Introduction

Infectious diseases (respiratory and diarrheal) are among the leading causes of death in children around the world. The immune system in children is not developed and is different from that of adults. Infants and young children under 2 years old are not capable of initiating a second humoral immune response as fast as adults due to the dysfunction of memory cells. In addition, similar to elderly and unlike young adults, neonates have notably lower T helper 1 (Th1) cell development and Th1 responses. These may be related to increased susceptibility to infection in children. The immune system plays a pivotal role in host defense against infectious agents. Membrane phospholipids of cells of the immune system have a high content of polyunsaturated fatty acids and are prime targets for free radical reactions. Release of reactive oxygen species by phagocytes upon encountering pathogens and rapid lymphocyte proliferation following antigenic stimulation expose the immune cells to high levels of oxidative stress. Vitamin E and selenium (Se) act synergistically in tissues to reduce free radical-induced damage to lipid membranes. In animal models and in humans, Se and vitamin E deficiencies have been shown to impair the immune response and decrease host resistance to infectious diseases. Furthermore, supplementation with higher than recommended levels of these nutrients in some, but not all, cases has been associated with improved immune response and resistance to certain bacterial and viral infections. Several comprehensive reviews have been written on the role of Se and vitamin E in the regulation of immune response and infectious
diseases. This review, therefore, is not intended to be comprehensive, rather it is a brief summary of past work, with emphasis on recent findings.

Vitamin E and Se Status in Children

Vitamin E

An adequate intake (AI) is used as the recommended intake level for infants. The AI is determined using the mean vitamin E intake of infants fed principally with human milk. The vitamin E concentrations determined by high-performance liquid chromatography in human milk vary from 2.3 [1] to 8 mg/l [2]. In general the vitamin E content of colostrum is high (average 6.8–23 mg/l), but the concentration decreases in transitional milk and in mature milk. The AI for infants 0–6 months is 4 and for those 7–12 months is 5 mg/day of RRR-\(\alpha\)-tocopherol. No upper limits of vitamin E intake have been determined for infants 0–12 months, as the only source of intake for infants should be from food and formula to prevent high levels of intake.

Premature infants are under severe oxidative stress as they are faced with an abrupt change to a relatively hyperoxic extraterrestrial environment and lower levels of antioxidant defenses. Premature infants are prone to vitamin E deficiency. Placental transfer of vitamin E is low in these babies and their tissue stores at birth are limited. Preterm infants have significantly lower vitamin E levels in cord blood compared to term infants [3]. In another study, while the median vitamin E levels in preterm infants were not different from that of term babies, a higher percentage of preterm infants exhibited vitamin E deficiency [4]. Vobecky et al. [5] determined serum vitamin E levels in 325 infants who were bottle- or breast-fed. The proportion of bottle-fed infants who had serum vitamin E levels of <0.35 mg/dl was 2 times higher than that of breast-fed infants. Low vitamin E status has been reported in malnourished children [6] and in those with cystic fibrosis [7].

In current clinical practice, premature infants usually receive vitamin E in a multivitamin preparation that is added to parenteral formula at a level of 2–3 IU/kg body weight [8]. Most of the vitamin E supplementation studies on premature infants focus on the outcomes related to retinopathy, bronchopulmonary dysplasia, necrotizing enterocolitis, and sepsis. The effect of vitamin E on the immune function of premature infants is not well documented. The use of vitamin E in premature infants has yielded conflicting results. The use of pharmacologic levels of \(\alpha\)-tocopherol combined with cryotherapy was found to be more effective than cryotherapy alone in decreasing the severity of threshold retinopathy of prematurity in infants weighing <1,250 g [9]. While Fish et al. [10] reported that necrotizing enterocolitis and sepsis did not occur more frequently in the neonates treated with intramuscular injections of vitamin E, Johnson et al. [11] reported increased incidence of necrotizing enterocolitis and neonatal sepsis associated with vitamin E treatment (oral, intravenous, or
intramuscular application). Necrotizing enterocolitis is a condition which results in widespread intestinal necrosis and frequently leads to perforation of the bowel and peritonitis. The difference in outcomes of the studies by Fish et al. [10] and Johnson et al. [11] might be due to the difference in target serum vitamin E levels. These were 0.5–3.5 mg/dl in the study by Fish et al. [10] and 5.0 mg/dl in the study by Johnson et al. [11]. In fact, about 43% of infants supplemented with vitamin E had serum vitamin E levels of >5.0 mg/dl in the study by Johnson et al. [11]. Sobel et al. [12] reported an increased incidence of necrotizing enterocolitis associated with serum levels of vitamin E of >3.5 mg/dl. Finer et al. [13] reported an increased incidence of necrotizing enterocolitis in association with a 200-mg oral dose of vitamin E, which may be due to the hyperosmolarity of the preparation.

