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# Nutrition and Immune Function: A Science Review of the Role of Micronutrients in the Immune System

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## Abstract

Almost all vitamins and minerals and essential fatty acids such as omega-3 fatty acids are essential for immune function. In the context of the COVID-19 pandemic, the importance of nutrition has been highlighted, but vitamins and minerals are often forgotten or intakes assumed to be adequate. Dietary surveys in the UK show that intakes of these essential micronutrients are below recommended intakes particularly in some population groups.

This review looks briefly at the immune system, its constituent organs and cells and how it functions to fight infection. The roles of micronutrients in immune function are also evaluated with consideration of the dietary intake of these nutrients in the UK and the potential impact of UK intakes on immune function. Given the below recommended intakes of micronutrients in the UK, this review also considers the role of supplementation, at least in currently recommended intakes for micronutrients with the possibility that higher intakes might be beneficial for optimal immune function.

## Introduction

Nutrition plays a key role in immune function. All immune cells, including neutrophils, monocytes, macrophages, mast cells, T and B lymphocytes require, amongst other factors, a variety of vitamins and minerals and essential fatty acids to function. The COVID-19 pandemic has focused some attention on nutrition and immune function but not to the extent that the importance of vitamins and minerals, with the exception of vitamin D, have gained significant attention of the public and healthcare professionals.

Almost all micronutrients are important for some aspects of immune function, in particular vitamins A (including beta-carotene), B6, folate, B12, C and D, and the minerals copper, iron, selenium and zinc, all of which have health claims for immune function allowed by the European Food Safety Authority (EFSA) [1]. Ensuring recommended intakes of all micronutrients are achieved offers an important way to optimize immune function and hence reduce the risk of infection [2,3].

However, dietary intakes of micronutrients in the UK as shown in the UK National Diet and Nutrition Survey (NDNS) fall below recommended intakes, particularly in some population groups [4]. The impact of low intakes of micronutrients is worthy of far more attention in the context of immune function and the COVID-19 pandemic. Some research from indirect data in COVID-19 patients, for example, suggests a possible benefit of supplementing the diet with micronutrients, including vitamins A, B vitamins, C, D and E [5] although robust clinical data would be required to support specific claims for micronutrients in COVID-19.

Immune function, which has not hitherto been of such concern in the UK is now likely to have a higher profile in the years ahead. According to a 2020 Mintel Survey, a quarter of the UK population had taken more vitamins and minerals because of a concern to protect their health in the context of the COVID-19 pandemic. Amongst supplement users, 36 percent had taken them to strengthen immune function [6]. This concern shows no signs of abating.

This review looks briefly at the immune system and evaluates the role of micronutrients in immune function, considers dietary intake of these nutrients in the UK, the impact of low intakes on immune function and the potential role of supplementation. Whilst the role of supplementation in COVID-19 is considered, the focus is on immune function overall, which is likely to be of most importance going forwards with clinical micronutrient knowledge from COVID-19 applied to other contexts where immune function many be prejudiced.

## The Immune System

The immune system exists to protect human beings (and animals) against pathogens, including viruses, bacteria, fungi, parasites, toxins

made by these antimicrobial agents, and other foreign bodies (or antigens) such as allergens [7]. To deal with these potential harms and drive an immune response, the immune system has developed over thousands of years to include a complex network of cells, communication channels between cells and responses to cellular messaging.

Immune cells include white cells (leukocytes) which are stored in the lymphoid organs including the bone marrow, spleen, thymus and lymph nodes [8]. One category of white cell is the phagocyte (of which there are several types including neutrophils, monocytes, macrophages and mast cells). A second category of white cell is the lymphocyte, of which there are two main types. The first are the B lymphocytes, which produce immunoglobulins or antibodies. The second type is the T lymphocytes including both helper T cells that co-ordinate the immune response and killer T cells or Natural Killer (NK) cells which destroy infected cells [8].

All these cells are involved in the immune response of which there are two types. First, the innate immune response, which we are born with. This is fast, general and non-specific and consists of physical barriers (e.g. the skin and the mucous membranes of the nose, mouth and gut) to prevent entry of pathogens and also a variety of phagocytes, neutrophils, macrophages and natural killer (NK) cells which recognise pathogens through expression of non-specific cell receptors and subsequent inflammatory processes [7]. The pathogen is then destroyed and damage to cells and tissue is repaired.

Second, the adaptive immune response, which is slower and more specific and builds up from infancy to young adulthood, declines after the age of around 50 years. The adaptive immune response depends on the so-called 'immunological memory' of previous pathogens and foreign bodies which allows for a fast response specific to a pathogen that has invaded the body before [7]. The adaptive immune response is engaged after the innate immune response and consists of immune cells (e.g. B lymphocytes which produce antibodies specific to the pathogen and T lymphocytes that co-ordinate the adaptive response and destroy any infected cell or foreign body).

Immune function varies considerably between individuals. Factors impacting on immune function include those specific to the individual (intrinsic factors) such as age, sex, genetics and co-morbidities [9] as well as extrinsic factors such as pre-existing immunity (to a specific infection), the makeup of the gut microbiota (i.e. the proportions of healthy and less healthy bacteria present), previous exposure to both infections and antibiotics [10]. Other factors that can impact on immune function include environmental factors such as geographic location globally and season. In addition, a range of behavioural and lifestyle factors, such as smoking, alcohol consumption, exercise, sleep and nutrition make an important contribution to immune function [11]. An important question is whether immune function was compromised in patients who developed COVID-19 and whether improved micronutrient intake could have reduced risk. It has been suggested that consumption of sufficient amounts of micronutrients would help support optimal immune function and help individuals deal with viruses and bacteria should they develop an infection [12].

## Nutrition and Immune Function

Good nutrition with an optimal intake and absorption of all vitamins, minerals and other essential substances, such as essential fatty acids and amino acids is vital for optimal immune function. Optimal intake of micronutrients and essential fatty acids makes it more likely that the immune system can respond to the challenges of harmful invaders. However, below recommended intakes of nutrients, may make it more challenging for the immune system to respond effectively [2].

Immune cells are never dormant, but entry of disease causing bacteria or a virus increases the activity and number of immune cells to facilitate the immune response. This increased immune cell activity results in an increased need for energy producing molecules such as glucose, amino acids and fatty acids. These molecules facilitate the synthesis of a variety of proteins, including immunoglobulins which fight infection as well as cytokines, prostaglandins and leukotrienes involved in the inflammatory response to infection [2]. The immune response also results in a greater need for Deoxyribonucleic Acid (DNA) and ribonucleic acid (RNA), as well as proteins and fatty acids needed inside the cells and for the construction of cell membranes.

