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ORIGINAL ARTICLE

Global and regional child mortality and burden of disease attributable to zinc deficiency

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Background/Objectives: Zinc is an essential micronutrient and deficiency can lead to an increased risk for infectious diseases and growth retardation among children under 5 years of age. We aimed to estimate disease-specific and all-cause mortality attributable to zinc deficiency.
Subject/Methods: We estimated the prevalence of zinc deficiency in Latin America, Africa and Asia, where based on zinc availability in the diet and childhood stunting rates, zinc deficiency is widespread. The relative risks of death among zinc-deficient children for diarrhea, malaria and pneumonia were estimated from randomized controlled trials. We used the comparative risk assessment methods to calculate deaths and burden of disease (measured in disability-adjusted life years, DALYs) from each of these three diseases attributable to zinc deficiency in these regions.
Results: Zinc deficiency was responsible for 453 207 deaths (4.4% of childhood deaths), and 1.2% of the burden of disease (3.8% among children between 6 months and 5 years) in these three regions in 2004. Of these deaths, 260 502 were in Africa, 182 546 in Asia and 10 159 in Latin America. Zinc deficiency accounted for 14.4% of diarrhea deaths, 10.4% of malaria deaths and 6.7% of pneumonia deaths among children between 6 months and 5 years of age.
Conclusions: Zinc deficiency contributes to substantial morbidity and mortality, especially from diarrhea. Zinc supplementation provided as an adjunct treatment for diarrhea may be the best way to target children most at risk of deficiency.
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Introduction

Zinc is an essential micronutrient for human health, growth and development (WHO, 1996). Human zinc deficiency was first recognized in the 1960s among adolescent boys in Iran and Egypt who showed signs of severe growth retardation and developmental delays (Prasad *et al*., 1963). Severe zinc deficiency, as was observed by Prasad *et al*. (1963), is easy to recognize through dwarfism, hypogonadism and severe developmental delays. However, many consequences of zinc deficiency, including stunting and increased rates of infectious diseases such as diarrhea and pneumonia, are also shared by other nutritional and environmental factors and are thus more difficult to recognize (Caulfield and Black, 2004).

Numerous randomized controlled trials of zinc supplementation have been conducted to quantify the effect of subclinical zinc deficiency through ongoing zinc supplementation on growth, morbidity and mortality among children under 5 years of age. These trials have helped establish hazardous effects of zinc deficiency on diarrhea, pneumonia and malaria morbidity and mortality. These studies now allow estimating the contribution of zinc deficiency to disease and death among children at the population level.

Here, we present the global burden of zinc deficiency as the attributable risk for death and disability-adjusted life years (DALYs), a summary measure of disease burden (Lopez *et al*., 2006). DALYs are an international standard for the measures of disease burden, including both years of life lost because of premature death and years lived with disability. We use the calculation of the number of DALYs that could

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be saved if zinc deficiency were eliminated to estimate the global burden of disease attributed to zinc deficiency. These estimates are important as interest in micronutrient malnutrition and its role in child mortality continues to grow. Because programs to prevent or treat zinc deficiency are not yet widespread, these estimates provide baseline values from which the effects of future programmatic efforts can be measured.

Materials and methods

We estimated the global burden of zinc deficiency in the regions of the world where there are the highest rates of zinc deficiency among children under 5 years of age. We first estimated the population prevalence of zinc deficiency for children under 5 years of age by utilizing stunting rates and the risk of inadequate zinc intake based on the estimated absorbable zinc in the diet. The fraction of disease-specific morbidity and mortality attributable to zinc deficiency was then estimated based on reductions in both morbidity and mortality as observed from randomized controlled supplementation trials. Finally, the attributable fraction was applied to the 2004 estimates for disease-specific deaths and DALYs among children 1–59 months of age to generate an estimate of the total number of deaths and DALYs that could be prevented if zinc deficiency were eliminated in this age group. Although the point estimates for potential reduction were calculated for children 1–59 months of age, we limited our final estimation of deaths and DALYs to only children 6–59 months of age because additional studies have demonstrated that the morbidity benefit is most pronounced in this age group. This method ensures the most conservative calculation for total deaths and DALYs.

