Review

Optimal Nutritional Status for a Well-Functioning Immune System is an Important Factor to Protect Against Viral Infections

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Abstract: Public health practices including handwashing and vaccinations help reduce the spread and impact of infections. Nevertheless, the global burden of infection is high, and additional measures are necessary. Acute respiratory tract infections, for example, are responsible for approximately 2.65 million deaths per year. The role nutrition plays in supporting the immune system is well-established. A wealth of mechanistic and clinical data show that vitamins, including vitamins A, B_6, B_{12}, C, D, E, and folate; trace elements, including zinc, iron, selenium, magnesium, and copper; and the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid play important and complementary roles in supporting the immune system. Inadequate intake and status of these nutrients are widespread, leading to a decrease in resistance to infections and as a consequence an increase in disease burden. Against this background the following conclusions are made: 1) Supplementation with the above micronutrients and omega-3 fatty acids is a safe, effective, and low-cost strategy to help support optimal immune function; 2) Supplementation above the RDA, but within recommended upper safety limits, for specific nutrients such as vitamins C and D is warranted; and 3) Public health officials are encouraged to include nutritional strategies in their recommendations to improve public health.

Keywords: immune system; viral infection; influenza; COVID-19; micronutrients; vitamins; omega-3 fatty acids; minerals; vitamin C; vitamin D

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1. Introduction

Acute respiratory tract infections are a major cause of morbidity and mortality across the globe, as illustrated both by both seasonal influenza epidemics, and the recent outbreak of the coronavirus disease, COVID-19. The WHO estimates that worldwide, seasonal influenza alone results in 3 – 5 million cases of severe illness that require hospitalization, and 290,000 – 650,000 deaths annually [1]. In aggregate, acute respiratory tract illnesses were estimated to be responsible for more than 2.65 million deaths worldwide in 2013 [2]. Indeed, severe lower respiratory tract infections were the most common cause of sepsis-related death globally from 1990 – 2017 [3].

A number of standard public health practices have been developed to help limit the spread and impact of respiratory viruses, such as regular hand washing, avoiding those showing symptoms of infection, and covering coughs [4]. For certain viruses, such as influenza, annual vaccination campaigns designed to prime the immune response in case of exposure exist in many countries. Influenza, like COVID-19, is a single-stranded RNA virus, and as such exhibits high mutation rates and rapid evolution, which may allow these viruses to escape from pre-existing neutralizing antibodies in the host [5]. Vaccination programs therefore must make predictions each year as to which strains to vaccinate against, with varying degrees of success. In the US, the Centers for Disease Control and Prevention estimate the current year influenza vaccine to be 45% effective for preventing medically attended, laboratory-confirmed influenza virus. This is consistent with estimates from the previous years when the influenza vaccines were antigenically matched to the circulating viruses [6]. Since the 2011 – 2012 season, vaccine efficacy has ranged from 19 – 54% [7].

The immune system is comprised of both the innate (fast, non-antigen specific) and adaptive (slower, antigen-specific) responses. The innate immune system is comprised of physical barriers that help prevent pathogen entry (e.g. skin, gut epithelium), antimicrobial peptides, the complement system, and a variety of phagocytic and other cells (e.g. neutrophils, macrophages, natural killer cells), that recognize the presence of pathogens via the expression of nonspecific pathogen-recognition receptors [8]. The innate system moves quickly to recognize and destroy "non-self" threats, typically via inflammatory processes, and then resolve the inflammation and repair the damage caused by these events [8]. However, innate immunity does not increase efficacy or speed of response with repeated exposure to a pathogen. Subsequent to the innate response, the adaptive response is engaged. The adaptive response includes antigen-specific cells, e.g. T lymphocytes, subsets of which coordinate the overall adaptive response or kill virally-infected cells, and B lymphocytes, which can be activated to secrete antibodies specific to the infecting pathogen [8]. While slower to respond than the innate system, the adaptive system is responsible for generating immunological "memory", whereby a repeated infection with the same pathogen will generate a vigorous, fast antigen-specific response [8]. The induction of immunological memory is the mechanism by which vaccines can provide protection against subsequent pathogen exposure.

Undoubtedly, public hygiene practices and, when available, vaccinations can be effective mechanisms to provide protection against infectious disease. However, vaccines can take years to create, are not available against all viruses (including the COVID-19 virus), and provide varying levels of protection. The morbidity and mortality numbers cited above highlight the need for additional strategies to support the immune system, in order to reduce the impact of respiratory and other infections.

2. Nutritional Impact on Immunity

Often missing in the public health discussions around immunity and infection are nutritional strategies to support the optimal function of the immune system. This is surprising, given that the importance that nutrition plays in immune function is well established. Several vitamins, including vitamins A, B_6, B_{12}, C, D, E, and folate; and trace elements, including zinc, iron, selenium, magnesium, and copper, play important and complementary roles in supporting both the innate and adaptive immune systems. Deficiencies or marginal status in micronutrients negatively affect immune function and can decrease resistance to infections [9–11]. Indeed, with the exceptions of vitamin E and magnesium, each of these micronutrients has been granted health claims in the European Union for contributing to the normal function of the immune system [12]. Other nutrients such as omega-3 fatty acids also support an effective immune system, specifically by helping to resolve the inflammatory response [13].