A range of vitamins and minerals are required for the immune response [12]. They act in many different ways. Firstly, many act as co-factors for enzymes that drive the biochemical reactions. Secondly, various micronutrients are required for the manufacture of DNA and RNA and in the production of immune cells. Thirdly, a part of the innate immune response is to facilitate a pro-oxidant environment, in which an inflammatory cascade develops, including the so-called 'cytokine storm' from which the individual needs protection [13]. In terms of micronutrients, this is achieved by those that act as antioxidants (e.g. vitamins C and E, selenium, zinc and copper) and/or support anti-oxidant enzymes (e.g. glutathione peroxidase and superoxide dismutase).

A low quality diet, high in a mix of fat, sugar and salt, and low in omega 3 fatty acids and vitamins and minerals, which is common in the UK and increasingly throughout the world because of the increasing intake of poor quality processed foods, is pro-inflammatory relative to a higher quality diet [14]. Evidence also shows that such a diet is linked with a less healthy gut microbiota which may, in part, give rise to excessive inflammation, compromising immune function [15]. That obesity also compromises immune function, as observed, for example, by the increased risk for serious COVID-19 disease in obese patients, is also related to inflammation. This is because obesity is considered to be a state of inflammation [11].

Overall, under nutrition prejudices immune function by firstly compromising the external barrier (e.g. nasal, skin and gastrointestinal) function [16] as nutrients, such as vitamin A, are involved in maintaining the external barriers. Secondly, poor nutrition may impact the development and growth of immune cells to fight infection and thirdly, poor nutrition may increase the risk of excessive inflammation in the face of a pathogenic challenge. High blood levels of certain nutrients, not necessarily due to high intakes, can also impair immune function. Iron is a case in point. Iron overload, as seen in patients with hereditary haemochromatosis, modifies numbers and distribution of immune cells, such as macrophages, monocytes and T lymphoctyes and reduces the antibody response [17].

## Micronutrients Involved in Immune Function

Many nutrients are involved in immune function, particularly micronutrients, including vitamins A, B2, B6, folic acid, B12, C, D, E, and iron, copper, magnesium, selenium and zinc (Micronutrients should be distinguished from macronutrients such as protein, carbohydrate and fat). These micronutrients have complementary, and in some cases, synergistic roles. Vitamins A, C, D, E, and zinc are important for the maintenance of the structure and function of the body's external and epithelial barriers, including the skin and respiratory and gastrointestinal tracts to pathogenic microbes [2,18].

Innate and adaptive immune function involves a range of processes, including recognition and destruction of pathogens, cell growth, antibody and cytokine production and the so-called 'respiratory or antioxidant burst'. All of these activities are dependent on sufficient amounts of vitamins including vitamins A, B6, B12, folate, C, D, E and minerals, including copper, iron, magnesium, selenium and zinc [2,18]. Omega 3 fatty acids are also important in immune function, mainly by helping to reduce the inflammatory response [19].

Vitamins, minerals and trace elements supporting immune function and the mechanisms (simplified) by which they act in immune function are summarised in table 1.

## Vitamin A

Vitamin A contributes to immune function through the restoration of the skin and respiratory and intestinal epithelium so contributing to the strength of these barriers which function to protect people against invading pathogens [20]. Vitamin A also plays a direct role in the growth and production of the different types of immune cells. Retinoic acid (one form of vitamin A) receptors are present in several immune cells such as T and B lymphocytes, natural killer (NK) and dendritic cells. Vitamin A helps to curb the inflammatory cytokine storm and contributes towards immune defence in the gut. It maintains the T helper cell antibody response by reducing the synthesis of some

**Table 1:** Nutrients that support immune function (adapted and summarised from [18]).

| Nutrient | Function in Immune System |
|---|---|
| Vitamin A | Plays a key role in the development and differentiation of the cells of the skin barrier and mucous tissues. |
| | Important in the defence of the oral, gut and urinary-genital mucosa. |
| | Reduces the toxicity of reactive oxygen species (ROS). |
| | Essential for the development and differentiation of B and T cells. |
| | Necessary for the B-cell mediated antibody response to antigens. |
| | Regulates the function of dendritic cells, NK cells and macrophages. |
| | Down regulates the production of anti-inflammatory interleukins. |
| Vitamin B6 | Involved in intestinal immune regulation. |
| | Important for lymphocyte activity, mediating lymphocyte migration into the intestine. |
| | Maintains or enhances NK cell activity. |
| | Maintains or enhances Th1-mediated immune response. |
| | Inhibits Th2 mediated cytokine-mediated activity. |
| | Required for the production of antibodies. |
| Vitamin B12 | Important for the gut barrier. |
| | Maintains or enhances NK cell activity. |
| | Facilitates production of T cells and helps to regulate balance between T helper cells and T killer (cytotoxic) cells. |
| | Important for antibody production and metabolism. |
| Folate | Essential for the survival of regulatory T cells in the intestine. |
| | Enhances NK cell activity. |
| | Supports Th-1 mediated response. |
| | Important for antibody production and metabolism. |
| Vitamin C | Promotes collagen formation. |
| | Protects cell membranes from ROS, supporting structure of skin and gut barrier and mucous membranes. |
| | Facilitates migration of white blood cells to the site of infection. |
| | Involved in the production, development and movement of T lymphocytes, particularly cytotoxic T cells, phagocytes (monocytes and neutrophils) and NK cells. |
| | Increases generation of antibodies, enhances killing of microbes and reduces tissue damage. |
| Vitamin D | Helps to modify the gut microbiota to a healthier composition. |
| | Supports the gut barrier. |
| | Enhances the barrier function of the cornea (the eye surface) and the kidney. |
| | Protects the lungs against infection. |
| | Vitamin D receptors are found in monocytes, macrophages and dendritic cells. |
| | Promotes activity of macrophages. |
| | Regulates proteins that kill pathogens. |
| | Reduces activity of pro-inflammatory cytokines and increases activity of anti-inflammatory cytokines. |
| | Promotes antigen processing. |
| | Suppresses antibody response. |
| | Contributes to innate and adaptive immunity. |
| Vitamin E | Protects cells against free radicals and inflammation. |
| | Supports the skin and gut barrier and mucous membrane barriers. |
| | Maintains or enhances NK cell activity. |
| | Enhances lymphocyte production and T cell-mediated functions. |
| | Increases proportion of memory T cells. |

