SUPPLEMENT

Nutrition, Immunosenescence, and Infectious Disease: An Overview of the Scientific Evidence on Micronutrients and on Modulation of the Gut Microbiota

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ABSTRACT

The immune system is key to host defense against pathogenic organisms. Aging is associated with changes in the immune system, with a decline in protective components (immunosenescence), increasing susceptibility to infectious disease, and a chronic elevation in low-grade inflammation (inflammaging), increasing the risk of multiple noncommunicable diseases. Nutrition is a determinant of immune cell function and of the gut microbiota. In turn, the gut microbiota shapes and controls the immune and inflammatory responses. Many older people show changes in the gut microbiota. Age-related changes in immune competence, low-grade inflammation, and gut dysbiosis may be interlinked and may relate, at least in part, to age-related changes in nutrition. A number of micronutrients (vitamins C, D, and E and zinc and selenium) play roles in supporting the function of many immune cell types. Some trials report that providing these micronutrients as individual supplements can reverse immune deficits in older people and/or in those with insufficient intakes. There is inconsistent evidence that this will reduce the risk or severity of infections including respiratory infections. Probiotic, prebiotic, or synbiotic strategies that modulate the gut microbiota, especially by promoting the colonization of lactobacilli and bifidobacteria, have been demonstrated to modulate some immune and inflammatory biomarkers in older people and, in some cases, to reduce the risk and severity of gastrointestinal and respiratory infections, although, again, the evidence is inconsistent. Further research with well-designed and well-powered trials in at-risk older populations is required to be more certain about the role of micronutrients and of strategies that modify the gut microbiota–host relationship in protecting against infection, especially respiratory infection. *Adv Nutr* 2022;13:1S–26S.

Statement of Significance: The article integrates the current state of knowledge around the impacts of aging, nutrition, and the gut microbiota on the immune system and then comprehensively reviews the influence of selected micronutrients (vitamins C, D, and E and zinc and selenium) and pro- and prebiotics on immunity, inflammation, and infection, particularly respiratory tract infection, focusing on trials conducted in older humans.

Keywords: immunity, inflammation, infection, aging, gut microbiota, vitamin C, vitamin D, vitamin E, zinc, selenium

Introduction

The immune system is key to host defense against pathogenic organisms. It is dispersed throughout the body, with cells moving between body compartments via the bloodstream and the lymph. The immune system is highly sophisticated and has barrier, recognition, elimination, and memory components. These are achieved as a result of the multiple cell types, cellular interactions, and chemical mediators that together form the immune response. Individuals with weakened immunity are at increased risk of infections and of infections becoming more severe. Thus, there is interest in those factors that support the immune system and those factors that weaken it. The diet and the gut microbiota are 2 interrelated factors that influence the

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immune response; among dietary components, a range of micronutrients have vital roles in the immune system. The immune system also changes through the life course and many older people show a decline in immune responses. This has been termed "immunosenescence" and predisposes older people to infections and also to weaker vaccination responses than seen in young and middle-aged adults. Older people can also show an elevation in inflammation, termed "inflammaging." This can be seen with the development of some chronic inflammatory conditions with age, but also with chronic low-grade inflammation which increases risks of the common noncommunicable diseases of aging. This review describes the effects of selected key micronutrients (vitamins C, D, and E and zinc and selenium) and strategies to beneficially alter the gut microbiota on the immune system and on infection risk and severity, with a focus on older people. The review starts with an overview of the immune system and the general effects of aging, the gut microbiota, and nutrition on it.

Overview of the Immune System and Its Components

The immune system acts to protect the host individual from infectious agents that occur in the environment (pathogenic bacteria, viruses, fungi, parasites) and from other noxious insults. It also plays a role in surveillance and destruction of tumor cells, in clearing dead and dying cells and cellular debris, in wound healing, and in enabling tolerance to harmless environmental constituents like food and commensal bacteria and to the host. The immune response involves various cell types distributed in many locations throughout the body. Cells move between these locations in the bloodstream and the lymph. Immune cells are organized into discrete lymphoid organs in some places in the body. Immune cells arise and mature in the primary lymphoid organs (bone marrow and thymus) and interact with one another and with antigens in the secondary lymphoid organs, which include lymph nodes and the spleen. The immune system has 2 general functional divisions. These are the innate (also termed "natural") immune system and the acquired (also termed "specific" or "adaptive") immune system (**Table 1**, **Figure 1**) (1, 2). These 2 parts of the immune system are functionally interlinked.

Physical barriers, soluble factors, and phagocytic cells contribute to innate immunity; indigenous commensal bacteria within the gastrointestinal tract may also be considered part of innate immunity (see section "The role of the gut microbiota in shaping and supporting the immune system"). The phagocytic cells are the granulocytes (also known as polymorphonuclear leukocytes and including neutrophils, basophils, eosinophils), monocytes, and macrophages. Inflammation is part of innate immunity. In general, inflammation acts to create an environment that is hostile to pathogens, it initiates pathogen killing, and it causes changes in the metabolism of the host. Many cell types play roles in the inflammatory response, which involves the production of, and responses to, a number of chemical mediators. The cardinal signs of inflammation are redness, swelling, heat, pain, and loss of function. These are all caused by the cellular activation and chemical mediator release that occur during the initiation and perpetuation of the inflammatory response. Although the inflammatory response is designed to be damaging to pathogens, the cellular activities and the chemical mediators that are involved in inflammation can also cause damage to host tissues. Fortunately, inflammation is normally self-limiting and resolves, often rapidly. This is because various inhibitory mechanisms are activated as inflammation runs its course. Loss of these regulatory processes can result in excessive, inappropriate, or ongoing inflammation that can cause irreparable damage to host tissues, leading to pathology and disease.

Although it has been traditionally considered that innate immunity has no memory and is therefore not influenced by prior exposure to a pathogenic organism, it is now thought that innate immunity can be primed or trained through exposure to general structural features of organisms, termed "microbe-associated molecular patterns." Phagocytic cells, the main effectors of innate immunity, express receptors that recognize microbe-associated molecular patterns; these receptors are termed "pattern recognition receptors" and include the Toll-like receptors (TLRs). Binding of bacteria to surface receptors on phagocytes triggers phagocytosis (engulfing) and subsequent destruction of the bacteria by toxic chemicals, such as superoxide radicals and hydrogen peroxide. Natural killer (NK) cells also possess surface receptors and destroy their target cells (virally infected cells, tumor cells) by the release of cytotoxic proteins. In this way, innate immunity provides a rapid first line of defense against invading pathogens. However, an immune response often requires the coordinated actions of both innate immunity and the more powerful and flexible acquired immunity.

Acquired immunity involves the specific recognition of molecules (termed "antigens") on an invading pathogen, which distinguish it as being foreign to the host. Lymphocytes are the main effector cells of acquired immunity. These are

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Abbreviations used: COVID-19, coronavirus disease 2019; CRP, C-reactive protein; GALT, gut-associated lymphoid tissue; MT, metallothionein; PG, prostaglandin; PGE_2, prostaglandin E_2; RCT, randomized controlled trial; ROS, reactive oxygen species; SARS-CoV, severe acute respiratory syndrome coronavirus; TCR, T-cell receptor; Th, T-helper type; TLR, Toll-like receptor; URTI, upper respiratory tract infection.

TABLE 1 The components of the immune system and their classification into innate and acquired immunity[1]

Innate (natural) immunity		Acquired (adaptive) immunity	
Barriers	**Cellular components**	**Cell-mediated immunity**	**Humoral immunity**
Skin Mucosal surfaces Mucus Antimicrobial proteins in secretions Acid pH of stomach	Granulocytes (neutrophils, basophils, eosinophils, mast cells) Phagocytes (neutrophils, macrophages, monocytes, dendritic cells) Inflammatory response NK cells Other innate cells (includes innate lymphoid cells, mucosal associated invariant T cells)	T lymphocytes (helper, cytotoxic, regulatory, others) Cytokines Memory response	B lymphocytes Antibodies

[1] Adapted from reference 1.

classified as T and B lymphocytes (also called T cells and B cells). B lymphocytes develop and mature in the bone marrow before being released into the circulation, while T lymphocytes develop in the bone marrow but mature in the thymus. Each individual lymphocyte carries surface receptors for a single antigen, meaning that the acquired immune system is highly specific. However, acquired immunity is extremely diverse; the lymphocyte repertoire in humans has been estimated to be able to recognize approximately 10^{11} antigens. The high degree of specificity, combined with the huge lymphocyte repertoire, means that only a relatively small number of lymphocytes will be able to recognize any given antigen. Therefore, acquired immunity involves proliferation of antigen-specific cells (called clonal expansion) to increase the number of lymphocytes that have the ability to recognize the antigen causing the initial response. This process takes time, meaning that the acquired immune response becomes effective over several days after the initial activation. It also persists for some time after the removal of the initiating antigen. This persistence gives rise to immunological memory, which is also a characteristic feature of acquired immunity. Memory is the basis for a stronger,