Measuring population prevalence of zinc deficiency

Individual zinc status can be assessed by quantifying the total body zinc mass via zinc tracer studies (Van Wouwe, 1995). Because these studies are intense and costly, this is not practical on a large scale and is not used routinely in developing countries. Plasma or serum zinc is the most commonly assessed biochemical indicator of zinc status; however, this measure is sensitive to both recent food intake and immune function and thus the accuracy as an indicator of individual zinc status is often challenged (Hambidge, 2000). Plasma zinc can be a useful indicator at the population level, but is rarely measured in population-based nutrition studies (Hess *et al*., 2007).

At the population level, alternative measures can be used in lieu of the distribution of serum zinc concentrations. The International Zinc Consultative Group estimated the absorbable zinc in the diet and percentage of bioavailable zinc based on Food and Agriculture Organization food balance sheets for each country to estimate the proportion of the population at risk of inadequate intake (Brown *et al*., 2004). This method allows for a comparison among countries but does not differentiate between subgroups within the population to estimate differences in probability of deficiency for high-risk groups such as young children.

To better identify population zinc deficiency among children, national stunting prevalence rates can also be used as a proxy indicator (Fischer Walker and Black, 2007). There have been more than 28 supplementation trials assessing the effect of zinc on growth. The magnitude of the effect size of zinc on height is dependent upon the baseline height for age *Z* score (HAZ) score of the population and thus zinc has a greater effect on linear growth when given in populations with the mean HAZ <-2. Using this data, it is recommended that childhood stunting prevalence rates $\geqslant 20\%$ serve as a proxy for identifying population zinc deficiency among children under 5 years of age (Fischer Walker and Black, 2007).

A combination of calculating zinc availability in the diet and childhood stunting rates to generate a likelihood of deficiency was previously used by International Zinc Consultative Group (Brown *et al*., 2004) and though the thresholds for classification have been updated, this remains the recommended method for assessing population-based zinc deficiency. Countries with a prevalence of stunting $\geqslant 20\%$ and a population at risk of inadequate zinc intake $\geqslant 25\%$ are classified at high risk; countries with a prevalence of stunting >10 and $<20\%$ and a population at risk of inadequate zinc intake >15 and $<25\%$ are classified at intermediate risk and countries with a prevalence of stunting $\leqslant 10\%$ and a population at risk of inadequate zinc intake $\leqslant 15\%$ are classified at low risk. Data from countries in 12 UN regions and subregions in Latin America, Asia and Africa were used to group countries for regional calculations (Table 1; Web Figure 1). All children less than 5 years of age living in countries with high or intermediate risk of zinc deficiency were included in these calculations. This was done to be consistent with the study populations of randomized controlled trials, which were conducted in the whole study community, not just among children with zinc deficiency at the baseline.

Hazardous effects of zinc deficiency on disease-specific mortality and morbidity

The effect of zinc supplementation on all-cause mortality among children 1–59 months of age was recently calculated in a meta-analysis of four randomized controlled trials conducted in unselected populations (Tielsch *et al*., 2007). Although mortality has been reported in other studies, these four studies are the only ones to have been powered to detect differences in mortality among a general population of children under 5 years of age (Muller *et al*., 2001; Brooks *et al*., 2005; Sazawal *et al*., 2007; Tielsch *et al*., 2007). Although the individual studies were not powered to detect the effect of zinc supplementation on cause-specific reductions in mortality (that is, diarrhea, pneumonia

Table 1 Countries by region

East Africa
- Burundi
- Comoros
- Djibouti
- Eritrea
- Ethiopia
- Kenya
- Madagascar
- Malawi
- Mauritius
- Mozambique
- Reunion
- Rwanda
- Seychelles
- Somalia
- Uganda
- United Republic of Tanzania
- Zambia
- Zimbabwe

