ImmuneFunction-HealthProfessional

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Dietary Supplements for Immune Function and Infectious Diseases  
Fact Sheet for Health Professionals  
  
This is a fact sheet intended for health professionals. For a general overview, see our consumer fact sheet.  
  
Introduction  
Interest in dietary supplement ingredients that might enhance immune function and reduce the risk of infectious diseases is high, especially after the emergence of COVID-19.  
  
The immune system defends the body from pathogens that cause disease and is comprised of innate responses, which are the first line of defense, and adaptive responses, which become engaged later [1-3].  
  
The innate immune system includes physical barriers, such as the skin and gut epithelium, that help prevent pathogen entry. It also includes leukocytes (white blood cells) such as neutrophils, macrophages (which release cytokines), and natural killer cells that attempt to find and eliminate foreign pathogens. However, these components are nonspecific, meaning that unlike the adaptive immune system, they do not recognize and respond to specific pathogens [1,2,4].  
  
The adaptive immune system consists of B lymphocytes (B cells) that secrete antibodies (a process known as humoral immunity) and T lymphocytes, which are also known as T cells (a process known as cell-mediated immunity), both of which are pathogen specific [3-5]. The adaptive response takes several days or weeks to develop, but it generates immunological memory; as a result, a subsequent exposure to the same pathogen leads to a vigorous and rapid immune response [1,3,5]. Vaccinations stimulate the adaptive immune system, protecting the body from future exposures [2].  
  
The body s immune response to pathogens can lead to inflammation, causing redness, swelling, heat, pain, and possible loss of tissue function [6]. Inflammation helps eliminate the pathogen and initiate the healing process, but it can also cause symptoms and severe pathologies [6,7]. For example, activation of CD8 T cells as part of the adaptive immune response can increase inflammation and cause pulmonary damage. This process can lead to acute respiratory distress syndrome (ARDS), which has occurred in some patients with COVID-19 [7].  
  
Consuming adequate amounts of several vitamins and minerals including vitamin A, vitamin C, vitamin D, vitamin E, selenium, and zinc is important for proper immune function, and clinical deficiencies of these nutrients weaken immunity and can increase susceptibility to infections [2,4,5,8-10]. Other ingredients (whether provided through foods or dietary supplements), such as botanicals and probiotics, are not essential in the body but might affect immune function.  
  
Measuring the impact of dietary supplement ingredients, such as vitamins, minerals, or other substances, on the immune system is difficult because the immune system is a complex network of organs, tissues, and cells [11,12]. No single, straightforward measure of immune system function and resistance to disease exists. Indirectly, immune function can be assessed by examining a person s risk and severity of infectious diseases.  
  
This fact sheet summarizes the effects of various dietary supplement ingredients on immune function and the risk of selected infectious diseases, including the common cold, influenza and other respiratory tract infections, infectious diarrhea, and HIV infection. These diseases can be caused by numerous pathogens. For example, the common cold is caused by a wide variety of respiratory viruses, most commonly rhinovirus, but also coronaviruses, adenoviruses, and other virus serotypes [13].  
  
Dietary supplement ingredients in each category are presented in alphabetical order. In some cases, cited research involves intravenous, enteral, or parenteral administration. Dietary ingredients administered by these routes are not classified as dietary supplements, but the information is included for completeness.  
  
For information on dietary supplements and COVID-19, please see the Office of Dietary Supplements (ODS) health professional fact sheet, Dietary Supplements in the Time of COVID-19.  
  
Vitamins and Minerals  
Consuming a nutritious variety of foods helps maintain overall good health and a strong immune system [14]. Obtaining adequate amounts of vitamins and minerals is also important for good health, and deficiencies of certain vitamins and minerals including vitamins A, B6, B12, C, D, E, and K; folate; and copper, iodine, iron, magnesium, selenium, and zinc might adversely affect immune function.  
  
Examples involving vitamins are as follows:  
  
Folate deficiency affects thymus and spleen function and decreases T-lymphocyte levels, and vitamin B12 deficiency decreases the phagocytic capacity of neutrophils [15].  
Vitamin A deficiency is associated with increased susceptibility to infections, altered immune responses, and an impaired ability of epithelial tissue to act as a barrier to pathogens [5,8,15].  
Vitamin E deficiency impairs humoral and cell-mediated immunity and is associated with reduced natural killer cell activity [16-18].  
Examples involving minerals are as follows:  
  
Copper deficiency is associated with altered immune responses and an increased risk of infection, especially in infants and older adults [16,19,20].  
Low magnesium status is associated with decreased immune cell activity, increased oxidative stress, and increased inflammation, including increased levels of some inflammatory cytokines, such as interleukin-6 [21-26].  
Selenium deficiency might adversely affect immune response as well as the pathogenicity of viruses [5,10,27].  
The European Society for Clinical Nutrition and Metabolism states that low intakes or status of several micronutrients including vitamins A, E, B6, and B12; zinc; and selenium are associated with worse outcomes in patients with viral infections [14]. If needed, vitamin and mineral supplementation can boost intakes to recommended levels. In the absence of deficiency, however, routine supplementation with micronutrients probably does little to prevent or treat specific infections [14,28].  
  