**Selenium**

As for vitamin E, the AI for Se is set for infants based on the observed mean intake of infants fed principally with human milk. The Se content of human milk is highest in colostrum (34–80 μg/l) [14], but decreases in transitional milk and mature milk [14]. The level of Se in breast milk varies depending on the region of the world and food supply content of Se. A significant correlation between selenium in human milk and maternal selenium intake has been reported [15]. Similarly the Se content of infant formulas varies depending on the protein source used [16]. The reported average Se concentration of human milk from mothers in Canada and the United States was 15–20 μg/l [17] and that of commercial formulas was 5.1–9.2 μg/l [18]. The AI, based on an average milk intake of 0.78 liters/day for infants 0–6 months old, is set at 15 μg/day. The AI for infants 7–12 months of age, extrapolated from that of infants 0–6 months old or by considering the Se intake from formula and table foods, is 20 μg/day. The upper limits for infants 2–6 and 7–12 months old are 45 and 60 μg/day, respectively.

Low plasma Se levels are common during early infancy. The plasma Se levels of infants fed formula without Se supplementation are less than in infants fed human milk. Plasma Se levels at birth are reported to be around 50 μg/l [16]. During the first few months infants fed human milk maintain the plasma Se levels at birth, whereas infants fed formula have decreased plasma Se levels compared to those at birth [19]. However, the plasma Se levels gradually increase during later infancy and early childhood to reach a plateau (100 μg/l) by around 20 years of age [16]. Low selenium status has been reported in premature infants, infants with protein energy malnutrition, those receiving parenteral nutrition without Se supplementation, infants suffering from diseases such as neural tube defects [20] and phenylketonuria, or those living in areas with Se-deficient soil such as New Zealand and parts of China [16]. Preterm infants are at risk of Se depletion due to low hepatic stores and rapid growth. Infants with chronic lung disease might be at further risk. Daniels et al. [21] reported that healthy preterm infants had a lower plasma Se status.
than term infants. Furthermore they showed that preterm infants fed parenteral nutrition for several weeks developed very low plasma Se levels. In those receiving either breast milk or formulas in conjunction with parenteral nutrition, the plasma Se level declined over the first 6 weeks of life. While the plasma Se level increased by 50% in breast milk-fed term infants, there was no increase in the plasma Se level of formula-fed term babies. Tyrala et al. [22] showed that Se supplementation of preterm and term infant formulas with Se significantly improved their Se status, however, there was no difference in growth rate between the 2 groups. Kumpulainen et al. [19] reported that infant formulas had to be supplemented with Se to maintain the plasma Se level comparable to that of the breast-fed infants. Se supplementation of infants receiving parenteral nutrition prevents Se depletion in newborns, but cannot achieve Se levels equivalent to those of breast-fed term infants. The effect of Se supplementation on the immune response or other biologic functions was not determined.

**Vitamin E, Immune Response and Infectious Disease**

Both deficiency and supplementation of vitamin E has been shown to affect the immune response and resistance against infection. The influence of vitamin E on immune function has been reported in a variety of species including rodents, chickens, calves, and humans, and has been shown to affect different aspects of immune function including T-cell response, antibody production, natural killer (NK) cell activity, phagocytic activity, production of immunoregulatory molecules. Here, effects of vitamin E deficiency and supplementation on immune functions and their clinical significance will be discussed.

**Vitamin E and Immune Function**

Vitamin E deficiency has been shown to impair both humoral and cell-mediated immune functions in animals and humans.