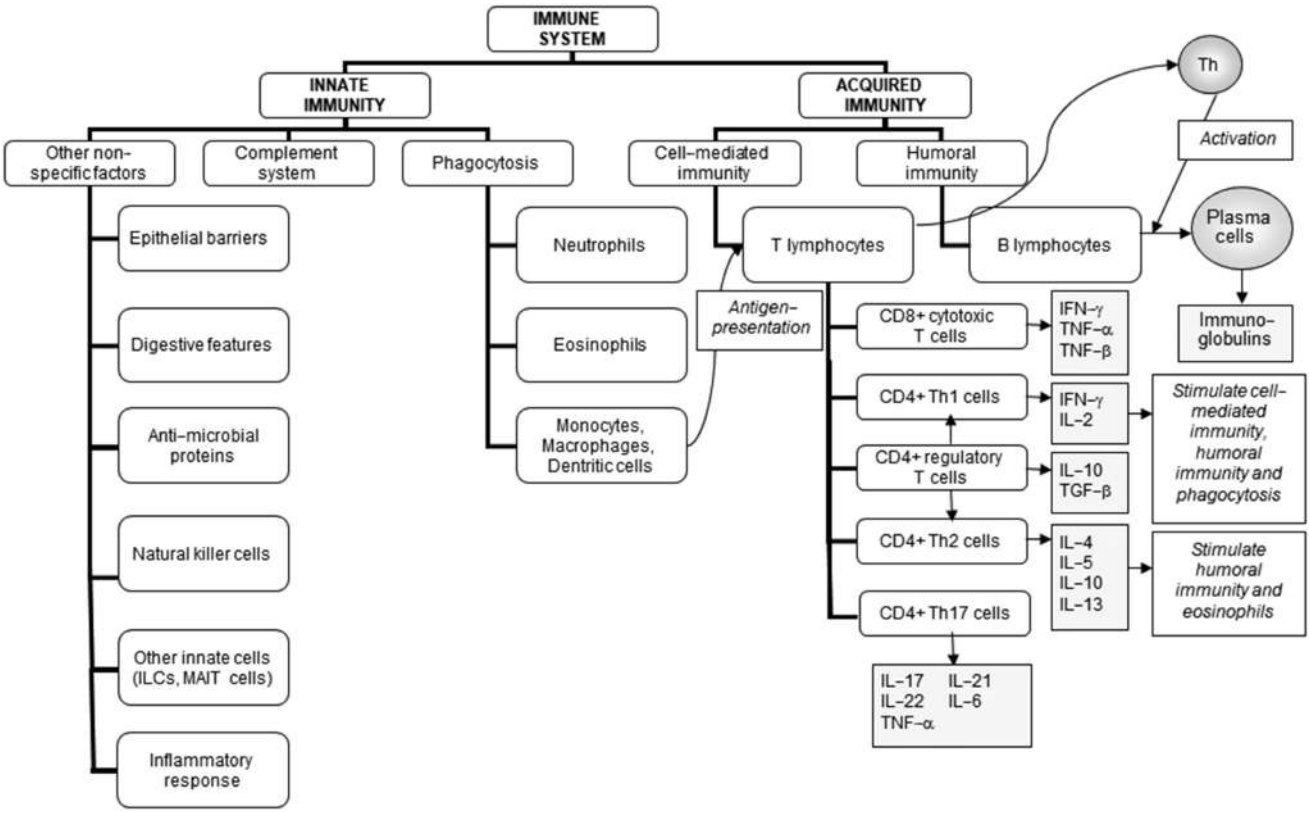

FIGURE 1 The components of the immune system and their division into innate and acquired immunity. ILC, innate lymphoid cell; MAIT, mucosal associated invariant T; TGF, transforming growth factor; Th, T helper. Reproduced from reference 2 .

more effective immune response upon re-exposure to an antigen (i.e., reinfection with the same pathogen) and is the basis of vaccination.

B lymphocytes are the immune cells that produce antibodies, which are antigen-specific immunoglobulins (Igs). This form of protection is called humoral immunity. B lymphocytes also carry Igs on their surface that are capable of binding an antigen. Binding of these surface Igs with antigen causes proliferation of the B lymphocyte and subsequent transformation into plasma cells, which secrete large amounts of antibody with the same specificity as the parent cell. There are 5 major classes of Igs (IgA, IgD, IgG, IgM, and IgE), each of which elicits different aspects of the humoral immune response. Antibodies can "neutralize" toxins or microorganisms by binding to them and preventing their attachment to host cells, and they can activate complement proteins in plasma, which, in turn, promote the destruction of bacteria by phagocytes.

Humoral immunity deals with extracellular pathogens (e.g., many bacteria). However, some pathogens, particularly viruses, but also certain bacteria, enter host cells, meaning they can escape humoral immunity. Instead, they are dealt with by cell-mediated immunity, which involves T lymphocytes. T lymphocytes express antigen-specific T-cell receptors (TCRs) on their surface. However, unlike B lymphocytes, T lymphocytes are only able to recognize antigens that are presented to them on a cell surface (the cell presenting the antigen to the T lymphocyte is termed an "antigen-presenting cell"). Dendritic cells are professional antigen-presenting cells, but other phagocytes also act in this way. Activation of the TCR results in T-lymphocyte proliferation. Activated T lymphocytes also synthesize and secrete the cytokine IL-2, which further promotes proliferation and differentiation. There are several types of T lymphocytes, including cytotoxic T cells, helper T cells, and regulatory T cells. Cytotoxic T lymphocytes carry the surface protein marker CD8 and kill infected cells and tumor cells by secretion of cytotoxic enzymes, which cause lysis of the target cell. Helper T lymphocytes carry the surface protein marker CD4 and eliminate pathogens by stimulating the phagocytic activity of macrophages and the proliferation of, and antibody secretion by, B lymphocytes. Helper T cells that have not previously encountered antigen produce mainly IL-2 upon the initial encounter with an antigen. These cells can differentiate into either T helper type (Th) 1 or Th2 cells. This differentiation is regulated by cytokines: IL-12 and IFN-γ promote the development of Th1 cells, while IL-4 promotes the development of Th2 cells. Th1 cells produce IL-2 and IFN-γ, which activate macrophages, NK cells, and cytotoxic T lymphocytes, which are the principal effectors of cell-mediated immunity against bacteria, viruses, and fungi. Th2 cells produce IL-4, which stimulates IgE production, and IL-5, an eosinophil-activating factor. Th2 cells are responsible for defense against helminthic parasites, which is due to IgE-mediated activation of mast cells and basophils. More recently characterized classes of helper T cells include Th17 cells, which are involved in inflammation and autoimmunity, and regulatory T cells, which produce IL-10 and transforming growth factor-β and suppress the activities of other T cells and B cells, so preventing inappropriate activation.

Factors That Influence Immunity

Overview

Any measurement of an immune or inflammatory biomarker in a group of individuals reveals significant heterogeneity (3–6). This heterogeneity relates to between-individual differences in the factors that influence the immune response. These include many unmodifiable factors such as genetics, sex, stage of the life course, and time of day, but many modifiable factors also influence the immune response. These include stress, physical fitness, frailty, body fatness, diet, and gut microbiota composition. Here, we focus on aging, the gut microbiota, and nutrition as factors influencing the immune response.

The effect of aging on the immune system: the dual burdens of immunosenescence and inflammaging

In comparison to younger adults, older adults are more susceptible to infectious diseases [e.g., influenza, pneumonia, tuberculosis, coronavirus disease 2019 (COVID-19)] and account for a greater proportion of the total infectious disease burden in high-income countries (7–13) and for higher use of antibiotics (14). It is increasingly recognized that older individuals experience prolonged infection periods, which are associated with an increased risk of morbidity and mortality (9, 13, 15). Vaccination is considered the optimal preventative measure against infections and mortality caused by them, yet vaccines often have reduced efficacy in older adults (9, 16–19). Thus, the aging population poses a unique challenge, requiring the identification and implementation of new preventative and therapeutic approaches to reduce infectious disease burden and enhance vaccine efficacy.

One important factor contributing to increased susceptibility to infection in older people is age-related immune decline, termed "immunosenescence" (20–24). Multiple changes to immune cell development, numbers, and function occur as part of immunosenescence (**Table 2**). First, there is decreased output of immune cells from bone marrow (25, 26), the site of origin of all immune cells. In addition, involution of the thymus with age decreases output of naive T lymphocytes with a loss in TCR diversity and an accumulation of memory T lymphocytes (27). The overall result of these changes is lowered numbers of T lymphocytes in the blood, changes in the ratio of different T lymphocytes (e.g., fewer naive and relatively more memory T cells), and impaired T-lymphocyte responsiveness. Immunosenescence also affects B lymphocyte numbers and function and the function of antigen-presenting cells and some components of innate immunity, including impairment of several fundamental aspects of neutrophil, macrophage, and NK-cell function (Table 2). Thus, aging can be associated with a reduced ability to mount an effective and appropriate immune response to both novel and previously encountered

TABLE 2 Summary of the key features of age-related immune decline (immunosenescence)[1]

Cell type	Effect seen in immunosenescence
T lymphocyte	• Decreased numbers in the circulation • Imbalances among different phenotypes (e.g., decreased ratio of $CD4^+$ to $CD8^+$ cells) • Decline in naive T-lymphocyte production and decreased numbers in the circulation • Accumulation of nonfunctional memory T lymphocytes • Diminished antigen receptor diversity • Impaired responsiveness • Impaired proliferation • Impaired production of cytokines (e.g., IL-2 and IFN-γ)
B lymphocytes	• Decreased numbers of naive B lymphocytes in the circulation • Accumulation of nonfunctional memory B lymphocytes in the circulation • Impaired responsiveness • Altered balance of immunoglobulins
Dendritic cells	• Decreased phagocytosis • Decreased TLR expression • Decreased responsiveness • Decreased type 1 IFN production
Neutrophils	• Numbers in the circulation are preserved • Impaired chemotaxis • Impaired oxidative burst and bacterial killing • Impaired phagocytosis • Decreased TLR expression • Decreased production of neutrophil extracellular traps • Decreased responsiveness
Monocytes	• Altered TLR expression • Decreased responsiveness • Altered pattern of cytokine production
Macrophages	• Impaired phagocytosis • Altered TLR expression • Increased prostaglandin E2 production
NK cells	• Increased numbers in the circulation • Imbalances among different phenotypes • Impaired cytotoxicity • Impaired responsiveness

[1] TLR, Toll-like receptor.

pathogens, which increases an individual's risk of severe disease and mortality. Additionally, loss of T-cell– and NK-cell–mediated immunity can increase an individual's risk for developing cancerous lesions and metastasis. Age-related changes in the immune response are exaggerated with frailty (28) and in those with poorer micronutrient status (29–31), suggesting that poor nutrition is one contributor to the immune decline seen in many older people.

While inflammation is necessary to orchestrate an appropriate immune response to an infection (see earlier), aging introduces a paradox: chronically raised low-grade inflammation, termed "inflammaging" (32–36). Inflammaging is seen as an increase in blood plasma or serum concentrations of the acute-phase protein C-reactive protein (CRP) and of inflammatory cytokines like IL-6 (32–36). This may reflect sensitized proinflammatory signaling pathways in older people. One of the current prevailing theories for the cause of chronic inflammation is the decreased turnover of "senescent cells" (37). In younger individuals, senescent cells are identified, eliminated, and replaced quickly. However, with age, the number of senescent cells can rapidly accumulate. In part, the accumulation of senescent cells occurs because there is a decrease in immune surveillance mechanisms, which are meant to remove damaged or necrotic host cells and maintain tissue homeostasis. Senescent cells are characterized by a chronic secretion of pro-tumorigenic and proinflammatory molecules, collectively referred to as the "senescence-associated secretory phenotype" (37). This array of secreted factors is considered to be a key contributor to inflammaging and is suggested to increase an older individual's risk for chronic disease (32–38) (**Figure 2**). Inflammation has been identified as a strong predictor of all-cause mortality in the elderly (39).

