effects which reduce morbidity incidence and duration/severity.

5. Burden of disease estimates

The estimated deaths and DALYs attributable to zinc deficiency are shown in Tables 5.6–5.7. When examined by region, the burden of zinc

Table 5.6 Deaths in children aged 0–4 years from zinc deficiency, by subregion

	Deaths (000s)		
Subregion	*Diarrhoea*	*Pneumonia*	*Malaria*
AFR-D	17	50	74
AFR-E	47	91	107
AMR-A	0	0	0
AMR-B	2	3	0
AMR-D	3	6	0
EMR-B	1	2	0
EMR-D	31	48	10
EUR-A	0	0	0
EUR-B	1	3	0
EUR-C	0	0	0
SEAR-B	2	6	0
SEAR-D	70	187	16
WPR-A	0	0	0
WPR-B	2	10	0
World	176	406	207

Table 5.7 Disease burden attributable to zinc deficiency, by subregion

	DALYs (000s)		
Subregion	*Diarrhoea*	*Pneumonia*	*Malaria*
AFR-D	604	1705	2729
AFR-E	1631	3105	3978
AMR-A	1	1	0
AMR-B	69	143	2
AMR-D	109	202	2
EMR-B	36	93	1
EMR-D	1071	1679	371
EUR-A	0	0	0
EUR-B	19	102	0
EUR-C	1	7	0
SEAR-B	84	244	21
SEAR-D	2456	6579	560
WPR-A	0	0	0
WPR-B	61	361	5
World	6142	14223	7669

deficiency and its consequences are borne most heavily by Africa, the Eastern Mediterranean and South-East Asia. This is true for both diarrhoea and pneumonia. The burden of malarial disease attributable to zinc deficiency is borne almost exclusively by those in the African Region.

6. Discussion

We estimated that zinc deficiency in children aged <5 years caused 176000 diarrhoea deaths, 406000 pneumonia deaths, and 207000 malaria deaths. The associated DALYs attributable to zinc deficiency were more than 28 million. This was because the risks of morbidity and mortality associated with zinc deficiency are relatively high, and because available data suggest that zinc deficiency—as defined by inadequate dietary zinc—is highly prevalent in many parts of the world, and particularly in parts of the world where the majority of deaths due to diarrhoea, pneumonia and malaria occur. This places zinc deficiency as a key factor conferring risk of morbidity and mortality to young children, one that is ostensibly preventable through public health action.

The evidence that zinc deficiency increases incidence risk is strong because it results from RCTs conducted in areas of the world with limited zinc available in the diet and where pneumonia, diarrhoea and malaria are public health problems. The risk estimates for diarrhoea and

pneumonia are particularly strong, based on results from nine and five RCTs, respectively. The estimated increased risk for malaria is less well studied. Our risk estimate was based on two RCTs with similar risk estimates in which clinic attack rates were the outcome of interest. We excluded the only other published RCT in which the effect of supplemental zinc on less severe malaria morbidity (detected through community surveillance) was studied and in which no increased risk of malaria was found. Clearly more research on the relation between zinc deficiency and malaria is needed to substantiate the risk estimates provided here.

The use of experimental designs has allowed for the characterization of the consequences of zinc deficiency, yet much work needs to be done in order to describe the magnitude and distribution of zinc deficiency throughout the world. This is an important task because the placement of zinc deficiency as a major contributor to the global burden of disease rests in its ubiquitous presence throughout the world. The approach used to characterize zinc deficiency was to estimate the proportion of the population living in areas with inadequate zinc in their food supply as determined from food balance sheet data compiled by FAO. This is far from the traditional approach of characterizing nutrient deficiencies using biochemical indicators. As stated earlier, however, there is no clear choice of biochemical indicator for zinc status, and the information available on zinc status based on plasma zinc concentration (the most commonly cited indicator of zinc status) would be limited to restricted samples of study participants conducted in selected regions of the world. To our knowledge, there are few if any national nutrition surveys utilizing biochemical indicators of zinc status and few laboratories capable of conducting trace mineral assays in developing countries due to the difficulties in eliminating contamination.

The advantage of the approach developed by IZiNCG is that a common methodology could be applied across similarly collected data from 172 countries, representing all 14 subregions. Further, because zinc is stored in the body in only limited amounts, and because certain key features of the diet (total energy content, animal protein availability, fibre/phytate content associated with the principal grain) largely determine the bioavailability of the zinc present in the food supply, the adequacy of dietary zinc intakes is an appropriate indicator to approximate the prevalence of zinc deficiency. There are multiple uncertainties inherent in this approach, and key assumptions include the following: (i) that per capita food availability data relates to actual dietary intake and ultimately to zinc status; (ii) that foods not included in the data (e.g. foraged foods) are not rich sources of zinc; (iii) that our knowledge of the composition of foods with respect to zinc, calcium, fibre and phytate is adequate for our purposes; (iv) that characterization of the bioavailability of zinc is correct; and (v) that we have the appropriate zinc requirement distribution and cut-point for defining adequacy of

intake. It is only through further research that we can determine the validity of the assumptions made, and judge the certainty with which we have characterized the prevalences of zinc deficiency in young children.

There are reasons to believe that the estimates presented here are conservative. First, food availability is usually greater than food intake. This effect, however, may be countered by underestimation of intake in the FAO data which do not always account for subsistence production. Second, the groups for which these numbers are likely to be most conservative are women of reproductive age and small children who may be particularly disadvantaged in terms of obtaining the best sources of zinc (animal products) in their diet. Third, dietary intake surveys, which more directly estimate the prevalence of inadequate intakes in populations, typically have estimated higher prevalences of inadequate zinc intakes than those depicted here (Parr 1992, 1996). On the other hand, because breastfeeding is an adequate source of zinc in the diets of infants aged less than six months, the same age when a large proportion of childhood mortality is concentrated, applying the risks to all children aged 0–4 years may result in substantial overestimation of disease burden in some populations.