The effect of vitamin E deficiency on humoral immune response in animals was demonstrated in experiments in which mice fed a diet deficient in vitamin E had lower plaque-forming cells and hemagglutination titer in response to sheep red blood cell injection than mice fed a diet adequate in vitamin E [23]. Depressed lymphocyte proliferation in response to T-cell mitogen concanavalin A (Con A) in rats fed vitamin E-deficient diet indicates that cell-mediated immune response is also impaired in vitamin E deficiency [24, 25]. Vitamin E deficiency has a significant impact on phagocytic functions. Harris et al. [26] reported that chemotactic and ingestive responses of polymorphonuclear leukocytes (PMNs) were impaired when rats were fed a vitamin E-deficient diet for 2 months. Warshauer et al. [27] also showed that vitamin E deficiency augmented the adverse effect of ozone-induced
impairments in pulmonary bactericidal capacity following prolonged exposure of rats to a low level of ozone. These effects of vitamin E deficiency might be due to increased free radical reactions, oxygen consumption and hydrogen peroxide release by phagocytosing PMNs from vitamin E-deficient animals [26].

In humans, a primary severe deficiency of vitamin E rarely occurs, while secondary deficiency is observed as a consequence of certain diseases such as primary biliary cirrhosis [28], cholestatic liver disease [29], cystic fibrosis [30], and intestinal malabsorption disorder [31]. Decreased plasma vitamin E levels were observed in patients with severe viral hepatitis and in HIV-1-infected children [32, 33]. In a case report by Kowdley et al. [31], in vivo and in vitro impairment of T-cell function, as well as polyneuropathy were observed in conjunction with vitamin E deficiency in a 59-year-old woman with progressive systemic sclerosis and malabsorption. Impaired mitogenic responses to Con A and phytohemagglutinin (PHA), interleukin (IL)-2 production, and delayed-type hypersensitivity (DTH) were improved following vitamin E supplementation.

Most premature low birth weight infants have a true deficiency of vitamin E at birth that requires early treatment. Vitamin E deficiency in preterm infants is associated with hemolytic anemia, bilirubinemia, intraventricular hemorrhage, and retinopathy of prematurity [8]. PMNs from neonates have impaired phagocytic ability, depressed oxidative metabolic responses, depressed bactericidal activity as well as a depressed ability to move toward defined chemotactic stimuli compared to normal adults [34]. In healthy 3-year-old children, lower serum vitamin E levels (<10th percentile) were associated with lower lymphocyte proliferation and serum IgM compared to those with higher vitamin E levels (>90th percentile) [35].

Vitamin E supplementation, when administered in quantities exceeding the established dietary requirements, has been shown to have immunostimulatory effects in a variety of species including humans. Vitamin E supplementation has been shown to affect both humoral and cell-mediated immune responses.

Dietary supplementation with vitamin E increased lymphocyte proliferation in response to T-cell and/or B-cell mitogens in mice [36], rats [25], and calves [37]. Meydani et al. [36] showed that dietary supplementation with 500 ppm vitamin E for 6 weeks increased lymphocyte proliferation and DTH response, and decreased prostaglandin (PG) E2 production in old mice. In addition, in vitro introduction of vitamin E increased the mitogenic response of splenic lymphocytes in mice [38]. In a co-culture study, Beharka et al. [39] showed that in vitro addition of vitamin E increased Con A-stimulated cell proliferation when macrophages from old mice were co-cultured with purified T cells from either old or young mice, or when macrophages from young mice were co-cultured with purified T cells from old mice. IL-2 production was also increased with vitamin E supplementation in co-cultures composed of macrophages from old mice and purified T cells from either old or young mice. The immunostimulatory effects of vitamin E supplementation seem to be transferred to the offspring. Chicks hatched from breeders fed diets
supplemented with vitamin E had significantly higher tetrahydrofuran-stimulated bursal lymphocyte proliferation and higher Con A and phorbol 12-myristate 13-acetate (PMA)-stimulated splenic lymphocyte proliferation compared to control chicks [40]. It is suggested that vitamin E’s immunostimulatory effect is mediated by either reducing PG synthesis [36] and/or decreasing free radical synthesis [38]. PGE2 has been shown to have a direct inhibitory effect on an early stage of T-cell activation, resulting in decreased IL-2 production, decreased IL-2 receptor expression, decreased responsiveness to exogenous IL-2, and decreased proliferation [41].