| | |
|---|---|
| Iron | Essential for development and growth of skin and gut barrier and mucous membranes. |
| | Involved in killing of bacteria by neutrophils. |
| | Component of enzymes critical for function of immune cells. |
| | Involved in cytokine production and inflammatory response. |
| Zinc | Helps to maintain integrity and function of the skin barrier and mucous membranes. |
| | Maintains or enhances NK cells activity. |
| | Promotes the killing activity of phagocytes. |
| Copper | Intrinsic antimicrobial properties. |
| | Defence against ROS and free radicals. |
| | Involved in the function of T cells (helps to regulate balance between T helper and T killer cells), macrophages, monocytes and neutrophils. |
| | Enhances NK cell activity. |
| | Important role in inflammatory response. |
| Selenium | Important for antioxidant defence system, counteracting ROS. |
| | Affects leukocyte and NK cell function. |
| | Regulates T cell and cytokine production. |
| | Involved in antibody production. |
| Magnesium | Involved in the regulation of leukocytes and antigen binding to macrophages. |
| | Protects against oxidative damage. |
| | Involved in antibody production. Role in antigen binding to macrophages. |
| Omega-3 fatty acids (EPA &DHA) | Reduces the pro-inflammatory response. |
| | Inhibits production of pro-inflammatory prostaglandins and leukotrienes. |

cytokines including Interleukin (IL)-12 and Tumour Necrosis Factor (TNF) alpha. Vitamin A is also needed for the normal functioning of B-cells, including the B-cell mediated antibody response to bacterial antigens [21]. Overall, vitamin A plays a vital role in immune function, particularly against respiratory and gastrointestinal infections [22]. Carotenoids also contribute to immune function, for example reducing the harm from toxic reactive oxygen species (ROS) and maintaining the structure and fluidity of cell membranes.

## B group vitamins

All eight vitamins of the B group are important in immune function. They act as co-factors to enzymes that facilitate energy metabolism and production of energy substrates, such as Adenosine Triphosphate (ATP) and the reduced form of Nicotinamide Adenine Dinucleotide (NADH), some of which highly active immune cells need for their metabolism [23]. Vitamin B6, B12 and folate act as one carbon donors in DNA and RNA synthesis in all cells, including immune cells. They are also involved in gastrointestinal immune regulation. Vitamin B6 influences lymphocyte entry into the gut, while folate is essential for the survival of T cells in the small intestine, and vitamin B12 is a co-factor for metabolic pathways in human gut microbes. All of these functions protect the gut barrier and reduce the risk of infection [2].

## Vitamin C

Vitamin C (ascorbic acid) is one of the most important water-soluble antioxidants. In terms of immune function, it protects immune cells from damage during the release of Reactive Oxygen Species (ROS). This is crucial for immune defence occurring in phagocytes as it facilitates the degradation of bacteria, viruses and other harmful antigenic particles [24]. Vitamin C is also essential for collagen synthesis and protects cell membranes from damage caused by free radicals, thus contributing to the maintenance of the respiratory and intestinal barriers. Vitamin C also contributes to the growth, movement and overall function of immune cells, including neutrophils, monocytes, and phagocytes. It is also involved in the activities of NK cells. Vitamin C is essential for the growth and function of T and possibly B-lymphocytes and for reducing the production of cytokines that cause inflammation in immune cells [24].

## Vitamin D

During recent years, and particularly in the context of the COVID-19 pandemic, vitamin D has been of special interest because of its multifunctionality in parts of the immune response. The vitamin D receptor is found on the surface of most immune cells including T and B lymphocytes, dendritic cells, monocytes and macrophages. The enzyme that converts vitamin D to its active form (calcitriol) is also present in these immune cells [25]. Calcitriol controls cathelicidin and β-defensins, antimicrobial proteins responsible for changing the balance of the intestinal bacteria towards a healthier composition whilst helping to maintain the gut barrier as well as protecting the lungs against infection [26]. Calcitriol also changes the balance of cytokines away from those that are pro-inflammatory towards those that are anti-inflammatory.

## Vitamin E

Vitamin E is the main fat-soluble antioxidant vitamin. It helps to prevent the transmission of the free radical reaction chains that can destroy fragile polyunsaturated fatty acids in cell membranes. In this role, vitamin E acts in immune function to protect cells, amino acids and fatty acids from ROS produced by pathogens during the oxidative burst [27]. Vitamin E also facilitates production and growth of T cells and antibodies and helps to regulate NK cell activity.

## Iron

Iron plays an important role in immune function. Many pathogens require iron to function and grow but iron concentration in different

parts of the body is tightly regulated to limit pathogens being able to access it. This is achieved largely in the context of absorption, as in the presence of infection, iron absorption is reduced and also taken into immune cells, particularly macrophages [20]. Iron also promotes the growth of T cells whilst iron deficiency alters the numbers of T and B lymphocytes which can reduce the ability of the immune system to eradicate harmful organisms. Iron is also involved in killing of bacteria by neutrophils and is a component of enzymes needed by immune cells (e.g. ribonucleotide reductase involved in DNA synthesis). With other nutrients, it regulates cytokine production and hence the inflammatory response [28].

### Zinc

The role of zinc in the immune system has been known for many years. For example, the zinc dependent thymulin protein which is involved in the development of T-lymphocytes in the thymus gland was discovered 40 years ago [29]. Zinc is a co-factor in at least 3,000 proteins and enzymic reactions including DNA replication. As a co-factor for enzymes zinc helps to maintain the structure and function of the skin and the gut barrier function. Zinc is also needed for the development of T-cells and the balance of T-cell subgroups and for NK cell cytotoxic activity it also enhances the phagocytic activity of monocytes and macrophages [29]. In cases of disrupted zinc homeostasis the function of these immune cells is impaired.

### Selenium

Selenium is a component of several enzymes involved in oxidation and reduction reactions. As a reflection of this redox activity, selenium helps to protect immune cells such as macrophages, NK cells and leukocytes from the oxidative damage caused by the entry of pathogens [30]. One selenoprotein (selenoprotein K) is highly expressed in immune cells. Selenium is also important for maintaining T cell function, including the antibody production which occurs in these immune cells [12].

### Copper

Copper is known to play an important part in immune function but its entire role remains to be elucidated. Copper supports the function of several immune cells including neutrophils, monocytes, macrophages and natural killer (NK) cells. It facilitates immune function activities such as those of T lymphocytes in the production of IL-2 [12].

