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Essential Role of Vitamin C and Zinc in Child Immunity and Health

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With the progressive elimination of dietary protein-energy deficits, deficiencies of micronutrients are emerging as the limiting factors in ensuring children's optimal health. Data from several countries in Asia and Latin America indicate that deficiencies of vitamin C and zinc continue to be at alarming levels. This article reviews the roles of vitamin C and zinc in supporting children's growth and development, with a particular focus on the complementary roles they play in supporting immune functions and combating infections. The contemporary relevance of vitamin C and zinc deficiency in the Asian and Latin American regions, both undergoing a rapid nutritional transition, are also discussed. Overall, there is increasing evidence that deficiency of vitamin C and zinc adversely affects the physical and mental growth of children and can impair their immune defences. Nutrition should be the main vehicle for providing these essential nutrients; however, supplementation can represent a valid support method, especially in developing regions.

KEY WORDS: Micronutrients; Paediatrics; Deficiencies; Stunting; Respiratory infections; Diarrhoea; Growth; Development; Immune system

Introduction

Diet and nutrition are important in the promotion and maintenance of good health throughout the entire lifespan and occupy a prominent position in prevention measures.[1 – 3] Both malnutrition and excessive caloric intake can have deleterious effects on health, especially when they occur during infancy and childhood.[4,5] Extensive research strongly suggests that nutrition in early life has a major effect on long-term health and well-being.[6] Negative consequences of an inadequate diet with insufficient micronutrient density include impairment of physical growth,[7,8] mental development[8 – 10] and immune function,[11,12] resulting in higher infection rates.

One out of every four children aged < 5 years – or 146 million children in the developing world – is underweight for their age and at increased risk of an early death.[13] Every year, it is estimated that undernutrition contributes to the death of about 5.6 million children aged < 5 years. Undernutrition, particularly in children, prevents individuals and even whole societies from achieving their full potential. Several organizations and committees worldwide[13 – 17] are heavily engaged in combating undernutrition and dietary micronutrient deficiencies, especially in developing countries, in order to reduce mortality and the burden of disease, and to improve growth, learning ability, overall health and work capacity and, thereby, ensure a better quality of life. At the same time, emerging regions, such as Asia and Latin America, are undergoing a rapid nutritional transition characterized by persistent nutritional deficiencies coexisting in the same country and, sometimes, even within the same individual, with a progressive rise in the prevalence of obesity, diabetes and other nutritional-related chronic diseases.[4,5] Even in industrialized countries, it is not uncommon for children not to receive adequate amounts of essential vitamins and minerals through their diet.[5,18] This can be due to dietary and cultural habits, socio-economic reasons (e.g. unemployment and working poors), frequent infections, and exposure to pollutants and passive smoke, but can also be due to a reduction in the micronutrient content of fruit and vegetables as a result of changes to their growth, transport and storage conditions.[12,18,19]

As they grow, children undergo major physiological, psychological and cognitive developmental processes. As part of its 'learning curve', the immune system is often challenged by pathogens unknown to the child's growing body and, indeed, children have more frequent infections compared with adults.[20,21] All these processes and the frequent immune challenges require adequate nutrient and micronutrient supplies,[5,22] which are not always easily achieved as poor eating habits are quite common in this age group.[4,23] Children have their food preferences and are also quite fussy about eating fruit and green leafy vegetables, thereby often compromising their intake of micronutrients from dietary sources even in situations of abundant dietary availability.[24,25]

Vitamin C (ascorbic acid) and zinc are essential micronutrients required to maintain the physiological functions and integrity of an organism.[26 – 29] Humans cannot synthesize them and depend on a continuous exogenous supply. This indispensability of regular intake is expressed in the need for official Recommended Dietary Allowances (RDAs), elaborated and published by the World Health Organization (WHO) and several other health authorities in various regions.[30,31] Table 1 shows children's vitamin C and zinc RDAs as set by the Institute of Medicine in the USA.

This article reviews the roles of vitamin C and zinc in supporting children's growth and development, with a particular focus on the complementary roles that these micronutrients play in supporting immune functions and combating various infections. The contemporary relevance of vitamin C and zinc deficiency, especially in the Asian and Latin American regions, both of which are undergoing a rapid nutritional transition, will also be discussed.

TABLE 1:
Recommended dietary allowances of vitamin C and zinc

	Age				
Micronutrient	0 – 12 months	1 – 3 years	4 – 8 years	9 – 13 years	References
Vitamin C (mg)	40 – 50	15	25	45	Institute of Medicine, 2000[30]
Zinc (mg)	2 – 3	3	5	8	Institute of Medicine, 2001[31]

General functions

Vitamin C is an essential micronutrient required for normal metabolic functioning of the body.[29,30,32] It is a cofactor for several enzymes involved in the biosynthesis of collagen, carnitine and neurotransmitters.[30,33,34] Unlike other water-soluble vitamins, vitamin C acts as a cosubstrate in these reactions, not as a coenzyme.[29,30,32] The chief biological function of vitamin C is as a water-soluble antioxidant,[29,30] with the potential to reduce cytochromes of the respiratory chain, as well as oxygen itself. Reduction of iron by vitamin C has also been implicated in enhanced gastrointestinal absorption of dietary non-haem iron.[29,30,32,35] Other proposed activities include maintenance of enzyme thiols in a reduced state and sparing of glutathione, an important intracellular antioxidant and enzyme cofactor. Finally, vitamin C has been implicated in strengthening of the immune system.[29,30,32,36]

Vitamin C deficiency results in a weakening of collagenous structures, causing tooth loss, joint pain, bone and connective tissue disorders, and poor wound healing, all of which are characteristic of scurvy.[29] Carnitine is essential for the transport of activated long-chain fatty acids into the mitochondria; as a result, fatigue and lethargy are early symptoms of vitamin C deficiency.[29] Vitamin C deficiency has also been shown to reduce significantly the delayed-type hypersensitivity responses that indicate compromised immunity.[37]

Zinc is one of the most abundant and important trace elements in the body, playing three major roles as a catalytic, structural and regulatory ion.[26,38] It is required for many biological functions, including reproduction, growth, immune function and defence against free radicals.[26,31,36,39 – 41] It is a component of over 1000 transcription factors, including DNA-binding proteins with zinc fingers, and is required in more than 300 zinc-containing metalloenzymes.[26,38] Worldwide, zinc deficiency is an important public health problem affecting two billion people.[41 – 43] It is even estimated that a considerable proportion of the Western population is at risk of marginal zinc deficiency.[41,43] Zinc deficiency increases the risk and severity of a variety of infections, restricts physical growth, results in hypogonadism in male adolescents, causes delayed wound healing, affects specific outcomes of pregnancy and may increase the risk of some chronic diseases, including cancer.[26,31,36,41,44,45] This link is attributed to the role of zinc in antioxidant defence and DNA damage repair.[43] Current indicators for zinc deficiency, such as plasma or hair zinc concentrations, have poor sensitivity and specificity, and do not change with marginal zinc deficiency.[43,46] Thus, the identification of more sensitive biomarkers of zinc status, especially at the individual level as opposed to the population level, is a critical issue in this field.[41,43,46,47] It has recently been shown that dietary zinc depletion in healthy men increases DNA damage, suggesting that marginal zinc deficiency could have significant health consequences because of its essential role in maintaining DNA integrity.[43] Notably, the study highlighted the sensitivity of DNA integrity to marginal dietary zinc depletion compared with traditional measures of zinc status.[43]

Role in growth and development

The health and well-being of children depend on the interaction between their genetic potential and external factors, such as adequate nutrition, environmental safety, social interaction and stimulation.[8] With the progressive elimination of protein-energy deficits in the diet, deficiencies of micronutrients are emerging as limiting factors to ensuring optimal growth and mental development.[8] There is increasing evidence that deficiencies of micronutrients, such as vitamin C and zinc, adversely affect the physical and mental growth of children.

Vitamin C supports growth via its role in collagen synthesis and, hence, the development of bone and soft tissues, and also indirectly by improving absorption of non-haem iron.[30,35,48] Although scurvy is a rare condition, at least in industrialized countries, it is still encountered in the daily practice of general paediatricians and paediatric rheumatologists. In children, scurvy is typically the result of a delay in starting weaning foods, improper dietary habits involving small amounts of fruit and vegetables, and developmental behaviour.[49 – 53] Among the observed symptoms are musculoskeletal complaints, weakness, limping and inability to walk, and debilitating bone pain.[49 – 53] Vitamin C has been convincingly shown to stimulate the absorption of non-haem iron from the diet by two mechanisms: the reduction of ferric to ferrous iron (i.e. to the form required for uptake into mucosal cells) and the prevention of the formation of insoluble and unabsorbable iron compounds. Vitamin C, therefore, counteracts the influence of ligands, such as phytates and polyphenols, that bind iron ions and inhibit iron absorption.[35,48,54 – 56] Thus, vitamin C contributes to combating anaemia,[57] another factor that negatively affects physical growth.[58]

A clinical study supplementing 44 pairs of monozygotic twins (18 male and 26 female pairs, aged 6 – 15 years) with 500 – 1000 mg/day vitamin C for 5 months resulted in enhanced growth only in the group of younger boys aged 6 – 11 years who received 500 mg/day vitamin C; on average, the active supplementation group showed an increase of 1.3 cm versus the untreated controls in this group of younger boys.[59]

Physical growth retardation is an early and prominent feature of zinc deficiency and was first reported in 1963 by Prasad *et al.*[60,61] During the last decade, several randomized, controlled trials have provided evidence that zinc deficiency, which can be reversed by zinc supplementation, contributes to stunting in children in both developing[47,62,63] and developed[64 – 66] countries. Table 2 shows the prevalence of nutritional stunting in children in various in Asia-Pacific, Latin American and Caribbean countries, plus India.[22,67 – 70] Several zinc-dependent enzymes are involved in the synthesis of nucleic acids and proteins and, hence, in the fundamental processes of cell replication and differentiation and, ultimately, growth.[26,31] Furthermore, zinc deficiency has been shown to reduce insulin-like growth factor I production and growth hormone levels.[71] The risk of stunting is greatest during the period of rapid body growth and development, and slows down after about 3 years of age.[72] Breast milk is an important source of zinc for infants. The bioavailability of zinc from human milk has been shown to be higher than from cow's milk and cow's milk-based formulas.[73] This difference may be explained by the higher proportion of zinc bound to citrate in human milk which, in turn, positively affects zinc absorption.[73 – 75] Although zinc citrate from breast milk is well absorbed[73 – 75] it becomes insufficient to support growth after 6 months of lactation.[76] Improvement of maternal zinc nutrition during pregnancy is the key to infant zinc nutritional support and the prevention of low zinc concentrations in breast milk.[77] Early stunting is likely to persist through

TABLE 2:
Prevalence of children with stunted growth in the Asia-Pacific, Latin American and Caribbean regions, plus India

	International Zinc Nutrition Consultative Group, 2006[67]		Additional data	
Region/Country	Stunting prevalence	Year	Stunting prevalence	References
Asia-Pacific			34.4%	Stephenson *et al.*, 2000[22]
South Central			43.7%	Stephenson *et al.*, 2000[22]
South-Eastern			32.8%	Stephenson *et al.*, 2000[22]
Indonesia	42%	2002		
China	14%	2000	14.3%	Ma *et al.*, 2007[68]
Philippines	32%	1998	25% – 52%	Khor and Sharif, 2003[69], Zalilah and Tham, 2002[70]
Malaysia	16%	1999		
Singapore	2%	2000		
Thailand	13%	1995		
Vietnam	37%	2000		
Cambodia	45%	2000		
India	45%	1999		
Latin America and Caribbean			12.6%	Stephenson *et al.*, 2000[22]
Caribbean			16.3%	Stephenson *et al.*, 2000[22]
Central America			24.0%	Stephenson *et al.*, 2000[22]
South America			9.3%	Stephenson *et al.*, 2000[22]
Brazil	11%	1996		
Argentina	12%	1996		
Mexico	18%	1999		
Venezuela	12%	2000		
Peru	25%	2000		
Bolivia	27%	2004		
Chile	1%	2004		
Colombia	12%	2005		
Ecuador	26%	1998		
Guatemala	49%	2002		
El Salvador	19%	2003		
Honduras	29%	2001		

adolescence if children remain in the same environment. Zinc supplementation has been shown to increase linear growth and weight gain in previously stunted or underweight children.[78 – 82] These results support the view that interventions to improve the zinc nutrition of children should be considered in populations at risk of zinc deficiency, especially if there are elevated rates of being underweight or stunting.[78]

Stunting in poor populations is usually associated with poor mental development.[22] Of course, many socio-cultural and economic disadvantages that coexist with stunted growth may also negatively affect mental development;[22] however, both vitamin C and zinc deficiencies on their own can also compromise mental development.