The role of the gut microbiota in shaping and supporting the immune system

The human gut is host to a significant number of bacteria and other microorganisms, which are collectively referred to as the gut microbiota. The large intestine has the greatest number and diversity of bacterial species, estimated at 10^{11} bacteria/g of colonic contents (40). In addition to hosting the largest quantity of microbes in the human body, the gut wall is also the largest site of immune tissue, known as the gut-associated lymphoid tissue (GALT). It is estimated that, in

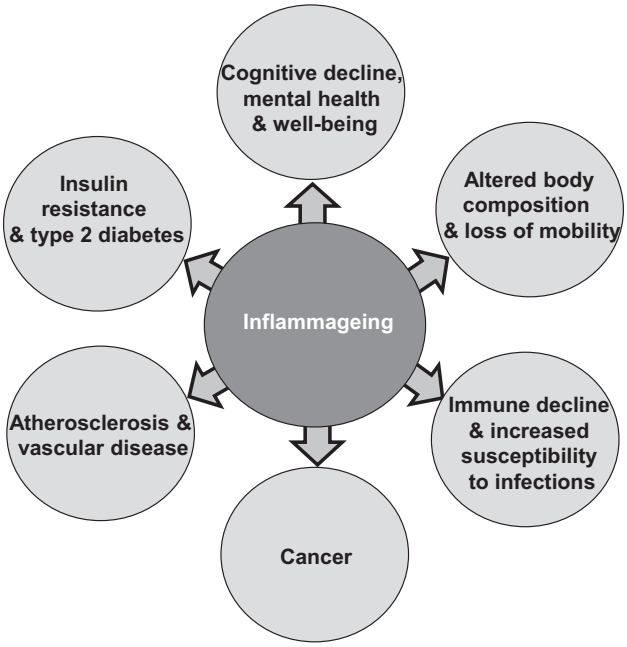

FIGURE 2 The central role of inflammaging in chronic conditions of aging. Adapted (color changes) from reference 33.

humans, 70% of immune cells are associated with the GALT, signifying its importance. The key roles of the GALT are surveillance of microorganisms and other sources of antigens (e.g., components of food) in the gut lumen and mounting either active or tolerogenic responses to these. Thus, the host immune system plays a role in regulating the composition of the gut microbiota. In turn, the gut microbiota plays a role in both the development and proper functioning of the host immune system (41–43) (**Figure 3**). Commensal bacteria of the microbiota seem to contribute to the development of a normally functioning immune system: in germ-free animal models, there are observable reductions in the size of all lymphoid organs, Ig production, and lymphocyte populations (44). The microbial communities that make up the gut microbiota have direct and indirect effects on host immune function (41–44). Indigenous commensal bacteria within the gastrointestinal tract play a role in host immune defense by creating a barrier against colonization by pathogens and they also compete with pathogenic bacteria for available nutrients. In addition to creating a physical barrier, many products of the metabolism of commensal bacteria, including lactic acid and antimicrobial proteins, can directly inhibit the growth of pathogens. As well as these direct interactions between commensal and pathogenic bacteria, they can interact with the host's gut epithelium and GALT (41–43). These communications with the host may occur through metabolites released from the bacteria or through direct cell-to-cell contact. Among the most important products of oligosaccharide metabolism by gut bacteria are the SCFAs (acetate, propionate, and butyrate), with butyrate being an important fuel for the gut epithelium and also regulating epithelial gene expression through histone modification. SCFAs increase gut mucosal barrier integrity by increasing mucus secretion, IgA production, and tight junction proteins (45, 46). Some lactobacilli convert tryptophan into kynurenine metabolites, which directly activate the aryl hydrocarbon receptor (47), which is necessary for proper gut barrier functionality and the development of specific immunoregulatory T cells (48, 49). Polysaccharide A produced by *Bacteroides fragilis* drives the differentiation of regulatory T cells, which are essential for keeping immune responses in check and for the development of oral tolerance (50). Thus, overall, the gut microbiota contributes to gut and immune development, to host immune defense, to maintenance of tolerance, and to control of inflammation.

The human gut microbiota demonstrates a high degree of variability among individuals (51), reflecting differing exposures to environmental factors and the influence of the host phenotype. The human gut microbiota is strongly influenced by habitual diet (52–55). Furthermore, aging and the presence or absence of diseases significantly influence the composition of the microbiota (56). For example, with aging, the abundance and diversity of bifidobacteria decline (57), while bacteria including streptococci, staphylococci, enterococci, and enterobacteria increase (58). There are significant differences in the microbiota of free-living older adults and those residing in residential care (59, 60), as shown in **Figure 4**. Aging also affects the GALT. In murine models, aging reduced gut mucosal secretory IgA responses, impaired oral tolerance to new antigens, and impaired mucosal dendritic cell function (61), as reviewed elsewhere (62–65). Given the role of the gut microbiota in supporting the host immune system, it is likely that age-related changes in the microbiota are linked with immunosenescence and inflammaging.

The role of nutrition in supporting the immune system

Foods and beverages provide macro- and micronutrients, as well as other bioactive components, that contribute to the normal functioning of the immune system, including supporting barrier function (66–69). Components of the diet act in a variety of ways to influence the immune response:

- Macronutrients act as fuels for energy generation by immune cells;
- Macronutrients provide substrate ("building blocks") for the biosynthesis that is involved in the immune response (e.g., amino acids for Igs, cytokines, new receptors, acute-phase proteins);
- Many micronutrients are regulators of molecular and cellular aspects of the immune response (e.g., iron, zinc, vitamin A, vitamin D);
- Some nutrients are substrates for the synthesis of chemicals involved in the immune response (e.g., arginine and nitric oxide; arachidonic acid and eicosanoids);
- Some micronutrients have specific anti-infection roles (e.g., zinc, vitamin D);

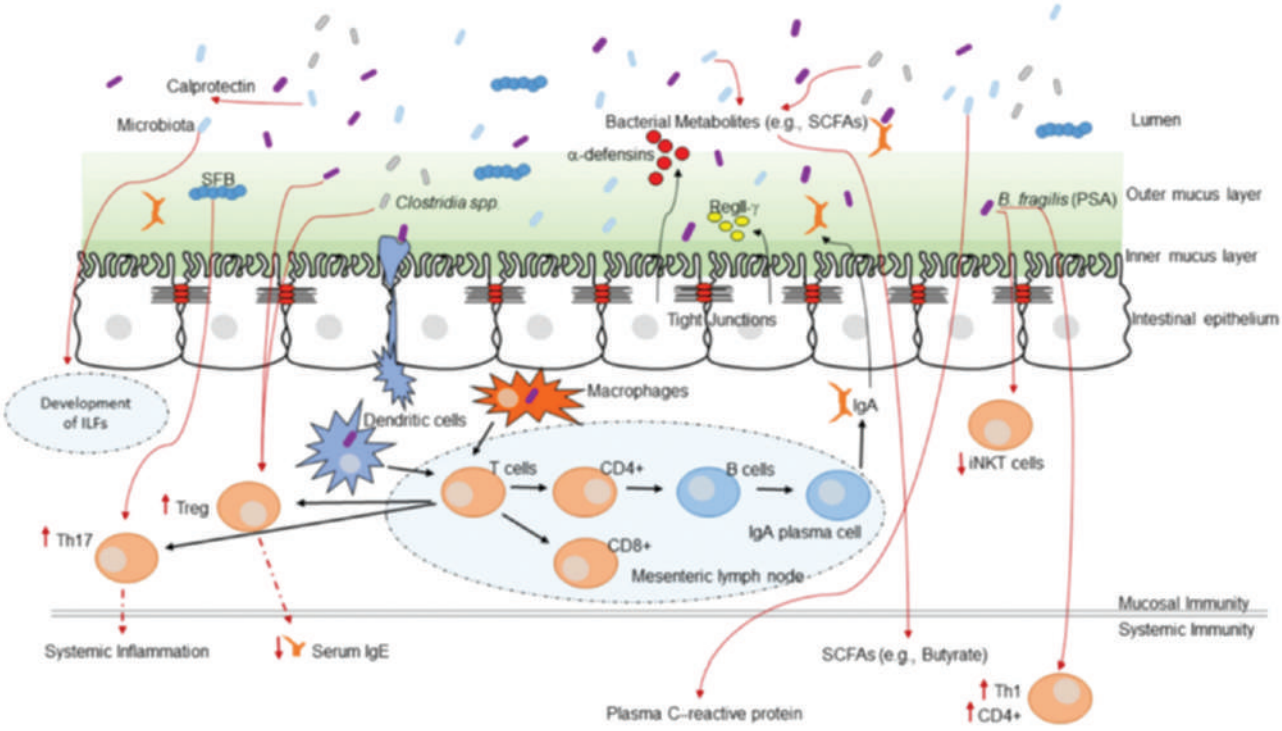

FIGURE 3 How the gut microbiota shapes host immunity. Multiple immune effectors function together to minimize bacterial-epithelial invasion. These include the mucus layer, epithelial antibacterial proteins, and IgA secreted by lamina propria plasma cells. Compartmentalization is accomplished by unique anatomic adaptations that limit commensal bacterial exposure to the immune system. Some microbes are sampled by intestinal dendritic cells. The loaded dendritic cells traffic to the mesenteric lymph nodes through the intestinal lymphatic but do not migrate to distal tissues. This compartmentalizes live bacteria and induction of immune responses to the mucosal immune system. Induced B cells and T-cell subsets recirculate through the lymphatic and the bloodstream back to mucosal sites, where B cells differentiate into IgA-secreting plasma cells. Thus, the intestinal microbiota shapes host mucosal as well as systemic immunity. ILF, isolated lymphoid follicle; iNKT, invariant natural killer T; PSA, polysaccharide A; SFB, segmented filamentous bacteria; Th, T helper. Treg, regulatory T cell. Reproduced from reference 43 with permission.

- Many nutrients and plant bioactives are involved in protection of the host from the oxidative and inflammatory stress imposed by the immune response (e.g., vitamin C, vitamin E, cysteine, zinc, copper, selenium, flavonoids);
- Many food components contribute to creating a diverse gut microbiota that supports the immune response (e.g., plant-derived fibers and nondigestible polysaccharides, prebiotic oligosaccharides).

These considerations suggest multiple sites of interaction of food components with the immune system. First, absorbed food components can act systemically to target the different components of the immune system (e.g., in bone marrow, the thymus, the bloodstream, secondary lymphoid organs, and other organs). Second, multiple food components can act to influence the immune system without being absorbed systemically. For example, they could have local actions on epithelial barrier function or on the GALT; they could modulate the gut microbiota composition, so influencing gut microbiota–immune system cross-talk; they could be fermented by the microbiota resulting in metabolites (e.g., SCFAs), which can act locally on epithelial and immune cells or be absorbed and act systemically; or they could train or prime immune cells involved in surveillance of the luminal contents of the gastrointestinal tract. Although these latter actions are primarily focused on the gastrointestinal tract, because of recirculation of cells from the GALT to other sites, including the respiratory tract, effects initiated at the gut level can have actions elsewhere, including the airways.