### Magnesium

Magnesium is required for both innate and adaptive immune function [12]. It is a co-factor of enzymes involved in DNA and RNA metabolism whilst stabilising the structure of these essential molecules. Magnesium is involved in DNA replication and repair and functions in antigen binding to macrophages as well as regulating the function of immune cells including leukocytes, lymphocytes, granulocytes and mononuclear phagocytes. Magnesium deficiency is associated with reduced levels of Immunoglobulin G (IgG) and increased Immunoglobulin E (IgE).

### Omega-3 fatty acid

Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) are long chain omega-3 fatty acids found mainly in fish oil and oily fish. These substances are capable of curbing several aspects of inflammation including interactions of leucocytes, production of prostaglandins and leukotrienes from the n-6 fatty cascade. Omega-3 fatty acids also reduce the production of pro-inflammatory cytokines and regulate the fatty composition of cell membranes and inhibition of various pro-inflammatory factors [19].

## Links between Poor Micronutrient Intake and Reduced Immune Function

It is well established that clinical micronutrient deficiencies adversely affect the immune system and predispose individuals to infection and increase the risk of severe illness and death from infections such as measles and pneumonia in low income countries. Whilst less is known about the impact of low intakes of micronutrients in the UK and other European countries, the below recommended intakes and poor to marginal status evident in UK dietary surveys, may compromise immune function and increase the risk of infection, particularly if low intakes continue in the medium to long term.

### Vitamin A

Vitamin A deficiency can result in excessive inflammation, diminish the oxidative burst of macrophages, decrease the number and growth of both T cells and B cells and compromise antibody-mediated immunity [21]. Vitamin A deficiency predisposes to infections such as measles, malaria and diarrhoea in low-income countries and low intakes can increase the risk that pathogens will invade the eye, and the respiratory and gastrointestinal tracts) [31].

### B vitamins

Low intakes of B vitamins reduce the ability to respond to pathogens. Vitamin B6 deficiency reduces IL-2 production, lowers the antibody response and reduces T helper 1 cell production whilst promoting T helper cell 2 cytokine mediated inflammation [31]. Deficiencies of both folate and vitamin B12 depress NK cell activity and T cell proliferation and reduce the antibody response. Folate deficiency suppresses RNA and DNA synthesis [31].

### Vitamin C

Vitamin C deficiency increases the risk of oxidative damage in immune cells and throughout the body which can predispose to infection affecting the severity of pneumonia and other infections mainly caused by increased oxidative damage [24,32]. Vitamin C deficiency leads to impaired function of the phagocytes and an increase in inflammation that is restored by vitamin C supplementation [24].

### Vitamin D

Poor vitamin D status, which is common in the UK, is associated with many features of poor immune function. These include a shift in the balance of the gut microbiota in an unhealthy direction, fewer lymphocytes, a reduced ability of macrophages to kill pathogens, reduced maintenance of the respiratory and gastrointestinal barrier function, impaired T and B cell movements in the intestine, reduced number and activity of NK cells and impaired innate immunity [18]. Poor vitamin D status also increases the risk of respiratory tract infections [33,34] and has been associated with increased risk and severity of COVID-19 [35]. Vitamin D deficiency has also been linked with auto-immune diseases such as type 1 diabetes, multiple sclerosis, rheumatoid arthritis and Systemic Lupus Erythematosus (SLE).

Low vitamin D levels (i.e. low serum levels of 25-hydroxyvitamin D) have been linked with increased risk of respiratory tract infection in several studies. Cross-sectional data from 6,789 participants in the nationwide 1958 British birth cohort who had measurements of serum 25-hydroxyvitamin D (25-OHD), lung function and respiratory infection data available from the age of 45 years indicated that the prevalence of respiratory infections reduced when 25-OHD concentrations increased. Each 10 nmol/L increase in 25-OHD was associated with a 7 percent reduced risk of respiratory infection (95

percent CI 3, 11 percent) combined with improved lung function [36]. A 2019 systematic review of epidemiological studies also found an increased risk of upper and lower respiratory tract infections when serum 25-OHD levels were low [37].

During 2020 a number of studies have examined the possible association between vitamin D status and risk of COVID-19. Two studies have found inverse associations between national estimates of vitamin D status and COVID-19 incidence and mortality in European countries [38,39]. Lower circulating 25-OHD concentrations have also been reported to be associated with susceptibility to SARS-CoV-2 infection [40] and COVID-19 severity [41].

An Israeli retrospective longitudinal study found independent associations between low pre-pandemic 25-OHD levels and subsequent incidence and severity of COVID-19 [42]. However, a recent UK Biobank Cohort study did not suggest a link between vitamin D concentrations and risk of COVID-19 infection [43]. However, both of these studies employed historic 25-OHD measurements which might not reflect vitamin D concentrations at the time of exposure to SARS-CoV-2.

Small studies in patients hospitalised with COVID-19 have suggested more chronic disease in those with low vitamin D levels. One small Irish observational study involving 33 male patients admitted to hospital for pneumonia associated with COVID-19 found lower vitamin D levels in those admitted to the Intensive Care Unit (ICU). Low vitamin D levels were also linked with a more than three times likelihood of needing to be put on a ventilator [44].

A retrospective analysis of patients hospitalised with COVID-19 in Spain compared vitamin D levels in these patients with those of a control group of healthy patients matched for age. The study included 216 patients (mean age 61 years, 62.4 percent male) of whom 19 were already taking vitamin D. Mean 25-OHD levels in COVID-19 patients were 13.8 (± 7.2 ng/ml) compared to 20.9 (± 7.4) ng/ml in control patients. Overall, vitamin D deficiency was recorded in 82.2 percent of patients with COVID-19 compared to 47.2 percent of the healthy controls. Compared to those who were vitamin D deficient, vitamin D replete patients had a reduced need for tocilizumab (17 percent *vs* 33.1 percent , p=0.032), less frequent radiological progressions (14.9 percent *vs* 30.2 percent, p=0.037), fewer intensive care admissions and a slightly shorter hospital stay (12 *vs* 8 days). However, the authors found no correlation between serum 25-OHD levels and the main composite severity endpoint, with an odds ratio of 1.13 (95 percent CL 0.27-4.77, p=0.865) [45].