The highest concentrations of vitamin C in the body are found intracellularly in brain neurons and the brain is known to retain vitamin C preferentially in cases of deficiency.[83,84] Animal experiments have demonstrated that vitamin C is crucial for early brain development.[85,86] Several mechanisms may be involved in neuronal damage induced by vitamin C deficiency. Ascorbate not only functions as the primary antioxidant reducing oxidative neurotoxic insults in the brain, but it also prevents additional neurotoxicity from the neurotransmitters, dopamine and glutamate, by catalysing the conversion of dopamine to noradrenaline and via glutamate–ascorbic acid heteroexchange.[87 – 91] Furthermore, vitamin C can affect synaptic neurotransmission because it is able to prevent the binding of neurotransmitters to receptors,[92 – 94] to modulate the release and reuptake of neurotransmitters[89] and to function as a cofactor in neurotransmitter synthesis.[95,96] Especially in the neonatal brain, the extensive growth during development increases the demand for antioxidants in order to prevent oxidative damage.[97] Poor vitamin C status has been postulated to deprive the brain of its primary antioxidant, thereby leading to neuronal damage during early brain development.[87,98]

Zinc is essential for brain development and central nervous system function and is present in synaptic vesicles in a group of glutamatergic neurons in the brain.[99 – 101] In this form, zinc may modulate responses for a number of neurotransmitters, both excitatory and inhibitory.[99,102 – 104] Zinc is concentrated in specific neuronal structures, notably in the nerve terminals of the hippocampus, cortex and pineal body, and deficiency alters autonomic nervous system regulation as well as hippocampal and cerebellar development.[101] Some, but not all, randomized clinical trials have, indeed, shown improvements of neurocognitive function in children aged 6 – 9 years,[82,105] improved psychomotor development in the first year of life in very low birth weight infants,[106] and improvements in behavioural aspects in both infants and children following zinc supplementation.[107 – 109] In a recent review, a relationship between low zinc concentrations and mental health problems (depression and attention-deficit hyperactivity disorder) in children was reported.[110]

Role in immune support

The immune system is a multifaceted and sophisticated network of specialized tissues, organs, cells, proteins and chemicals (including free radicals), which has evolved in order to protect the host from a range of dangerous agents, such as bacteria, viruses, fungi and parasites, as well as cancer cells and foreign substances or matter, as for example organ transplants and other noxious insults.[111 – 113] The immune system can be divided into epithelial barriers, and cellular and humoral constituents of either so-called innate (unspecific) immunity or acquired (specific) immunity, as well as into organs (lymph nodes, gut-associated lymphoid tissue, spleen and bone marrow) and special transport systems such as the lymphatic system.[111 – 113] These constituents interact in multiple and highly complex ways and networks, and both vitamin C and zinc have been shown to be crucial players in immunonutrition.[36]

The immune-enhancing role of vitamin C has been previously reviewed.[36,114 – 116] Vitamin C regulates the immune system because of its antioxidant properties and its role in collagen synthesis required for stabilization of epithelial barriers.[37] It plays a role in phagocytic function and has an immunostimulatory effect on lymphocyte cells.[116] Vitamin C is highly concentrated in leucocytes and is used rapidly during infection.[117,118] In fact, it has been defined as a stimulant of leucocyte functions, especially of neutrophil and monocyte movement.[116,119] High vitamin C levels in neutrophils are necessary to counteract the extremely high levels of oxidative stress to which they are exposed following reactive oxygen species (ROS) production.[119 – 121] ROS are generated during the respiratory burst to kill pathogens and are elevated in the inflammatory response. The oxidant–antioxidant balance is an important determinant of the immune function and immune cells are particularly sensitive to changes in this balance because of the higher percentage of polyunsaturated fatty acids in their plasma membranes.[122] Oxidative damage can lead to a loss of membrane integrity, altered membrane fluidity and result in alterations in the transmission of signals both within and between different immune cells.[123] Vitamin C supplements have been shown to enhance neutrophil chemotaxis in healthy children, whereas no effects on antibody production have been detected.[117] Vitamin C may also play a significant role in regulation of the inflammatory response.[124,125] Large doses of vitamin C are able markedly to lower blood histamine levels and this reduction is inversely related to leucocyte chemotaxis.[126,127] Vitamin C stimulated interferon production *in vitro* when incubated with cultured mouse cells and *in vivo* when administered to mice.[128] Some evidence is available suggesting that ascorbic acid may have antiviral activity in humans.[129 – 131] Vitamin C deficiency is associated with a decreased resistance to disease, while high supplemental intakes can stimulate phagocytic and T-lymphocytic activities.[36,132,133] Administration of vitamin C results in improvement in several components of the human immune response, such as antimicrobicidal and natural killer (NK) cell activities, lymphocyte proliferation, chemotaxis and delayed-type hypersensitivity response.[37,133]

Several recent reviews have documented the ever increasing immune-related functions of zinc.[26,36,45,134 – 138] Zinc is considered key for optimal functioning of both innate and acquired immunity, and impaired immune function because of inadequate zinc status may be the most common cause of secondary immunodeficiency in humans.[139] Zinc deficiency impairs cellular mediators of innate immunity, such as phagocytosis of macrophages and neutrophils, NK cell activity, generation of the oxidative burst and complement activity.[140 – 144] Deficiency also cause thymus involution[145,146] and zinc is required for the activity of thymulin,[147] a hormone involved in T-cell differentiation and enhancement of T-cell and NK cell actions.[148] Zinc deficiency depresses lymphocyte proliferation, Th1 cytokine production (interleukin-2 and interferon-γ), causes Th1/Th2 imbalance[44,149,150] and depresses delayed-type hypersensitivity skin responses and antibody responses to T-cell dependent antigens. Zinc homeostasis influences the development and function of immune cells (particularly T-cells),[44,140,150] the activity of stress-related and antioxidant proteins and helps to maintain genomic integrity and stability. In addition to its effects on cell-mediated immunity, zinc is also an anti-inflammatory and antioxidant agent.[26,45,138]

The latest advances in understanding the role of zinc homeostasis on immunity are only the tip of the iceberg and new roles are constantly emerging.[38,134,135] For example, recent findings in murine mast cells, indicate that zinc is a novel second messenger with the potential to influence many aspects of cellular signalling through its effects on zinc-binding proteins.[38,45,151]

COMPLEMENTARY ROLES OF VITAMIN C AND ZINC

The complementary roles of vitamin C and zinc in immune functions are visualized in Fig. 1 and shown in Table 3.[12,36,152 – 154] Vitamin C and zinc are required to support the functions of innate immunity, such as epithelial barriers and the cellular components involved in phagocytosis. While vitamin C and zinc both support epithelial barriers, although by different mechanisms, they target different populations of phagocytic cells, thereby complementing each other to ensure an effective phagocytic response.[30,31,36,153,155] With regard to adaptive immunity, zinc is the key player. Zinc is essential for the process that causes stem cells in the bone marrow to form lymphocytes, and for the subsequent differentiation into B- and T-lymphocytes. It is also required for the proper functioning of T-lymphocytes, for the production of antibodies by B-lymphocytes, and for efficient interaction between B- and T-lymphocytes.[36,134,153,156 – 161]

An effective immune response to an external or internal threat can only occur when all the sophisticated components of the immune system work properly together. Among the micronutrients required to ensure proper immune function, vitamin C and zinc play a central role through their

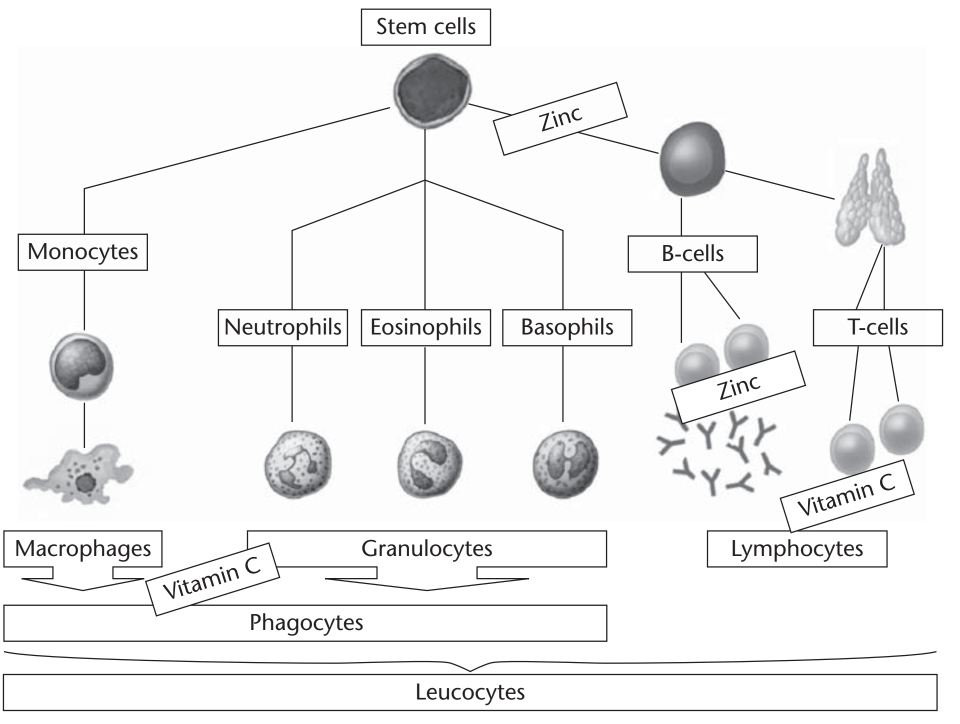

FIGURE 1: Complementary effects of vitamin C and zinc on the cellular immune system in haematopoiesis[12,36,152 – 154]

TABLE 3:
The complementary roles of vitamin C and zinc in body defences[12,36,152 – 154]

Defence	Vitamin C	Zinc
Skin and mucosal barriers	Collagen synthesis (improved strength)	Cellular proliferation (thickness maintenance)
Neutrophils and macrophages	Protection of neutrophils against reactive oxygen species-induced damage Improved motility and chemotaxis Enhanced killing Overall improvement of phagocytosis	Deficiency impairs phagocytosis
B lymphocytes and T lymphocytes	Proliferation	Proliferation of stem cells Proliferation and appropriate response B and T cell differentiation B and T cell interaction Balance of T helper (Th) 1 and Th2 Antibody production by B cells Destruction of infected tissue cells and tumours
Interferon	Enhanced production	

complementary roles in supporting components of both innate and adaptive immunity, such as epithelial barriers, cellular proliferation and antibody production. Finally, both vitamin C and zinc provide complementary antioxidant protection to exogenously derived and endogenously generated ROS.[12,36,152,153] There is, therefore, a good scientific rationale that the combination of vitamin C and zinc support immune functions and reduce the risk of infections as described further in the following sections.

COMMON COLD, RESPIRATORY TRACT INFECTIONS AND ASTHMA

Viral respiratory tract infections, such as the common cold and influenza, are among the most common illnesses in humans, with significant health and economic consequences especially for vulnerable groups such as children.[162] Acute respiratory tract infections have been reported as being one of the leading causes of death in children aged < 5 years and can lead to severe lower respiratory tract disease, such as pneumonia, bronchiolitis and other conditions.[163]

Vitamin C is a major antioxidant present in the airway surface fluid of the lungs.[164] Based on its immunostimulatory and antiviral properties, vitamin C was already postulated in 1960 to be effective in ameliorating the symptoms of upper respiratory tract infections, especially the common cold. Furthermore, plasma and leucocyte vitamin C concentrations fall rapidly with the onset of infection and return to normal with the amelioration of symptoms, suggesting that vitamin C could be beneficial for the recovery process.[165] In recent decades, a large number of placebo-controlled studies have been carried out, including several studies with schoolchildren.[59,166 – 168] A recent meta-analysis of all well-conducted, available studies concluded that vitamin C administration provides significant benefit with respect to the duration and severity of common cold symptoms when taking ≥ 200 mg/day as a prophylactic agent. The effect on the duration of cold symptoms was shown to be stronger for children compared with the effects on adults (14% and 8%, respectively). No consistent prophylactic effect on the incidence of the common cold could be seen from the pooled analysis.[21]

Hyper-responsiveness to histamine is associated with many of the symptoms seen in respiratory tract infections, allergic disorders and bronchial asthma. In view of its antihistaminic effects, high doses of vitamin C may be beneficial in such cases.[126,127] In addition, an acute dose of 2 g vitamin C significantly reduced bronchial responsiveness to inhaled histamine in patients with allergy.[130] The observed antihistamine property may contribute to the prophylactic effect of supplemental vitamin C in people with asthma and attenuate the severity of symptoms seen with respiratory infections.[169,170] Low vitamin C intake is associated with pulmonary dysfunction[171] and children with asthma have lower concentrations of vitamin C compared with normal subjects.[172] In the latest Cochrane review, however, the current evidence was considered insufficient to recommend a specific role of vitamin C in the treatment of asthma in children, and large-scale, randomized, controlled trials were advocated in order to address the potential effectiveness.[173] Recently, the role of ω-3 fatty acids, vitamin C and zinc, either singly or in combination, was evaluated in 60 children with moderately persistent asthma.[174] Childhood asthma control test (C-ACT), pulmonary function tests and sputum inflammatory markers were evaluated at the beginning of the study and at the end of each therapeutic phase. There was significant improvement in the C-ACT, pulmonary function tests and sputum inflammatory markers with diet supplementation for 6 weeks with ω-3 fatty acids, vitamin C and/or zinc. There was also significant improvement with combined use of the three supplementations compared with the single use of any one of them.[174]