The following subsections describe research on the effects of dietary supplements containing more commonly studied vitamins and minerals vitamins A, C, D, and E, selenium, and zinc on immune function.  
  
Vitamins  
Vitamin A  
Many foods contain vitamin A, an essential nutrient. Two sources of vitamin A are available in the human diet: preformed vitamin A (retinol and retinyl esters) and provitamin A carotenoids (beta-carotene, alpha-carotene, and beta-cryptoxanthin). Preformed vitamin A is present in foods from animal sources, including dairy products, eggs, fish, and organ meats. Provitamin A carotenoids come from plant foods, including leafy green vegetables, orange and yellow vegetables, tomato products, fruits, and some vegetable oils. The Recommended Dietary Allowance (RDA) for vitamin A is 300 to 1,200 mcg retinol activity equivalents (RAE) for infants and children, depending on age, and 700 to 1,300 mcg RAE for adults, including those who are pregnant or lactating [29].  
  
Vitamin A plays a critical role in vision and growth. It is also required for the formation and maintenance of epithelial tissue and the differentiation, maturation, and function of macrophages and other cells of the innate immune system [5,15,30]. Vitamin A s impact on adaptive immunity is less clear, but it is involved in the maturation of CD4+ T cells, the function of B cells, and the regulation of inflammatory cytokines [5,15]. Vitamin A deficiency is associated with increased susceptibility to infections, altered immune responses, and impairment in the ability of epithelial tissue to act as a barrier to pathogens [5,15,30,31].  
  
Although vitamin A deficiency is rare in the United States, it is common in many low- and middle-income countries and is one of the top causes of preventable blindness in children [32-36]. It is also associated with an increased risk of respiratory diseases, diarrhea, and measles. For this reason, the World Health Organization (WHO) and other expert groups recommend universal vitamin A supplementation for children younger than 5 years (including those who have HIV) in populations with a high risk of vitamin A deficiency [33,37]. Recommended doses in these populations are 30,000 mcg RAE (100,000 International Units [IU]) vitamin A once for infants age 6 11 months and 60,000 mcg RAE (200,000 IU) every 4 6 months for children age 1 5 years [37]. The authors of a 2022 analysis concluded that vitamin A supplementation has reduced child mortality rates in sub-Saharan Africa, although rates are still substantial in many countries in this region [38].  
  
Efficacy  
Diarrhea in children  
Vitamin A deficiency can decrease resistance to pathogens in the mucosa of the digestive tract and increase the risk of diarrhea [30]. Vitamin A deficiency also increases the risk of mortality from diarrhea in young children [39]. A 2015 analysis of data from 83 countries found that 94,500 deaths from diarrhea in children were associated with vitamin A deficiency [39]. In addition, more than 95% of these deaths occurred in sub-Saharan Africa and south Asia.  
  
For these reasons, researchers have examined the effects of vitamin A supplementation on childhood diarrhea. Results from these studies suggest that vitamin A supplementation reduces the risk and severity of diarrhea in children in low- and middle-income countries but does not appear to benefit very young infants.  
  
A 2011 systematic review of studies that examined the effects of vitamin A on childhood diarrhea included 13 clinical trials in a total of 37,710 participants that examined risk of diarrhea and 7 clinical trials in a total of 90,951 children age 6 months to 5 years, mostly in low- or middle-income countries, that examined the risk of death from diarrhea [40]. Vitamin A doses ranged from 6,000 mcg RAE (20,000 IU) to 61,800 mcg RAE (206,000 IU), depending on age, and were administered in a single dose or in several doses administered weekly or every few months for up to 24 months. Vitamin A supplementation decreased the risk of diarrhea by 15% and the risk of death due to diarrhea by 28%. Similarly, a 2017 Cochrane Review that included 15 clinical trials in a total of 77,946 children age 6 months to 5 years found that 15,000 mcg RAE (50,000 IU) to 60,000 mcg RAE (200,000 IU) vitamin A, depending on age, reduced the risk of diarrhea by 15% [33]. In addition, results from 9 studies in a total of 1,098,538 children showed that vitamin A reduced the risk of death due to diarrhea by 12%.  
  
In very young infants, however, limited evidence suggests that vitamin A supplementation does not affect diarrhea morbidity or mortality. A 2016 Cochrane Review that examined the effects of vitamin A supplementation in children age 1 to 6 months found that 7,500 mcg RAE (25,000 IU) to 15,000 mcg RAE (50,000 IU) vitamin A administered three times during the first few months of life did not reduce the risk of diarrhea or of death due to diarrhea [41]. However, these findings were based on only two clinical trials that examined the incidence of diarrhea in 5,183 participants and one trial that examined mortality from diarrhea in 210 participants.  
  