Middle Africa
- Angola
- Cameroon
- Central African Republic
- Chad
- Congo
- Democratic Republic of Congo
- Equatorial Guinea
- Gabon
- Sao Tome & Principe

Northern Africa
- Algeria
- Egypt
- Lybian Arab Jamahiriya
- Morocco
- Sudan
- Tunisia
- Western Sahara

Southern Africa
- Botswana
- Lesotho
- Namibia
- South Africa
- Swaziland

Eastern Asia
- China
- Hong Kong SAR
- Democratic People's Republic of Korea
- Japan
- Macau
- Mongolia
- Republic of Korea

Western Africa
- Benin
- Burkina Faso
- Cape Verde
- Cote d'Ivoire
- Gambia
- Ghana
- Guinea
- Guinea-Bissau
- Liberia
- Mali
- Mauritania
- Niger
- Nigeria
- St Helena
- Senegal
- Sierra Leone
- Togo

South-central Asia
- Afghanistan
- Bangladesh
- Bhutan
- India
- Iran (Islamic Republic of)
- Kazakhstan
- Kyrgyzstan
- Maldives
- Nepal
- Pakistan
- Sri Lanka
- Tajikistan
- Turkmenistan
- Uzbekistan

South-eastern Asia
- Brunei Darussalam
- Cambodia
- Indonesia
- Lao (People's Democratic Republic of)
- Malaysia
- Myanmar
- Philippines
- Singapore
- Thailand
- Timor Leste (Democratic Republic)
- Vietnam

Western Asia
- Armenia
- Bahrain
- Cyprus
- Georgia
- Iraq
- Israel
- Jordan
- Kuwait
- Lebanon
- Occupied Palestinian Territory
- Oman
- Qatar
- Saudi Arabia
- Syrian Arab Republic
- Turkey
- United Arab Emirates
- Yemen

Caribbean
- Anguilla
- Antigua & Barbuda
- Aruba
- Bahamas
- Barbados
- British Virgin Island
- Cayman Islands
- Cuba
- Dominica
- Dominican Republic
- Grenada
- Guadeloupe
- Haiti
- Jamaica
- Martinique
- Montserrat
- Netherlands
- Antilles
- Puerto Rico
- St Kitts & Nevis
- St Lucia
- St Vincent & the Grenadines
- Trinidad & Tobago
- Turks & Caicos Islands
- US Virgin Islands

Central America
- Belize
- Costa Rica
- El Salvador
- Guatemala
- Honduras
- Mexico
- Nicaragua
- Panama

South America
- Argentina
- Bolivia
- Brazil
- Chile
- Colombia
- Ecuador
- Falkland Islands
- French Guyana
- Guyana
- Paraguay
- Peru
- Suriname
- Uruguay
- Venezuela

and malaria), a meta-analysis of these cause-specific effects provides the best estimates available and these results are used in this analysis. Using the inverse of the reductions in each cause of death, the relative risk (RR) of death has been estimated at 1.27 (95% confidence interval (CI) 0.96–1.63) for diarrhea (Brooks *et al*., 2005; Sazawal *et al*., 2007; Tielsch *et al*., 2007), 1.18 (95% CI 0.90–1.54) for pneumonia (Brooks *et al*., 2005; Sazawal *et al*., 2007; Tielsch *et al*., 2007) and 1.11 (95% CI 0.94–1.30) for malaria (Muller *et al*., 2001; Sazawal *et al*., 2007) (S Sazawal, personal communication).