Despite the mixed results in trials of vitamin C supplementation, the significant association of low vitamin C dietary intakes with increased odds for asthma and wheezing have been newly confirmed in a recent meta-analysis.[175] It is well established that exposure to oxidants from different sources, including cigarette smoke[176,177] or air pollutants, can deplete antioxidants such as vitamin C and lead to increased asthma incidence or severity.[164,178] A study on children with asthma living in Mexico City showed that supplementation with vitamins C and E provided some protection against the acute effects of ozone on their lungs.[179] It is also interesting to note that a higher body mass index in children aged 6 – 16 years was also found to be associated with an increased risk of self-reported current asthma and wheezing.[164] The authors suggested that body fat *per se* may play a role in asthma prevalence and found that low vitamin C intake was marginally related to self-reported wheezing.[164]

Many of the changes observed in zinc deficiency are considered important contributors to the increased susceptibility to infections, especially for children. In children, low concentrations of circulating zinc are associated with an increased risk of respiratory tract morbidity.[180,181] Zinc supplementation to maintain a normal serum concentration may help to reduce the mean incidence of infections (i.e. common cold, cold sores and flu)[180] and was shown in children to reduce the incidence of pneumonia by 40% – 45%, as well as reduce its duration.[182] These findings were subsequently confirmed by other trials, where a 26% – 30% reduction in the risk of pneumonia was observed.[183,184] While some researchers are in agreement regarding the benefits of zinc supplementation for pneumonia in children,[185,186] others consider that, for this disease, the role of zinc is less established than its efficacy in diarrhoea (discussed below) and advocate further evaluation.[187] Finally, preventive supplementation with zinc was shown in a meta-analysis to reduce acute lower respiratory tract infections by about 15%.[188]

HELICOBACTER PYLORI

Infection with *Helicobacter pylori* occurs generally during childhood and is prevalent in approximately 50% of the world's population, with an even higher prevalence in developing countries; although variations by geographic area, age, race, ethnicity and socioeconomic status also occur.[189 – 191] *H. pylori* has been recognized as the major aetiological factor in the development of chronic gastritis, peptic ulcer disease and, possibly, gastric cancer in adults and children.[191]

In chronic diseases, such as *H. pylori* infection, an active inflammatory response is induced by neutrophil infiltration. These neutrophils, macrophages and/or monocytes, produce free radicals that can cause DNA damage that has, in turn, been implicated in increased cancer risk.[192 – 194] Additional deleterious effects include a membrane peroxidation cascade leading to mucosal damage; a polarized (Th1 cell-mediated) response with interferon-γ release activating phygocytic cells.[195,196] Inflammation induced by *H. pylori* in the stomach causes enhanced consumption of vitamin C and has been shown to reduce significantly its secretion into gastric juice, thereby impairing systemic bioavailability of dietary vitamin C[192,197] and creating a vicious circle.[198]

Vitamin C is not only an antioxidant and a free radical scavenger but it also shows antimicrobial activity both *in vitro* and *in vivo*,[192] and is able to inhibit *H. pylori* growth *in vitro*.[199,200] Several investigators[201,202] have suggested that vitamin C supplementation may be important in the management of *H. pylori* infection in adults and children, and vitamin C intake has been found to modify favourably the relationship between *H. pylori* and gastric cancer.[193] Park *et al*.[201] demonstrated that vitamin C levels in whole blood, plasma and gastric juice, and the pH of gastric juice in Korean children were closely related to the severity of *H. pylori* infection and histological changes in the stomach. These data suggest that vitamin C may play a role in determining infection and its progression, and that vitamin C supplementation may be an important axis for the management of *H. pylori* infection in children. These findings are in line with a population-based study in Colombian children aged 2 – 9 years in which children with a daily dietary vitamin C intake of < 40 mg had greatly increased odds of *H. pylori* infection.[203]

Since available data strongly indicate a preventive effect of vitamin C against carcinogenesis in the stomach associated with *H. pylori* infection, an adequate intake of vitamin C is warranted, especially during childhood when children are most susceptible to *H. pylori* infection.[204,205] High dietary intake of vitamin C might also decrease the risk of *H. pylori* re-infection.[206]

DIARRHOEA

Despite improving trends in mortality rates, diarrhoea still causes 18% of all deaths in children aged < 5 years and accounts for nearly two million child deaths in developing countries every year.[207,208] On average, in developing countries, a child aged < 5 years will have approximately 3.2 episodes of diarrhoea each year, based on data published between 1992 and 2000.[209] Diarrhoea is also an important cause of malnutrition, particularly when it is prolonged.[210] Zinc cannot be stored in the body and zinc excretion through the gastrointestinal tract is increased during episodes of diarrhoea.[211]

It is anticipated that over half of deaths caused by diarrhoea could be averted through the successful application of zinc as a treatment for childhood diarrhoea.[212] Given this potential reduction in mortality and the strength of the evidence at hand in support of zinc treatment,[161,182,213 – 220] the WHO/United Nations Children's Fund (UNICEF) issued a joint statement on updated guidelines for the management of childhood diarrhoea.[221] This included the recommendation that all children aged < 5 years be treated with zinc (20 mg/day if aged 6 – 59 months and 10 mg/day if aged < 6 months) for 10 – 14 days. A recent Cochrane review re-enforced the importance of zinc for treating diarrhoea and concluded that research evidence shows that zinc is clearly of benefit in children aged ≥ 6 months.[211]

In addition to its role in the treatment of diarrhoea, a recent meta-analysis focused on the preventive role of zinc supplementation for diarrhoea.[188] Zinc supplementation (typical dosage 10 mg) was found to reduce the incidence of diarrhoea by about 20% among children in low-income countries, although the evidence indicated that this beneficial effect was limited to children aged > 12 months.[188] Among the subset of studies that enrolled children with a mean initial age > 12 months, the relative risk of diarrhoea was reduced by as much as 27%.[188]

The possible mechanisms for the beneficial effect of zinc in diarrhoea include improved absorption of water and electrolytes by the intestine,[222 – 224] faster regeneration of gut epithelium,[225 – 228] increased levels of enterocyte brush-border enzymes,[229,230] and enhanced immunological mechanisms for the clearance of infection. Supplementation of zinc, resulting in an improved immune reponse,[231 – 233] may also promote rapid clearance of diarrhoea pathogens from the intestine, which is in line with the major role of zinc in supporting the immune system.[181]

It is now > 5 years since the WHO and UNICEF released their joint statement recommending low osmolarity oral rehydration salts and zinc supplementation for diarrhoea management, but millions of children continue to die since few of them in developing countries are receiving these life-saving interventions. For nearly all countries, zinc availability continues to be a major obstacle.[234] Experts in the field have recently emphasized that a revitalization of diarrhoea management must become an international priority in order to reduce the burden of deaths from diarrhoea and overall child mortality worldwide.[234]

OTHER INFECTIONS/DISEASES

There are limited data relating zinc supplementation to a decrease in the incidence of febrile illnesses with malaria infections (pooled reduction of 36%).[155,235,236] The Zinc Against Plasmodium Study Group evaluated the therapeutic effect of zinc as an adjunct therapy to standard treatment in large, double-blind, controlled trials, but could not confirm any effect on malaria episodes.[237]

Deficiencies: relevance and prevalence

Deficiency of vitamin C may start with mild symptoms, such as lassitude or fatigue, and may develop into a life-threatening deficiency (scurvy). Plasma vitamin C concentrations < 0.2 mg/dl (< 11 µmol/l) indicate deficiency, while concentrations of 0.2 – 0.5 mg/dl (11 – 28 µmol/l) characterize a marginal deficiency state with inadequate tissue stores.[118] The clinical features of vitamin C deficiency include follicular hyperkeratosis, inflamed and bleeding gums, perifollicular haemorrhages and impaired wound healing.[118,238,239] Deficiency in infants may result in bone abnormalities, such as impaired bone growth and disturbed ossification, haemorrhagic symptoms and resultant anaemia.[240]

While scurvy is rare in modern societies (as previously discussed), subclinical vitamin C deficiency is relatively common even in affluent societies. In particular, plasma and leucocyte concentrations of vitamin C are significantly decreased during acute and chronic infections and disease.[37,241] This is also seen during the first days of a common cold with a significant reduction in leucocyte ascorbic acid concentrations.[165] Furthermore, children with *H. pylori* have reduced vitamin C levels.[201] Another risk group is children exposed to environmental tobacco smoke via passive smoking. Even at a low amount of smoke exposure, children showed reduced plasma ascorbate concentrations, by an average of 3.2 µmol/l compared with unexposed children who received equivalent quantities of vitamin C.[176] Plasma ascorbic acid concentrations in passive smokers were intermediate between levels found in smokers and those found in non-exposed non-smokers.[242] Hypovitaminosis C (i.e. < 23 µmol/l or < 0.5 mg/dl) was observed in 12% of passive smokers, indicating that they may have lowered body ascorbic acid pools.[242] Vitamin C supplementation was found to decrease the oxidative stress biomarker F_2-isoprostane in the plasma of non-smokers exposed to environmental tobacco smoke.[243] Exposure of non-smokers to second-hand smoke for only 30 min in a smoke-filled room was shown to result in a significant decline in serum vitamin C concentration, and increased lipid peroxidation and oxidized low-density lipoprotein.[177] These findings seem of considerable importance, since low vitamin C concentrations (< 17 µmol/l) are strongly predictive of all-cause and cardiovascular disease mortality in later life.[3]

Table 4 summarizes the data on vitamin C deficiency or inadequate dietary intake in Asia-Pacific and Latin American countries.[69,244 – 250] Although vitamin C deficiency is not the public health problem that zinc deficiency is, suboptimal vitamin C intake/status is still seen in a non-negligible proportion of the paediatric population. During the past 50 years, in both developed countries and cities in developing countries there have been many changes in the way fruit, vegetables and other crops are grown, stored, transported and distributed. These changes have resulted in lower micronutrient content and densities, including vitamin C, in many foods.[19] On the other hand, countries less affected by these changes have experienced a significant decline of fruit intake due to dietary and habit changes. In Brazil, for instance, the annual *pro capita* fruit intake halved in only 16 years (from 48 kg/year in 1987 to 24.5 kg/year in 2003).[251]

There is no specific zinc storage tissue in the body and a restriction in dietary zinc is rapidly followed by signs of zinc deficiency.[252] Nearly 50% of zinc excretion takes place through the gastrointestinal tract

TABLE 4:
Inadequate intake and prevalence of vitamin C deficiency amongst children in the Asia-Pacific and Latin American regions

Country	Age	*n*	Marker	Results	Comments	References
Mexico	< 2 years	85	Serum concentration	~30% high risk of deficiency	Probalistic sample from National Nutrition Survey, 1999	Villapando *et al.*, 2003[244]
Mexico	< 12 years	1815	Serum concentration	25% at moderate to high risk of deficiency	Probalistic sample from National Nutrition Survey, 1999	Villapando *et al.*, 2003[244]
Mexico	< 5 years	8011	Serum concentration	25% deficient	Conclusions of the Mexican National Nutrition Survey, 1999. Cut-off for deficiency < 0.2 mg/dl	Rivera and Sepúlveda Amor, 2003[245]
Mexico	5 – 11 years	11 415	Serum concentration	30% deficient	Conclusions of the Mexican National Nutrition Survey 1999. Cut-off for deficiency < 0.2 mg/dl	Rivera and Sepúlveda Amor, 2003[245]
Mexico (Tabasco)	< 6 years	149	Serum concentration	47% deficient	Cut-off for deficiency < 0.2 mg/dl	Dewey, 1983[246]
Argentina	6 – 23 months	NA	Dietary intake	57% with inadequate intake		Encuesta Nacional de Nutrición y Salud (ENNyS), 2006[247]
Argentina	2 – 5 years	NA	Dietary intake	41% with inadequate intake		Encuesta Nacional de Nutrición y Salud (ENNyS), 2006[247]
Philippines	16 months	1089	Dietary intake	1% – 25% meeting WHO needs (depending on number of feeds/day and geography)	Dietary intake from complementary foods	Perlas *et al.*, 2004[248]
Philippines	22 months	454	Dietary intake	9% – 75% meeting WHO needs (depending on number of feeds/day and geography)	Dietary intake from complementary foods	Perlas *et al.*, 2004[248]
Malaysia	1 – 3 years	29	Dietary intake	63% of RDA	24-h recalls for 2 days	Khor and Sharif, 2003[69]
Malaysia	4 – 6 years	28	Dietary intake	74% of RDA	24-h recalls for 2 days	Khor and Sharif, 2003[69]

TABLE 4 (continued): Inadequate intake and prevalence of vitamin C deficiency amongst children in the Asia-Pacific and Latin American regions

Country	Age	*n*	Marker	Results	Comments	References
Thailand (north-east)	6 – 13 years	220	Dietary intake	22 mg mean intake, i.e. 50% of DRI for 9 – 13 years	24-h recalls	Gibson *et al.*, 2007[249]
Hong Kong	1 – 7 years	~170	Dietary intake	Intake corresponds to > 60% of DRI	Dietary history, 24-h recall and food frequency	Leung *et al.*, 2000[250]

NA, not available; WHO, World Health Organization, RDA, recommended dietary allowance; DRI, dietary reference intake.

and is increased by diarrhoea. Young children regularly exposed to gastrointestinal pathogens and with diets low in animal products and high in phytate-rich foods are most at risk.[211]