Vitamin E has been shown to increase antibody production by enhancing the humoral immune response or by acting as an adjuvant. Dietary vitamin E supplementation increased the number of plaque-forming cells and hemagglutination titers following immunization with sheep red blood cells and tetanus toxoid in mice [42]. Enhancement of the humoral immune response to Venezuelan equine encephalomyelitis-attenuated live-virus vaccine was observed in guinea pigs given intramuscular injections of vitamin E before and after immunization [43]. Oral supplementation of vitamin E, begun 2 weeks prior to and continued for 3 weeks after vaccination, did not have an effect on humoral response in this study. Vitamin E supplementation, 20 mg vitamin E/kg diet for 10 weeks, in lambs stimulated a secondary humoral immune response following parainfluenza-3 virus challenge [44]. The adjuvant effect of vitamin E was reported by Francini et al. [45]. Vitamin E, which partially replaced mineral oil in viral-inactivated emulsified vaccines, increased the hemagglutination inhibition titers to the viral antigen (Newcastle disease virus) in chicks.

Several studies have shown that vitamin E supplementation affects the immune response in humans. Baehner et al. [46] showed that administration of 1,600 mg/day of vitamin E for 1 week increased the rate of neutrophil phagocytic activity, but decreased bactericidal activity, which correlated with a reduced level of hydrogen peroxide (H₂O₂) release. Vitamin E supplementation has been shown to enhance the immune response in the elderly. In a double-blind, placebo-controlled study, Meydani et al. [47] showed that DTH scores, mitogenic response of peripheral blood mononuclear cells (PBMCs) to Con A, and IL-2 production were significantly higher in elderly subjects over 60 years of age supplemented with 800 mg/day vitamin E for 30 days. Decreased PGE₂ production by PBMCs and plasma lipid peroxide levels were also observed. In a more recent study, the effect of long-term vitamin E supplementation on in vivo indices of immune response in healthy elderly subjects was evaluated [48]. After 4 months of vitamin E supplementation at 60, 200, or 800 mg/day, DTH and antibody titer to hepatitis B were significantly increased in the groups supplemented with 200 and 800 mg/day. The largest increase was observed in the 200-mg/day group, which also showed a significant increase in antibody titer to tetanus vaccine. This long-term vitamin E supplementation did not adversely affect the elderly subjects [49]. Vitamin E supplementation had no significant effects on plasma concentrations of other...
nutrients, serum autoantibodies (anti-DNA and anti-thyroglobulin), liver enzyme function (glutathione peroxidase and superoxide dismutase), or on cytotoxic ability of neutrophils against *Candida albicans*.

Mino [50] investigated the effect of oral vitamin E supplementation on leukocyte function of premature infants. There was no effect of vitamin E supplementation on zymosan-induced superoxide anion formation by PMNs following the administration of 40 mg/kg of all-rac-tocopherol nicotinate for 8–14 days to premature infants. Chirico et al. [51] reported improved neutrophil function with intramuscular injection of 120 mg/kg vitamin E to healthy premature infants during the first 13 days after birth. An enhanced index and frequency of phagocytosis were observed at 5 days of age. Since clinical outcomes of vitamin E therapy in premature infants vary with dose, route of administration, and preparation of the vitamin E used, administration to premature infants should be done with caution, with dose and route of administration carefully examined.

**Vitamin E and Infection**

Beck et al. [52] showed that vitamin E deficiency can be detrimental to the mice infected with Coxsackievirus. Vitamin E deficiency in mice exacerbated the cardiac damage caused by a virulent, myocarditic strain of the Coxsackievirus and allowed the non-virulent, amyocarditic CVB3/0 to become myocarditic. Viral passage experiments demonstrated that the increased virulence of both viral strains was due to a phenotypic change in the viruses as a consequence of replication in a vitamin E-deficient host. It is thought that a nonspecific effect of oxidative stress is responsible for these results as N,N′-diphenyl-p-phenylenediamine, a synthetic antioxidant structurally unrelated to vitamin E, was active in protecting vitamin E-deficient mice against the cardiotoxic effects of the Coxsackievirus [53]. On the other hand, prooxidant dietary conditions (menhaden fish oil-enriched and vitamin E deficient) produce beneficial effects against lethal *Plasmodium yoelii* infection in mice that lack the ability to produce an acquired antimalarial immune response [54].