For morbidity, we estimated the RR as the inverse of the risk reduction summarized in meta-analyses of zinc supplementation trials for diarrhea and pneumonia (Aggarwal *et al*., 2007) and for malaria (Caulfield and Black, 2004). Trials included in these meta-analyses were those that provided ongoing supplementation and excluded trials

designed to provide a short course of therapeutic zinc. The RR of morbidity in areas with high or intermediate risk of zinc deficiency is 1.09 (95% CI 1.01–1.18) for diarrhea, 1.25 (95% CI 1.09–1.43) for pneumonia and 1.56 (95% CI 1.29–1.89) for malaria. Using the RR estimates for morbidity and mortality, we calculated the deaths and DALYs from diarrhea, pneumonia and malaria attributable to zinc deficiency in children 6–59 months of age.

Estimating the burden of morbidity and mortality attributable to zinc deficiency

For the numbers of deaths and DALYs by cause (that is, diarrhea, pneumonia and malaria), we used a revision for 2004 employing the methods of the Global Burden of Disease project (Lopez *et al*., 2006). We estimated deaths and DALYs attributable to zinc deficiency using the methodology previously described by the Comparative Risk Assessment (CRA) project (Ezzati *et al*., 2002, 2004). In brief, we calculated the population-attributable fractions (PAF) for zinc deficiency for diarrhea, pneumonia and malaria deaths and DALYs by estimating the reduction in morbidity and mortality if the risk of zinc deficiency was reduced to a theoretical minimum risk exposure among children 6–59 months of age. The estimated percentage reduction in morbidity and mortality is not based on programmatic feasibility; rather it is an estimate of the greatest attainable mortality reduction for diarrhea, pneumonia and malaria if zinc deficiency was not present. The PAF for zinc deficiency was calculated separately for diarrhea, pneumonia and malaria mortality and incidence.

The estimated total number of deaths attributable to zinc deficiency for each disease was calculated by multiplying the PAF of deaths by the total number of cause-specific annual diarrhea, pneumonia or malaria deaths among children 6–59 months of age. The number of DALYs for each disease attributable to zinc deficiency was found by multiplying the PAF by the years of life lost to death and the years lived with disability, and adding these. All DALY- and disease-specific death estimates were based on the Global Burden of Disease 2004 database (Lopez *et al*., 2006).

Results

According to these analyses, zinc deficiency is responsible for an estimated 453 207 deaths, 4.4% of deaths among children 6–59 months of age and 1.0% of all deaths globally (Table 2). The largest number of these deaths is in Africa while the lowest is in Latin America. Differences in the total number of attributable deaths are a result of variation in exposure and overall child mortality rates. The highest rates of zinc deficiency are in both Africa and Asia, while most countries in Latin America are at slightly lower risk. Overall, child mortality remains highest in Africa and some Asian countries, while mortality rates are much lower in many Latin American countries. The largest number of deaths attributable to zinc deficiency in Asia is found in India, which contributes 18.6% of all zinc deficiency deaths globally. In Africa, Nigeria has the largest number of deaths attributable to zinc deficiency contributing 11.6% of all zinc deficiency deaths globally. The five countries with the highest numbers

Table 2 Total deaths attributable to zinc deficiency by cause and UN region

UN regions/subregions	*Cause of death*			
	Diarrhea (% of <5/total)	*Malaria (% of <5/total)*	*Lower respiratory infection (% of <5/total)*	*Total (% of <5/total)*
Africa	114 014 (14.5/13.1)	80 426 (10.4/9.0)	66 062 (6.8/4.7)	260 502 (5.3/2.1)
Eastern Africa	39 683	20 531	22 762	82 976
Middle Africa	24 788	16 123	14 963	55 874
Northern Africa	5030	2743	2379	10 152
Southern Africa	1165	6	565	1736
Western Africa	43 349	41 024	25 392	109 765
Asia	126 164 (14.5/12.9)	11 582 (10.4/9.1)	48 800 (6.7/2.3)	182 546 (3.7/0.6)
Eastern Asia	10 953	25	4022	15 000
South-central Asia	96 207	5163	37 340	138 709
South-eastern Asia	12 131	1943	4055	18 129
Western Asia	6874	451	3382	10 707
Latin America	6890 (13.4/11.4)	134 (9.5/8.3)	3315 (6.2/1.8)	10 159 (2.8/0.3)
Caribbean	945	20	472	1437
Central America	1327	22	746	2094
South America	4618	92	1918	6628
All[a]	247 068 (14.4/12.9)	88 142 (10.4/9.0)	117 997 (6.7/3.2)	453 207 (4.4/1.0)