HIV infection  
HIV infection can lower appetite and impair the body s absorption and use of nutrients. It can also increase the risk of comorbidities, including diarrhea and respiratory diseases [42]. HIV progression can be measured by CD4+ T-cell counts; lower cell counts indicate more advanced disease, and a count below 200 cells/microliter (mcL) indicates AIDS [43]. HIV is treated with a combination of medicines called antiretroviral therapy (ART), which can reduce the risk of HIV transmission from one individual to another by reducing viral load and help people with HIV live longer [44].  
  
The results of studies of the effects of vitamin A supplementation on risk of HIV transmission or disease outcomes in children and adults have been mixed.  
  
Two Cochrane Reviews found that vitamin A supplements improved some but not all outcomes examined in children but offered no benefit in adults with HIV infection. A 2013 Cochrane Review included three clinical trials in a total of 262 infants and children with HIV age 5 years or younger [45]. It found that vitamin A supplementation (15,000 mcg RAE [50,000 IU] to 60,000 mcg RAE [200,000 IU], depending on age, administered up to four times per year) reduced the risk of all-cause mortality by 45% but had inconsistent effects on the risk of diarrhea or respiratory infections. Another Cochrane Review examined the effects of vitamin A supplementation in four clinical trials that included a total of 919 adults with HIV infection (mostly women age 18 to 45) [46]. This review found that 90,000 mcg RAE (180,000 mcg) beta-carotene or 3,000 mcg RAE (10,000 IU) vitamin A supplementation daily for 4 to 6 weeks or a single dose of 60,000 mcg RAE (200,000 IU) or 90,000 mcg RAE (300,000 IU) vitamin A did not have clinically significant effects on CD4+ T-cell counts or viral load. None of the trials was adequately powered to assess mortality or morbidity outcomes.  
  
Results were negative in another 2017 Cochrane Review [47]. It included five clinical trials conducted in sub-Saharan Africa with a total of 7,298 pregnant participants with HIV. Participants took vitamin A daily during pregnancy (3,000 mcg RAE [10,000 IU] or 1,500 mcg RAE [5,000 IU] plus 30 mg beta-carotene), a single dose immediately after delivery (60,000 to 120,000 mcg RAE [200,000 to 400,000 IU] to the mother and/or 15,000 mcg RAE [50,000 IU] to the newborn), or both. Vitamin A supplementation did not affect the risk of mother-to-child transmission of HIV. Largely because of the findings from this analysis, the WHO does not recommend vitamin A supplementation in people with HIV who are pregnant in order to reduce the risk of mother-to-child transmission of HIV [48].  
  
Most of the findings were also negative in a 2022 systematic review of vitamin A supplementation that included 17 clinical trials, conducted mostly in sub-Saharan Africa, in a total of 12,585 children and adults (mostly pregnant women) with HIV [31]. Vitamin A dosing schedules varied widely but commonly included 1,500 to 3,000 mcg RAE (5,000 to 10,000 IU) daily or one-time doses of 15,000 to 120,000 mcg RAE (50,000 to 400,000 IU) at baseline or delivery. Vitamin A supplementation did not affect viral load, CD4+ or CD8+ T-cell counts, or interleukin-1b levels. In addition, it did not affect rates of gastrointestinal and HIV symptoms. However, in one trial included in the review, vitamin A supplementation (120,000 mcg RAE [400,000 IU] at delivery) reduced the number of clinic visits for some health conditions in women with HIV postpartum and in another trial, supplementation with 15,000 to 60,000 mcg RAE (50,000 to 200,000 IU) vitamin A (depending on age) five times per year reduced rates of diarrhea in children with HIV. Supplements (1,500 mcg RAE [5,000 IU] daily plus 60,000 mcg RAE [200,000 IU] at delivery) also reduced the risk of preterm birth in one study in pregnant women with HIV.  
  
Whether maternal vitamin A supplementation affects the morbidity and mortality of breastfed infants was the focus of a cross-sectional study in lactating people with HIV from sub-Saharan Africa [49]. The study included 838 mothers, 309 of whom took vitamin A supplements after giving birth (doses and frequency not reported); the other 529 did not. Vitamin A supplementation did not affect infant mortality rates or the risk of cough with difficulty breathing, diarrhea, or fever in the breastfed infants.  
  
Measles in children  
In 2019, measles was responsible for more than 207,500 deaths around the world, mostly in young children in low-income countries [50]. A major risk factor for severe measles is low vitamin A status [5]. Research suggests that vitamin A supplementation reduces the risk of measles in children who are at high risk of vitamin A deficiency. However, whether vitamin A supplementation reduces the risk of death from measles is less clear.  
  
Evidence supporting vitamin A s role in reducing the risk of death from measles comes from a 2013 WHO analysis of data from 83 countries showing that 11,200 deaths from measles in children were associated with vitamin A deficiency, and more than 95% of these deaths occurred in sub-Saharan Africa and south Asia [39]. In a pooled analysis of clinical trials within this study, vitamin A supplementation was associated with a 26% lower risk of dying from measles.  
  
