Global Distribution and Disease Burden Related to Micronutrient Deficiencies

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Abstract
Micronutrients are vitamins and minerals that are essential for human life and health. Deficiencies in these micronutrients are common because of poor quality diets and frequent infectious diseases in low- and middle-income countries. The high prevalence of deficiencies and their important adverse consequences on mortality, morbidity and disability result in a substantial disease burden. In particular, deficiencies of vitamin A and zinc increase the risk of child mortality, and zinc deficiency increases infectious morbidity and reduces linear growth as well. Deficiencies of iodine and iron are significant primarily for their effects on development and cognition and consequent disabilities. Programs targeting each of these micronutrients are underway and, particularly for vitamin A and iodine, have some success. Greater efforts to address these and the full set of micronutrients are needed to reduce their global burden of diseases.

Introduction
Essential vitamins and minerals, referred to collectively as micronutrients, have critical roles in human metabolism, immunity and other body functions. The deficiency of some can cause a unique clinical syndrome, yet it is the more insidious effects of some of the micronutrients that have the greatest effects on health and human capacity. Even as the classical clinical manifestations have diminished, the deficiencies of many vitamins and minerals have persisted with
important adverse consequences, especially in low- and middle-income countries. This review will focus on the deficiencies of selected micronutrients because of their important global distribution and disease burden, namely vitamin A, zinc, iodine and iron.

**Vitamin A Deficiency**

The characteristic clinical feature of vitamin A deficiency is xerophthalmia, with severity ranging from night blindness to corneal ulceration keratomalacia, leading to corneal scarring and possibly blindness. The more severe forms of xerophthalmia are now very infrequent, possibly due to additional vitamin A intake, especially from programs that provide high-dose supplements every 6 months as well as control of measles and other infectious diseases that may precipitate the clinical conditions. However, night blindness continues to be common in some populations. The World Health Organization (WHO) estimates that 7.8% (7.0–8.7%) of pregnant women are afflicted with night blindness, affecting nearly 10 million women worldwide [1]. Vitamin A deficiency is also assessed by serum retinol concentrations with <0.70 μmol/l indicating deficiency. WHO estimates that 15.3% (7.4–23.2%) of pregnant women have subclinical deficiency, affecting 19 million women. Pre-school children are also at risk of vitamin A deficiency. WHO estimates the global prevalence of night blindness to be 0.9% (0.3–1.5%), affecting 5 million children, and the prevalence of subclinical deficiency based on serum retinol concentrations to be 33.3% (31.1–35.4%), affecting 90 million children [1].

Maternal night blindness has been associated with increased rates of babies born with low birthweight and with infant mortality [2, 3]. The relationship of maternal vitamin A deficiency with these outcomes, as studied in supplementation trials in pregnancy, has not been found to be significant when the three trials are combined; however, subclinical vitamin A deficiency in children has important consequences for mortality. A meta-analysis of the trials of vitamin A supplementation found a 23% reduction in deaths in the 6–59 months age group, a statistically significant benefit for diarrhea deaths and a suggestive one for measles deaths [4].

We calculated the deaths that could be attributed to vitamin A deficiency using estimated deaths due to diarrhea and measles in 2011 [5]. The risk of vitamin A deficiency was said to be the inverse of the trial effects on these two causes of death, adjusted with the assumption that all of the effect was in the subset of the population that had subclinical deficiency in the trial populations. This adjusted relative risk was then applied to the current prevalence of subclinical deficiency. The estimated deaths for 2011 attributed to current vitamin A deficiency is
157,000, two thirds of which would be in Africa and nearly all of the rest in Asia. Nearly all of these deaths were related to diarrhea, because measles deaths are low due to extensive vaccination programs.

**Zinc Deficiency**

Zinc is an essential mineral with many biological functions in humans. The characteristic clinical features of rash, alopecia, hypogonadism and reduced immunocompetence occur with severe dietary zinc deficiency and with acrodermatitis enteropathica, a genetic defect in zinc absorption, but these are rarely seen. Instead, subclinical zinc deficiency that does not have overt manifestations of deficiency but does have important consequences is common. Recent estimates based on analysis of national food balances suggest that 17% of the world’s population may consume a diet that has inadequate amounts of bioavailable zinc [6]. Based on dietary intakes in pregnancy, it has also been estimated that as many as 82% of pregnant women may have inadequate zinc intakes [7]. Likewise, pre-school children may have prevalences of zinc deficiency higher than the population average because of their limited consumption of animal-source foods and the cereal-based complementary food diets containing phytates that reduce the bioavailability of zinc.