While vitamin E deficiency has an effect on the outcome of infection, infection can alter the vitamin E status of the host as well, leading to further exacerbation of infection. In animals, a decreased vitamin E concentration in the lung and liver was observed following influenza infection [55]. Furthermore, retrovirus infection significantly reduced liver, spleen, and thymus vitamin E levels [56]. These decreases in vitamin E levels may be due to increased oxidative stress following viral infection. In humans, plasma vitamin E levels were significantly lower in patients with acute or chronic viral hepatitis with high activity of disease [32]. Furthermore, significantly lower levels of α-tocopherol in serum were observed in papillomavirus-positive patients with cervical intraepithelial neoplasia [57]. Circulating α-tocopherol values were considerably lower in HIV-infected patients; this decrease was correspondent with increased malondialdehyde levels [58]. Results from a study by Tang et al.
suggest that high serum levels of vitamin E may be associated with lower HIV-1 disease progression. Men in the highest quartile of serum vitamin E levels showed a 34% lower risk of progression to AIDS compared with those in the lowest quartile.

The immunostimulatory effect of vitamin E supplementation was shown to render resistance against infection with different pathogens in different species of animals. Lower mortality due to Escherichia coli infection in chicks [60], lower clinical cases of mastitis in cows [61], faster recovery from chlamydia infection in lambs [62], higher survival from Diplococcus pneumoniae type-I infection in mice [63], higher resistance to Mycoplasma pulmonis infection in rats [64], and lower influenza viral titers in mice [65] were observed with vitamin E supplementation. In a study by Hayek et al. [65], dietary supplementation with 500 ppm vitamin E significantly reduced lung viral titers in old mice infected with influenza virus. It was suggested that the effect of vitamin E may be due, in part, to preservation of antioxidant status and NK cell activity and, in part, due to enhanced Th1 response [66]. Wang et al. [67] also reported that vitamin E supplementation prevented retrovirus-induced suppression of splenocyte proliferation and NK activity and partially restored production of IL-2 and interferon (IFN)-γ by splenocytes. In vitro addition of RRR-α-tocopheryl succinate to splenocytes from avian erythroblastosis virus-infected chickens resulted in normalization of the T-cell response to Con A and PHA which is suppressed in infected animals [68].

Few studies have investigated the direct effect of vitamin E supplementation on the incidence of infectious diseases in humans. Harman and Miller [69] supplemented 103 patients in a chronic care facility with 200 or 400 mg of vitamin E daily for 6 months and determined the serum antibody titers to influenza virus vaccine and the number of cases of pulmonary, urinary tract, and other infections. There was no effect of vitamin E on the serum titers or the incidence of infectious diseases. Unfortunately, because the data on the subjects’ health status, medication use, and other relevant parameters were not reported, it is hard to determine the effect of confounding factors. Meydani et al. [48] reported a nonsignificant (p = 0.09) 30% lower incidence of self-reported infection in vitamin E-supplemented elderly compared to the placebo group. Chandra [70] supplemented 96 healthy elderly individuals with a multinutrient formulation for 12 months. The supplemented group had a higher antibody response to influenza vaccine and less infection-related illness than the placebo group. It is impossible to attribute the effect to a particular nutrient since the intervention included multinutrients. However, vitamin E was the only nutrient provided at 440% of the recommended dietary allowance (RDA) level; other nutrients were provided at 30–200% RDA levels. Results from the Alpha-Tocopherol Beta-Carotene Cancer Prevention study showed no effect of 50 mg/day vitamin E supplementation on symptoms of chronic obstructive pulmonary disease, such as chronic cough, phlegm, or dyspnea over a 5- to 8-year period in male smokers [71].
Vitamin E supplementation has been used to improve the clinical outcomes of several infectious disease states including viral hepatitis, chronic respiratory tract infection, and sepsis in human and animals. In a randomized, double-blind, placebo-controlled study by von Herby et al. [72], treatment of hepatitis C patients with 800 IU RRR-α-tocopherol/day for 12 weeks improved clinical parameters indicative of liver damage. Alanine aminotransferase and aspartate aminotransferase levels were lowered after 12 weeks of vitamin E treatment. Andreone et al. [73] also reported improved biochemical and virologic outcomes in chronic hepatitis B with 3 months of vitamin E supplementation (600 mg/day). However, Yurdakök and Kanra [74] did not observe beneficial effects of vitamin E therapy (300 mg/day intramuscular injection for 7 days) on children with acute viral hepatitis. These conflicting results may be due to differences in the duration of therapy.