Micronutrients, Immunity, and Infection with an Emphasis on Older People

Micronutrients to support the immune system in older people

Nutritional status is considered to be a major contributor to immune system development (70) and function (66–69). It follows that nutrient status can be a determinant of susceptibility to, or severity of, infection (71, 72). Furthermore, the relation between nutrition, immunity, and infection suggests that specific nutrients and other dietary components could be used to favorably modulate immune

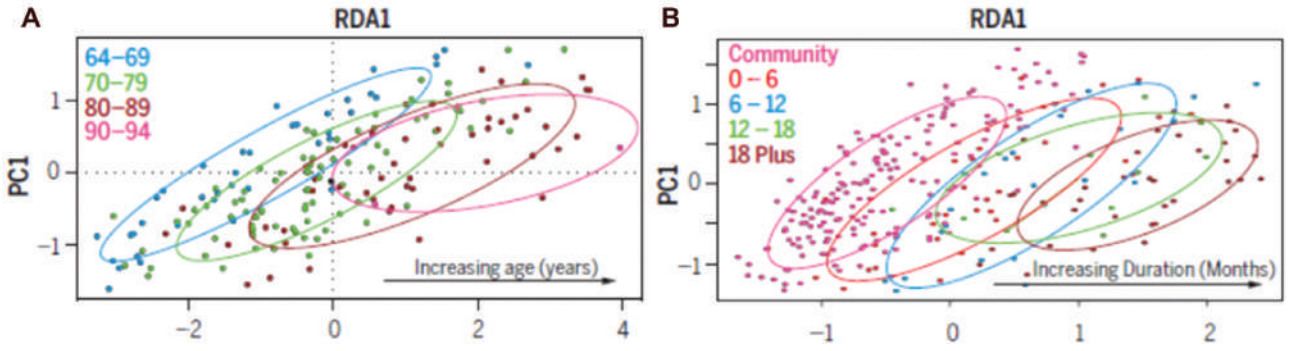

FIGURE 4 Changes to the gut microbiota with age and with duration of residential care. Redundancy analysis plot of microbiota composition (log-transformed OTU dataset) of (A) community-dwelling individuals by age (years) ($n = 176$; $P < 0.002$). (B) Full dataset of community and long-term residential care individuals by duration in care (months) ($n = 282$; $P < 0.001$). OTU, operational taxonomic unit. Reproduced from reference 59 with permission from American Association for the Advancement of Science (AAAS). PC, principal component; RDA, redundancy analysis.

cell function, inflammatory responses, and infectious disease susceptibility and prognosis (2, 66–69, 73, 74). This is particularly important in older people, because many have generally poor nutritional status and, in particular, habitual intakes of a number of vitamins and minerals that are below those that are recommended (75–79). Since micronutrients are important to supporting the immune response and controlling inflammation (2, 66, 67, 80, 81), insufficient intake may deleteriously impact immune competence, contributing to increasing the susceptibility of older people to infection. Hence, it has been suggested that micronutrient supplementation at or above recommended intakes may be beneficial in older individuals (82, 83). Among the micronutrients, the roles of vitamins A, C, D, and E and the minerals zinc, copper, iron, and selenium are well explored, but B vitamins, vitamin K, magnesium, and others all have roles. Here we review the roles of vitamins C, D, and E and zinc and selenium on immunity and infection with a focus on older people.

Vitamin C

Vitamin C contributes to supporting innate and adaptive immune defenses, as well as to the physical barriers that limit entry to pathogens (84, 85). Vitamin C helps to maintain the integrity of the internal and external barriers acting as a cofactor of enzymes required in collagen synthesis and cross-linking and in connective tissue healing (86). Many innate immune cells, particularly granulocytes and macrophages, produce reactive oxidative species (ROS) to lyse bacteria or promote apoptosis of infected host cells. However, ROS can cause unintended damage to both the cell producing them and to neighboring, uninfected host cells. Vitamin C, as a potent antioxidant, helps to protect against such damage. Neutrophils have specific transport systems for vitamin C uptake and accumulation (87, 88) and to recycle oxidized vitamin C (89) in order to protect against the damage caused by ROS. During infection, granulocytes such as neutrophils produce a high concentration of ROS for microbial killing, which, in turn, increases vitamin C uptake in a nonspecific manner and increases the host requirement for vitamin C to protect itself (90). Vitamin C is required for apoptosis and macrophage-mediated clearance of dead immune cells and can promote chemotaxis of neutrophils (84). Vitamin C supports differentiation, proliferation, and function of T and B cells (80, 81, 84, 91). Incubation of mononuclear cells isolated from the blood of older adults with severe community-acquired pneumonia with vitamin C decreased oxidative stress, DNA damage, and inflammatory cytokine production (92). A vitamin C–deficient diet in healthy young-adult humans decreased mononuclear cell vitamin C content by 50% and decreased the T-lymphocyte–mediated immune responses to recall antigens (93).

The ability of supplemental vitamin C to enhance immune function has been investigated in adults, including older adults, in several studies. One study reported that 6 wk of vitamin C supplementation (1000 mg/d) in elderly women (mean age: 72.8 y) resulted in no significant changes in leukocyte expression of genes encoding the proinflammatory markers IL-1, IL-6, and CRP or the anti-inflammatory marker IL-10 (94). However, a clear trend of decreasing IL-6 and increasing in IL-10 mRNA was observed (94). A 6-wk randomized controlled trial (RCT) of vitamin C (1000 mg/d) in patients aged 45 to 60 y with diagnosed type 2 diabetes and poor glycemic control reported increased phagocytosis and oxidative burst by granulocytes (95). Vitamin C (500 mg/d) restored multiple indices of immune function in both older men and women (mean age: 74 y), bringing them closer to the levels seen in young adults (mean age: 38 y) (96), effects that were maintained 6 mo postsupplementation. The combination of vitamin C (1000 mg/d) and vitamin E (200 mg/d) resulted in a significant increase in lymphocyte proliferation and in granulocyte phagocytosis in both healthy

older women and in older women (mean age: 72 y) with major depressive disorders or coronary artery disease (97).

If vitamin C is needed to support the immune system, then vitamin C deficiency would lead to increased susceptibility to, and severity of, infectious disease. In fact, recognition of the connection between vitamin C and infectious disease dates to the early 20th century when it was found that vitamin C deficiency was associated with scurvy and its related infections, including pneumonia (98). In the 1970s, the Nobel Laureate Linus Pauling suggested that high doses of vitamin C might decrease the incidence and duration of the common cold (99). Thereafter, a number of trials investigating vitamin C supplementation for the prevention and treatment of the common cold were conducted, but comparisons of the different studies have been complicated because of the variations in the dosage administered and the participants studied and inadequate control groups (98). A meta-analysis of 24 RCTs involving children and adults was conducted to determine whether vitamin C has an effect on the incidence, duration, and severity of the common cold at a dosage of at least 200 mg/d (100). Overall, there was little benefit in consuming vitamin C to decrease the incidence of the common cold for the general population of participants who used vitamin C regularly for a period of 2 wk to 5 y (risk ratio: 0.95; 95% CI: 0.92, 0.98). However, when the trials were subgrouped into whether participants had "no physical stress" or "heavy acute stress," vitamin C supplementation was found to benefit those who experienced heavy acute stress (i.e., physical activity). The risk ratio of the "no physical stress" trials was 0.97 (95% CI: 0.94, 1.00) while the risk ratio of the "heavy acute stress" trials was 0.48 (95% CI: 0.35, 0.64). Participants undertaking acute physical activity included marathon runners, skiers, and soldiers conducting subarctic exercises. Those who engage in short-term exposure to extreme physical stress may have higher antioxidant intake requirements because of the increased ROS production compared with the general population. In the same meta-analysis, regular supplementation with vitamin C appeared to decrease the duration of colds: high-dose (>200 mg/d), regular intake of vitamin C significantly reduced the duration of cold symptoms by 8% in adults and 14% in children (100). These high doses also prevented the onset of symptoms in extreme athletes (100). Vitamin C supplementation had a modest effect on the severity of colds, defined as days confined to the home (100). It is possible that granulocytes and other immune cells can better respond to an infection and the related increased metabolic requirements for vitamin C in those who have consumed these higher doses of vitamin C, resulting in more rapid resolution of symptoms.

Vitamin C supplementation (200 mg/d) for 4 wk in hospitalized older adults with acute respiratory tract infections who were identified to have very low vitamin C concentrations reduced respiratory symptom scores (101). Several studies report an association between low vitamin C status and increased susceptibility to, and severity of, COVID-19 [e.g., (102)]. However, such studies cannot be used to infer cause and effect. A small retrospective case study in patients with severe (mean age: 63 y) or critical (mean age: 55 y) COVID-19 pneumonia reported that a high dose of intravenous vitamin C (~170 mg/kg body weight daily) significantly decreased CRP concentrations at day 3 and 7, and found that blood lymphocyte and T-helper cell counts in severe patients reached normal levels at day 3 (103). There was a trend to improved airway function and reduced Sequential Organ Failure Assessment (SOFA) score (103). In contrast, a small open-label RCT in patients (mean age: 57.5 y for cases and 61 y for controls) with severe COVID-19 infection did not find significantly better outcomes at discharge in the group treated with a high dose of vitamin C (6 g/d) in addition to the standard treatment regimen (104). Trials of vitamin C in patients with COVID-19 have been reviewed recently (105).

In summary, vitamin C supports many aspects of innate and acquired immunity and vitamin C deficiency results in immune impairments. Supplemental vitamin C seems to enhance immune cell functions at the doses tested and in older adults. Trials of vitamin C in relation to respiratory infection are inconsistent, perhaps relating to dose and the characteristics of the participants studied. Despite conflicting results, the effects of vitamin C may be useful to prevent or reduce the severity of respiratory diseases in groups most at risk for severe disease, such as older adults and/or those who have low concentrations of vitamin C (98). Future work should aim to confirm or refute the proposed benefits of vitamin C on respiratory disease in older adults through conduct of well-designed and adequately powered studies.

Vitamin D

The precursor to the active form of vitamin D can be acquired from the diet or be produced via UVB irradiation of the skin. Subsequent hydroxylation reactions involving the enzymes 25-hydroxylase and 1-α-hydroxylase, located in the liver and kidney, respectively, produce the active form, 1-α,25-dihydroxyvitamin D, also known as calcitriol. Some immune cells, including macrophages and dendritic cells, also express 1-α-hydroxylase activity, and so can produce calcitriol (106, 107). Calcitriol binds to the vitamin D receptor, which is a transcription factor acting to regulate cellular gene expression. Many immune cell types express the vitamin D receptor and respond to vitamin D, including dendritic cells, monocytes, macrophages, T cells, and B cells, and so vitamin D is now considered to also be an important regulator of immune function and inflammation (108–115).

Vitamin D enhances epithelial integrity and induces antimicrobial peptide (e.g., cathelicidin) synthesis in epithelial cells and macrophages (108, 116), directly enhancing host defense. The effects of vitamin D on the cellular components of immunity are rather complex. Vitamin D promotes differentiation of monocytes to macrophages and increases phagocytosis, superoxide production, and bacterial killing by innate immune cells (81). It also promotes antigen processing by dendritic cells, although antigen presentation may be impaired (117–119); this has been interpreted as a pro-tolerogenic role for vitamin D. Vitamin D is also

reported to inhibit $CD4^+$ and $CD8^+$ T-cell proliferation and production of cytokines by Th1 lymphocytes and of antibodies by B lymphocytes (120–122), highlighting the paradoxical nature of its effects. Effects on Th2 responses are not clear, but vitamin D seems to increase the number of regulatory T lymphocytes (119, 123, 124). Incubation of human memory T cells with vitamin D promoted a switch from a proinflammatory to an anti-inflammatory phenotype (125). Incubation of blood mononuclear cells from older people with vitamin D resulted in higher IL-10 production in response to LPS (126). An RCT of a vitamin D analog in older adults (mean age: 73 y) reported an increase in LPS-induced production of IL-10 by isolated blood mononuclear cells, an increased ratio of $CD4^+$ to $CD8^+$ cells in the blood, and a decrease in the number of $CD8^+CD28^-$ cells (127); LPS-induced production of IL-6 and IFN-γ was not affected (127). A cross-sectional study identified that older men (but not women) who were replete in vitamin D had a lower risk of having very low NK activity, in comparison to older men with low vitamin D (128). Low-dose vitamin D (10 μg/d) in healthy adults (40–55 y) did not affect the blood regulatory T-cell population but attenuated the seasonal increase in IFN-γ production by T cells (129). Several studies have investigated the association between vitamin D status and response to seasonal influenza vaccination, with inconsistent findings: a meta-analysis of 4 studies identified that vitamin D deficiency reduces seroprotection to the H3N2 and B components, but not to the H1N1 component, but has no effect on seroconversion to any of the components (130).