However, other studies have found no effect of vitamin A supplementation on risk of death from measles. A 2011 systematic review included six clinical trials in a total of 19,566 children younger than 5 years that examined the effect of vitamin A supplementation on risk of measles and five clinical trials in a total of 88,261 children that examined the risk of death from measles. Most studies were conducted in low- and middle-income countries [40]. Vitamin A doses ranged from 2,500 mcg RAE (8,333 IU) to 60,000 mcg RAE (200,000 IU), depending on age, and were administered as single doses or over weeks or months. Vitamin A supplementation decreased the risk of measles by 50% but did not affect the risk of death due to measles. Similarly, a 2017 Cochrane Review of 15,000 mcg RAE (50,000 IU) to 60,000 mcg RAE (200,000 IU), depending on age, vitamin A supplementation in six clinical trials in a total of 19,566 children age 6 months to 5 years found that supplementation reduced the risk of new cases of measles by 50% [33]. However, the supplements did not affect risk of death due to measles, according to the results of six clinical trials in a total of 1,088,261 children.  
  
Again, findings were mostly negative in a 2022 systematic review of 13 clinical trials conducted in India or sub-Saharan Africa of vitamin A supplementation for measles in a total of 1,061,373 infants and children [31]. Vitamin A supplementation did not reduce the risk of measles in healthy infants and children or mortality rates in those with measles. The supplements also had no effect on immunological responses, except for higher levels of immunoglobulin G antibodies in children taking vitamin A in one study. However, a few trials found that vitamin A supplementation reduced the risk of a few measles-related complications, such as pneumonia, especially among children with vitamin A deficiency, and severe diarrhea.  
  
Pneumonia and other respiratory tract infections in children  
Vitamin A deficiency is associated with recurrent respiratory tract infections in children [33,51]. However, findings have been mixed from trials of the effects of vitamin A supplementation on the risk and severity of pneumonia and other respiratory tract infections in children [33,52]. In addition, some evidence suggests that doses of vitamin A supplementation that are higher than the WHO recommends might increase the risk of respiratory tract infections among children with normal nutritional status [53].  
  
Effects were mixed in a meta-analysis of 15 clinical trials in a total of 3,021 children (age not specified) that examined the effects of 450 mcg RAE (1,500 IU) to 120,000 mcg RAE (400,000 IU) vitamin A supplementation for several days or weeks on the risk of morbidity and mortality from pneumonia [52]. Vitamin A supplementation shortened the durations of hospital stays and of signs and symptoms, including fever, cough, and abnormal chest X-rays. However, it did not reduce the risk of death due to pneumonia.  
  
Other clinical trials have found that vitamin A supplements do not reduce the risk of respiratory tract infections or of death from these infections. A 2017 Cochrane Review that included 11 clinical trials in a total of 27,540 children age 6 months to 5 years found that 15,000 mcg RAE (50,000 IU) to 60,000 mcg RAE (200,000 IU), depending on age, vitamin A supplementation did not significantly affect the risk of lower respiratory tract infections [33]. In addition, vitamin A supplements did not affect the risk of death due to these infections, according to the results of nine studies in a total of 1,098,538 children that examined this outcome. A separate Cochrane Review also found that vitamin A supplementation (7,500 mcg RAE [25,000 IU] or 15,000 mcg RAE [50,000 IU] given three times during the first 14 weeks of life) did not reduce the risk of respiratory tract infections or death due to such infections in very young infants age 1 to 6 months, although the review included only one trial for each outcome [41]. Similarly, a 2022 systematic review of 16 clinical trials that combined nine trials in a meta-analysis in a total of 32,129 children found that vitamin A supplementation did not reduce the risk of respiratory tract infections [54].  
  
Another meta-analysis found that taking vitamin A supplements to reduce the risk of respiratory tract infections might even be harmful in some circumstances [53]. The analysis included 26 clinical trials that examined acute or lower respiratory tract infections in a total of 50,994 children from birth to age 11 years. Vitamin A doses ranged from 15,000 mcg RAE (50,000 IU) to 370,800 mcg RAE (1,236,000 IU) depending on age and were administered as a single dose or over days, weeks, months, or years. Overall, vitamin A supplementation did not affect the risk, severity, or duration of acute or lower respiratory tract infections. However, in subgroup analyses, higher-than-standard vitamin A doses (more than 30,000 mcg RAE [100,000 IU] for children up to 11 months of age and more than 60,000 mcg RAE [200,000 IU] every 4 to 6 months for children age 12 months to 11 years) increased the risk of acute respiratory tract infections by 66% in participants with normal nutritional status, but these doses did not affect this risk in participants with stunted and wasted nutritional status.  
  
Safety  
Up to 600 to 2,800 mcg/day preformed vitamin A in foods and dietary supplements is safe for children, depending on age, and up to 3,000 mcg/day is safe for adults, including those who are pregnant or lactating [29]. These tolerable upper intake levels (ULs, maximum daily intake unlikely to cause adverse health effects), however, do not apply to people taking vitamin A under the care of a physician.  
  