Studies in people of South Asian origin find low intakes of vitamin D and also 25-OHD levels below 25 nmol/L throughout the year even in summer. Low vitamin D status may contribute to the higher observed rates of COVID-19 in black and minority ethnic people. In the UK Biobank cohort, 55 percent of the 6,433 South Asians with a 25-OHD measurement had a 25-OHD <25 nmol/L (severe deficiency) and 92 percent had a 25-OHD <50 nmol/L (insufficiency). One fifth (20 percent) of those with a measurement had a 25-OHD concentration <15 nmol/L (very severe deficiency) [46]. When 824 additional participants with undetectable (<10 nmol/L) 25-OHD measurements were included, 29 percent had 25-OHD <15 nmol/L, 60 percent had 25-OHD <25 nmol/L and 93 percent had 25-OHD <50 nmol/L. However, low vitamin D levels in the UK Biobank Study did not explain the pattern of COVID-19 related to ethnic origin. This suggests that factors underlying ethnic differences in COVID-19 are complex and different avenues of research need to be pursued.

### Vitamin E

Vitamin E deficiency may impair B and T cell function which can prejudice adaptive immunity [31,47]. Deficiency reduces T cell maturation and may reduce resistance to infection [47].

### Iron

Iron deficiency is associated with alterations in T lymphocyte numbers, poor maturation of T helper cells reduced NK cell activity, lower IL-6 levels, impaired microbial killing by polymorphonuclear leukocytes and a reduced antibody response [18,31]. Respiratory tract infections occur more frequently and last longer in children with iron deficiency [48].

### Zinc

Zinc deficiency has widespread impact on immune function, altering cytokine production, impairing NK and T cells, with decreased T cell function, impaired oxidative burst and impaired antibody response [29,31]. Susceptibility to antimicrobial (bacteria, viral, fungal) infection of the respiratory and gastrointestinal tract is increased [49].

### Copper

Copper deficiency is associated with a poor response to infections with reduced T cell proliferation, poor neutrophil function (i.e. poor phagocytic ability) and reduced IL-2 production even in marginal deficiency [50]. It is associated overall with poor immune defence to infection [21].

### Selenium

Selenium deficiency may impair the response to vaccination, as well as cell-mediated immunity and immunoglobulin production [21]. Deficiency has also been linked with respiratory tract infection in young children [18]. Deficiency of selenium, like that of vitamin D, has been also been associated with greater risk of COVID 19 [51].

### Magnesium

Magnesium deficiency reduces NK cell activity, increases levels of cytokines such as IL-6 and increases inflammation. It has also been shown to reduce resistance to bacterial, viral and fungal infections [52].

### Omega 3s

Nutritional deficiencies in these fatty acids can result in delayed or suboptimal resolution of inflammation [19] which can prejudice immune response.

## Intakes of Micronutrients in the UK

The UK National Diet and Nutrition Survey (NDNS) measures intakes and status of several nutrients of importance in immune function. The most recent data from the NDNS Rolling Programme (NDNS-RP) [53] indicate that whilst mean intakes across the UK population of most micronutrients measured in the survey are close to the Reference Nutrient Intake (RNI), which is the amount of a nutrient considered sufficient for 95 percent of the population, a significant proportion of the population has intakes of several micronutrients, including those discussed above of relevance to immune function, which fall below the Lower Reference Nutrient Intake (LRNI). (The LRNI is the amount of a nutrient that is enough for only the small number of people with low needs). Below LRNI intakes would be considered to be inadequate and increase the risk of deficiency. Increased susceptibility to infections, including respiratory tract

infections, and poorer outcomes from such infections has been seen in cases of inadequate micronutrient intakes [12].

According to NDNS-RP time trend data, since 2008/9 there has been a decline in the intakes of some of these micronutrients, such as vitamin A, vitamin D, B vitamins (riboflavin and folate) and iron, in some age groups. Table 2 summarises dietary intake data relative to the LRNI for micronutrients monitored in the NDNS since 2008/9. Vegetarian and vegan diets, which are increasing in popularity, can also be low in nutrients of importance in immune function, such as vitamin B12, vitamin D, copper, iron, selenium and zinc as well as the omega-3 long-chain fatty acids DHA and EPA [54]. In addition, emerging opinion suggests that recommended intakes of micronutrients may not be high enough to support optimal immune function [12].

Micronutrient intakes of teenagers and young adults continue to be of concern with declines in intakes in some nutrients over the past two decades. Thus, almost one third (30 percent) of 11-18 year olds fail to achieve the LRNI for iron, which is a 6 percent increase in the proportions of youngsters not achieving even that low intake from 2008/9. Just under a fifth (18 percent) did not achieve the LRNI for vitamin A compared with 13 percent in 2008/9; 9 percent did not achieve the LRNI for folate compared with 4 percent in 2008/9. For zinc respective figures were 18 *vs* 16 percent (i.e. the situation for zinc has improved slightly but more than one in six in this age group still fail to achieve the LRNI).

These micronutrient shortfalls and declines in intakes are worst in teenage girls. A substantial 43 percent of teenage girls failed to achieve the LRNI for iron in 2008/9, and this has increased since, ranging from 48 to 54 percent over the 10 year survey period from 2008/9 to 2018/2019. Similarly in 2008/9, 14 percent of 11-18 year-old girls did not achieve the LRNI for vitamin A, a figure that has increased to as high as 24 percent in recent years. Respective figures for riboflavin were 18 percent in 2008/9, increasing to as high as 26 percent in recent years, and for folate were 6 percent in 2008/9 increasing to 10 percent in the most recent data, with a peak of 15 percent during the NDNS-RP period.

Micronutrient intakes in women of childbearing age and middle years (19-64 years) have also fallen since 2008/9. The proportion not achieving the LRNI for folate has increased from 3 to 7 percent. Figures for vitamin A are 5 and 8 percent respectively with a peak of 10 percent in the course of the survey, and for iron 21 and 25 percent respectively with a peak of 27 percent.

Older people, too, have shortfalls in micronutrient intake. There have been increases in the proportions of people over 65 failing to achieve the LRNI for vitamin A, iron, magnesium, and zinc since 2008/9. In older women, the proportion not achieving the LRNI for iron has increased from 1 percent to 5 percent with a peak of 10 percent over the survey period. For zinc respective figures are 1 percent and 4 percent.

Consideration is now given to the NDNS findings for specific nutrients of importance in immune function.

## Vitamin A

The most recent NDNS RP report [53] showed that mean intake of vitamin A was above or close to the RNI in all age/sex groups. However, a significant proportion of the population is hidden by this statistic in that below LRNI intakes occur in 10 percent of adults aged 19-64, 8 percent of adults of 65 and over, 18 percent of 11-18 year olds, 11 percent of 4-10 year olds and 9 percent of children aged 18 months to 3 years. Vitamin A intake overall has fallen since 2008/9 by 21 and 23 percent in children and teenage age groups respectively, by 13 percent in adult groups and by 29 percent in people of 65 and over.