If vitamin D is needed to support the immune system, then vitamin D deficiency would lead to increased susceptibility to, and severity of, infectious disease. In the 19th and early 20th centuries it was found that cod liver oil and exposure to the sun helped treat tuberculosis (131), although the role of vitamin D itself was not immediately evident. Niels Ryberg Finsen was awarded the Nobel Prize for Medicine in 1903 for demonstrating the benefits of UV light to patients with tuberculosis of the skin—lupus vulgaris—which either cured or improved the disease in approximately 95% of patients (132), and by 1920, phototherapy was routinely used to treat pulmonary tuberculosis. While UV therapy can affect immune function in the skin, independent of the effect on vitamin D synthesis, these early studies had findings that are consistent with the later-demonstrated effects of vitamin D on immune function. Research in the early 21st century showed that TLR activation of macrophages upregulates the vitamin D receptor and vitamin D-1-α-hydroxylase genes, which, in turn, induce the expression of the antimicrobial peptide cathelicidin, which has activity against *Mycobacterium tuberculosis* (108, 116, 133). Furthermore, there is a positive relation between circulating vitamin D and cathelicidin, consistent with the idea that sufficient vitamin D status supports this antibacterial mechanism (134). Clinical trials have examined the efficacy of vitamin D intervention on treatment of tuberculosis, often using the rate of sputum conversion from a positive to a negative culture result as the key outcome, during the lengthy antimicrobial treatment period for patients with active pulmonary tuberculosis. In a meta-analysis of RCTs (135), high-dose vitamin D supplementation given after the initiation of antimicrobial treatment did not speed the recovery in patients infected with tuberculosis, but recovery was more rapid in those who were infected with the multidrug-resistant strains of *M. tuberculosis* where drug therapy would have been ineffective, thus allowing the benefit of vitamin D treatment to, perhaps, become more apparent.

Observational findings have linked low concentrations of vitamin D to increased risk of viral acute respiratory infection. For example, Berry et al. (136) described an inverse linear relation between serum 25-hydroxyvitamin D concentrations and respiratory tract infections in a cross-sectional study of 6789 British adults. Similarly, data from the US Third NHANES, which included 18,883 adults, showed an independent inverse association between serum 25-hydroxyvitamin D and recent upper respiratory tract infection (URTI) (137). Other studies also reported that individuals with low vitamin D status have a higher risk of viral respiratory tract infections (138, 139). A recent meta-analysis of RCTs involving 48,488 participants (140) examined the relation between vitamin D supplementation and the prevention of acute respiratory infections and found a small, but significant, protective effect of daily administration of 400 to 1000 IU vitamin D taken for 12 mo or less against 1 or more acute respiratory infection compared with the placebo (OR: 0.70; 95% CI: 0.55, 0.89). Baseline vitamin D status was not associated with a protective benefit, although the authors speculated that the heterogeneity of the studies examined may have masked a potentially greater benefit for supplement use in those with vitamin D insufficiency or deficiency at baseline (140).

There has been significant interest in vitamin D and COVID-19 (141, 142). Numerous trials report associations between low vitamin D status and increased susceptibility to, and severity of, COVID-19 [e.g., (143)] and meta-analyses of such studies report that vitamin D deficiency is associated with increased risk of severe COVID-19, hospitalization with COVID-19, and mortality from COVID-19 [e.g., (144, 145)]. A prospective study from the UK Biobank involving 8297 adults who had COVID-19 test results and records of their use of vitamin D supplements, serum 25-hydroxyvitamin D, and a number of covariates found a 34% lower risk of COVID-19 infection associated with the habitual use of vitamin D supplements, although there was no association with baseline vitamin D status (146). One large-scale retrospective study suggests a possible role of vitamin D in suppressing CRP and proinflammatory cytokine production implicated during the cytokine storm in COVID-19 infections, thus reducing COVID-19 severity (147). A study in an Italian residential care home reported that a bolus of vitamin D reduced mortality from COVID-19 (148). Some studies report that vitamin D supplementation

in patients hospitalized with COVID-19 reduced COVID-19 severity (e.g., need for intensive care unit admission, mortality) (149, 150), although not all such studies reported benefits from vitamin D (151). Further studies are needed to determine whether inadequate vitamin D status is associated with a higher risk of more severe COVID-19 and whether vitamin D can be used to reduce disease severity.

In summary, vitamin D has pleiotropic effects on immunity, but it does support many aspects of both innate and acquired immunity, promoting antibacterial and antiviral defenses while also promoting a pro-tolerogenic environment. Supplemental vitamin D seems to reduce the risk, and perhaps severity, of respiratory tract infections. The effects of vitamin D may be useful to prevent or reduce the severity of respiratory diseases in groups most at risk for severe disease, such as older adults, and/or those who have low concentrations of vitamin D; this is important since, globally, vitamin D intake and status are low, especially in older people (78, 79). Future work should aim to confirm or refute the proposed benefits of vitamin D on respiratory disease in older adults through conduct of well-designed and adequately powered studies. In terms of understanding the effects of supplemental vitamin D and in the design of trials, consideration should be given to the genetic polymorphisms found in the vitamin D binding protein and the vitamin D receptor, as they have been associated with respiratory disease outcomes (152–154), as well as sex-related differences in how vitamin D might affect immune responses (128, 155).

Vitamin E

Vitamin E, or tocopherol, is a potent lipid-soluble antioxidant that can prevent oxidative stress-induced damage to cellular lipids (156). Vitamin E has also been demonstrated to have anti-inflammatory activities independent of its antioxidant properties (157, 158). In animal models, vitamin E has anti-inflammatory, anti-atherosclerotic, and antitumor properties (159, 160). In immune cells, vitamin E modulates lipid microdomain formation in membranes (161), signal transduction (162), and prostaglandin (PG) E_2 (PGE_2) synthesis (163). In laboratory animals, vitamin E deficiency decreases lymphocyte proliferation, NK-cell activity, specific antibody production following vaccination, and phagocytosis by neutrophils (159, 164, 165). Vitamin E has been shown to support T-cell differentiation in the thymus of rats (166) and to enhance the immune response of aged mice (163). In healthy adults aged over 60 y a positive association between plasma vitamin E and cell-mediated immune responses and a negative association between plasma vitamin E and the risk of infections were reported (167).

In general, vitamin E has been demonstrated to improve age-associated impairments in immune function in the elderly (164, 168). A study conducted in healthy older men and women (mean age: 70.4 y) found that a variety of immune functions (e.g., neutrophil chemotaxis and phagocytosis, lymphocyte proliferation and IL-2 production, NK-cell activity) were enhanced after 3 mo of vitamin E supplementation (200 mg/d) (169). However, some of these effects were not maintained 6 mo postsupplementation (169), suggesting that continual supplementation may be required in older adults and/or that dietary vitamin E intake habits in this population were inadequate. The combination of vitamin E and vitamin C (200 and 1000 mg/d, respectively) could restore several blood neutrophil and lymphocyte functions in healthy older men and women to closer to those observed in young adults (96). High-dose vitamin E (800 mg/d) for 30 d increased lymphocyte proliferation and delayed-type hypersensitivity in older participants (170). A follow-up RCT using 3 doses of vitamin E (60, 200, and 800 mg/d) showed dose-dependent increases in lymphocyte proliferation, IL-2 production, delayed-type hypersensitivity, and responses to some vaccinations including to hepatitis B virus in older adults (171). The effect of vitamin E may be mediated by a decrease in PGE_2 and/or other lipid-peroxidation products (170).

In aged mice, vitamin E supplementation has been reported to decrease influenza viral titer, which was linked to an enhancement of Th1 cytokines and reduced PGE_2 production (172, 173). Similarly, in mice, vitamin E has been shown to modulate neutrophil responses and enhance resistance to *Streptococcus pneumoniae* (174). *S. pneumoniae* infection is a key driver of morbidity and mortality in older patients and is typically associated with an uncontrolled pulmonary infiltration of neutrophils and neutrophil-driven pulmonary inflammation. Surprisingly, baseline levels of pneumococcal-induced transepithelial migration by granulocytes from young or elderly individuals are reported to be indistinguishable (175). Furthermore, granulocytes from older individuals are reported to be more efficient at killing bacteria ex vivo than those from younger individuals (175). Interestingly, the higher antimicrobial activity found for granulocytes from older adults correlated with increased activity of neutrophil elastase, a protease that is required to kill *S. pneumoniae* (175). Incubation with vitamin E increased elastase activity in granulocytes from young individuals and boosted their ability to kill *S. pneumoniae* (175), while incubation with granulocytes from older individuals diminished their migration, which was associated with reduced inflammation (175). Supporting the use of vitamin E to help combat pneumonia, a secondary analysis of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study in Finland reported that the incidence of pneumonia was significantly lower in the group receiving vitamin E (176). However, the older adults who participated in this study were smokers, and thus these results may not be applicable to nonsmoking older adults. One RCT reported that vitamin E supplementation (200 IU or ∼135 mg/d) for 1 y decreased the risk of URTIs and the common cold in older people in nursing homes (177), but another study did not see an effect of supplemental vitamin E (200 mg/d) on the incidence, duration, or severity of respiratory tract infections in an elderly population (178). Interestingly, polymorphisms for genes encoding various cytokines, including IL-2 and IL-10, have been associated with respiratory tract infections (179), while polymorphisms for genes encoding various

cytokines have been shown to influence the effect of vitamin E on production of those cytokines (180). Thus, genetic polymorphisms may, in part, determine the ability of vitamin E on lower respiratory tract infection risk in older people, and this should be considered when testing the efficacy of vitamin E on respiratory disease outcome.

AS03A is an α-tocopherol oil-in-water emulsion-based adjuvant system that has recently been used in combination with a H1N1 and H9N2 influenza vaccine. AS03A was reported to enhance the longevity of B- and T-cell–mediated responses to vaccination, mitigating the negative effects of age-associated impairments in adaptive immunity (181–183). However, the exact underlying mechanisms for the α-tocopherol–induced protection are not clear (184). Similar studies had been previously conducted in farm animals, in which vitamin E has been utilized as an adjuvant to augment humoral immunity (185).