The risk of inadequate zinc status in a population group can be estimated by measuring serum zinc concentrations. The suggested cut-off levels for the 2.5th percentile are 11.3 µmol/l (74 µg/dl) in fasting men, 10.7 µmol/l (70 µg/dl) in fasting women (age group ≥ 10 years) and 9.9 µmol/l (65 µg/dl) for unfasting children aged < 10 years.[253] Serum zinc concentrations, although convenient to measure, are physiologically insensitive and may not indicate overall zinc status because concentrations remain within the accepted range even at zinc intakes of 2.6 – 3.6 mg/day, which is below the recommended daily intake.[254] Other measures of zinc deficiency include hair zinc, functional measures such as height- or length-for-age, and incidence of infectious diseases (diarrhoea and pneumonia).[255] Recently, DNA breaks have been proposed as a sensitive marker for marginal zinc deficiency.[43,255] Since the central role of zinc is in cell division and protein synthesis, infants, children and adolescents are, therefore, considered to be high-risk groups in zinc undernutrition and deficiency.[26,41,256]

Zinc deficiency, which is highly prevalent in low- and middle-income countries, is related to growth retardation in children, skin changes, impaired immune response, increased susceptibility to infection, delayed wound healing, abnormal dark adaptation, delayed sexual maturation and impaired fertility.[28,42,161,257 – 260] Zinc deficiency arises mainly as a result of inadequate dietary intake.[181,261] High levels of zinc are found in ’expensive foods’ (e.g. meat and fish). Zinc is also present in nuts, seeds, legumes and wholegrain cereal; however, the high phytate content of these foods interferes with its absorption.[181,211] Vegetarians, and especially vegans, whose major food staples are grains and legumes and whose diet has a phytate:zinc ratio > 15:1, may have as much as a 50% higher zinc requirement due to lowered bioavailability, but no special RDA has been set by the Institute of Medicine due to insufficient data.[31] Other health authorities have, however, taken into account dietary composition in setting their RDAs. The Food and Agriculture Organization of the United Nations (FAO)/WHO[262] as well as the proposed zinc RDAs for Southeast Asia[263] take into consideration the bioavailability of zinc from the diet and the fact that, compared with western diets, those in Asia generally tend to have lower amounts of animal products and higher amounts of plant-based foods containing phytate.

Table 5 summarizes data on zinc deficiency or inadequate dietary intake in Asia-Pacific and Latin American countries.[68,245,249,264 – 279] These data show that suboptimal zinc intake/status is still present in a considerable part of the paediatric population. Considering that, for example, marginal zinc deficiency is associated with about a 50% increased risk and number of days with diarrhoea[181] and that, overall, zinc-deficient children are at a three-fold increased risk of acute respiratory infection,[259,260] these figures are disturbing and urgently require intervention.[234]

Regions such as Asia and Latin America are undergoing profound socioeconomic transformations accompanied by a nutritional transition, and are experiencing a progressive increase in obesity and nutrition-related chronic diseases. In these transitional countries, stunting and micronutrient deficiencies (including zinc and vitamin C) in children coexist with obesity, representing energetic ‘overnutrition’, and nutrition-related chronic diseases resulting in a double burden of nutritional disease.[4] Acting early in life with strategies to correct micronutrient deficiencies and prevent obesity and chronic diseases can save healthy life years and also significant resources that address the health and well-being of populations.

Conclusions

Diet and nutrition are important in the promotion and maintenance of good health throughout a person’s entire life. Especially in early life, an inadequate diet with insufficient micronutrient density results in impairment of physical growth, mental development and immune function, and in increased risk of chronic diseases later in life. Despite the joint efforts of several international organizations, undernutrition is still contributing to over five million deaths in children aged < 5 years and it continues to prevent individuals and even whole societies from achieving their full potential.

Infants and children undergo major developmental processes that will influence their future life and they also suffer more frequently from infections compared with adults. These events need to be adequately supported by proper nutrition, including essential micronutrients provided at appropriate levels.

Many children in low- to middle-income countries do not have adequate access to micronutrient-rich foods and sometimes the discriminating food preferences typically observed in children (e.g. dislike for green leafy vegetables and fruit) further exacerbate micronutrient intake. At the same time, emerging countries especially in Asia and Latin America are experiencing major

TABLE 5:
Inadequate intake and prevalence of zinc deficiency amongst children in Asia-Pacific and Latin American regions

Country	Age	*n*	Marker	Results	Comments	References
USA (Mexican)	6 – 7 years	54	Hair zinc	42% zinc deficiency	Mexican children in the USA consume ethnic foods (maize tortilla, refried beans, etc.) known to inhibit intestinal zinc absorption	Sandstead *et al.*, 2008[264]
Mexico	< 5 years	8011	Serum concentration	33% zinc deficient	Cut-off: serum zinc < 65 µg/dl. National Nutrition Survey, 1999	Rivera and Sepúlveda Amor, 2003[245]
Mexico	5 – 11 years	11 415	Serum concentration	20% zinc deficient	Cut-off: serum zinc < 65 µg/dl. National Nutrition Survey, 1999	Rivera and Sepúlveda Amor, 2003[245]
Mexico	< 2 years	4955	Serum concentration	13% and 28% zinc deficiency in rural and urban areas, respectively	Cut-off: serum zinc < 65 µg/dl	Duque *et al.*, 2007[265]
Brazil	3 – 6 years	229	Serum concentration	74% zinc deficiency	Cut-off: serum zinc < 40 µg/g haemoglobin. Survey in North East Brazil (Teresina)	da Costa *et al.*, 2008[266]
Brazil (Pernambuco)	7 – 11 months	948	Dietary intake	57% with inadequate intake	State of Pernambuco. 24-h recall	Martins Ferreira Fidelis and Osório, 2007[267]
Brazil (Pernambuco)	1 – 4 years		Dietary intake	53% with inadequate intake	State of Pernambuco. 24-h recall	Martins Ferreira Fidelis and Osório, 2007[267]
China	< 6 years	NA	Dietary intake	31% of boys and 33% of girls with intake less than 0.5 RDA	Results based on 1992 data (National Nutrition Survey). 3 days inventory change plus food weighing and 24-h recalls for 3 days	Ge and Chang, 2001[268]
China[a]	2 – 3 years	NA	Dietary intake	7% and 24% deficient in urban and rural areas, respectively	China National Nutrition and Health Survey, 2002. 24-h recalls for 3 consecutive days	Ma *et al.*, 2007[68,269]
China[a]	4 – 6 years	NA	Dietary intake	12% and 16% deficient in urban and rural areas, respectively	China National Nutrition and Health Survey, 2002. 24-h recalls for 3 consecutive days	Ma *et al.*, 2007[68,269]

TABLE 5 (continued):
Inadequate intake and prevalence of zinc deficiency amongst children in Asia-Pacific and Latin American regions

Country	Age	*n*	Marker	Results	Comments	References
China[a]	7 – 10 years	NA	Dietary intake	8% and 14% deficient in urban and rural areas, respectively	China National Nutrition and Health Survey, 2002. 24-h recalls for 3 consecutive days	Ma *et al.*, 2007[68,269]
China (Jiangsu Province)	6 – 9 years	297	Serum concentration and hair zinc	0.7% deficient based on serum and 15% based on hair zinc	Jiangsu is a rural area with low soil zinc concentrations	Qin *et al.*, 2009[270]
China (Beijing)	< 6 years	303	Hair zinc	34% with very low zinc	Cut-off < 70 μg/g	Chen *et al.*, 1985[271]
China	19 – 25 months	43	Plasma concentration	48% low zinc	Low zinc: < reference 2.5th percentile	Sheng *et al.*, 2006[272]
China	< 6 years	NA	Hair zinc	50% marginal deficiency or zinc deficiency	Cut-off < 100 μg/g	Zhao, 1992[273]
Indonesia (West Java)	2.4 – 10.5 months	155	Serum and urinary zinc concentration	20% deficient	West Java is a rural area	Dijkhuizen *et al.*, 2001[274] and 2003[275]
Vietnam	6 – 24 months	~150	Serum concentration	36% zinc deficient	Hai Duong Province (80 km North of Hanoi)	Thu *et al.*, 1999[276]
Vietnam	1 – 6 years	~240	Serum concentration	87% zinc deficient	Thai Nguyen Province (rural) (150 km North of Hanoi)	Van Nhien *et al.*, 2008[277]
Thailand (north-east)	6 – 13 years	220	Dietary intake	4.4 mg mean intake corresponding to 55% of DRI for 9 – 13 years old	24-h recalls	Gibson *et al.*, 2007[249] and Krittaphol *et al.*, 2006[278]
Thailand (north-east)	6 – 13 years	567	Serum concentration	57% low zinc		Thurlow *et al.*, 2006[279]

[a]Estimated population affected by zinc intake inadequacy and stunting in Chinese children: 86 million and 10 million, respectively.[68,269]
NA, not available; RDA, recommended dietary allowance; DRI, dietary reference intake.

socioeconomic and dietary habit changes. The rapid nutritional transition observed in these regions is characterized by persistent nutritional deficiencies coexisting in these same regions, and sometimes even in individuals, with a progressive rise in the prevalence of obesity, diabetes and other nutritional-related chronic diseases.

Vitamin C and zinc are essential micronutrients with profound effects on children's physical and mental development, health maintenance and well-being. Both are required for optimum immune response and are, therefore, important for disease prevention and combating infections. Vitamin C is a cofactor for several enzymes involved in the biosynthesis of collagen, carnitine and neurotransmitters; it is a water-soluble antioxidant and enhances gastrointestinal absorption of dietary non-haem iron. Marginal vitamin C deficiency results in fatigue, lack of well-being and poor concentration, whereas severe deficiency causes weakening of collagenous structures, resulting in tooth loss, joint pains, bone and connective tissue disorders (e.g. impaired bone growth and disturbed ossification), poor wound healing and a compromised immunity. Zinc is required in numerous transcription factors and enzymes, it plays a central role in cellular differentiation and proliferation, and its deficiency causes growth retardation, skin changes, impaired immune response, increased susceptibility to infections, delayed wound healing, abnormal dark adaptation, delayed sexual maturation and impaired fertility.

The health and well-being of children depend upon the interaction between their genetic potential and external factors, such as adequate nutrition, environmental safety, and social interaction and stimulation. With the progressive elimination of protein–energy deficits in the diet, deficiencies of micronutrients are emerging as the restriction to ensuring optimal health in growing children. Data from several countries in Asia and Latin America indicate that deficiencies of vitamin C and, particularly, zinc continue to be present at disturbing levels. Data on zinc deficiency are backed up by matching data reporting stunted growth.

Overall, there is increasing evidence that deficiencies in micronutrients, such a vitamin C and zinc, adversely affect the physical and mental growth of children and can impair their immune defences. Nutrition should be the main vehicle for providing adequate amounts of these essential nutrients; however, supplementation can represent a valid support especially in developing regions.

Conflicts of interest

Silvia Maggini and Susanne Wenzlaff are employed by Bayer Consumer Care, a manufacturer of multivitamins. Dietrich Hornig is a retired employee of Roche Vitamins.

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References

1 World Health Organization (WHO)/Food and Agriculture Organization: *Diet, Nutrition and the Prevention of Chronic Diseases*. WHO Technical Report Series, No. 916. Geneva: World Health Organization, 2003 (available at: http://whqlibdoc.who.int/trs/WHO_TRS_916.pdf).
2 Fairfield KM, Fletcher RH: Vitamins for chronic disease prevention in adults: scientific review. *JAMA* 2002; **287:** 3116 – 3126.
3 Fletcher RH, Fairfield KM: Vitamins for chronic disease prevention in adults: clinical