## B Vitamins

**Folate:** The most recent NDNS-RP report [53] found that 10 percent of 11-18 year old girls and 7 percent of 19-64 year old women had below LRNI intakes for folate. Blood folate concentrations have also decreased considerably since 2008/9 for most population groups, and there has been an increase in the proportion of participants with folate concentrations indicating risk of anaemia.

In women of child bearing age (16 to 49 years) [53] red blood cell

**Table 2:** Micronutrient intake changes of particular relevance for immune function between 2008/9 and 2018/19 by gender (per cent with intakes below LRNI) (Data from NDNS 2018/2019) [43].

| | 2008/2009-2009/2010 | | | | 2016/2017 - 2018/2019 | | | | | | Trend | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 4-10 y | 11-18y | 19-64y | 65+ y | 4-10y | 11-18y | 19-64y | 65+y | 4-10y | 11-18y | 4-10y | 11-18y | 19-64y | 65+ |
| **Males** | | | | | | | | | | | | | | |
| Vitamin A (µg/d) | 3 | 12 | 10 | 5 | 9 | 18 | 12 | 10 | 7 | 14 | ↓ | ↓ | ↓ | ↓ |
| Riboflavin (mg/d) | 0 | 8 | 3 | 2 | 1 | 13 | 4 | 5 | 0 | 8 | ↓ | ↓ | ↓ | ↓ |
| Folate (µg/d) | 0 | 2 | 1 | 1 | 1 | 9 | 2 | 2 | 0 | 5 | ↓ | ↓ | ↓ | ↓ |
| Iron (mg/d) | 0 | 6 | 1 | 3 | 1 | 11 | 2 | 1 | 1 | 9 | ↓ | ↓ | ↔ | ↑ |
| Magnesium (mg/d) | 0 | 26 | 16 | 18 | 1 | 33 | 12 | 14 | 0 | 27 | ↓ | ↓ | ↑ | ↑ |
| Selenium (µg/d) | 0 | 21 | 24 | 30 | 1 | 24 | 26 | 34 | 1 | 23 | ↓ | ↓ | ↓ | ↓ |
| Zinc (mg/d) | 5 | 12 | 9 | 11 | 8 | 20 | 6 | 9 | 4 | 17 | ↓ | ↓ | ↑ | ↑ |
| **Females** | | | | | | | | | | | | | | |
| Vitamin A (µg/d) | 5 | 14 | 5 | 1 | 13 | 8 | 8 | 7 | 12 | 18 | ↓ | ↓ | ↓ | ↓ |
| Riboflavin (mg/d) | 0 | 18 | 11 | 2 | 2 | 22 | 13 | 10 | 1 | 20 | ↓ | ↓ | ↓ | ↓ |
| Folate (µg/d) | 0 | 7 | 3 | 2 | 1 | 10 | 7 | 4 | 0 | 8 | ↓ | ↓ | ↓ | ↓ |
| Iron (mg/d) | 1 | 43 | 21 | 1 | 2 | 49 | 25 | 5 | 3 | 48 | ↓ | ↓ | ↓ | ↓ |
| Magnesium (mg/d) | 1 | 51 | 9 | 8 | 3 | 47 | 11 | 11 | 3 | 48 | ↓ | ↑ | ↓ | ↓ |
| Selenium (µg/d) | 1 | 49 | 53 | 51 | 2 | 41 | 46 | 59 | 2 | 44 | ↓ | ↑ | ↑ | ↓ |
| Zinc (mg/d) | 10 | 20 | 4 | 1 | 15 | 16 | 7 | 4 | 13 | 22 | ↓ | ↑ | ↓ | ↓ |

Data is from food sources only. ↓Intakes have gone down. ↔ Intake

folate decreased by 20 percent over the survey period. Time-trend analysis of the proportion of women of childbearing age (16 to 49 years) with a red blood cell folate concentration below the threshold for increased risk of pregnancies affected by a neural tube defect (748 nmol/L) increased from approximately two thirds to almost 90 percent over the course of the survey [53].

### Vitamin B12

Since 2008/9, overall intakes of vitamin B12 have continued to meet recommendations. However, vitamin B12 is found in animal foods such as meat and dairy foods and in some fortified plant-based foods such as some breakfast cereals. Vegans are at particular risk from low vitamin B12 intakes as they consume no animal produce, but the growing number of vegetarians and people following plant based diets could also be at risk if they do not plan their food intake carefully.

### Vitamin C

Vitamin C intake and status is not analysed in the recent NDNS. However, earlier iterations of the NDNS and other UK studies indicate that vitamin C insufficiency is not uncommon in the UK [55]. The Norfolk arm of the European EPIC study evaluated more than 22,400 subjects (aged 40-79 years), and found a vitamin C deficiency (plasma concentration <11 micromol/L) prevalence of 1.4 percent (2.2 percent for men and 0.8 percent for women) with 12 percent of participants (17 percent of men, 8 percent of women) having low vitamin C (plasma concentration of <28 micromol/L) [56] Data from the UK National Diet and Nutrition Survey carried out in 1994/1995 in more than 1,300 elderly participants (aged ≥ 65 years) showed a lower vitamin C status and a higher prevalence of deficiency (14 percent ) [57] whilst the third MONICA study, carried out in Glasgow in 1992 in over 1,200 adults, found that 20 percent of the cohort (26 percent for men and 14 percent for women) were deficient in vitamin C whilst 44 percent (52 percent of men, 36 percent of women) had low vitamin C [58].

### Vitamin D

Poor vitamin D status is common in the UK. The most recent UK National Diet and Nutrition Survey data (NDNS) shows that 16 percent of adults (aged 19-64 years) (18 percent of women, 15 percent of men), have 25-OHD plasma levels below 25 nmol/L (the UK threshold indicating deficiency) [53]. Amongst young people, 2 percent of 4-10-year olds (1 percent of boys, 3 percent of girls) and 19 percent of 11-18-year olds (21 percent of boys, 17 percent of girls) also have low blood levels. A study in UK primary care found that amongst 210,502 patients who had a vitamin D test, one third were deficient (with deficiency identified as a blood level below 30 nmol/L). Deficiency among minority groups ranged from 43 percent among those of mixed ethnicity to 66 percent in Asian people [59].