**Selenium, Immune Response and Infectious Diseases**

Numerous studies indicated that deficiency of Se impairs the immune response and host defense against infectious diseases [75, 76]. There is also evidence that Se supplementation above the recommended level in some, but not all cases, improves the immune response of the host [75, 76].

**Selenium and Immune Function**

Se deficiency has been shown to decrease T-cell proliferation and differentiation, expression of IL-2 receptor on T cells, lymphocyte cytotoxicity [77, 78] and neutrophil killing, and enhance neutrophil adherence to endothelial cells. These changes have been indicated to contribute to an increased risk of viral diseases as well as cancer associated with low Se levels. On the other hand supplementation with Se has been shown to increase T-cell proliferation, cytotoxic T lymphocytes and NK cell activity in mice and humans [76–79].

Recent animal studies have indicated that Se supplementation might improve the immune response in the aged. Kiremidjian-Schumacher and Roy [79] showed that 24-month-old mice supplemented with 2.0 ppm Se for 8 weeks had higher mitogenic response to PHA and cytolytic T-lymphocyte activity against malignant cells. This effect was not due to increases in IL-1, IL-2, or IFN-γ production but was related to the ability of Se to enhance the expression of α(p55) and/or β(p70/75) subunits of the IL-2 receptor on the surface of activated cells.

A 6-month, double-blind, placebo-controlled trial of Se supplementation (100 μg/day as Se-enriched yeast) in institutionalized elderly (mean age 78 years; n = 22) revealed significantly greater lymphocyte proliferation in response to pokeweed mitogen [80]. This increase in proliferative response was limited to B cells and was not exhibited in proliferative responses to T-cell mitogens PHA or OKT3. No significant correlations between plasma Se levels
and lymphoproliferative responses were established, although it is interesting to note that the greatest increases in B-cell proliferation occurred in subjects who had the lowest plasma Se levels at baseline. Based on this, the authors concluded that Se supplementation enhances the immune response in the elderly. This conclusion, however, is not supported by the data presented. As mentioned above, age-related changes in immune function occur in mainly T-cell-mediated function. Se supplementation did not improve the mitogenic response to T-cell mitogens, thus Se supplementation in this study was not effective in changing the age-associated defect in T cells.

Potential mechanisms through which Se may enhance lymphocyte proliferation may revolve around Se being an integral component of the enzyme glutathione peroxidase, a member of the antioxidant enzyme system. Glutathione peroxidase is involved in reducing the oxygen metabolites H2O2, which has been shown to impair lymphocyte proliferation and lipid hydroperoxides, which can be deleterious to cellular membranes and also lead to impaired immune responses [81]. A reduction in the activity of erythrocyte glutathione peroxidase has been reported with aging, which may be due to significantly lower plasma levels of Se with aging [82], therefore restoration of Se pools through supplementation could work to restore glutathione peroxidase activity and, in turn, restore some measures of immune function. The reason why the restoration of lymphocyte proliferation would be selective to B cells is not known, and remains to be explored. Additional studies among the elderly are warranted to determine if the aging immune response will benefit from additional Se supplementation.

__Selenium and Infectious Diseases__

Se deficiency has been linked to the occurrence, virulence and pathogenesis of certain viral infections [83, 84].