applications. *JAMA* 2002; **287:** 3127 – 3129.
4 Uauy R, Kain J, Mericq V, *et al*: Nutrition, child growth, and chronic disease prevention. *Ann Med* 2008; **40:** 11 – 20.
5 Fanjiang G, Kleinman RE: Nutrition and performance in children. *Curr Opin Clin Nutr Metab Care* 2007; **10:** 342 – 347.
6 Koletzko B: Early nutrition and its later consequences: new opportunities. *Adv Exp Med Biol* 2005; **569:** 1 – 12.
7 Ramakrishnan U, Nguyen P, Martorell R: Effects of micronutrients on growth of children under 5 y of age: meta-analyses of single and multiple nutrient interventions. *Am J Clin Nutr* 2009; **89:** 191 – 203.
8 Singh M: Role of micronutrients for physical growth and mental development. *Indian J Pediatr* 2004; **71:** 59 – 62.
9 Bellisle F: Effects of diet on behaviour and cognition in children. *Br J Nutr* 2004; **92(suppl 2):** S227 – S232.
10 Bourre JM: Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 1: micronutrients. *J Nutr Health Aging* 2006; **10:** 377 – 385.
11 Chandra RK: Nutrition and the immune system from birth to old age. *Eur J Clin Nutr* 2002; **56(suppl 3):** S73 – S76.
12 Maggini S, Beveridge S, Sorbara PJP, *et al*: Feeding the immune system: the role of micronutrients in restoring resistance to infections. *CAB Reviews: Perspectives in Agriculture, Veterinary Science, Nutrition and Natural Resources* 2008; **3(98):** 1 – 21.
13 UNICEF: *Progress for Children: a Report Card on Nutrition,* number 4. New York: UNICEF, May 2006 (available at: http://www.unicef.org/progressforchildren/2006n4/files/PFC4_EN_8X11.pdf).
14 Katzen-Luchenta J: The declaration of nutrition, health, and intelligence for the child-to-be. *Nutr Health* 2007; **19:** 85 – 102.
15 Copenhagen Consensus Center: *Copenhagen Consensus 2008 – Results*. Frederiksberg: Copenhagen Consensus Center, 2008 (available at: http://www.copenhagenconsensus.com/Default.aspx?ID=953).
16 The World Bank Group: *Enriching Lives: Overcoming Vitamin and Mineral Malnutrition in Developing Countries*. Washington DC: The World Bank Group (available at: http://web.worldbank.org/WBSITE/EXTERNAL/TOPICS/EXTHEALTHNUTRITIONANDPOPULATION/EXTNUTRITION/0,,contentMDK:20205924~menuPK:282594~pagePK:148956~piPK:216618~theSitePK:282575,00.html).
17 World Health Organization: *Revised WHO Global Burden of Disease (GBD) 2002 Estimates*. Geneva: World Health Organization, 2003 (available at: http://www.who.int/healthinfo/global_burden_disease/estimates_regional_2002_revised/en/).
18 James WP, Nelson M, Ralph A, *et al*: Socioeconomic determinants of health. The contribution of nutrition to inequalities in health. *BMJ* 1997; **314:** 1545 – 1549.
19 Davis DR, Epp MD, Riordan HD: Changes in USDA food composition data for 43 garden crops, 1950 to 1999. *J Am Coll Nutr* 2004; **23:** 669 – 682.
20 Bhaskaram P: Micronutrient malnutrition, infection, and immunity: an overview. *Nutr Rev* 2002; **60:** S40 – S45.
21 Douglas RM, Hemilä H, Chalker E, *et al*: Vitamin C for preventing and treating the common cold. *Cochrane Database Syst Rev* 2007; CD000980.
22 Stephenson LS, Latham MC, Ottesen EA: Global malnutrition. *Parasitology* 2000; **121(suppl):** S5 – S22.
23 Bhutta ZA: Micronutrient needs of malnourished children. *Curr Opin Clin Nutr Metab Care* 2008; **11:** 309 – 314.
24 Ricketts CD: Fat preferences, dietary fat intake and body composition in children. *Eur J Clin Nutr* 1997; **51:** 778 – 781.
25 Liem DG, Zandstra LH: Children's liking and wanting of snack products: influence of shape and flavour. *Int J Behav Nutr Phys Act* 2009; **6:** 38.
26 Stefanidou M, Maravelias C, Dona A, *et al*: Zinc: a multipurpose trace element. *Arch Toxicol* 2006; **80:** 1 – 9.
27 Deruelle F, Baron B: Vitamin C: is supplementation necessary for optimal health? *J Altern Complement Med* 2008; **14:** 1291 – 1298.
28 Bhatnagar S, Natchu UC: Zinc in child health and disease. *Indian J Pediatr* 2004; **71:** 991 – 995.
29 Carr AC, Frei B: Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. *Am J Clin Nutr* 1999; **69:** 1086 – 1107.
30 Institute of Medicine: Vitamin C. In: *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. Washington, DC: National Academy Press, 2000; pp 95 – 185.
31 Institute of Medicine: Zinc. In: *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: National Academy Press, 2001; pp 442 – 501.
32 Bruno EJ Jr, Ziegenfuss TN, Landis J: Vitamin C: research update. *Curr Sports Med Rep* 2006; **5:** 177 – 181.
33 Park JB, Levine M: Purification, cloning and expression of dehydroascorbic acid-reducing activity from human neutrophils: identification as glutaredoxin. *Biochem J* 1996; **315:** 931 – 938.
34 Himmelreich U, Drew KN, Serianni AS, *et al*: ^{13}C NMR studies of vitamin C transport and its redox cycling in human erythrocytes.

Biochemistry 1998; **37:** 7578 – 7588.
35 Atanassova BD, Tzatchev KN: Ascorbic acid – important for iron metabolism. *Folia Med (Plovdiv)* 2008; **50:** 11 – 16.
36 Wintergerst ES, Maggini S, Hornig DH: Immune-enhancing role of vitamin C and zinc and effect on clinical conditions. *Ann Nutr Metab* 2006; **50:** 85 – 94.
37 Jacob RA, Kelley DS, Pianalto FS, *et al*: Immunocompetence and oxidant defense during ascorbate depletion of healthy men. *Am J Clin Nutr* 1991; **54(6 suppl):** 1302S – 1309S.
38 Haase H, Rink L: Functional significance of zinc-related signaling pathways in immune cells. *Annu Rev Nutr* 2009; **29:** 133 – 152.
39 Powell SR: The antioxidant properties of zinc. *J Nutr* 2000; **130(5S suppl):** 1447S – 1454S.
40 Salgueiro MJ, Zubillaga M, Lysionek A, *et al*: Zinc status and immune system relationship: a review. *Biol Trace Elem Res* 2000; **76:** 193 – 205.
41 Tuerk MJ, Fazel N: Zinc deficiency. *Curr Opin Gastroenterol* 2009; **25:** 136 – 143.
42 Brown KH, Rivera JA, Bhutta Z, *et al*: International Zinc Nutrition Consultative Group (IZiNCG) technical document #1. Assessment of the risk of zinc deficiency in populations and options for its control. *Food Nutr Bull* 2004; **25(1 suppl 2):** S99 – S203.
43 Song Y, Chung CS, Bruno RS, *et al*: Dietary zinc restriction and repletion affects DNA integrity in healthy men. *Am J Clin Nutr* 2009; **90:** 321 – 328.
44 Prasad AS: Zinc and immunity. *Mol Cell Biochem* 1998; **188:** 63 – 69.
45 Prasad AS: Zinc: role in immunity, oxidative stress and chronic inflammation. *Curr Opin Clin Nutr Metab Care* 2009; **12:** 646 – 652.
46 Hess SY, Peerson JM, King JC, *et al*: Use of serum zinc concentration as an indicator of population zinc status. *Food Nutr Bull* 2007; **28(3 suppl):** S403 – S429.
47 Hess SY, Lönnerdal B, Hotz C, *et al*: Recent advances in knowledge of zinc nutrition and human health. *Food Nutr Bull* 2009; **30(1 suppl):** S5 – S11.
48 Sandström B: Micronutrient interactions: effects on absorption and bioavailability. *Br J Nutr* 2001; **85(suppl 2):** S181 – S185.
49 Vitale A, La Torre F, Martini G, *et al*: Arthritis and gum bleeding in two children. *J Paediatr Child Health* 2009; **45:** 158 – 160.
50 Ratanachu-Ek S, Sukswai P, Jeerathanyasakun Y, *et al*: Scurvy in pediatric patients: a review of 28 cases. *J Med Assoc Thai* 2003; **86(suppl 3):** S734 – S740.
51 Weinstein M, Babyn P, Zlotkin S: An orange a day keeps the doctor away: scurvy in the year 2000. *Pediatrics* 2001; **108:** E55.
52 Akikusa JD, Garrick D, Nash MC: Scurvy: forgotten but not gone. *J Paediatr Child Health* 2003; **39:** 75 – 77.
53 Olmedo JM, Yiannias JA, Windgassen EB, *et al*: Scurvy: a disease almost forgotten. *Int J Dermatol* 2006; **45:** 909 – 913.
54 Siegenberg D, Baynes RD, Bothwell TH, *et al*: Ascorbic acid prevents the dose-dependent inhibitory effects of polyphenols and phytates on nonheme-iron absorption. *Am J Clin Nutr* 1991; **53:** 537 – 541.
55 Hallberg L, Hulthén L: Prediction of dietary iron absorption: an algorithm for calculating absorption and bioavailability of dietary iron. *Am J Clin Nutr* 2000; **71:** 1147 – 1160.
56 Teucher B, Olivares M, Cori H: Enhancers of iron absorption: ascorbic acid and other organic acids. *Int J Vitam Nutr Res* 2004; **74:** 403 – 419.
57 Mao X, Yao G: Effect of vitamin C supplementations on iron deficiency anemia in Chinese children. *Biomed Environ Sci* 1992; **5:** 125 – 129.
58 Iannotti LL, Tielsch JM, Black MM, *et al*: Iron supplementation in early childhood: health benefits and risks. *Am J Clin Nutr* 2006; **84:** 1261 – 1276.
59 Miller JZ, Nance WE, Norton JA, *et al*: Therapeutic effect of vitamin C. A co-twin control study. *JAMA* 1977; **237:** 248 – 251.
60 Prasad AS, Miale A, Farid Z, *et al*: Biochemical studies on dwarfism, hypogonadism, and anemia. *Arch Intern Med* 1963; **111:** 407 – 428.
61 Prasad AS, Miale A, Farid Z, *et al*: Zinc metabolism in patients with the syndrome of iron deficiency anemia, hepatosplenomegaly, dwarfism, and hypognadism. *J Lab Clin Med* 1963; **61:** 537 – 549.
62 Ferguson EL, Gibson RS, Opare-Obisaw C, *et al*: The zinc nutriture of preschool children living in two African countries. *J Nutr* 1993; **123:** 1487 – 1496.
63 Rivera JA, Ruel MT, Santizo MC, *et al*: Zinc supplementation improves the growth of stunted rural Guatemalan infants. *J Nutr* 1998; **128:** 556 – 562.
64 Hambidge KM, Walravens PA, Brown RM, *et al*: Zinc nutrition of preschool children in the Denver Head Start program. *Am J Clin Nutr* 1976; **29:** 734 – 738.
65 Walravens PA, Hambidge KM: Growth of infants fed a zinc supplemented formula. *Am J Clin Nutr* 1976; **29:** 1114 – 1121.
66 Walravens PA, Chakar A, Mokni R, *et al*: Zinc supplements in breastfed infants. *Lancet* 1992; **340:** 683 – 685.
67 International Zinc Nutrition Consultative Group: *Prevalence of Nutritional Stunting in Children Under 5 Years of Age*. Dakar Yoff, Senegal: International Zinc Nutrition Consultative Group, 2006 (available at: http://www.izincg.org/stunt.php#).
68 Ma G, Li Y, Jin Y, *et al*: Assessment of intake inadequacy and food sources of zinc of people in China. *Public Health Nutr* 2007; **10:** 848 – 854.