Severe zinc deficiency in pregnancy is associated with fetal growth restriction, preterm delivery and maternal morbidity, including hemorrhage [8, 9]. A recent systematic review of randomized controlled trials found that women who received zinc supplements in pregnancy had a 14% reduction in preterm deliveries [10]. Subclinical zinc deficiency in children is associated with increased incidence rates of and mortality from diarrhea, pneumonia and possibly other infectious diseases. Because observational studies are unable to discern causal relationships with the common childhood diseases, a number of randomized controlled trials have been done and subjected to meta-analyses. A recent review found that zinc-supplemented pre-school children had a 9% reduction in all-cause mortality (RR 0.91, 95% CI 0.82–1.01) of borderline statistical significance [11]. Another analysis of available trials found an 18% reduction in deaths in children 12–59 months of age (RR 0.82, 95% CI 0.70–0.96) [12]. In these meta-analyses, there were suggestive benefits for diarrhea mortality (RR 0.82, 95% CI 0.64–1.05) and pneumonia mortality (RR 0.85, 95% CI 0.65–1.11) [11]. There were also statistically significant reductions in diarrhea incidence (RR 0.87, 95% CI 0.81–0.94) and pneumonia incidence (RR 0.81, 95% CI 0.73–0.90). Zinc deficiency also reduces linear growth in young children [11].

To estimate the deaths attributed to zinc deficiency in children, we used the inverse of the reductions in cause-specific mortality in children 1–4 years old ad-
adjusted with the assumption that all the benefit was in the subset of the trial populations that was at risk of zinc deficiency based on the availability of zinc in national diets \[5, 6\]. This adjusted risk estimate was then applied to the current estimated prevalence of inadequate zinc intake in countries. It is estimated that for 2011 116,065 child deaths, about equally split between diarrhea and pneumonia, could be attributed to zinc deficiency; 57% of the deaths were in Africa and 42% in Asia.

**Iodine Deficiency**

Severe iodine deficiency during pregnancy causes cretinism \[13\]. In addition, studies done in highly endemic areas of iodine deficiency found average deficits of about 13 IQ points in the offspring of mothers likely to have been iodine deficient in pregnancy \[14, 15\]. It is questionable if less severe levels of iodine deficiency have an effect on brain development and cognition \[16, 17\].

The measure of iodine deficiency is a population one not an individual one. The median urinary iodine concentration in school-age children is used to assess the iodine status of a population. Median values of <100 μg/l are considered to represent deficiency. Iodine requirements increase 50% in pregnancy, and deficiency is defined as <150 μg/l for a population of pregnant women; however, the data from children are largely used to establish national and global prevalences of deficiency. Recent estimates are that 28.7% of the world’s population, in some regions up to 50%, or 1.9 billion people are deficient \[16–18\]. This is largely mild deficiency, the consequences of which are unclear, but there may be some individuals still who have severe deficiency in spite of widespread use of iodized salt to increase intake.

Iodine deficiency rarely causes death, but it can result in disability. Our previous estimates were that in 2004 it resulted in a loss of 2.6 million disability-adjusted life years (DALYs) or 0.5% of the DALYS in children under 5 years old \[19\]. New estimates from the Global Burden of Disease Project are that iodine deficiency resulted in a loss of 4.0 million DALYs in 2010 \[20\].

**Iron Deficiency**

Iron deficiency as a cause of anemia is globally prevalent. We estimate that the prevalence of anemia that responds to iron supplementation (referred to hereafter as iron deficiency anemia or IDA) ranges from 11 to 16% for pre-school children and 10–15% for pregnant women for UN regions, the highest prevalence in Africa followed closely by Asia (table 1) \[5\].
Maternal anemia is a risk factor for death during labor and delivery. A recent analysis of 10 observational studies found an odds ratio of 0.71 (95% CI 0.60–0.85) for maternal mortality for a 10 g/l increase in hemoglobin in pregnancy [21]. There is a possible link between maternal IDA and adverse birth outcomes. A meta-analysis of 11 trials of iron or iron/folic acid supplementation in pregnancy found a statistically significant 20% (RR 0.80, 95% CI 0.71–0.90) lower rate of low birthweight in the iron versus control group; rates of small for gestational age or preterm births were not significantly different [22]. Trials also find a reduction in neonatal and child mortality in offspring of iron-supplemented mothers during pregnancy [23, 24]. On the other hand, iron supplementation in childhood appears to have no mortality benefit.