It is also important to note that maternal or gestational zinc deficiency may affect immunological development in the newborn in ways that compromise immune function throughout the lifespan irrespective of zinc status (Caulfield et al. 1998; Shankar and Prasad 1998). Although this is well demonstrated in certain animal models, it has not been well characterized in humans, but a recent study by Osendarp et al. (2001) provides intriguing evidence of potential long-term effects on infant health in the first year of life due to maternal prenatal zinc deficiency. Fetal accumulation of zinc is a function of maternal zinc status, and therefore, newborn zinc deficiency (assessed as low serum zinc concentration) is likely among women with inadequate dietary zinc intakes during pregnancy (Caulfield et al. 1999). This deficiency is likely transitory for all but the most vulnerable (preterm or low-birth-weight infants) because the zinc content of colostrum is high and some zinc becomes available to the infant as part of the haematological changes accompanying the transition to extrauterine life (WHO 1996). Beginning at around six months of age, however, breast milk intake no longer provides sufficient zinc to meet requirements (Krebs 2000), making zinc-rich complementary foods necessary (Brown et al. 1998b). If zinc-rich sources are not available on a routine basis, zinc deficiency develops over time and persists until changes in the diet are made. Thus, it must be recognized that removal of the global burden of disease due to zinc deficiency will likely require improvements in child *and* maternal zinc intakes. In this chapter, we have considered only the burden of disease for children aged 0–4 years since no available evidence on the role of zinc in morbidity and mortality among other age groups was available. Thus, it may

be true that zinc deficiency contributes greatly to death and disability among other age groups. Defining these risk relations should be a priority area for future research.

Because low weight-for-age (usually described as underweight) also increases risk of morbidity and mortality from diarrhoea, pneumonia and malaria (see chapter 2), there is overlap between zinc deficiency and underweight as risk factors for morbidity and mortality from these causes in young children. The degree of overlap cannot be quantified empirically, but evidence from studies can provide insight in this issue. In the meta-analysis of zinc RCTs (Zinc Investigators' Collaborative Group 1999), the authors found that the effects of zinc supplementation on risk of diarrhoea and pneumonia across studies did not depend on the underlying level of malnutrition as characterized by the average *z*-score in the study subjects. However, the study by Umeta et al. (2000) did find greater reductions in morbidity in stunted as opposed to non-stunted children. Zinc supplementation has reduced morbidity with no detectable changes in growth rates (Meeks-Gardner et al. 1998). Overall, limited evidence shows that the efficacy of zinc supplementation for reducing morbidity is more substantial than for reducing growth faltering in studies in which both outcomes have been characterized. There are also studies in the literature in which improvements in immune function have been observed with zinc supplementation in well-nourished subjects (e.g. those with adequate weight); thus, although most of the research on the benefits to health from zinc supplements has been conducted in populations similarly characterized by underweight or stunting, the potential reductions in the global burden of disease due to zinc deficiency should not be limited to those who are also underweight or stunted. In the case of malaria, Shankar (2000) describes how zinc deficiency exerts fairly specific effects on malaria morbidity (increasing febrile illness accompanied by hyperparasitaemia), whereas low anthropometric status appears to exert more generalized effects. With these considerations, we conclude that although zinc deficiency and underweight co-exist in many populations, and both are risk factors for the disease outcomes described here, the majority of the disease burden attributable to zinc deficiency is not restricted to children who are generally malnourished.

In summary, the available evidence suggests that zinc deficiency contributes substantially to death and disability throughout the world, and particularly in Africa, the Eastern Mediterranean, and South-East Asia. Because epidemiological evidence is limited to studies conducted among preschool children and this analysis considers only three causes of death and disability, it is clear that further research on the role of zinc in morbidity, mortality and disability due to other causes and in other age groups is urgently needed. Further research is needed to identify indicators of exposure to zinc deficiency as well as effective strategies to reduce zinc deficiency and its consequences.

7. Projections of exposure

Currently, there are no programmes or policy initiatives in place to specifically improve the zinc intakes of human populations. This is true with respect to improving the zinc supply in foods (e.g. interventions to improve intakes of animal products which are good sources of zinc or to reduce phytates in foods which impair zinc absorption). Further, there are no examples of programmes utilizing supplemental zinc to improve zinc status, although some are beginning to use supplemental zinc as adjuvant therapy during diarrhoeal illness, based on research demonstrating the efficacy of zinc in shortening the duration of the current episode and prolonging the time until the next episode in paediatric populations with heavy disease burden. Because of the general lack of policy or programmatic initiatives to address zinc deficiency, we project that the magnitude and distribution of zinc deficiency will remain the same for the years 2010 and 2020, as presented here.

Acknowledgements

We are grateful for the support of Kenneth H. Brown in providing us with the data on the prevalence of inadequate zinc intakes in 172 countries; Sunil Sazawal for updating the pooled analyses of zinc and risk of diarrhoea and pneumonia, and Anuraj H. Shankar for conducting the pooled analysis of zinc and malaria and for his insights into the various dimensions of malarial morbidity.

This manuscript was supported in part by the Family Health and Child Survival (FHACS) Cooperative Agreement between the United States Agency for International Development, Office of Health and Nutrition, the Johns Hopkins Bloomberg School of Public Health, Department of International Health, and by the World Health Organization.

Note

1 See preface for an explanation of this term.

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