69 Khor GL, Sharif ZM: Dual forms of malnutrition in the same households in Malaysia – a case study among Malay rural households. *Asia Pac J Clin Nutr* 2003; **12:** 427 – 437.
70 Zalilah MS, Tham BL: Food security and child nutritional status among Orang Asli (Temuan) households in Hulu Langat, Selangor. *Med J Malaysia* 2002; **57:** 36 – 50.
71 Cole CR, Lifshitz F: Zinc nutrition and growth retardation. *Pediatr Endocrinol Rev* 2008; **5:** 889 – 896.
72 World Health Organization (1995) Physical Status: The Use and Interpretation of Anthropometry 1995 WHO Geneva, Switzerland. Technical Report Series no. 854. (available at: http://whqlibdoc.who.int/trs/WHO_TRS_854.pdf).
73 Sandström B, Cederblad A, Lönnerdal B: Zinc absorption from human milk, cow's milk, and infant formulas. *Am J Dis Child* 1983; **137:** 726 – 729.
74 Lönnerdal B: Trace element absorption in infants as a foundation to setting upper limits for trace elements in infant formulas. *J Nutr* 1989; **119:** 1839 – 1844.
75 Lönnerdal B, Stanislowski AG, Hurley LS: Isolation of a low molecular weight zinc binding ligand from human milk. *J Inorg Biochem* 1980; **12:** 71 – 78.
76 Umeta M, West CE, Verhoef H, *et al*: Factors associated with stunting in infants aged 5 – 11 months in the Dodota-Sire District, rural Ethiopia. *J Nutr* 2003; **133:** 1064 – 1069.
77 Dórea JG: Zinc deficiency in nursing infants. *J Am Coll Nutr* 2002; **21:** 84 – 87.
78 Brown KH, Peerson JM, Rivera J, *et al*: Effect of supplemental zinc on the growth and serum zinc concentrations of prepubertal children: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2002; **75:** 1062 – 1071.
79 Yang YX, Han JH, Shao XP, *et al*: Effect of micronutrient supplementation on the growth of preschool children in China. *Biomed Environ Sci* 2002; **15:** 196 – 202.
80 Sayeg Porto MA, Oliveira HP, Cunha AJ, *et al*: Linear growth and zinc supplementation in children with short stature. *J Pediatr Endocrinol Metab* 2000; **13:** 1121 – 1128.
81 Lind T, Lönnerdal B, Stenlund H, *et al*: A community-based randomized controlled trial of iron and zinc supplementation in Indonesian infants: effects on growth and development. *Am J Clin Nutr* 2004; **80:** 729 – 736.
82 Sandstead HH, Penland JG, Alcock NW, *et al*: Effects of repletion with zinc and other micronutrients on neuropsychologic performance and growth of Chinese children. *Am J Clin Nutr* 1998; **68 (2 suppl):** 470S – 475S.
83 Rice ME, Russo-Menna I: Differential compartmentalization of brain ascorbate and glutathione between neurons and glia. *Neuroscience* 1998; **82:** 1213 – 1223.
84 Tsukaguchi H, Tokui T, Mackenzie B, *et al*: A family of mammalian Na^+-dependent L-ascorbic acid transporters. *Nature* 1999; **399:** 70 – 75.
85 Sotiriou S, Gispert S, Cheng J, *et al*: Ascorbic-acid transporter Slc23a1 is essential for vitamin C transport into the brain and for perinatal survival. *Nat Med* 2002; **8:** 514 – 517.
86 Wilson JX: Regulation of vitamin C transport. *Annu Rev Nutr* 2005; **25:** 105 – 125.
87 Tveden-Nyborg P, Lykkesfeldt J: Does vitamin C deficiency result in impaired brain development in infants? *Redox Rep* 2009; **14:** 2 – 6.
88 Venkataraman P, Muthuvel R, Krishnamoorthy G, *et al*: PCB (Aroclor 1254) enhances oxidative damage in rat brain regions: protective role of ascorbic acid. *Neurotoxicology* 2007; **28:** 490 – 498.
89 Levine M, Morita K, Heldman E, *et al*: Ascorbic acid regulation of norepinephrine biosynthesis in isolated chromaffin granules from bovine adrenal medulla. *J Biol Chem* 1985; **260:** 15598 – 15603.
90 Berman SB, Zigmond MJ, Hastings TG: Modification of dopamine transporter function: effect of reactive oxygen species and dopamine. *J Neurochem* 1996; **67:** 593 – 600.
91 Miele M, Boutelle MG, Fillenz M: The physiologically induced release of ascorbate in rat brain is dependent on impulse traffic, calcium influx and glutamate uptake. *Neuroscience* 1994; **62:** 87 – 91.
92 Todd RD, Bauer PA: Ascorbate modulates 5-[^{3}H]hydroxytryptamine binding to central 5-HT_3 sites in bovine frontal cortex. *J Neurochem* 1988; **50:** 1505 – 1512.
93 Majewska MD, Bell JA: Ascorbic acid protects neurons from injury induced by glutamate and NMDA. *Neuroreport* 1990; **1:** 194 – 196.
94 Majewska MD, Bell JA, London ED: Regulation of the NMDA receptor by redox phenomena: inhibitory role of ascorbate. *Brain Res* 1990; **537:** 328 – 332.
95 Levine M, Morita K, Pollard H: Enhancement of norepinephrine biosynthesis by ascorbic acid in cultured bovine chromaffin cells. *J Biol Chem* 1985; **260:** 12942 – 12947.
96 Paterson IA, Hertz L: Sodium-independent transport of noradrenaline in mouse and rat astrocytes in primary culture. *J Neurosci Res* 1989; **23:** 71 – 77.
97 Lykkesfeldt J, Moos T: Age-dependent change in vitamin C status: a phenomenon of maturation rather than of ageing. *Mech Ageing Dev* 2005; **126:** 892 – 898.
98 Tveden-Nyborg P, Johansen LK, Raida Z, *et al*: Vitamin C deficiency in early postnatal life impairs spatial memory and reduces the number of hippocampal neurons in guinea pigs. *Am J Clin Nutr* 2009; **90:** 540 – 546.

99 Frederickson CJ, Suh SW, Silva D, *et al*: Importance of zinc in the central nervous system: the zinc-containing neuron. *J Nutr* 2000; **130(5S suppl):** 1471S – 1483S.
100 Wallwork JC: Zinc and the central nervous system. *Prog Food Nutr Sci* 1987; **11:** 203 – 247.
101 Georgieff MK: Nutrition and the developing brain: nutrient priorities and measurement. *Am J Clin Nutr* 2007; **85:** 614S – 620S.
102 Frederickson CJ: Neurobiology of zinc and zinc-containing neurons. *Int Rev Neurobiol* 1989; **31:** 145 – 238.
103 Smart TG: Uncultured lobster muscle, cultured neurons and brain slices: the neurophysiology of zinc. *J Pharm Pharmacol* 1990; **42:** 377 – 387.
104 Xie XM, Smart TG: A physiological role for endogenous zinc in rat hippocampal synaptic neurotransmission. *Nature* 1991; **349:** 521 – 524.
105 Penland JG, Sandstead HH, Alcock NW, *et al*: A preliminary report: effects of zinc and micronutrient repletion on growth and neuropsychological function of urban Chinese children. *J Am Coll Nutr* 1997; **16:** 268 – 272.
106 Friel JK, Andrews WL, Matthew JD, *et al*: Zinc supplementation in very-low-birth-weight infants. *J Pediatr Gastroenterol Nutr* 1993; **17:** 97 – 104.
107 Ashworth A, Morris SS, Lira PI, *et al*: Zinc supplementation, mental development and behaviour in low birth weight term infants in northeast Brazil. *Eur J Clin Nutr* 1998; **52:** 223 – 227.
108 Sazawal S, Bentley M, Black RE, *et al*: Effect of zinc supplementation on observed activity in low socioeconomic Indian preschool children. *Pediatrics* 1996; **98:** 1132 – 1137.
109 Bentley ME, Caulfield LE, Ram M, *et al*: Zinc supplementation affects the activity patterns of rural Guatemalan infants. *J Nutr* 1997; **127:** 1333 – 1338.
110 DiGirolamo AM, Ramirez-Zea M: Role of zinc in maternal and child mental health. *Am J Clin Nutr* 2009; **89:** 940S – 945S.
111 Delves PJ, Roitt IM: The immune system – first of two parts. *N Engl J Med* 2000; **343:** 37 – 49.
112 Delves PJ, Roitt IM: The immune system – second of two parts. *N Engl J Med* 2000; **343:** 108 – 117.
113 Parkin J, Cohen B: An overview of the immune system. *Lancet* 2001; **357:** 1777 – 1789.
114 Webb AL, Villamor E: Update: effects of antioxidant and non-antioxidant vitamin supplementation on immune function. *Nutr Rev* 2007; **65:** 181 – 217.
115 Ströhle A, Hahn A: Vitamin C and immune function. *Med Monatsschr Pharm* 2009; **32:** 49 – 54 [in German].
116 Thomas WR, Holt PG: Vitamin C and immunity: an assessment of the evidence. *Clin Exp Immunol* 1978; **32:** 370 – 379.
117 Anderson R, Oosthuizen R, Maritz R, *et al*: The effects of increasing weekly doses of ascorbate on certain cellular and humoral immune functions in normal volunteers. *Am J Clin Nutr* 1980; **33:** 71 – 76.
118 Levine M, Conry-Cantilena C, Wang Y, *et al*: Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. *Proc Natl Acad Sci USA* 1996; **93:** 3704 – 3709.
119 Levine M, Dhariwal KR, Wang Y, *et al*: Ascorbic acid in neutrophils. In: *Natural Antioxidants in Health and Disease* (Frei B, ed). San Diego: Academic Press, 1994; pp 469 – 488.
120 Patrone F, Dallegri F, Bonvini E, *et al*: Effects of ascorbic acid on neutrophil function. Studies on normal and chronic granulomatous disease neutrophils. *Acta Vitaminol Enzymol* 1982; **4:** 163 – 168.
121 Levy R, Shriker O, Porath A, *et al*: Vitamin C for the treatment of recurrent furunculosis in patients with impaired neutrophil functions. *J Infect Dis* 1996; **173:** 1502 – 1505.
122 Meydani SN, Wu D, Santos MS, *et al*: Antioxidants and immune response in aged persons: overview of present evidence. *Am J Clin Nutr* 1995; **62(6 suppl):** 1462S – 1476S.
123 Knight JA: Review: Free radicals, antioxidants, and the immune system. *Ann Clin Lab Sci* 2000; **30:** 145 – 158.
124 Härtel C, Puzik A, Göpel W, *et al*: Immunomodulatory effect of vitamin C on intracytoplasmic cytokine production in neonatal cord blood cells. *Neonatology* 2007; **91:** 54 – 60.
125 Härtel C, Strunk T, Bucsky P, *et al*: Effects of vitamin C on intracytoplasmic cytokine production in human whole blood monocytes and lymphocytes. *Cytokine* 2004; **27:** 101 – 106.
126 Johnston CS, Retrum KR, Srilakshmi JC: Antihistamine effects and complications of supplemental vitamin C. *J Am Diet Assoc* 1992; **92:** 988 – 989.
127 Johnston CS, Martin LJ, Cai X: Antihistamine effect of supplemental ascorbic acid and neutrophil chemotaxis. *J Am Coll Nutr* 1992; **11:** 172 – 176.
128 Flodin NW (ed): Vitamin C. In: *Pharmacology of Micronutrients*. New York: Alan R Liss, 1988; pp 201 – 244.
129 Mortola E, Okuda M, Ohno K, *et al*: Inhibition of apoptosis and virus replication in feline immunodeficiency virus-infected cells by N-acetylcysteine and ascorbic acid. *J Vet Med Sci* 1998; **60:** 1187 – 1193.
130 Bucca C, Rolla G, Farina JC: Effect of vitamin C on transient increase of bronchial responsiveness in conditions affecting the airways. *Ann NY Acad Sci* 1992; **669:** 175 – 186.

131 Jariwalla RJ, Harakeh S: Antiviral and immunomodulatory activities of ascorbic acid. In: *Subcellular Biochemistry Ascorbic Acid: Biochemistry and Biomedical Cell Biology* (Harris JR, ed). New York: Plenum Press, 1996; pp 215 – 231.
132 Anderson R, Smit MJ, Joone GK, *et al*: Vitamin C and cellular immune functions. Protection against hypochlorous acid-mediated inactivation of glyceraldehyde-3-phosphate dehydrogenase and ATP generation in human leukocytes as a possible mechanism of ascorbate-mediated immunostimulation. *Ann NY Acad Sci* 1990; **587:** 34 – 48.
133 Panush RS, Delafuente JC, Katz P, *et al*: Modulation of certain immunologic responses by vitamin C. III. Potentiation of *in vitro* and *in vivo* lymphocyte responses. *Int J Vitam Nutr Res Suppl* 1982; **23:** 35 – 47.
134 Prasad AS: Zinc in human health: effect of zinc on immune cells. *Mol Med* 2008; **14:** 353 – 357.
135 Rink L, Haase H: Zinc homeostasis and immunity. *Trends Immunol* 2007; **28:** 1 – 4.
136 Mocchegiani E: Zinc and ageing: third Zincage conference. *Immun Ageing* 2007; **4:** 5.
137 Haase H, Rink L: Signal transduction in monocytes: the role of zinc ions. *Biometals* 2007; **20:** 579 – 585.
138 Overbeck S, Rink L, Haase H: Modulating the immune response by oral zinc supplementation: a single approach for multiple diseases. *Arch Immunol Ther Exp (Warsz)* 2008; **56:** 15 – 30.
139 Tapiero H, Tew KD: Trace elements in human physiology and pathology: zinc and metallothioneins. *Biomed Pharmacother* 2003; **57:** 399 – 411.
140 Prasad AS: Effects of zinc deficiency on immune functions. *J Trace Elem Exp Med* 2000; **13:** 1 – 20.
141 Keen CL, Gershwin ME: Zinc deficiency and immune function. *Annu Rev Nutr* 1990; **10:** 415 – 431.
142 Ravaglia G, Forti P, Maioli F, *et al*: Effect of micronutrient status on natural killer cell immune function in healthy free-living subjects aged ≥ 90 y. *Am J Clin Nutr* 2000; **71:** 590 – 598.
143 Allen JI, Perri RT, McClain CJ, *et al*: Alterations in human natural killer cell activity and monocyte cytotoxicity induced by zinc deficiency. *J Lab Clin Med* 1983; **102:** 577 – 589.
144 Wellinghausen N, Kirchner H, Rink L: The immunobiology of zinc. *Immunol Today* 1997; **18:** 519 – 521.
145 Fraker PJ, Haas SM, Luecke RW: Effect of zinc deficiency on the immune response of the young adult A/J mouse. *J Nutr* 1977; **107:** 1889 – 1895.
146 Fraker PJ, DePasquale-Jardieu P, Zwickl CM, *et al*: Regeneration of T-cell helper function in zinc-deficient adult mice. *Proc Natl Acad Sci USA* 1978; **75:** 5660 – 5664.
147 Dardenne M, Pléau JM, Nabarra B, *et al*: Contribution of zinc and other metals to the biological activity of the serum thymic factor. *Proc Natl Acad Sci USA* 1982; **79:** 5370 – 5373.
148 Bach JF, Dardenne M: Thymulin, a zinc-dependent hormone. *Med Oncol Tumor Pharmacother* 1989; **6:** 25 – 29.
149 Prasad AS: Effects of zinc deficiency on Th1 and Th2 cytokine shifts. *J Infect Dis* 2000; **182(suppl 1):** S62 – S68.
150 Beck FW, Prasad AS, Kaplan J, *et al*: Changes in cytokine production and T cell subpopulations in experimentally induced zinc-deficient humans. *Am J Physiol* 1997; **272:** E1002 – E1007.
151 Yamasaki S, Sakata-Sogawa K, Hasegawa A, *et al*: Zinc is a novel intracellular second messenger. *J Cell Biol* 2007; **177:** 637 – 645.
152 Maggini S, Wintergerst ES, Beveridge S, *et al*: Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses. *Br J Nutr* 2007; **98(suppl 1):** S29 – S35.
153 Beveridge S, Wintergerst ES, Maggini S, *et al*: Immune-enhancing role of vitamin C and zinc and effect on clinical conditions. *Proc Nutr Soc* 2008; **67:** E83.
154 Maggini S, Wintergerst ES, Beveridge S, *et al*: Contribution of selected vitamins and trace elements to immune function. *Proc Nutr Soc* 2008; **67:** E84.
155 Shankar AH, Prasad AS: Zinc and immune function: the biological basis of altered resistance to infection. *Am J Clin Nutr* 1998; **68(2 suppl):** 447S – 463S.
156 Huse M, Eck MJ, Harrison SC: A Zn^{2+} ion links the cytoplasmic tail of CD4 and the N-terminal region of Lck. *J Biol Chem* 1998; **273:** 18729 – 18733.
157 Lin RS, Rodriguez C, Veillette A, *et al*: Zinc is essential for binding of $p56^{lck}$ to CD4 and CD8 . *J Biol Chem* 1998; **273:** 32878 – 32882.
158 Ibs KH, Rink L: Zinc-altered immune function. *J Nutr* 2003; **133(5 suppl 1):** 1452S – 1456S.
159 Ibs KH, Rink L: Zinc. In: *Diet and Human Immune Function* (Hughes DA, Darlington LG, Bendich A, eds). Totowa, NJ: Humana Press, 2004; pp 241 – 259.
160 Fraker PJ, King LE: Reprogramming of the immune system during zinc deficiency. *Annu Rev Nutr* 2004; **24:** 277 – 298.
161 Fischer Walker C, Black RE: Zinc and the risk for infectious disease. *Annu Rev Nutr* 2004; **24:** 255 – 275.
162 Fendrick AM, Monto AS, Nightengale B, *et al*: The economic burden of non-influenza-related viral respiratory tract infection in the United States. *Arch Intern Med* 2003; **163:** 487