In summary, vitamin E supports many aspects of innate and acquired immunity and has anti-inflammatory effects including reduction in PGE_2 production. Animal studies clearly demonstrate the ability of vitamin E to reverse age-related immune impairments. Supplemental vitamin E seems to enhance immune cell functions at the doses tested and in older adults, but these intakes are high compared with those that are recommended. Trials of vitamin E in relation to respiratory infection are inconsistent, perhaps relating to dose and the characteristics of the participants studied, including genotype. Future work should aim to confirm or refute the proposed benefits of vitamin E on respiratory disease in older adults considering confounding factors.

Zinc

Zinc is required for the activity of enzymes involved in a number of processes such as cell proliferation and differentiation, cell membrane integrity, and DNA and RNA synthesis. Systemic and intracellular concentrations of zinc are tightly regulated, with the vast majority of the body's zinc being closely bound to intracellular metallothioneins (MTs), enzymes, transcription factors, and other proteins. The expression of MT genes is highly responsive to zinc concentrations, viral infections, and to a lesser extent to oxidative stress (186, 187). Adequate zinc status is needed for a well-functioning immune system (188–191). Zinc participates in regulating intracellular signaling pathways in innate and adaptive immune cells, and has been demonstrated to have anti-inflammatory, antioxidant, and antiviral properties (192, 193). Zinc status, as determined by serum or plasma zinc concentrations, has been correlated with alterations in total immune cell numbers, particularly helper T cells, and in immune cell function (31,188–191), which together are associated with increased susceptibility to infections (194, 195). Zinc deficiency has a marked impact on bone marrow, decreasing the number immune precursor cells, with reduced output of naive B lymphocytes, and causes thymic atrophy, reducing output of naive T lymphocytes (196). Therefore, zinc is important in maintaining T- and B-lymphocyte numbers. Zinc deficiency impairs many aspects of innate immunity, including phagocytosis, respiratory burst, and NK-cell activity (188–191). Zinc also supports the release of neutrophil extracellular traps that capture microbes (197). There are marked effects of zinc deficiency on acquired immunity. Circulating $CD4^+$ T-lymphocyte numbers and function (e.g., IL-2 and IFN-γ production) are decreased and there is a disturbance in favor of Th2 cells (188–191). Likewise, B-lymphocyte numbers and antibody production are decreased in zinc deficiency (188–191). Zinc supports proliferation of $CD8^+$ cytotoxic T lymphocytes (188–191), key cells in antiviral defense. Moderate or mild zinc deficiency or experimental zinc deficiency in humans results in decreased NK-cell activity, T-lymphocyte proliferation, IL-2 production, and cell-mediated immune responses, which can all be corrected by zinc repletion (198–200).

Zinc deficiency is prevalent in older individuals (201). For example, in 1 study in the United States, 30% of nursing home residents were zinc deficient (202). Interestingly, many of the perturbations observed in zinc deficiency parallel those that occur in aging, such as a reduction in thymic activity, an imbalance in T-helper cell numbers, blunted immune response to vaccination, and general impairments in the functions of immune cells (31, 203, 204). Zinc supplementation has been associated with general improvements in age-related impairments of immune function, reductions in inflammatory markers, and, in some instances, with reduced incidence of infection. For example, zinc supplementation (45 mg/d) for 3 mo increased the number of helper T cells and cytotoxic T cells in the blood of older participants residing in nursing homes (mean age: 79.5 y) and there was a strong trend to increased lymphocyte proliferation (205). In another study, older participants (>70 y of age) received zinc (50 mg/d) for 1 mo: there was an increase in the number of blood T cells, in the delated-type hypersensitivity response, and in the antibody response to tetanus vaccination (206). In that study there was no effect of zinc on lymphocyte proliferation (206). In a more recent study, zinc supplementation (30 mg/d) for 3 mo in elderly nursing home residents with low zinc status enhanced the proliferative capacity of T cells (207). Further, there was a strong positive correlation between zinc concentrations and T-cell proliferation and total number of T cells in the blood (207).

Aside from its potential roles in enhancing immunity and decreasing inflammation (see above), free zinc ions can act on the buccal membranes of the oral cavity and nasopharyngeal tissues by interfering with the capsid assembly of rhinoviruses (208), suggesting a nonimmunologic mechanism by which zinc supplementation above that required to maintain adequate zinc status might affect the incidence or severity of the common cold. A meta-analysis of RCTs of zinc supplementation in children and adults (209) found that the overall duration of the cold was 1.03 d shorter with zinc than in the placebo group (95% CI: −1.72, −0.34 d) when given within 24 to 48 h after the onset of cold symptoms. When studies were subgrouped by zinc dosage, administered in the form of zinc acetate or zinc gluconate lozenges, a zinc intake of more than 75 mg/d reduced the

duration of the cold by 1.97 d (95% CI: −3.09, −0.85), with significant heterogeneity in findings. There was no significant reduction in the duration of cold symptoms with a zinc intake of less than 75 mg/d (mean difference: 0.13 d; 95% CI: −0.54, 0.79). The high heterogeneity seen in the >75-mg/d subgroup may be explained by a placebo effect (i.e., the taste of zinc lozenges is difficult to mask) and/or the amount of zinc released in the oral cavity. Zinc lozenges that use additives such as citrate, tartrate, or glycine bind zinc tightly, thus releasing less free zinc ions in the oral cavity. In addition, other variable components of lozenges, such as oils, and the processing temperature used, may impact the solubility of zinc from its complex and deliver a lower zinc dose than indicated (210). When adults and children were studied as subgroups (209), adults had a reduced duration of cold symptoms with oral zinc supplementation by 1.12 d (95% CI: −2.17, −0.06) while children had a reduced duration by only 0.62 d (95% CI: −0.82, −0.42). This difference may be explained by the different zinc formulations given to the adults and children; adults received zinc acetate or zinc gluconate in the form of lozenges while children received either zinc sulfate syrup or zinc gluconate lozenges. Zinc lozenges would dissolve slowly in the oral cavity, thus giving more time for zinc to exert its effects on the buccal membranes than syrup, which is immediately swallowed. The meta-analysis (209) also examined whether prophylactic administration of zinc decreases the incidence of the common cold. Two trials involving children who were given RDA levels of zinc sulfate in the form of syrup or tablets for 5 to 7 mo showed significantly decreased incidence of the cold by 36% compared with the placebo group (incident rate ratio: 0.64; 95% CI: 0.70, 0.88) with high heterogeneity. In addition, children missed fewer days of school when supplemented with zinc compared with the placebo group (mean difference: −0.66 d; 95% CI: −0.99, −0.33).

Zinc deficiency is suggested to be a risk factor for pneumonia in older adults (211). Low serum zinc concentrations were linked to a higher risk of pneumonia and longer duration of pneumonia episodes as well as increased antibiotic use in older adults in nursing homes (202). In a murine model of *S. pneumoniae* infection, dietary zinc restriction resulted in a reduced ability to control bacterial growth, leading to increased virulence and infection, and a much greater inflammatory response (212). Interestingly, the activation and infiltration of phagocytic cells into the infected region were not affected by zinc restriction. Rather, zinc-supplemented phagocytic cells had higher concentrations of intracellular zinc, which promoted lysis of phagocytized bacteria, demonstrating that zinc can act as an antimicrobial agent. While these findings are promising, a study in hospitalized adults (>50 y of age) with community-acquired pneumonia found that zinc (25 mg twice daily for 4 d in combination with standard treatment) did not improve outcomes (213). It is possible that the duration of zinc supplementation was too short to have a benefit. However, a meta-analysis revealed that, in children, zinc supplementation significantly reduced mortality caused by severe pneumonia (214). Given the data linking zinc deficiency and pneumonia susceptibility and health outcomes, and the rising rate of resistance of *S. pneumoniae* to conventional antibiotics (215), further research is warranted to determine the efficacy of supplemental zinc in attenuating *S. pneumoniae* infection and disease-associated mortality in older adults.

In vitro models of influenza infection have demonstrated that zinc can inhibit influenza virus RNA polymerase activity and significantly reduced viral titers (216, 217). Similarly, in vitro studies have demonstrated that zinc can inhibit RNA-dependent RNA polymerases of severe acute respiratory syndrome coronavirus (SARS-CoV)-1 (218), which has high homology with SARS-CoV-2, the virus responsible for COVID-19. Multiple studies report an association between low zinc status and increased susceptibility to, and severity of, COVID-19 [e.g. (219)], although such studies cannot demonstrate cause and effect. Zinc supplementation in patients hospitalized with COVID-19 is reported to reduce the risk of poor outcome, including mortality in some studies (220, 221) but not others (222). Clearly more, and better, studies are needed in this area.

Centenarians (those aged 90–100 y) are a useful model for understanding healthy aging, and studies comparing changes in immunity between older individuals (65–80 y) and centenarians may yield mechanistic insights, including about the role of zinc. One study reported differences in NK activity, MT and cytokine concentrations, and DNA-repair enzyme activity between older adults and healthy centenarians (223). The authors suggest that centenarians have lower MT mRNA, resulting in greater zinc ion bioavailability, supporting NK-cell activity and a higher capacity for DNA repair. MT polymorphisms have also been demonstrated to be involved in maintaining innate immune responses and intracellular zinc availability in the aged, suggesting that mechanisms that maintain adequate zinc homeostasis/metabolism in immune cells are associated with healthy aging and longevity (224). Given that responses to nutritional interventions are highly variable between participants despite similarities in anthropometrics, age, and sex, personalized nutrition may be leveraged in the future to address differences in response to dietary interventions and immune/inflammatory responses associated with specific gene polymorphisms.

It is important to note that, while low zinc status is associated with a weakened immune system, long-term and high-dose supplementation of zinc can lead to copper deficiency (225), highlighting a potential adverse effect of high-dose or prolonged zinc supplementation.

In summary, zinc supports many aspects of innate and acquired immunity and has anti-inflammatory and antioxidant effects. Supplemental zinc seems to promote immune cell functions at the doses tested and in older adults, but these intakes are sometimes high compared with those that are recommended. Trials of zinc in relation to respiratory infection are inconsistent, perhaps relating to dose and formulation and the characteristics of the participants studied, including genotype, and there are few

such studies in older adults. Future work should aim to confirm or refute the proposed benefits of zinc on respiratory disease in older adults through conduct of well-designed and adequately powered studies.

Selenium

Selenium, most often ingested as selenomethionine, is an essential micronutrient that is incorporated into selenoproteins as selenocysteine. Selenoproteins, such as glutathione peroxidases and iodothyronine deiodinase, are involved in multiple biological processes, such as redox signaling, antioxidant defenses, thyroid hormone production, and both immune and inflammatory responses (226). Thus, unsurprisingly, selenium deficiency has been linked to increased mortality and cancer risk, as well as impaired immune defenses (227). Mutations in the selenocysteine insertion sequence have been associated with impaired lymphocyte proliferation, abnormal cytokine secretion, and telomere shortening, highlighting the importance of selenoproteins in immune cells (228). While selenium deficiency is rare in the United States and Canada, people in other countries such as those living in parts of China, Europe, and Russia, are at risk for selenium deficiency. Selenium intake in these countries is inadequate due to low soil selenium concentrations, resulting in variable levels of selenium incorporation into food and, thus, an inadequate intake to support the optimal expression of the selenoproteins (229).