Maternal iron supplementation may have other benefits for maternal mental health and maternal-child relations, perhaps related to reduced fatigue [25, 26]. Maternal iron supplementation may also benefit the offspring’s development, including IQ and executive functioning at school age [27, 28].

Iron supplementation in school-aged children with IDA generally benefits their cognition, but in pre-school children this has not been demonstrated [29–31]. Of 7 randomized, controlled trials of iron supplementation in young children, only one found a benefit in mental development, while 5 showed benefits in motor development [32–39].

There are very few deaths in children that could be attributed to iron deficiency or IDA, so the estimation of disease burden depends on the disability from anemia. Our previous estimate for the disease burden in children was a loss of about 2 million DALYs in 2004 [19]. The recent Global Burden of Disease Project estimate is about 15 million childhood DALYs [20].

<table>
<thead>
<tr>
<th>UN region</th>
<th>Vitamin A deficiency</th>
<th>Zinc deficiency</th>
<th>Iodine deficiency</th>
<th>Iron deficiency anemia</th>
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<tr>
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<td>children &lt;5 years</td>
<td>pregnant women</td>
<td>children 6–12 years</td>
<td>total population</td>
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<td></td>
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<td>serum retinol &lt;0.70 μmol/l</td>
<td>urine iodine &lt;100 μg/l</td>
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<td>14.3</td>
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<tr>
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</table>
Implications for Nutrition Programs

Deficiencies of vitamin A, zinc, iodine and iron, among all the possible deficiencies of micronutrients deserve focus because they have a high global prevalence and important health effects. These deficiencies may coexist in populations and even in individuals with deficiencies of other vitamins and minerals. Of note in this regard is that poor folate status at the time of conception may lead to neural tube defects in the fetus, particularly in women who are genetically susceptible and thus need more folate. Deficiencies of some of the B vitamins and vitamin D may also have adverse effects on women in pregnancy, on the fetus and on the young child and are subjects of active investigation.

There are programs in low- and middle-income countries to reduce these micronutrient deficiencies or ameliorate their negative effects. Supplementation with high-dose vitamin A reaches a high proportion of children living in areas with deficient diets. As a result, the number of deaths attributed to vitamin A deficiency is reduced; however, without continued intervention, the deaths would increase because the dietary inadequacy has not been corrected except in a few countries with food fortification programs. Zinc is now recommended for use in treatment of childhood diarrhea, and as coverage increases, this should have benefits both for treatment of that episode of illness and for prevention of subsequent infectious diseases. It would still be desirable to have programs that increase the consumption of zinc in the diet or provide zinc supplements to vulnerable age groups including pregnant women and young children. Iodine deficiency is being addressed primarily through programs to fortify salt with iodine, and this is now reaching more than 70% of the world’s population [40]. IDA remains a problem with only limited programmatic efforts. Iron and folic acid is to be taken by all pregnant women, but the adherence to this recommendation is low. Iron supplementation in children is increasing through the use of micronutrient powders and fortified products, but coverage is still very low.

Given the possible occurrence of a number of micronutrient deficiencies, the limited data on the distribution of deficiencies in populations and the difficulty of diagnosing deficiencies in individuals, additional efforts are needed. There is increasing evidence on the value of giving a multiple micronutrient supplement in pregnancy instead of iron and folic acid. Similarly, there would be value in approaches that ensure dietary adequacy of micronutrients, as well as calories, protein and essential fatty acids, possibly through fortification of foods for specific target population groups such as young children.

The disease burden caused by micronutrient deficiencies is substantial, but completely preventable. More precise quantification of the prevalence of these deficiencies within countries and in vulnerable groups should guide the interven-
tions available and encourage innovative approaches. Better assessment of the consequences, throughout the life course, of these deficiencies may help to motivate action and give greater priority to nutritional interventions and programs.

Disclosure Statement

R.E. Black is a member of the governing boards of the Micronutrient Initiative and Vitamin Angels.

References