### Iron

During the past 10 years, there has been a 5 percent reduction in iron intakes. Mean intakes of iron were below the RNI in some groups with intakes below the LRNI in others, including girls aged 11 to 18 years and women aged 19 to 64 years. Nearly half (49 percent) of girls aged 11-18 years and a quarter (25 percent) of women aged 19-64 have intakes of iron below the LRNI, a level which is associated with risk of iron deficiency anaemia [53].

### Zinc

The most recent NDNS RP report [53] showed that mean intake of zinc was above or close to the RNI in all population groups apart from children aged 4 to 10 and 11 to 18 years. Nearly one in five (18 percent) of 11-18 year olds, 11 percent of 4-10 year olds, 6 percent of both 19-64 year olds and people aged 65 and over have a zinc intake below the LRNI [53].

Red meat makes a particularly good contribution to zinc intakes, more so than for iron, particularly in women. Reducing meat intake amongst those with lower intakes of zinc as well as those with lower iron intakes could increase the risk of deficiency of these essential minerals [60].

### Selenium

Selenium intakes have changed little over the NDNS-RP survey period. However, in the 2020 NNDS-RP [53] 32 percent of 11-18 year olds, 36 percent of 19-64 year olds and 47 percent of those aged 65 and over had selenium intakes below the LRNI. Amongst women, the figures were 41 percent, 46 percent and 59 percent respectively.

### Magnesium

In the latest iteration of the NDNS-RP [53], 40 percent of 11-18 year olds, 12 percent of 19-64 year olds and 13 percent of those aged 65 and over had selenium intakes below the LRNI. For women across these age ranges the figures were 47 percent, 11 percent and 11 percent respectively.

### Omega 3 fatty acids

Omega 3 fatty acid intake is a reflection of oily fish intake, the main source of the long chain omega-3s, EPA and DHA. Amongst 11-18 years olds oily fish intake is 21 g weekly and in adults is only 56 g weekly. These intakes are substantially lower than the recommended 140 g weekly.

## Micronutrient Intakes to Optimise Immune Function

Good immune function depends on adequate intakes of most if not all vitamins and minerals and essential fatty acids, particularly omega-3 fatty acids. The European Food Safety Authority (EFSA) has authorised nutrient function health claims for several micronutrients including vitamins A (including beta-carotene), B6, folate, B12, C and D, and the minerals zinc, selenium, iron and copper [1].

What is clear from the UK NDNS data, however, is that a significant proportion of the population has below recommended intakes of essential micronutrients increasing their risk of deficiency. Such low intakes may also prejudice immune function. Hence, there exists a rationale to supplement the diet to top up micronutrient intakes at least to recommended levels. In some instances, intakes of vitamins and minerals above recommended intakes may be required for optimal immune function. This applies in particular to vitamin C [2], where the Nutrient Reference Value (the daily amount of a vitamin or mineral needed by a healthy person to prevent deficiency and set by the European Union (EU) for the purpose of food labelling) is 80 mg daily [61]. However, supplementation of vitamin C (≥ 200 mg/d) in patients with pneumonia was found to restore plasma vitamin C levels and improve respiratory symptom scores with an inverse relationship between length of stay in hospital and dose of vitamin C [62].

Micronutrient supplementation has been shown to improve several specific immune functions particularly where micronutrient deficiencies exist.

### Vitamin C

High doses of vitamin C have been shown to stimulate the activity of T lymphocytes and phagocytes. Such doses also protect leukocytes and lymphocytes from damage from oxidative stress [21]. A recent meta-analysis reported a significantly lower risk of pneumonia

amongst people supplementing with vitamin C, particularly in those with low dietary intakes [63]. In older people, severity of pneumonia and mortality risk was reduced with vitamin C use particularly when plasma vitamin C was low. Vitamin C supplementation has also been shown to reduce the length of time an upper respiratory tract infection such as the common cold lasts, as well as its severity. Additional vitamin C has also been shown to reduce the risk of infection in people under physical stress [64]. In terms of dose, doses of ≥ 200 mg/day saturate vitamin C concentrations in the blood [65], and have been shown to reduce the risk, duration and severity of upper and lower respiratory tract infections [62]. The presence of infection increases vitamin C requirements.

### Vitamin D

The active form of vitamin D (calcitriol) when given as a supplement helps to restore optimal macrophage function [66]. Intramuscular injection of vitamin D (30,000 units) has been shown to reduce IL-6 levels in patients on ventilators. A 2017 systematic review of 25 randomised controlled clinical trials (11,321 participants aged 0 to 95 years) found that the risk of acute respiratory tract infection was reduced by 12 percent with vitamin D supplementation. They found a 19 percent reduction in those receiving daily or weekly vitamin D without additional bolus doses but not in those receiving one or more bolus doses. Among those receiving daily or weekly vitamin D, protective effects were stronger in those with 25-hydroxyvitamin D levels <25 nmol/L at the start than in those with 25-hydroxyvitamin D levels ≥ 25 nmol/L [34].

A 2020 meta-analysis of 45 RCTs (73,384 participants) [67] and a 2021 update of the same meta-analysis including 46 RCTs (75,541 participants) [67] found that a significantly lower proportion of participants in the vitamin D supplementation group had one or more acute respiratory tract infections. Analysis by initial vitamin D plasma concentration showed no difference in benefit but protective effects of supplementation were observed in trials in which vitamin D was given in a dose of 400-1,000 IU (10-25 micrograms) daily for 12 months or less [67].

### Vitamin E

Vitamin E supplementation may also have a positive role in immune function, particularly in older people amongst whom a decline in T-cell mediated immune function is especially evident as people age [68]. Vitamin E supplementation improved antibody response to hepatitis B and tetanus vaccine in a RCT in healthy older people (>65 years) [69]. In another vitamin E supplementation study, vitamin E improved NK cell activity and other immune function parameters bringing their values close to those of younger adults [70]. Vitamin E supplementation of 200 IU daily for 12 months reduced risk of upper respiratory tract infections in a nursing home study involving 617 residents [71].