In mice, selenium has been shown to be vital for both adaptive and innate immune cells, particularly for NK- and T-cell function (230, 231). Experimental data in aged mice suggest that selenium supplementation may augment immune function: splenocytes from aged mice that were supplemented with selenium for 8 wk had increased proliferation capacity after stimulation with mitogens (232). Additionally, in vivo alloantigen-activated lymphocytes from selenium-supplemented aged mice contained significantly higher numbers of cytotoxic T lymphocytes, which resulted in an enhanced capacity to destroy tumor cells (232). This effect occurred in the absence of changes in the ability of the cells to produce IL-2, suggesting that selenium restored the age-related defect in cell proliferation through an increase in the number of IL-2 receptors (232). Selenium deficiency in mice increases susceptibility to viral infection and permits viral mutation, including of influenza viruses, and so allowing normally weak viruses to become more virulent (233–236). The permissive effect of selenium deficiency on viral mutation and virulence seems to relate to the higher oxidative stress that exists in the absence of selenium. The effects of selenium on antiviral immunity have been comprehensively reviewed recently (237–239).

A study in older women (90–106 y), linked both zinc and selenium deficiency to a reduced percentage of NK cells in the blood (240). Selenium supplementation (100–400 μg/d depending on the study) has been shown to improve various aspects of immune function in humans (241–243), including in the elderly. Older people in nursing homes received 100 μg selenium daily as selenium-enriched yeast for 6 mo: lymphocyte proliferation in response to mitogens increased (244). An RCT in older people (57–84 y), demonstrated that 6 mo of selenium supplementation (400 μg/d) increased the number of T cells, $CD4^+$ T cells, and NK cells in blood and increased NK-cell activity (245). However, the impact of supplementation was not sustained postsupplementation. Two other RCTs of selenium in younger adults are also of particular interest. Broome et al. (246) conducted a 15-wk RCT of 2 doses of selenium (50 or 100 μg/d) in adults (20–47 y of age) with marginal selenium status. After 6 wk, participants received the live attenuated oral poliomyelitis vaccine. Selenium resulted in a dose-dependent increase in blood T-cell numbers and in ex vivo mononuclear cell responses (proliferation, IFN-γ production) to the vaccine. Selenium-supplemented individuals also showed more rapid clearance of the poliovirus and had a lower number of virus mutants appearing in their feces (246). A more recent RCT compared 3 doses of selenium (50, 100, and 200 μg/d) from selenium-enriched yeast over 12 wk in adults (mean age: 56 y); participants received the seasonal influenza vaccine after 10 wk (247). Selenium (100 μg/d) increased blood cytotoxic T-cell numbers before influenza vaccination. Two weeks postvaccination, blood mononuclear cells were stimulated ex vivo with the influenza vaccine. Selenium supplementation increased T-cell proliferation and production of IL-8 and IL-10. However, the highest dose of selenium decreased the granzyme B content of cytotoxic T cells (247). There was no effect of selenium on mucosal influenza-specific antibodies.

An observational study found that selenium concentrations were significantly lower in patients with tuberculosis than in controls (248, 249). Similarly, low redox status, high oxidative stress, and low serum selenium status were observed in patients with pulmonary tuberculosis and anti-tuberculosis treatment steadily increased the concentration of selenium (250). Selenium and vitamin E supplementation, in combination with standard anti-tuberculosis treatment, reduced malondialdehyde, a marker of oxidative damage, in patients with newly diagnosed tuberculosis, in comparison to controls who only received standard treatment (251). However, it should be noted that *M. tuberculosis* requires selenium for its own survival and replication (252). No studies have assessed the impact of selenium on immune responses during tuberculosis infection in older individuals. Some studies report an association between low selenium status and increased susceptibility to, and severity of, COVID-19 [e.g., (219)].

In summary, selenium supports many aspects of innate and acquired immunity and has anti-inflammatory effects. Animal studies clearly demonstrate the importance of selenium to antiviral immunity. Supplemental selenium seems to enhance immune cell functions at the doses tested and in older adults. There are few trials of selenium in relation to respiratory infection. Future work should aim to identify whether selenium has benefits on respiratory disease, especially in older adults, through conduct of well-designed and adequately powered studies.

Immune Enhancement through Targeting the Gut Microbiota

Modulation of gut microbiota and immunity

There are a variety of foods, food components, and supplements that modulate the gut microbiota, supporting the growth of bacteria that are considered favorable to health and well-being (53–55, 253). The proposed health benefits include favorably modulating the immune response and helping to control inflammation.

Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (254). Commonly used probiotics include different lactobacilli and bifidobacteria, although other bacterial genera and some yeasts are also used as probiotics (254). Whether many probiotics survive stomach acid and populate the intestine is still under debate (255), although live probiotic organisms can be cultured from fecal samples from individuals consuming those organisms. Even though they are defined as "live" microbes (254), there is increasing evidence that many probiotic preparations may not contain high numbers of live organisms but instead contain dead organisms, bacterial cell walls, bacterial metabolites, or bacteriophages that could all be biologically active (256). Indeed, organisms do not have to be alive to elicit immunological benefits (257), giving rise to the concepts of parabiotics and postbiotics (258, 259).

Prebiotics were previously largely restricted to fructo-oligosaccharides and inulins that promote the growth of bifidobacteria [see discussion in (260)]; however, the definition has been broadened to include "a substrate that is selectively utilized by host microorganisms conferring a health benefit" (260). Oligo- and polysaccharides remain the most commonly used prebiotics, and foods such as onions, Jerusalem artichokes, leeks, garlic, bananas, and asparagus have some of the highest potential to provide these prebiotics. Mushrooms, some species of yeast, and some seaweeds may exert prebiotic effects through B-glucans (261, 262), although B-glucans appear to also act through immune-training mechanisms (263, 264). Polyphenols in spices have also been shown to affect gut microbiota and may be considered as prebiotics (260, 265). The culinary herbs, black pepper, cayenne pepper, cinnamon, ginger, Mediterranean oregano, and rosemary demonstrated prebiotic-like activity by promoting the growth of beneficial bacteria and suppressing the growth of pathogenic bacteria in vitro. Synbiotics are combinations of at least 1 prebiotic with at least 1 probiotic (266).

Many studies have examined the effect of various probiotic organisms, either alone or in combination, on immune function, infection, and inflammatory conditions in humans (267), including in older people (268). Probiotic organisms increased NK-cell activity in older people in several studies (269–272), and increased phagocytosis by monocytes (269) and granulocytes (273) and monocyte oxidative burst (274). The effects of probiotics on NK-cell activity, phagocytosis, and oxidative burst were seen with live but not dead organisms. Probiotics increased production of IFN-α (273) and of IFN-γ, IL-5, and IL-10 (275) by blood mononuclear cell cultures stimulated with a T-cell agonist. However, T-cell proliferation was not affected by probiotics in several studies (269, 276, 277). Most studies of prebiotics and immunity in older people have used either fructo-oligosaccharides or galacto-oligosaccharides (278). There are reports that prebiotics increase NK-cell activity (279, 280) and granulocyte phagocytosis of bacteria (279).

The effect of probiotics and prebiotics on seasonal influenza vaccination in older people has been investigated in a number of studies, with variable findings (281–290) according to the probiotic organism or prebiotic used. Recent systematic reviews and meta-analyses confirm that probiotics or oligosaccharide-type prebiotics enhance the response to seasonal influenza vaccination in adults (291, 292). Antibody titers to the H1N1 strain of the influenza virus were higher in individuals receiving probiotics, prebiotics, and either pro- or prebiotics than in those in placebo groups (291). Antibody titers to the H3N2 strain of the influenza virus were higher in individuals receiving probiotics and either pro- or prebiotics, while antibody titers to the B strain were higher in individuals receiving either pro- or prebiotics (291). This meta-analysis did not perform any subgroup analysis by age, so the overall effect in older people is not clear. However, a separate meta-analysis of RCTs reported effects on seroprotection and seroconversion post-seasonal influenza vaccination in adults and included subgroup analysis according to age (292). This meta-analysis identified higher seroprotection to the H1N1 and H3N2 strains in individuals receiving pre- or probiotics than in those in placebo groups (OR, H1NI: 1.83; 95% CI: 1.19, 2.82; OR, H3N2: 2.85; 95% CI: 1.59, 5.10). Seroprotection to the B strain was not affected by pre- or probiotics. There was higher seroconversion to the B strain in individuals receiving pre- or probiotics than in placebo groups (OR: 2.11; 95% CI: 1.38, 3.21) with a trend (both $P = 0.07$) for higher seroconversion to the H1N1 and H3N2 strains (OR, H1N1: 1.52; 95% CI: 0.75, 3.09; OR, H3N2: 2.54; 95% CI: 0.93, 6.91).

Subgroup analysis according to whether probiotics or prebiotics were used indicated that probiotics increased seroconversion to the H3N2 and B components and increased seroprotection to the H3N2 component (292). Prebiotics increased seroprotection to the H1N1 and H3N2 components (292).

Subgroup analysis according to age indicated that an effect of pre- or probiotics on seroconversion and seroprotection to H1N1 was seen in healthy older adults (OR seroconversion: 2.93; 95% CI: 1.47, 5.87; OR seroprotection: 2.46; 95% CI: 1.15, 5.26) but not in healthy younger/middle-aged adults (292). There was also an effect of pre- or probiotics on seroprotection to H1N1 in hospitalized older adults (OR: 2.06; 95% CI: 1.11, 3.82), but there was no effect on seroconversion. Greater seroconversion to H3N2 was seen with pre- or probiotics than with placebo in healthy older adults (OR: 3.68; 95% CI: 1.11, 12.25) and there was a trend to higher seroprotection in both healthy older adults (OR: 2.27;

95% CI: 0.94, 5.47) and hospitalized older adults (OR: 2.83; 95% CI: 0.97, 8.21). Both seroprotection and seroconversion were higher with pre- or probiotics than with placebo in healthy younger/middle-aged adults. Seroconversion to the B component was greater with pre- or probiotics than placebo in healthy older adults (OR: 2.69; 95% CI: 1.51, 4.78) and there was a trend to greater seroconversion with pre- or probiotics in hospitalized older adults (OR: 2.05; 95% CI: 0.92, 4.58). These findings indicate that pre- or probiotics increase responses to the seasonal influenza vaccine in adults, including in older adults. However, the number of studies included in the subgroup analyses was small (e.g., only 1 study in hospitalized older adults).