Abbreviation: UN, United Nations.
[a]Restricted to developing countries included in this analysis and listed in Table 1.

of total deaths attributable to zinc deficiency (India, Nigeria, Democratic Republic of Congo, Ethiopia and Afghanistan) together account for 47% of all attributable deaths. The large population size, high risk of deficiency and high child mortality rates all contribute to the large numbers of deaths attributable to zinc deficiency in these countries.

Diarrhea has the highest percentage of deaths attributed to zinc deficiency followed by malaria and pneumonia (Table 2). Diarrhea is the leading cause of death attributable to zinc deficiency in each UN region/subregion and accounts for more than half of all zinc deficiency deaths globally. Although zinc deficiency likely accounts for a smaller proportion of pneumonia deaths than malaria deaths (6.7 versus 10.4%), the much greater number of pneumonia than malaria deaths results in a larger total number of pneumonia deaths attributed to zinc deficiency. Although the percentage of cause-specific deaths attributable to zinc deficiency is similar among regions, the total number by cause varies by overall disease-specific prevalence rate. For example, though zinc deficiency contributes to 10.4% of all malaria deaths in Africa and 9.5% of all malaria deaths in Latin America, the high prevalence of malaria in Africa versus the relatively low prevalence in Latin America translates to a difference in total deaths of 80 426 in Africa versus 134 in Latin America.

Zinc deficiency as a risk factor accounts for an estimated 3.8% of all DALYs among children under 5 years of age and 1.2% of all DALYs globally (Table 3). As with deaths, diarrhea has the highest percentage of DALYS, which is followed by malaria and pneumonia (Table 3). India and Nigeria also contribute the largest number of DALYs in Asia and Africa, respectively. India accounts for 18.3% and Nigeria accounts for 11.7% of the DALYs globally where zinc is the risk factor.

Discussion

Zinc deficiency results in a substantial disease burden predominantly among children less than 5 years of age who are most affected by diarrhea, malaria and pneumonia. Zinc deficiency may result in approximately 453 000 deaths and 16 million DALYS each year. In comparison, malaria causes approximately 980 000 deaths and 37.5 million DALYs each year. It is inappropriate to compare deaths and DALYs attributable to zinc deficiency with those attributable to other nutritional deficiencies, such as vitamin A, because there have been programmatic interventions to prevent vitamin A deficiency for several years; thus, attributable mortality and disability have been declining.

Previous estimates of the zinc global burden of disease were published as part of the CRA project (Caulfield and Black, 2004). The CRA project estimated that zinc deficiency was responsible for 176 000 diarrhea deaths compared to our estimate of 247 000; 406 000 pneumonia deaths compared to our estimate of 118 000 and 207 000 malaria deaths compared to our estimate of 88 000. The CRA estimates were based on RRs calculated in epidemiological studies that had measured the effects of zinc deficiency on disease-specific morbidity, and had used the same RRs for mortality, while we utilized new data from large-scale mortality trials to better estimate mortality risks. We also used a new meta-analysis