The mechanistic roles that micronutrients play to optimize immune function have been well-described recently [9,11]. Most micronutrients exhibit pleiotropic roles in supporting immune function. With respect to innate immunity, the vitamins and minerals listed above collectively function to support the development and maintenance of physical barriers; production and activity of antimicrobial proteins; growth, differentiation and motility/chemotaxis of innate cells; phagocytic and killing (e.g. oxidative burst) activities of neutrophils and macrophages; and promotion of and recovery from inflammation (e.g. cytokine production and antioxidant activity). They also support adaptive immunity, via lymphocyte differentiation, proliferation and homing; cytokine production;

antibody production; and the generation of memory cells. The roles that vitamins C and D play in immunity are particularly well elucidated. Vitamin C has roles in several aspects of immunity, including supporting epithelial barrier function, growth and function of both innate and adaptive immune cells, white blood cell migration to sites of infection, phagocytosis and microbial killing, and antibody production [9]. Many immune cells have vitamin D receptors that affect their function after ligand binding, and as such vitamin D profoundly influences immunity. Vitamin D, for example, promotes differentiation of monocytes to macrophages and increases their killing capacity; modulates the production of inflammatory cytokines; and supports antigen presentation. Furthermore, vitamin D metabolites appear to regulate production of specific antimicrobial proteins that directly kill pathogens, and thus are likely to help reduce infection including in the lungs [14,15].

As mentioned above, inflammation is a key component of the immune response. This response is caused by a variety of pro-inflammatory mediators, produced by several different types of cells, resulting in the influx of fluid, immune cells, and other mediators that function to eliminate the infection. Inflammation typically resolves quickly at the end of the immune response, due to activation of specific negative-feedback mechanisms. Among these, the omega-3 fatty acids EPA and DHA present at the site of inflammation are enzymatically converted to pro-resolving mediators known as resolvins, protectins, and maresins. These molecules, along with others, function together to orchestrate the resolution of inflammation and to support healing, including in the respiratory tract [13,16]. Notably, nutritional deficiencies in these essential fatty acids can result in delayed or suboptimal resolution of inflammation [16].

It is not surprising, then, that deficiencies and even marginal status of these nutrients can impair immune functions. Depending on the deficient nutrient or nutrients, there can be decreases in the numbers of lymphocytes, impairment of phagocytosis and microbial killing by innate cells, altered production of cytokines, reduced antibody responses, and even impairments in wound healing [11]. These functional impairments are, presumably, what lead to the clinical immune-related manifestations of deficiency. Indeed, people deficient in vitamin C are susceptible to severe respiratory infections such as pneumonia [9,17]. A recent meta-analysis reported a significant reduction in the risk of pneumonia with vitamin C supplementation, particularly in individuals with low dietary intakes [18]. In older patients, disease severity and risk of death were reduced with supplementation, particularly in the case where initial plasma levels of vitamin C were low [18]. Vitamin C supplementation has also been shown to decrease the duration and severity of upper respiratory tract infections, such as the common cold, and significantly decrease the risk of infection in people under enhanced physical stress [17,19]. Likewise, vitamin D deficiency increases the risk for respiratory infection. Observational studies report an association between low blood concentrations of 25-hydroxyvitamin D (the major vitamin D metabolite) and susceptibility to acute respiratory tract infections [20,21]. Consistent with these findings, several recent meta-analyses have concluded that vitamin D supplementation can reduce the risk of respiratory tract infections in both children and adults [10,22–26]. Finally, marginal zinc deficiency can also impact immunity. Those deficient in zinc, particularly children, are prone to increased diarrheal and respiratory morbidity [27,28].

Furthermore, data from animal models and epidemiological studies in people indicate that deficiency in specific nutrients, particularly selenium and vitamin E, can lead to reproducible genetic mutations and increased virulence of certain viruses, including coxsackievirus, poliovirus, and murine influenza [29,30]. These data suggest that suboptimal nutrient status in the host population could lead to the emergence of more pathogenic strains of viral diseases, thereby increasing the risks and burdens associated with these illnesses.

Optimal intake of all these nutrients ideally would be achieved through the consumption of a well-balanced and diverse diet, but this can be difficult to accomplish for the general population. Indeed, even populations in developed countries exhibit inadequate micronutrient intakes versus the Recommended Daily Allowance (RDA) [11,31,32]. In the United States, for example, intakes below recommendations are common for most of the immune supporting micronutrients listed above, but particularly vitamins A, C, D, and E, magnesium and zinc. Vitamin B6 intake is low in the elderly, and folate, iron and copper intake are often below recommendations in females [11,32–34]. In Europe, intakes of vitamins D, E, folate and selenium are low in all age groups, with other micronutrients including vitamin C also below recommendations in specific age groups [11]. In China, inadequacies in both intake and status of the immune-supporting micronutrients are also quite common, including for vitamins A, C, D and E, folate, iron, zinc, selenium, and magnesium [35–37]. It should also be noted that optimal nutritional support for the immune system can require intakes above the RDA for some micronutrients, while at the same time infections and other stressors can reduce micronutrient status in the body. For example, vitamin C stores decrease during times of infection and higher intakes are required to restore normal blood levels [9,38]. In addition to micronutrient inadequacies, omega-3 fatty acid (EPA + DHA) intake and status are also commonly below recommendations, including in the Americas, Europe, the Middle East, and parts of Asia including China [32,39–41].