Modulation of gut microbiota and infections

As a result of their dual influence on the gut microbiota and on the host's gut epithelium and immune system, probiotics are proposed to reduce infections. This would be most obvious for gastrointestinal infections. In accordance with this, several lactobacilli strains have been shown to reduce the incidence, duration, and severity of diarrhea in children (293–297). Recent studies have identified that heat-killed lactobacilli decreased the risk and duration of diarrhea in children (298). In adults, there is evidence that probiotics protect against antibiotic-associated diarrhea (299–303). Systematic reviews and meta-analyses identify that probiotics (again, especially some lactobacilli stains) reduce the incidence and duration of antibiotic-associated diarrhea and of *Clostridium difficile*–associated diarrhea in adults (304–306) and may be effective in treating these conditions (307). However, although probiotics are effective in preventing and treating diarrhea in both children and adults, there are considerable differences in the effects of different probiotic species and strains and the effects observed with 1 type of probiotic cannot be extrapolated to another.

The gut microbiota seems to play a role in determining infections at sites distant from the gut, including in the respiratory tract (308, 309), suggesting a gut–lung axis of some importance in maintaining respiratory health that may be amenable to modulation by probiotics. There are a number of studies of probiotics in respiratory disease, mainly in children, and mainly using different lactobacilli and bifidobacteria. Many of these studies report that probiotics reduce the incidence or severity of respiratory tract infections, as indicated by systematic reviews and meta-analyses (310–318). A meta-analysis of 20 RCTs in children and adults (all adults were young or middle-aged) that used a variety of probiotic organisms found that, compared with placebo, probiotics reduced the number of days of illness and the number of days absent from daycare, school, or work (313). A second meta-analysis of 12 RCTs in children and adults identified that probiotics reduced the risk of URTIs compared with placebo (OR: 0.53; 95% CI: 0.37, 0.76) and reduced the duration of URTIs (mean duration: −1.89 d; 95% CI: −2.03, −1.75 d) and the need for antibiotic prescription to treat the URTI (314). While probiotics were superior to placebo in this meta-analysis, the quality of the included studies was considered to be low. These meta-analyses combined trials in children and adults and did not include trials in older people. However, a recent meta-analysis of 22 RCTs investigated effects of probiotic fermented dairy products on respiratory tract infections in children, adults, and older people (319). Compared with placebo, consumption of probiotics reduced the risk of respiratory tract infections in all age groups combined (RR: 0.81; 95% CI: 0.74, 0.89) and separately in children (RR: 0.82; 95% CI: 0.73, 0.93), in adults (RR: 0.81; 95% CI: 0.66, 1.00), and in the elderly population (RR: 0.78; 95% CI: 0.61, 0.98). Disease-specific analysis identified that probiotics decreased the risk of URTIs (RR: 0.83; 95% CI: 0.73, 0.93), pneumonia (RR: 0.76; 95% CI: 0.61, 0.95), and the common cold (RR: 0.68; 95% CI: 0.49, 0.96) and tended ($P = 0.06$) to decrease the risk of lower respiratory tract infections (RR: 0.78; 95% CI: 0.60, 1.01). Taken together, these findings provide evidence that probiotics, in particular some lactobacilli and bifidobacteria, reduce the incidence, and improve the outcomes, of respiratory infections in humans, including the elderly.

Another recent meta-analysis investigated the effect of synbiotics on respiratory tract infections (320). It included 16 RCTs conducted in infants, children, and adults. The synbiotics mostly included lactobacilli or bifidobacteria as probiotics and fructo-oligosaccharides, galacto-oligosaccharides, or inulin as prebiotics. Compared with placebo, synbiotics decreased the incidence of respiratory tract infection (rate ratio: 0.84; 95% CI: 0.73, 0.96) and the risk of developing a respiratory tract infection (risk ratio: 0.84; 95% CI: 0.74, 0.95). Subgroup analysis demonstrated that synbiotics decreased the incidence of respiratory tract infection in adults (rate ratio: 0.68; 95% CI: 0.57, 0.81) but not in infants and children.

Modulation of gut microbiota and inflammation

There is some evidence that probiotics may reduce the inflammation associated with aging, as discussed elsewhere recently (321). Probiotics decrease the proinflammatory cytokines IL-1, IL-6, and TNF-α (322) and increase transforming growth factor-β made by regulatory T cells (323). Furthermore, probiotics have been shown to increase antioxidant activity (glutathione) in a meta-analysis of 16 clinical studies (324).

Conclusions and Perspectives

Aging is associated with changes in the immune system, with a decline in protective components (immunosenescence), so increasing susceptibility to infectious disease (and also contributing to the development of autoimmunity and malignancy, which are not discussed herein), and a chronic elevation in low-grade inflammation, so increasing the risk of multiple noncommunicable diseases. Thus, the age-related changes in the immune system increase the risk of both communicable and noncommunicable diseases in the population, contributing to stress on health care and social care systems.

TABLE 3 Summary of the effects of selected micronutrients on different aspects of immunity[1]

Micronutrient	Role in barrier function	Role in cellular aspects of innate immunity	Role in T-cell–mediated immunity	Role in B-cell–mediated immunity
Vitamin C	Promotes collagen synthesis and connective tissue healing; protects against oxidative damage; promotes wound healing	Supports function of neutrophils, monocytes and macrophages including phagocytosis; promotes neutrophil chemotaxis; supports NK-cell activity	Promotes production, differentiation and proliferation of T cells, especially cytotoxic T cells; regulates IFN-γ production	Promotes production and proliferation of B cells; promotes antibody production
Vitamin D	Promotes epithelial integrity; promotes production of antimicrobial proteins (cathelicidin, β-defensin); promotes homing of T cells to the skin	Promotes differentiation of monocytes to macrophages; promotes macrophage phagocytosis, oxidative burst and bacterial killing; supports NK-cell activity	Promotes antigen processing but can inhibit antigen presentation; can inhibit T-cell proliferation, Th1-cell function, and cytotoxic T-cell function; promotes the development of regulatory T cells; inhibits differentiation and maturation of dendritic cells; regulates IFN-γ production	Can decrease antibody production
Vitamin E	Protects against oxidative damage	Reduces inflammation; supports NK-cell activity; promotes neutrophil phagocytosis	Promotes interaction between dendritic cells and T cells; promotes T-cell proliferation and function, especially Th1 cells; regulates (promotes) IL-2 production	Supports antibody production
Zinc	Maintains integrity of the skin and mucosal membranes; Promotes complement activity	Reduces inflammation; supports monocyte and macrophage phagocytosis; promotes formation of neutrophil extracellular traps; supports NK-cell activity	Promotes Th1-cell response; promotes proliferation of cytotoxic T cells; promotes development of regulatory T cells; regulates (promotes) IL-2 and IFN-γ production; reduces development of Th9 and Th17 cells	Supports antibody production, IgG
Selenium	—	Reduces inflammation; supports NK-cell activity	Regulates differentiation and proliferation of T cells; regulates (promotes) IFN-γ production	Supports antibody production

[1] Adapted from reference 2. Th, T-helper;

Age-related immune decline also contributes to poor vaccine efficacy, resulting in wasted resource and creating a false sense of security in recipients. The higher rate of infections among older people means they are significant users of antibiotics, contributing to the development of antibiotic resistance. For these reasons, age-related immune decline (the combination of immunosenescence and inflammaging) is a major public health challenge that requires solutions. This is especially important because the number of older people is increasing (325–327) and also because changes in the environment and weather conditions, due to climate change, may alter the dynamics and geographic range of existing, and favor the emergence of, novel infectious diseases (328–330).

Nutrition is a determinant of immune cell development and function and of the gut microbiota. In turn, the gut microbiota shapes and controls the immune and inflammatory responses. Many older people show changes in food intake, with many not meeting micronutrient recommendations or consuming enough protein. Older people also show changes in the gut microbiota, which can be accelerated by moving into residential care. Hence it seems likely that the age-related changes in immune competence, low-grade inflammation, and gut dysbiosis are interlinked and all relate, at least in part, to the age-related changes in nutrition.

Multiple micronutrients play multiple roles within the immune system (**Table 3**). There is evidence that, through restoring status, micronutrient supplements can reverse immune deficits in older people and/or in those with insufficient intakes. Nevertheless, there are inconsistencies in the literature reporting on micronutrient trials and immune outcomes in humans. These inconsistencies relate in part to the large between-individual differences in immune markers that exist (3–5), meaning that sample sizes of human trials have sometimes been too small to identify the hypothesized

effect. This is particularly important because the effect size of nutritional interventions may be modest. Despite the evidence that individual micronutrients can improve immune outcomes, the evidence that this will reduce the risk or severity of infections is inconsistent. Therefore, further research with well-designed and well-powered trials in at-risk older populations is required to be more certain about the role of micronutrients on infection, especially respiratory infection. In this regard, rationally designed micronutrient combinations using appropriate levels of intake (there are many trials of medium to high doses of single micronutrients, some showing benefit and some not) should be examined and there should be more studies of the effects on responses to common vaccinations, including both immune responses (e.g., antibody titers) and clinical protection. It is clear that a sizeable fraction of older adults fall short in the intake of many micronutrients, particularly of those with known immunomodulatory effects (i.e., vitamins C, D, and E and zinc and, in some countries, also selenium). Thus, promoting the intake of these micronutrients to correct marginal deficiencies may have a considerable impact on the aged immune system and help in the battle against infectious disease. With regard to individual micronutrients, most studies have investigated single doses at 1 or only a few time points; more needs to be known about the dose-response effects in older people of all the micronutrients discussed herein. It is known that very high intakes of some micronutrients (e.g., zinc) impair the immune response and therefore more clarity is needed on upper limits of intake from the immune system perspective. Other areas to be explored include sex-related differences in immunosenescence and inflammaging and how these relate to nutrient intake and micronutrient supplementation and how micronutrients interact with genetic polymorphisms to determine immune and infectious outcomes.

Probiotic, prebiotic, or synbiotic strategies that modulate the gut microbiota, especially by promoting the colonization of some strains of lactobacilli and bifidobacteria, have been demonstrated to modulate some immune and inflammatory biomarkers in older people and, in some cases, to reduce the risk and severity of gastrointestinal and respiratory infections. However, it is important to note that the evidence is again inconsistent and, in some cases, considered to be of low quality. One reason for the inconsistency is likely to be that the effects of probiotic organisms are species and strain specific. Better definitions of those organisms that have immune benefits should be a focus for future research, which should use well-designed and well-powered studies and appropriate outcomes. It is now evident that some effects of probiotics do not require them to be alive. This has given rise to the concepts of postbiotics and parabiotics, which include dead organisms, bacterial extracts, bacterial cell wall components, and metabolic products of bacteria such as SCFAs. Another consideration is the matrix used to deliver probiotics, which might be important in determining their effects, and the matrix and exact chemical form of micronutrients, which might affect their bioavailability and function. Clearly, this is an area that is ripe for research in the context of immunity, inflammation, and infection, but to generate high-quality evidence (for or against the food component being investigated), serious consideration needs to be given to the number of factors that could influence the outcome of human trials.

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