Table 3 Total DALYs attributable to zinc deficiency by cause and UN region

UN regions/subregions	*Cause of DALYs*			
	Diarrhea (% of <5/total)	*Malaria (% of <5/total)*	*Lower respiratory infection (% of <5/total)*	*Total (% of <5/total)*
Africa	3 969 019 (14.4/13.6)	3 089 379 (10.5/9.5)	2 350 194 (6.9/5.2)	9 408 591 (4.8/2.2)
Eastern Africa	1 376 775	822 727	804 820	3 004 323
Middle Africa	855 626	621 511	529 373	2 006 510
Northern Africa	178 293	100 373	86 228	364 894
Southern Africa	41 440	1098	19 671	62 208
Western Africa	1 516 885	1 543 670	910 101	3 970 656
Asia	4 403 809 (14.3/12.7)	277 108 (10.4/6.9)	1 839 854 (7.1/4.4)	6 520 771 (3.1/0.8)
Eastern Asia	386 865	1484	160 089	548 438
South-central Asia	3 350 026	189 118	1 379 724	4 918 868
South-eastern Asia	428 013	69 774	172 686	670 473
Western Asia	238 906	16 733	127 355	382 993
Latin America	247 312 (13.0/10.1)	5737 (9.8/3.9)	159 157 (7.5/5.0)	412 206 (2.1/0.4)
Caribbean	33 485	755	20 110	54 350
Central America	49 822	1222	38 219	89 264
South America	164 005	3760	100 827	268 592
All[a]	8 620 140 (14.3/13.0)	3 772 255 (10.5/9.2)	4 349 204 (7.0/4.8)	16 341 569 (3.8/1.2)

Abbreviations: DALY, disability-adjusted life year; UN, United Nations.
[a]Restricted to developing countries included in this analysis and listed in Table 1.

of zinc supplementation trials to estimate morbidity risks (Aggarwal *et al*., 2007). The same analytic methods can be used to estimate the effects of programmatic efforts aimed at reducing zinc deficiency.

There are several limitations to this type of analysis. The data used to provide rates of national-level zinc deficiency are still an aggregate of childhood stunting rates, as a proxy for zinc deficiency, and estimates of dietary zinc availability. While these data are the best available, national surveys of individual zinc status, especially among young children would improve upon these estimates. In addition, we used a RR based on only four large-scale mortality trials and then used this single RR for all populations. These studies represent four countries in the world, thus may not represent the true effect of zinc on morbidity and mortality. Although study sites were large and assumed to be representative of children throughout the country, they were not conducted in every district thus they may not be representative of the national population; this may be an additional limitation. To estimate morbidity, we used the results from three and two studies for diarrhea and pneumonia, and malaria, respectively. Again, the limited number of large-scale studies to produce these estimates increases our uncertainty bounds.

There are likely variations by age, which may be non-negligible. We excluded infants less than 6 months of age because results from nonspecific trials have shown the greatest effect among children older than 6 months. There have been studies demonstrating a positive effect of zinc supplementation among low birth weight and small for gestational age babies (Sazawal *et al*., 2001; Sur *et al*., 2003), but because those are very specific subsets of the infant population we did not include those estimates. Additional age-specific data would be helpful for subsequent analyses. We did estimate deaths and DALYs attributable to zinc deficiency by sex, but did not present this data here. Although trials have shown small differences in the RR by sex, when these differences are used to calculate the PAF and applied to the total number of deaths and DALYs, the differences are small.

Finally, there is uncertainty in the cause-specific number of deaths and DALYs as calculated by Global Burden of Disease estimates. Because developing countries do not have national data available documenting the cause of every death, estimates are generated using all available data.

Very little is currently being done to prevent zinc deficiency in comparison with the prevention and treatment of specific childhood diseases and some of their other risk factors. In 2004, WHO and UNICEF (2004) released a global recommendation supporting the use of zinc supplementation as an adjunct treatment for all episodes of diarrhea in children under 5 years of age. Targeting children with diarrhea has been proven as an effective method for decreasing diarrhea morbidity and mortality as well as decreasing diarrhea and pneumonia morbidity in the months following treatment. Given the large number of deaths and DALYs attributable to zinc deficiency, more must be done to increase the widespread use of zinc for diarrhea treatment, a proven intervention, in the developing world. Additional efforts are also needed to improve dietary zinc intake, which may include supplementation of target populations, fortification and dietary diversification.

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Conflict of interest

The authors have no competing interests.

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