Higher intakes can cause severe headache, blurred vision, nausea, dizziness, aching muscles, and coordination problems. In severe cases, cerebral spinal fluid pressure can increase, leading to drowsiness and, eventually, coma [55]. Regular consumption of high doses of preformed vitamin A from foods or supplements can cause dry skin, painful muscles and joints, fatigue, depression, and abnormal liver test results. High intakes of preformed vitamin A can also cause congenital birth defects [35].  
  
Unlike preformed vitamin A, beta-carotene is not known to be teratogenic or lead to reproductive toxicity. Therefore, beta-carotene does not have an established UL [56].  
  
Vitamin A might interact with some medications. For example, orlistat, a weight-loss medication, can decrease the absorption of vitamin A, resulting in low plasma levels in some patients [57]. In addition, synthetic retinoids derived from vitamin A that are used as oral prescription medicines, such as acitretin used to treat psoriasis, increase the risk of hypervitaminosis A when taken in combination with vitamin A supplements [57].  
  
More information on vitamin A is available in the ODS health professional fact sheet on vitamin A.  
  
Vitamin C  
Vitamin C, also called ascorbic acid, is an essential nutrient contained in many fruits and vegetables, including citrus fruits, tomatoes, potatoes, red and green peppers, kiwifruit, broccoli, strawberries, brussels sprouts, and cantaloupe. The RDA for vitamin C is 15 to 115 mg for infants and children, depending on age, and 75 to 120 mg for nonsmoking adults, including those who are pregnant or lactating; people who smoke need 35 mg more per day [56].  
  
Vitamin C plays an important role in both innate and adaptive immunity, probably because of its antioxidant effects, antimicrobial and antiviral actions, and effects on immune system modulators [5,32,58-62]. Vitamin C helps maintain epithelial integrity, enhance the differentiation and proliferation of B cells and T cells, enhance phagocytosis, normalize cytokine production, and decrease histamine levels [4,5,60]. It might also inhibit viral replication [13].  
  
Vitamin C deficiency impairs immune function and increases susceptibility to infections [5,58,60]. Some research suggests that supplemental vitamin C enhances immune function [63], but its effects might vary depending on an individual s vitamin C status [64].  
  
Vitamin C deficiency is uncommon in the United States, affecting only about 7% of individuals age 6 years and older [65]. People who smoke and those whose diets include a limited variety of foods (such as some older adults and people with alcohol or drug use disorders) are more likely than others to obtain insufficient amounts of vitamin C [61,63].  
  
Efficacy  
Common cold  
Vitamin C s antioxidant action might help reduce oxidative stress during infections. In addition, regular consumption of vitamin C might reduce the duration of the common cold and the severity of its symptoms, but taking vitamin C supplements only after symptom onset does not provide consistent benefits [5,59].  
  
Several clinical trials have examined whether vitamin C supplementation reduces the risk of developing the common cold in the general population and those exposed to extreme physical stress. One trial included 92 runners and a control group of 92 nonrunners (mostly male, age 25 years or older) who took 600 mg per day vitamin C or placebo for 21 days before a 90-kilometer ultramarathon [66]. During the 2 weeks after the race, 68% of the runners who took a placebo but only 33% of those who took vitamin C reported developing an upper respiratory tract infection. Among nonrunners, however, the incidence of upper respiratory tract infections was not different between supplement and placebo users. In addition, the duration of symptoms in nonrunners who took vitamin C was shorter (mean 4.2 days) than in those who took a placebo (5.6 days), but symptom duration did not differ between the runners who took vitamin C and those who took a placebo.  
  
A 2013 Cochrane Review included 29 clinical trials (including the one described above) that examined the effects of vitamin C supplementation in 11,306 participants [13]. Most trials had participants from the general population, but five trials involved 598 people exposed to extreme physical stress, including marathon runners, skiers, and soldiers in subarctic areas. Taking 200 mg/day or more vitamin C regularly did not affect the risk of developing the common cold in the general population. However, among people exposed to extreme physical stress, vitamin C supplementation reduced the risk of developing a cold by 52%. In addition, regular use of vitamin C supplements shortened the duration of colds by about 8% in adults and about 14% in children; it also reduced cold severity. The authors noted that extreme physical stress generates oxidative stress, and the antioxidant action of vitamin C might help counteract this effect in people exposed to this type of physical stress [13].  
  
Findings were positive in a 2021 systematic review and meta-analysis that included 24 clinical trials in a total of 10,961 adults [67]. Daily doses of vitamin C ranged from less than 250 mg to 2,000 mg for 5 days to 5 years. The supplementation reduced the risk of the common cold and other acute respiratory infections by 4%. However, effects differed by sex, with an 18% reduced risk among men, but no significant effect among women. Vitamin C supplementation also shortened the duration of symptoms by 9%.  
  
Some evidence suggests that vitamin C supplementation might be more effective in people with low vitamin C status [64]. For example, a 2014 clinical trial included 28 healthy, nonsmoking men age 18 to 35 years who took 1,000 mg vitamin C or placebo daily for 8 weeks during the peak of the cold season, January through April [68]. Approximately half of the participants had either inadequate (less than 28 mcmol/L) or deficient (less than 11 mcmol/L) plasma vitamin C concentrations. Participants who took vitamin C had a 45% lower risk of developing the common cold than those who took placebo.  
  