3. Recommendations and Conclusions

Thus, a set of clear nutritional recommendations is needed (Table 1). First, supplementation with micronutrients and omega-3 fatty acids is a safe, effective, and low-cost way to help eliminate nutritional gaps and support optimal immune function, and therefore reduce the risk and consequences of infections [9,11]. Intakes should follow recommended upper safety limits set by expert authorities, such as the European Food Safety Authority and, in the United States, the Institute of Medicine. Thus, a multivitamin and mineral supplement that supplies the basic micronutrient requirements (e.g. RDA) for vitamins and minerals is recommended in addition to the consumption of a well-balanced diet.

Second, we recommend supplementation above the RDA for vitamins C and D. As noted above, recent meta-analyses concluded significant reductions in the risk and impact of both upper and lower respiratory tract infections such as the common cold and pneumonia, including disease severity and risk of death in older patients, with vitamin C supplementation [18,19,42]. Based on this evidence, a daily intake of at least 200 mg/day for healthy individuals is recommended. This level is above the US RDA of 75 and 90 mg/day for female and male adults, respectively [43]. It should be noted that vitamin C requirements depend on health status, and 1 – 2 g/day are recommended to restore normal blood levels in individuals who are sick. These levels are within the US Tolerable Upper Limit (TUL) for adults of 2 g/day (note that the upper limit for children aged 1 - 3 years is 400 mg/day) [43].

Several recent meta-analyses have concluded that vitamin D supplementation reduces the risk of respiratory tract infections in both children and adults [10,22–26]. Protective effects were seen with those receiving daily or weekly vitamin D, but not with less frequent bolus doses [10,23]. A daily intake of 2000 IU (50 μg) is recommended. This is above the US RDA of 400 – 800 IU (depending on age), but below the TUL for those over 1 year of age (2,500 – 4000 IU) [44].

A third recommendation involves the omega-3 fatty acids EPA and DHA. An adequate intake supports the resolution of inflammation via the production of anti-inflammatory metabolites of these fatty acids, including in the respiratory tract [13,16]. An intake of 250 mg EPA + DHA per day is recommended, consistent with global, regional and national expert recommendations [39,40,45].

Public health practices, such as vaccinations and hygiene measures, are important measures that help limit the spread and impact of infections, including against acute respiratory viruses. However, the present situation with COVID-19 and the annual morbidity and mortality figures for respiratory infections overall make it clear that these practices alone are not sufficient. New strains of influenza continuously emerge, necessitating development of new vaccines with varying efficacy, and outbreaks of novel viruses can be enormously difficult to contain. As such, additional safe, effective, and cost-effective strategies are needed to support the immune system, and further protect individuals and populations from harm. One compelling strategy is to provide sufficient nutritional support for the immune system. As described above, optimal nutrient intake, including supplementing above the RDA for certain immune-supporting vitamins, promotes optimal immune function, helps to control the impact of infections, and could help limit the emergence of novel, more virulent strains of pathogenic viruses. We therefore strongly encourage public health officials to also include nutritional strategies in their arsenal to improve public health and to limit the impact of seasonal and emerging viral infections.

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Table 1. Recommended intakes of selected nutrients to support optimal immune function.

Nutrient	Rationale	Recommendation
Vitamins and trace elements	These micronutrients play important roles in supporting the cells and tissues of the immune system. Deficiencies or marginal status in these micronutrients negatively affect immune function and can decrease resistance to infections.	A multivitamin & trace element supplement that supplies the nutrient requirements (e.g. 100% US RDA for age and gender) [31] for vitamins and trace elements including vitamins A, B_6, B_{12}, C, D, E, and folate, and trace elements including zinc, iron, selenium, magnesium and copper. This is in addition to the consumption of a well-balanced diet.
Vitamin C	Doses of ≥ 200 mg/day provide saturating levels in the blood, and support reduction in the risk, severity and duration of upper and lower respiratory tract infections. Requirements for vitamin C increase during infection.	Daily intake of at least 200 mg/day for healthy individuals. In individuals who are sick, 1-2 g/day is recommended.
Vitamin D	Daily supplementation of vitamin D reduces the risk of upper respiratory tract infections.	Daily intake of 2000 IU/day (50 µg/day).
Zinc	Marginal zinc deficiency can impact immunity. Those deficient in zinc, particularly children, are prone to increased diarrheal and respiratory morbidity.	Daily intake in the range of 8-11 mg/day.
Omega-3 fatty acids (EPA + DHA)	Omega-3 fatty acids support an effective immune system, including by helping to resolve inflammation.	Daily intake of 250 mg/day of EPA + DHA.

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