### Zinc

Zinc deficiency is associated with infectious diarrhoeal illness in children in low-income countries. A 2016 Cochrane analysis of 33 studies including 10,841 children found that zinc supplementation may be of benefit in diarrhoea in areas where zinc malnutrition is high [72]. Zinc supplementation has also been shown to reduce the risk of acute upper respiratory tract infection in zinc deficient children living in low income countries [73]. Findings on zinc supplementation and the common cold have been mixed. A study involving U.S. military cadets found that 15 mg zinc gluconate taken daily for 7 months did not have any significant effect on cold prevention. However, cold frequency was 11 percent lower in the zinc group than in the placebo group (zinc group: 56.7 percent, 135 self-reported cold episodes of 238 survey entries; placebo group: 67.9 percent, 163 self-reported cold episodes of 240 survey entries) [74].

### Selenium

Selenium supplementation has shown variable effects on immunity, and more trials are needed to demonstrate clarity. In a 12 week study in healthy adults with marginal selenium status, selenium supplementation improved T-cell function and concentrations of IL-8 and IL-10 after an influenza vaccine challenge. However, these beneficial changes were contrasted with some more detrimental changes such as reduction in TNF alpha synthesis [75]. A small trial in 22 adult UK subjects found that those with marginal selenium status had suboptimal immune status. When challenged with polio vaccination those with poor selenium status displayed impaired handling of the virus. Supplementation with selenium improved the cellular immune response (e.g. T cell proliferation and T-helper cell increase) but without impact on humoral immune cell response [76].

### Multivitamins

Several peer-reviewed papers have evaluated the effect of multivitamins and other nutrients on immune function. A 12-week RCT in 42 older adults (>65 years) found that multivitamin and multimineral supplementation reduced duration of minor illness, improved vitamin C and zinc status but did not change measures of immune function or vitamin D levels [77].

In a study using data from adult (>19 years) participants in the NDNS-RP (2008-2016) there was a significant inverse association between the intake of vitamin A and E from diet and supplements and respiratory complaints. For vitamin D, intake from supplements, but not diet, was also inversely associated with respiratory complaints. No association between vitamin C and respiratory complaints was found [78].

A further RCT in 477 healthy adults (mean age = 36 years) found the incidence of viral infections of the respiratory tract was 13.6 percent lower (but statistically non-significant) in the group taking a multivitamin/mineral with a probiotic supplement compared with the placebo group. Symptoms of common cold and influenza were reduced in the supplemented group but there was no change in the length of time the illness lasted. During the first 14 days, compared with the placebo group, the vitamin C group had significantly higher leukocytes, lymphocytes and monocytes [79].

Most recently, a study from King's College London [80] looked at dietary supplement use amongst 445,840 subscribers of a COVID-19 app that collected self-reported health related data. In 372,720 UK participants, 175,652 of whom said they used supplements and 197,068 said they did not, there was a 14 percent lower risk of SARS-CoV-2 infection amongst those taking probiotics, omega-3 fatty acids, multivitamins or vitamin D. Self-reported vitamin C, zinc or garlic supplementation had no effect. After adjusting for sex, age and Body Mass Index (BMI), the protective associations in individuals taking probiotics, omega-3 fatty acids, multivitamins and vitamin D were observed in women across all ages and BMI groups, but not in men.

## Discussion

Nutrition has a significant impact on immune function. Evidence for this is recognised in the European Food Safety Authority's (EFSA) authorised nutrient function health claims for the vitamins A (including beta-carotene), B6, folate, B12, C and D, and the minerals

copper, iron, selenium and zinc. These permitted claims are based on scientific assessment of their "contributions to the normal functioning of the immune system" [1].

The evidence base indicates that, at the very least, recommended intakes of all micronutrients, in particular those recognised as essential for normal immune function, and omega 3 fatty acids, should be achieved. It is clear, however, that the UK population does not achieve these intakes, with below LRNI intakes across the board, particularly in younger adults and particularly for trace minerals. The recent UK NDNS-RP data show a worsening of dietary intakes over the period of the programme (2008/2009 to 2018/2019) with below recommended intakes of several of the nutrients involved in supporting normal immune functions. These include vitamins A and D, magnesium and the trace minerals iron, zinc selenium and copper. Omega-3 intakes as a reflection of oily fish intake also fall below recommended intakes.

Of additional importance is that the immune system undergoes some adverse changes during and throughout ageing [81]. Some older people have poor nutritional status due to poor appetite, poor food intake and various co-morbidities, which further affects an already impaired immune function. Immune function may be improved by increasing and maintaining micronutrients at recommended levels, thereby increasing resistance to infection and potentially supporting faster recovery from an infectious illness.

Poor vaccine response has been linked with low micronutrient intakes. This is of potential relevance for COVID-19 and other vaccinations [82]. A systematic review and meta-analysis of nine studies involving 2,367 individuals found lower protection to influenza A virus subtype H3N2 and to influenza B virus in those who were vitamin D deficient [83]. A meta-analysis of 20 RCTs found that probiotics and prebiotics improved immune function in people inoculated with influenza vaccine [84]. Vitamin E in doses of 60 or 200mg daily demonstrated improvement in response to some vaccines in individuals aged over 65 years [69]. Selenium supplementation (50 or 100 micrograms/day) improved some aspects of immune response to a poliovirus vaccine in selenium deficient adults in the UK and also reduced the emergence of mutant viral strains [76].

Supplementation of micronutrients including vitamins, C, D and E, zinc and selenium and/or multivitamins/multiminerals has demonstrated benefits in terms of reducing the risk of infection including that of COVID-19 [80].

Some authors have advised higher-than-recommended intakes of micronutrients for immune function [2]. Such intakes would be difficult to achieve from the diet. Suggested intakes include, in addition to a healthy diet, supplements as follows [2].

- A multivitamin/mineral providing the Nutrient Reference Value (NRV) of a wide range of micronutrients, particularly those involved in immune function.
- ≥ 200 mg vitamin C
- 50 micrograms vitamin D
- 8-11 mg zinc
- 250 mg of the omega-3 long chain fatty acids Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA).

Of note is that these suggestions require validation in robust clinical trials.

## Conclusion

- Nutrition is important for immune function.
- The EFSA has permitted immune function claims for vitamins A (including beta-carotene), B6, folate, B12, C and D, and the minerals copper, iron, selenium and zinc.
- Recommended intakes of all vitamins and minerals should be achieved by everyone in the population for overall health, including immune health.
- Higher than recommended intakes of micronutrients may be beneficial for optimal immune function but clinical trials are required to identify specific doses for specific nutrients.
- In the meantime, the best policy would appear to be to improve the below recommended nutrient intakes and marginal nutrient status which are evident in the UK population by recommending a multivitamin and multimineral supplement in recommended amounts plus an omega-3 supplement providing a total of 250 mg daily of omega-3s each day.

## Competing Interests Statement

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