Sepsis (vitamin C administered intravenously, not as a dietary supplement)  
Sepsis is a life-threatening condition that occurs when the body s extreme inflammatory response to an infection causes widespread organ and tissue damage. Some researchers believe that high-dose intravenous vitamin C (which is classified as a drug in the United States) might mitigate the damage caused by sepsis, but evidence from clinical trials is mixed, and some evidence suggests that this treatment may cause harm.  
  
Evidence on the potential harms of intravenous vitamin C for sepsis comes from a 2022 clinical trial in Canada, France, and New Zealand that included 872 men and women (mean age 65 years) with an infection who were in the intensive care unit (ICU) for 24 hours or less and were treated with vasopressor medications [69]. Patients received an infusion of vitamin C (50 mg/kg) or placebo every 6 hours for up to 96 hours. On day 28, those treated with intravenous vitamin C had a higher risk of death or organ dysfunction than those treated with a placebo.  
  
Other trials have had mixed findings. For example, in a clinical trial in 167 ICU patients (mean age 55 years) with sepsis and ARDS for less than 24 hours, 50 mg/kg every 6 hours for 96 hours intravenous vitamin C did not improve organ dysfunction scores or markers of inflammation and vascular injury compared with placebo [70]. However, patients treated with intravenous vitamin C had a lower risk of 28-day all-cause mortality.  
  
Two 2022 systematic reviews and meta-analyses that examined the effects of intravenous vitamin C in critically ill patients also had mixed findings [71,72]. One of these analyses included 15 clinical trials (including the 2019 trial described above but not the 2022 trial) in a total of 2,490 patients that administered high-dose intravenous vitamin C (10,000 mg/day or more, which is equal to about 33 mg/kg every 6 hours for a 165-pound person) and low dose (less than 10,000 mg/day) [71]. In some studies, intravenous vitamin C was combined with thiamin and hydrocortisone. Vitamin C infusion did not affect overall mortality risk. However, high-dose intravenous vitamin C reduced overall mortality rates by 30%, whereas low dose intravenous vitamin C did not. The other analysis included 17 trials that administered less than 6,000 mg/day to more than 12,000 mg/day intravenous vitamin C, sometimes in combination with thiamin, glucocorticoids, or both [72]. The intravenous vitamin C did not affect organ dysfunction, length of ICU stay, or risk of death 90 days to 1 year after study enrollment.  
  
Safety  
Up to 400 to 1,800 mg/day vitamin C from foods and dietary supplements is safe for children, depending on age, and up to 2,000 mg/day is safe for adults, including those who are pregnant or lactating [56]. These ULs, however, do not apply to people taking vitamin C under the care of a physician.  
  
Higher vitamin C intakes can cause diarrhea, nausea, and abdominal cramps. High intakes might also cause falsely high or low readings on some blood glucose meters that are used to monitor glucose levels in people with diabetes [73-75]. In people with hemochromatosis, high doses of vitamin C could exacerbate iron overload and damage body tissues [56,61].The Food and Nutrition Board of the National Academies of Sciences, Engineering, and Medicine recommends that people with hemochromatosis be cautious about consuming vitamin C doses above the RDA [56].  
  
Vitamin C supplementation might interact with some medications. For example, it might reduce the effectiveness of radiation therapy and chemotherapy by protecting tumor cells from the action of these agents [76]. Vitamin C might also enhance the absorption of levothyroxine when taken at the same time [77].  
  
More information on vitamin C is available in the ODS health professional fact sheet on vitamin C.  
  
For information on vitamin C and COVID-19, please see the ODS health professional fact sheet, Dietary Supplements in the Time of COVID-19.  
  
Vitamin D  
Vitamin D exists in two forms: vitamin D2 and vitamin D3. It is an essential nutrient that is naturally present in only a few foods, such as fatty fish (including salmon and tuna) and fish liver oils. In addition, beef liver, cheese, and egg yolks contain small amounts. Fortified foods, especially fortified milk, provide most of the vitamin D in the diets of people in the United States. The RDA for vitamin D is 10 to 15 mcg (400 IU to 600 IU) for children, depending on age, and 15 to 20 mcg (600 to 800 IU) for adults, including those who are pregnant or lactating [78]. The body can also synthesize vitamin D as a result of sun exposure.  
  
Vitamin D obtained from sun exposure, foods, and supplements is biologically inert until it undergoes two hydroxylations in the body for activation. The first hydroxylation, which occurs in the liver, converts vitamin D to 25-hydroxyvitamin D [25(OH)D]. The second hydroxylation occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [1,25(OH)2D].  
  
Serum concentration of 25(OH)D is the main indicator of vitamin D status [78]. Although researchers have not definitively identified serum concentrations of 25(OH)D associated with deficiency and adequacy, the Food and Nutrition Board advises that levels below 30 nmol/L (12 ng/mL) are associated with vitamin D deficiency, and levels of 50 nmol/L (20 ng/mL) or more are considered adequate for bone and overall health in most people [78]. However, 25(OH)D levels defined as deficient or adequate vary from study to study.  
  