– 494.
163 Fuchs SC, Fischer GB, Black RE, *et al*: The burden of pneumonia in children in Latin America. *Paediatr Respir Rev* 2005; **6:** 83 – 87.
164 Romieu I, Mannino DM, Redd SC, *et al*: Dietary intake, physical activity, body mass index, and childhood asthma in the Third National Health And Nutrition Survey (NHANES III). *Pediatr Pulmonol* 2004; **38:** 31 – 42.
165 Hume R, Weyers E: Changes in leucocyte ascorbic acid during the common cold. *Scott Med J* 1973; **18:** 3 – 7.
166 Ritzel G: Critical evaluation of vitamin C as a prophylactic and therapeutic agent in colds. *Helv Med Acta* 1961; **28:** 63 – 68 [in German].
167 Ludvigsson J, Hansson LO, Tibbling G: Vitamin C as a preventive medicine against common colds in children. *Scand J Infect Dis* 1977; **9:** 91 – 98.
168 Bancalari A, Seguel C, Neira F, *et al*: Prophylactic value of vitamin C in acute respiratory tract infections in schoolchildren. *Rev Med Chil* 1984; **112:** 871 – 876 [in Spanish].
169 Cohen HA, Neuman I, Nahum H: Blocking effect of vitamin C in exercise-induced asthma. *Arch Pediatr Adolesc Med* 1997; **151:** 367 – 370.
170 Hatch GE: Asthma, inhaled oxidants, and dietary antioxidants. *Am J Clin Nutr* 1995; **61(3 suppl):** 625S – 630S.
171 Schwartz J, Weiss ST: Relationship between dietary vitamin C intake and pulmonary function in the First National Health and Nutrition Examination Survey (NHANES I). *Am J Clin Nutr* 1994; **59:** 110 – 114.
172 Aderele WI, Ette SI, Oduwole O, *et al*: Plasma vitamin C (ascorbic acid) levels in asthmatic children. *Afr J Med Med Sci* 1985; **14:** 115 – 120.
173 Ram FS, Rowe BH, Kaur B: Vitamin C supplementation for asthma. *Cochrane Database Syst Rev* 2004: CD000993.
174 Biltagi MA, Baset AA, Bassiouny M, *et al*: Omega-3 fatty acids, vitamin C and Zn supplementation in asthmatic children: a randomized self-controlled study. *Acta Paediatr* 2009; **98:** 737 – 742.
175 Allen S, Britton JR, Leonardi-Bee JA: Association between antioxidant vitamins and asthma outcome measures: systematic review and meta-analysis. *Thorax* 2009; **64:** 610 – 619.
176 Preston AM, Rodriguez C, Rivera CE, *et al*: Influence of environmental tobacco smoke on vitamin C status in children. *Am J Clin Nutr* 2003; **77:** 167 – 172.
177 Valkonen M, Kuusi T: Passive smoking induces atherogenic changes in low-density lipoprotein. *Circulation* 1998; **97:** 2012 – 2016.
178 Health effects of outdoor air pollution. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. *Am J Respir Crit Care Med* 1996; **153:** 3 – 50.
179 Romieu I, Sienra-Monge JJ, Ramírez-Aguilar M, *et al*: Antioxidant supplementation and lung functions among children with asthma exposed to high levels of air pollutants. *Am J Respir Crit Care Med* 2002; **166:** 703 – 709.
180 Prasad AS: Zinc: mechanisms of host defense. *J Nutr* 2007; **137:** 1345 – 1349.
181 Larson CP, Roy SK, Khan AI, *et al*: Zinc treatment to under-five children: applications to improve child survival and reduce burden of disease. *J Health Popul Nutr* 2008; **26:** 356 – 365.
182 Bhutta ZA, Black RE, Brown KH, *et al*: Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. Zinc Investigators' Collaborative Group. *J Pediatr* 1999; **135:** 689 – 697.
183 Bhandari N, Bahl R, Taneja S, *et al*: Effect of routine zinc supplementation on pneumonia in children aged 6 months to 3 years: randomised controlled trial in an urban slum. *BMJ* 2002; **324:** 1358.
184 Brooks WA, Yunus M, Santosham M, *et al*: Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial. *Lancet* 2004; **363:** 1683 – 1688.
185 Black RE: Zinc deficiency, infectious disease and mortality in the developing world. *J Nutr* 2003; **133(5 suppl 1):** 1485S – 1489S.
186 Brown KH, Baker SK, IZiNCG Steering Committee: Galvanizing action: conclusions and next steps for mainstreaming zinc interventions in public health programs. *Food Nutr Bull* 2009; **30(1 suppl):** S179 – S184.
187 Haider BA, Bhutta ZA: The effect of therapeutic zinc supplementation among young children with selected infections: a review of the evidence. *Food Nutr Bull* 2009; **30(1 suppl):** S41 – S59.
188 Brown KH, Peerson JM, Baker SK, *et al*: Preventive zinc supplementation among infants, preschoolers, and older prepubertal children. *Food Nutr Bull* 2009; **30(1 suppl):** S12 – S40.
189 Brown LM: *Helicobacter pylori*: epidemiology and routes of transmission. *Epidemiol Rev* 2000; **22:** 283 – 297.
190 Pounder RE, Ng D: The prevalence of *Helicobacter pylori* infection in different countries. *Aliment Pharmacol Ther* 1995; **9(suppl 2):** 33 – 39.
191 Salgueiro J, Zubillaga M, Goldman C, *et al*: Review article: is there a link between micronutrient malnutrition and *Helicobacter pylori* infection? *Aliment Pharmacol Ther* 2004; **20:** 1029 – 1034.
192 Akyön Y: Effect of antioxidants on the

immune response of *Helicobacter pylori*. *Clin Microbiol Infect* 2002; **8:** 438 – 441.
193 Kim DS, Lee MS, Kim YS*, et al*: Effect modification by vitamin C on the relation between gastric cancer and *Helicobacter pylori*. *Eur J Epidemiol* 2005; **20:** 67 – 71.
194 Hahm KB, Lee KJ, Kim JH*, et al*: *Helicobacter pylori* infection, oxidative DNA damage, gastric carcinogenesis, and reversibility by rebamipide. *Dig Dis Sci* 1998; **43(9 suppl):** 72S – 77S.
195 Blanchard TG, Czinn SJ: Review article: Immunological determinants that may affect the *Helicobacter pylori* cancer risk. *Aliment Pharmacol Ther* 1998; **12(suppl 1):** 83 – 90.
196 Lindholm C, Quiding-Järbrink M, Lönroth H*, et al*: Local cytokine response in *Helicobacter pylori*-infected subjects. *Infect Immun* 1998; **66:** 5964 – 5971.
197 Woodward M, Tunstall-Pedoe H, McColl K: *Helicobacter pylori* infection reduces systemic availability of dietary vitamin C. *Eur J Gastroenterol Hepatol* 2001; **13:** 233 – 237.
198 Annibale B, Capurso G, Delle Fave G: Consequences of *Helicobacter pylori* infection on the absorption of micronutrients. *Dig Liver Dis* 2002; **34(suppl 2):** S72 – S77.
199 Wang X, Willén R, Wadström T: Astaxanthin-rich algal meal and vitamin C inhibit *Helicobacter pylori i*nfection in BALB/cA mice. *Antimicrob Agents Chemother* 2000; **44:** 2452 – 2457.
200 Chatterjee A, Bagchi D, Yasmin T*, et al*: Antimicrobial effects of antioxidants with and without clarithromycin on *Helicobacter pylori*. *Mol Cell Biochem* 2005; **270:** 125 – 130.
201 Park JH, Kim SY, Kim DW*, et al*: Correlation between *Helicobacter pylori* infection and vitamin C levels in whole blood, plasma, and gastric juice, and the pH of gastric juice in Korean children. *J Pediatr Gastroenterol Nutr* 2003; **37:** 53 – 62.
202 Sasazuki S, Sasaki S, Tsubono Y*, et al*: The effect of 5-year vitamin C supplementation on serum pepsinogen level and *Helicobacter pylori* infection. *Cancer Sci* 2003; **94:** 378 – 382.
203 Goodman KJ, Correa P, Tenganá Aux HJ*, et al*: Nutritional factors and *Helicobacter pylori* infection in Colombian children. *J Pediatr Gastroenterol Nutr* 1997; **25:** 507 – 515.
204 Kikuchi S: Epidemiology of *Helicobacter pylori* and gastric cancer. *Gastric Cancer* 2002; **5:** 6 – 15.
205 Zhang ZW, Farthing MJ: The roles of vitamin C in *Helicobacter pylori* associated gastric carcinogenesis. *Chin J Dig Dis* 2005; **6:** 53 – 58.
206 Jarosz M, Rychlik E, Siuba M*, et al*: Dietary and socio-economic factors in relation to *Helicobacter pylori* re-infection. *World J Gastroenterol* 2009; **15:** 1119 – 1125.
207 Boschi-Pinto C, Velebit L, Shibuya K: Estimating child mortality due to diarrhoea in developing countries. *Bull World Health Organ* 2008; **86:** 710 – 717.
208 Bryce J, Boschi-Pinto C, Shibuya K*, et al*: WHO estimates of the causes of death in children. *Lancet* 2005; **365:** 1147 – 1152.
209 Kosek M, Bern C, Guerrant RL: The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. *Bull World Health Organ* 2003; **81:** 197 – 204.
210 Brown KH: Diarrhea and malnutrition. *J Nutr* 2003; **133:** 328S – 332S.
211 Lazzerini M, Ronfani L: Oral zinc for treating diarrhoea in children. *Cochrane Database Syst Rev* 2008: CD005436.
212 Jones G, Steketee RW, Black RE*, et al*: How many child deaths can we prevent this year? *Lancet* 2003; **362:** 65 – 71.
213 Bhutta ZA, Bird SM, Black RE*, et al*: Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. *Am J Clin Nutr* 2000; **72:** 1516 – 1522.
214 Brooks WA, Santosham M, Naheed A*, et al*: Effect of weekly zinc supplements on incidence of pneumonia and diarrhoea in children younger than 2 years in an urban, low-income population in Bangladesh: randomised controlled trial. *Lancet* 2005; **366:** 999 – 1004.
215 Rahman MM, Vermund SH, Wahed MA*, et al*: Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomised double blind controlled trial. *BMJ* 2001; **323:** 314 – 318.
216 Baqui AH, Zaman K, Persson LA*, et al*: Simultaneous weekly supplementation of iron and zinc is associated with lower morbidity due to diarrhea and acute lower respiratory infection in Bangladeshi infants. *J Nutr* 2003; **133:** 4150 – 4157.
217 Bahl R, Bhandari N, Saksena M*, et al*: Efficacy of zinc-fortified oral rehydration solution in 6- to 35-month-old children with acute diarrhea. *J Pediatr* 2002; **141:** 677 – 682.
218 Gupta DN, Mondal SK, Ghosh S*, et al*: Impact of zinc supplementation on diarrhoeal morbidity in rural children of West Bengal, India. *Acta Paediatr* 2003; **92:** 531 – 536.
219 Bhatnagar S, Bahl R, Sharma PK*, et al*: Zinc with oral rehydration therapy reduces stool output and duration of diarrhea in hospitalized children: a randomized controlled trial. *J Pediatr Gastroenterol Nutr* 2004; **38:** 34 – 40.
220 Al-Sonboli N, Gurgel RQ, Shenkin A*, et al*: Zinc supplementation in Brazilian children with acute diarrhoea. *Ann Trop Paediatr* 2003; **23:** 3 – 8.
221 World Health Organization (WHO)/United Nations Children's Fund (UNICEF):