In mice, Beck et al. [83] showed that the avirulent Coxsackievirus (CVB3/0) mutates to the virulent cardiotoxic form when it is passaged through the Se-deficient host and exerts similar effects to that of the virulent type, CVB3/20. The observation that Keshan disease occurs in Se-deficient areas of China suggested that nutrient (Se) and viral interaction is involved in the development of the disease. Coxsackievirus has been isolated from the blood and tissues of people with Keshan disease, and the presence of Se deficiency in the area suggests that viral mutation leading to the myocarditis seen in Keshan disease might also occur in humans. In addition, Se was shown to reduce the pathogenesis of hepatitis virus B or C [85].

Se has been indicated in the susceptibility to and pathogenesis of HIV. In vitro Se supplementation was shown to reduce viral proliferation [86]. Several investigators have reported a decline in plasma Se in parallel with the loss of CD4 T cells in patients infected with HIV [84, 87–89]. Plasma Se seems to be a strong predictor of HIV prognosis [84]. Of interest to this review is the observation that low plasma Se and vitamin E levels have been reported in
neonates with high infection risk suggesting that the low status of these nutrients predisposes infants to infection.

The underlying mechanisms for the effect of Se on viral resistance is under investigation; both improvement of the immune response and a direct effect on viral virulence and replication have been suggested [53].

Conclusions

Vitamin E and Se deficiency, both in animal models and humans, impairs the immune response and renders the host more susceptible to infectious diseases. Severe primary vitamin E deficiency rarely occurs. However, marginal deficiency is observed in premature infants, in malnourished children, and following viral and bacterial infection. Secondary vitamin E deficiency is reported in association with lipid absorption abnormalities, and cystic fibrosis. Low Se status has been observed in areas of the world with low levels of Se in the soil such as China and New Zealand, in early infancy, in malnourished children, those receiving parenteral nutrition without Se supplementation, in infants suffering from diseases such as neural tube defects and phenylketonuria, and in association with viral infections. Further studies are needed to determine the role of vitamin E and Se status in the resistance of premature and term infants to infectious disease.

Clinical trials in the aged with vitamin E and Se have been shown to result in significant improvement in immune response. The evidence is stronger for vitamin E than that for Se. The effect of vitamin E in animal models is associated with increased resistance to influenza infection. Such information is not yet available in humans for vitamin E or in animals and humans for Se. Similarities exist between immunological changes in the elderly and early childhood as well as with malnourished children. The success of vitamin E and Se supplementation in improving the immune response in the elderly suggests that vitamin E and Se may produce similar results in children, particularly in those with low Se and E status.

Research is needed to determine: (1) the mechanisms by which vitamin E and Se exert their effect, and (2) to determine the role of vitamin E and Se supplementation in maintaining the host defense of well-nourished, malnourished, and low birth weight infants against pathogens. Such information will help in developing more effective intervention strategies. In particular, such information is needed to determine the type of infection and host conditions most conducive to effective interventions.

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**Discussion**

*Dr. Abbasy:* I followed up a young girl with Down syndrome, whose doctors had advised that she be given a selenium supplementation. I don't think that selenium plays a role in Down syndrome, but it was just given to potentiate her immune system. Is that so?

*Dr. Meydani:* I tend to agree with you that the children with Down syndrome might have higher oxidative stress and they do have an impaired immune response. There have been some studies indicating that supplementation with either selenium or vitamin E could be beneficial as far as improving antioxidant status and decreasing chromosomal damage in lymphocytes [1, 2].

*Dr. Abbasy:* But selenium is not available in vitamin preparations. So what advice would you give us for her?
Dr. Meydani: I am not quite sure what you mean by not being available in oral preparations because we find them in most of the supplements; they are available in the US anyway. I am not quite sure how to answer that question but I am sure that there are oral forms of selenium available. I have certainly seen them in different shops and pharmacies and in multivitamin preparations.

Dr. El Hodhod: We conducted a survey on the soil content of selenium in our country and it ranges between 0.5 and 1.5 μg/g. Do you think this level is low, very low or average, so that we can consider supplementation in different locations in our country?

Dr. Meydani: I don’t remember what the soil level should be to provide an adequate level in plants. Are there particular regions that have this level and do you see signs of selenium deficiency in these areas? Have you looked at the status in the children for example or in adults living in those areas, if they are adequate or not? I don’t remember what the level in the soil should be to provide adequate contents but I think the best way is to look at the status of selenium in people who are living in those areas to know whether in fact it is adequate or not.

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