In addition to its well-known effects on calcium absorption and bone health, vitamin D plays a role in immune function [5,58,79-82]. Vitamin D appears to lower viral replication rates, suppress inflammation, and increase levels of T-regulatory cells and their activity [16,58,83-88]. In addition, almost all immune cells (e.g., B lymphocytes and T lymphocytes) express the vitamin D receptor, and some immune cells (e.g., macrophages and dendritic cells) can convert 25(OH)D to the active 1,25(OH)2D form. These capabilities suggest that vitamin D can modulate both innate and adaptive immune responses [5,16,80-82,85,87,88].  
  
Vitamin D deficiency affects the body s susceptibility to infection, partly by weakening tissue barriers, and has been associated with an increased risk of influenza and other respiratory tract infections, hepatitis C, HIV, and other viral infections [5,14,81,89]. It also impairs macrophage function and interleukin-10 production [5].  
  
Dietary surveys indicate that most people in the United States consume less than recommended amounts of vitamin D [90]. Nevertheless, according to a 2011 2014 analysis of serum 25(OH)D concentrations, most people in the United States age 1 year and older have adequate vitamin D status [91]. Sun exposure, which increases serum 25(OH)D levels, is one of the reasons serum 25(OH)D levels are usually higher than would be predicted on the basis of dietary vitamin D intakes alone [78].  
  
Efficacy  
Influenza, pneumonia, and other respiratory tract infections  
Researchers have investigated whether higher vitamin D status can reduce the risk of seasonal infections, having observed that low vitamin D status (due to less sun exposure) and higher risk of upper respiratory tract infections are more common in the winter [87,92]. An analysis of data on the association between 25(OH)D levels and recent upper respiratory tract infections in 18,883 participants age 12 years and older from the third National Health and Nutrition Examination Survey (1988 1994) suggests that lower vitamin D levels are associated with a higher risk of respiratory tract infections [93]. In this analysis, 24% of participants with 25(OH)D levels less than 10 ng/mL reported recent upper respiratory tract infections. In contrast, only 20% of participants with levels of 10 to less than 30 ng/mL and 17% of those with levels of 30 ng/mL or higher reported recent upper respiratory tract infections. In another analysis, vitamin D insufficiency and deficiency were associated with a higher mortality risk from respiratory diseases than vitamin D sufficiency during 15 years of follow-up in 9,548 adults age 50 75 years in Germany [94].  
  
Results from clinicals trials have been mixed but suggest that vitamin D supplementation might modestly reduce the risk of respiratory tract infections. For example, in a clinical trial in Japan, 430 children age 6 to 15 years took 30 mcg (1,200 IU) vitamin D3 or placebo daily during 4 winter months [95]. Children who took vitamin D3 were 42% less likely to develop influenza A than those who took a placebo. Another trial, in contrast, found that 50 mcg (2,000 IU)/day vitamin D3 for 12 weeks during the winter failed to reduce the incidence of upper respiratory tract infections or the duration or severity of symptoms when compared with placebo in 162 adults age 18 to 80 years [96]. In this trial, both groups had adequate mean 25(OH)D levels for bone and overall health at baseline. Weekly supplementation with 350 mcg (14,000 IU) vitamin D3 for 3 years also failed to reduce the risk of tuberculosis or acute respiratory infection in comparison with placebo in 8,851 children age 6 to 13 in Mongolia, almost all of whom had serum 25(OH)D levels below 20 ng/mL at baseline [97].  
  
Results have been mixed from systematic reviews and meta-analyses that have examined the effects of vitamin D supplementation on the risk of pneumonia and other respiratory tract infections. Results were negative in a 2016 Cochrane Review that evaluated the use of vitamin D supplementation for preventing infections, including pneumonia, in children younger than 5 years [98]. The review included two trials that examined pneumonia incidence in a total of 3,134 participants; one trial was placebo controlled, and the other had a control group that received no treatment. Vitamin D3 (10 mcg [402 IU]/day for 12 months or 2,500 mcg [100,000 IU] every 3 months for 18 months) did not reduce the risk of pneumonia.  
  
A 2017 systematic review and meta-analysis of vitamin D supplementation to prevent acute respiratory tract infections (mostly upper respiratory tract infections) had mixed findings. This analysis included 25 clinical trials and a total of 10,933 participants from newborns to adults age 95 years [99]. Study durations ranged from 7 weeks to 1.5 years, and vitamin D supplementation schedules varied widely (e.g., one 2,500 mcg bolus, 25 mcg daily, or 500 mcg weekly). Vitamin D supplementation resulted in a 12% lower risk of acute respiratory tract infections than placebo. However, vitamin D supplementation was beneficial only in participants who took supplements daily or weekly, not in those who took one or more bolus doses. In addition, protective effects were stronger in those with baseline 25(OH)D levels less than 25 nmol/L (10 ng/mL) than in those with higher levels.  
  