WHO/UNICEF Joint Statement. Clinical Management of Acute Diarrhoea (WHO/FCH/CAH/04.7 or UNICEF/PD/Diarrhoea/01). Geneva: WHO/New York: UNICEF, 2004 (available at: http://rehydrate.org/diarrhoea/pdf/acute-diarrhoea.pdf).
222 Ghishan FK: Transport of electrolytes, water, and glucose in zinc deficiency. *J Pediatr Gastroenterol Nutr* 1984; **3:** 608 – 612.
223 Patrick J, Golden BE, Golden MH: Leucocyte sodium transport and dietary zinc in protein energy malnutrition. *Am J Clin Nutr* 1980; **33:** 617 – 620.
224 Patrick J, Michael J, Golden MN*, et al*: Effect of zinc on leucocyte sodium transport *in vitro*. *Clin Sci Mol Med* 1978; **54:** 585 – 587.
225 Bettger WJ, O'Dell BL: A critical physiological role of zinc in the structure and function of biomembranes. *Life Sci* 1981; **28:** 1425 – 1438.
226 Elmes ME, Jones JG: Ultrastructural changes in the small intestine of zinc deficient rats. *J Pathol* 1980; **130:** 37 – 43.
227 Moran JR, Lewis JC: The effects of severe zinc deficiency on intestinal permeability: an ultrastructural study. *Pediatr Res* 1985; **19:** 968 – 973.
228 Roy SK, Behrens RH, Haider R*, et al*: Impact of zinc supplementation on intestinal permeability in Bangladeshi children with acute diarrhoea and persistent diarrhoea syndrome. *J Pediatr Gastroenterol Nutr* 1992; **15:** 289 – 296.
229 Gebhard RL, Karouani R, Prigge WF*, et al*: The effect of severe zinc deficiency on activity of intestinal disaccharidases and 3-hydroxy-3-methylglutaryl coenzyme A reductase in the rat. *J Nutr* 1983; **113:** 855 – 859.
230 Jones PE, Peters TJ: Oral zinc supplements in non-responsive coeliac syndrome: effect on jejunal morphology, enterocyte production, and brush border disaccharidase activities. *Gut* 1981; **22:** 194 – 198.
231 Luecke RW, Fraker PJ: The effect of varying dietary zinc levels on growth and antibody-mediated response in two strains of mice. *J Nutr* 1979; **109:** 1373 – 1376.
232 Fraker PJ: Zinc deficiency: a common immunodeficiency state. *Surv Immunol Res* 1983; **2:** 155 – 163.
233 Sazawal S, Jalla S, Mazumder S*, et al*: Effect of zinc supplementation on cell-mediated immunity and lymphocyte subsets in preschool children. *Indian Pediatr* 1997; **34:** 589 – 597.
234 Fischer Walker CL, Fontaine O, Young MW*, et al*: Zinc and low osmolarity oral rehydration salts for diarrhoea: a renewed call to action. *Bull World Health Organ* 2009; **87:** 780 – 786.
235 Bates CJ, Evans PH, Dardenne M*, et al*: A trial of zinc supplementation in young rural Gambian children. *Br J Nutr* 1993; **69:** 243 – 255.
236 Gibson RS, Huddle JM: Suboptimal zinc status in pregnant Malawian women: its association with low intakes of poorly available zinc, frequent reproductive cycling, and malaria. *Am J Clin Nutr* 1998; **67:** 702 – 709.
237 Zinc Against Plasmodium Study Group: Effect of zinc on the treatment of *Plasmodium falciparum* malaria in children: a randomized controlled trial. *Am J Clin Nutr* 2002; **76:** 805 – 812.
238 Baker EM, Hodges RE, Hood J*, et al*: Metabolism of ^{14}C- and ^{3}H-labeled L-ascorbic acid in human scurvy. *Am J Clin Nutr* 1971; **24:** 444 – 454.
239 Levine M, Katz A, Padayatty SJ: Vitamin C. In: *Modern Nutrition in Health and Disease,* 10th edn (Shils ME, Shike M, Ross AC*, et al*, eds). Baltimore: Lippincott Williams & Wilkins, 2006; pp 507 – 524.
240 Jacob RA: Vitamin C. In: *Modern Nutrition in Health and Disease,* 9th edn (Shils ME, Olsen JA, Shike M*, et al*, eds). Philadelphia: Lippincott Williams & Wilkins, 1999; pp 467 – 483.
241 Schorah CJ: Vitamin C status in population groups. In: *Vitamin C (Ascorbic Acid)* (Counsell JN, Hornig DH, eds). London: Applied Science, 1981; pp 23 – 47.
242 Tribble DL, Giuliano LJ, Fortmann SP: Reduced plasma ascorbic acid concentrations in nonsmokers regularly exposed to environmental tobacco smoke. *Am J Clin Nutr* 1993; **58:** 886 – 890.
243 Dietrich M, Block G, Benowitz NL*, et al*: Vitamin C supplementation decreases oxidative stress biomarker F_2-isoprostanes in plasma of nonsmokers exposed to environmental tobacco smoke. *Nutr Cancer* 2003; **45:** 176 – 184.
244 Villalpando S, Montalvo-Velarde I, Zambrano N*, et al*: Vitamins A, and C and folate status in Mexican children under 12 years and women 12 – 49 years: a probabilistic national survey. *Salud Publica Mex* 2003; **45(suppl 4):** S508 – S519.
245 Rivera JA, Sepúlveda Amor J: Conclusions from the Mexican National Nutrition Survey 1999: translating results into nutrition policy. *Salud Publica Mex* 2003; **45(suppl 4):** S565 – S575.
246 Dewey KG: Nutrition survey in Tabasco, Mexico: nutritional status of preschool children. *Am J Clin Nutr* 1983; **37:** 1010 – 1019.
247 Encuesta Nacional de Nutrición y Salud: *Documento de Resultados*. Buenos Aries: Ministerio de Salud de la Nacion, 2006 (available at: http://www.msal.gov.ar/htm/site/ennys/) [in Spanish].
248 Perlas LA, Gibson RS, Adair LS: Macronutrient and selected vitamin intakes from complementary foods of infants and toddlers from Cebu, Philippines. *Int J Food Sci Nutr*

2004; **55:** 1 – 15.
249 Gibson RS, Manger MS, Krittaphol W, *et al*: Does zinc deficiency play a role in stunting among primary school children in NE Thailand? *Br J Nutr* 2007; **97:** 167 – 175.
250 Leung SS, Chan SM, Lui S, *et al*: Growth and nutrition of Hong Kong children aged 0 – 7 years. *J Paediatr Child Health* 2000; **36:** 56 – 65.
251 Instituto Brasileiro de Geografia e Estatística (IBGE): Pesquisa de Orçamentos Familiares 2002 – 2003. Análise da Disponibilidade Domiciliar de Alimentos e do Estado Nutricional no Brasil. In: *IBGE, Coordenação de Índices de Preços*. Rio de Janeiro: IBGE, 2004 [in Portuguese].
252 King JC, Cousins RJ: Zinc. In: *Modern Nutrition in Health and Disease,* 10th edn (Shils ME, Shike M, Ross AC, *et al*, eds). Baltimore: Lippincott Williams & Wilkins, 2006; pp 271 – 285.
253 Hotz C, Peerson JM, Brown KH: Suggested lower cutoffs of serum zinc concentrations for assessing zinc status: reanalysis of the second National Health and Nutrition Examination Survey data (1976 – 1980). *Am J Clin Nutr* 2003; **78:** 756 – 764.
254 Maret W, Sandstead HH: Zinc requirements and the risks and benefits of zinc supplementation. *J Trace Elem Med Biol* 2006; **20:** 3 – 18.
255 Gibson RS, Hess SY, Hotz C, *et al*: Indicators of zinc status at the population level: a review of the evidence. *Br J Nutr* 2008; **99(suppl 3):** S14 – S23.
256 Prasad AS: Discovery of human zinc deficiency: impact on human health. *Nutrition* 2001; **17:** 685 – 687.
257 Hambidge M: Human zinc deficiency. *J Nutr* 2000; **130(5S suppl):** 1344S – 1349S.
258 Aggett PJ, Comerford JG: Zinc and human health. *Nutr Rev* 1995; **53:** S16 – S22.
259 Bahl R, Bhandari N, Hambidge KM, *et al*: Plasma zinc as a predictor of diarrheal and respiratory morbidity in children in an urban slum setting. *Am J Clin Nutr* 1998; **68(2 suppl):** 414S – 417S.
260 Bhandari N, Bahl R, Hambidge KM, *et al*: Increased diarrhoeal and respiratory morbidity in association with zinc deficiency a preliminary report. *Acta Paediatr* 1996; **85:** 148 – 150.
261 Wagstaff A, Bustreo F, Bryce J, *et al*: Child health: reaching the poor. *Am J Public Health* 2004; **94:** 726 – 736.
262 Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO): Zinc: In *Human Vitamin and Mineral Requirements. Report of a Joint FAO/WHO Expert Consultation*. Rome: FAO/Geneva: WHO, 2002, pp 257 – 270.
263 Tee ES, Florentino R: *Recommended Dietary Allowances (RDA) Harmonization in Southeast Asia*. Monograph Series. Singapore: International Life Sciences Institute, Southeast Asia Region, 2005.
264 Sandstead HH, Prasad AS, Penland JG, *et al*: Zinc deficiency in Mexican American children: influence of zinc and other micronutrients on T cells, cytokines, and antiinflammatory plasma proteins. *Am J Clin Nutr* 2008; **88:** 1067 – 1073.
265 Duque X, Flores-Hernández S, Flores-Huerta S, *et al*: Prevalence of anemia and deficiency of iron, folic acid, and zinc in children younger than 2 years of age who use the health services provided by the Mexican Social Security Institute. *BMC Public Health* 2007; **7:** 345.
266 da Costa GA, do Nascimento Marreiro D, Eulálio JM, *et al*: Erythrocytary zinc and the infant growth profile in northeast Brazil. *Biol Trace Elem Res* 2008; **126(suppl 1):** S15 – S20.
267 Martins Ferreira Fidelis C, Osório MM: Dietary intake of macro and micronutrients by children under five years of age in the State of Pernambuco, Brazil. *Rev Bras Saúde Matern Infant* 2007; **7:** 63 – 74.
268 Ge KY, Chang SY: Dietary intake of some essential micronutrients in China. *Biomed Environ Sci* 2001; **14:** 318 – 324.
269 Ma G, Li Y, Jin Y, *et al*: Phytate intake and molar ratios of phytate to zinc, iron and calcium in the diets of people in China. *Eur J Clin Nutr* 2007; **61:** 368 – 374.
270 Qin Y, Melse-Boonstra A, Zhao J, *et al*: Stunting and zinc deficiency among primary school children in rural areas with low soil zinc concentrations in Jiangsu Province, China. *Asia Pac J Clin Nutr* 2009; **18:** 15 – 21.
271 Chen XC, Yin TA, He JS, *et al*: Low levels of zinc in hair and blood, pica, anorexia, and poor growth in Chinese preschool children. *Am J Clin Nutr* 1985; **42:** 694 – 700.
272 Sheng XY, Hambidge KM, Zhu XX, *et al*: Major variables of zinc homeostasis in Chinese toddlers. *Am J Clin Nutr* 2006; **84:** 389 – 394.
273 Zhao XH: Nutritional situation of Beijing residents. *Southeast Asian J Trop Med Public Health* 1992; **23(suppl 3):** 65 – 68.
274 Dijkhuizen MA, Wieringa FT, West CE, *et al*: Concurrent micronutrient deficiencies in lactating mothers and their infants in Indonesia. *Am J Clin Nutr* 2001; **73:** 786 – 791.
275 Dijkhuizen MA, Wieringa FT, West CE, *et al*: Micronutrient deficiency and supplementation in Indonesian infants. Interactions between micronutrients. *Adv Exp Med Biol* 2003; **531:** 359 – 368.
276 Thu BD, Schultink W, Dillon D, *et al*: Effect of daily and weekly micronutrient supplementation on micronutrient deficiencies and growth in young Vietnamese children. *Am J Clin Nutr* 1999; **69:** 80 – 86.
277 Van Nhien N, Khan NC, Ninh NX, *et al*:

Micronutrient deficiencies and anemia among preschool children in rural Vietnam. *Asia Pac J Clin Nutr* 2008; **17:** 48 – 55.
278 Krittaphol W, Bailey KB, Pongcharoen T, *et al*: Low zinc, iron, and calcium intakes of Northeast Thai school children consuming glutinous rice-based diets are not exacerbated by high phytate. *Int J Food Sci Nutr* 2006; **57:** 520 – 528.
279 Thurlow RA, Winichagoon P, Pongcharoen T, *et al*: Risk of zinc, iodine and other micronutrient deficiencies among school children in North East Thailand. *Eur J Clin Nutr* 2006; **60:** 623 – 632.

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