A subsequent systematic review and meta-analysis by the same research team that included 46 clinical trials and a total of 75,541 participants age 0 to 95 years found some benefits of vitamin D supplementation [100]. Participants who took vitamin D supplements had an 8% lower risk of developing one or more acute respiratory infections. Similarly, another 2021 systematic review and meta-analysis of 20 clinical trials in a total of 9,902 adults found that vitamin D supplements reduced the risk of acute respiratory infections by 3% and shortened the duration of symptoms by 6% [67].  
  
Other systematic reviews and meta-analyses have also found that vitamin D supplementation helps reduce the risk of respiratory tract infections and influenza in children and adults [101-103] and that vitamin D deficiency is associated with an increased risk of community-acquired pneumonia in children and adults [104]. In addition, serum 25(OH)D concentrations are inversely associated with risk and severity of acute respiratory tract infections [105]. In contrast, a meta-analysis of 30 clinical trials in a total of 30,263 participants age 3 to 81 years found that vitamin D supplementation did not reduce the risk of respiratory tract infections [106]. Mixed findings were reported in a meta-analysis of six trials in a total of 6,843 children and seven trials in a total of 3,994 adults [54]. It found that 25 to 100 mcg (1,000 to 4,000 IU)/day vitamin D supplementation reduced the risk of respiratory tract infections by 11% in adults, but 25 to 50 mcg (1,000 to 2,000 IU)/day did not affect risk in children.  
  
Vitamin D supplementation did not reduce the risk of respiratory tract infections in adolescents and adults in two clinical trials whose results were published in 2022 [107,108]. In one of these trials, 34,601 men and women age 18 to 75 years in Norway who were not taking daily vitamin D supplements took 5 mL cod liver oil containing 10 mcg (400 IU) vitamin D3 or placebo for up to 6 months during the winter [107]. The cod liver oil did not reduce the incidence of acute respiratory infections. The other trial involved 6,200 participants age 16 years or older in the United Kingdom who were not taking vitamin D supplements [108]. Half of the participants were offered a vitamin D blood test. Those whose 25(OH)D level was less than 75 nmol/L (30ng/mL) received a 6-month supply of a lower dose (20 mcg [800 IU]/day) or a higher dose (80 mcg [3,200 IU]/day) of vitamin D3. The other participants were not offered vitamin D tests or supplementation, and the study did not use a placebo. Neither lower nor higher doses of vitamin D3 reduced the risk of acute respiratory tract infections.  
  
Researchers have also examined whether vitamin D supplementation helps treat respiratory tract infections, but results suggest that it has limited, if any, benefits. A 2022 meta-analysis included 18 clinical trials in a total of 3,648 participants with mean ages between 12 months and 62 years [109]. It assessed whether one-time, daily, or occasional vitamin D doses ranging from 15 to 15,000 mcg (600 IU to 600,000 IU), depending on dosing schedule, for up to 8 months helped treat respiratory infections. Treatment outcomes differed among trials but included sputum conversion (for pulmonary tuberculosis), survival rate, and no need for ICU admission. Vitamin D supplementation had some small beneficial effects on treatment outcomes, but when the authors analyzed only the 12 high-quality trials, the differences between groups in the trials were no longer statistically significant.  
  
HIV infection  
People with HIV may be more likely to have vitamin D deficiency because many medications that treat HIV/AIDS increase vitamin D catabolism [110,111]. Inflammation and comorbidities from HIV infection may also contribute to low vitamin D levels [112]. Low vitamin D levels could partly explain why people with HIV appear to have a higher risk of major bone fractures [113]. Many, but not all studies, also show associations between vitamin D deficiency and decreased CD4+ T-cell counts [111].  
  
Vitamin D deficiency might also increase HIV infection severity [114]. Observational studies show associations between low vitamin D status and increased risk of pulmonary tuberculosis and mortality in people with HIV [115]. In addition, low levels of vitamin D in pregnant people with HIV are associated with poor fetal and infant growth [116].  
  
Results from clinical trials, however, have not shown that vitamin D supplementation improves outcomes in people with HIV [115,116]. In one clinical trial in Tanzania, 4,000 men and women (mean age about 39 years) with HIV who had serum 25(OH)D levels lower than 30 ng/mL at ART initiation took 1,250 mcg (50,000 IU) vitamin D3 weekly for 4 weeks, followed by daily doses of 50 mcg (2,000 IU) for 11 additional months or placebo [115]. Vitamin D3 supplementation did not affect rates of mortality or pulmonary tuberculosis. Moreover, vitamin D3 supplementation did not affect secondary outcomes, including risk of HIV progression, viral suppression, comorbidities (nausea, vomiting, cough, fever, or diarrhea), changes in body weight, or depression [112].  
  
Another clinical trial in Tanzania examined the effects of vitamin D3 supplementation during pregnancy and lactation in 2,300 people with HIV [116]. Participants took 75 mcg (3,000 IU)/day vitamin D3 or placebo from the second trimester of pregnancy (12 27 weeks) until 1 year after delivery. Vitamin D3 supplementation did not affect the risk of maternal HIV progression or death. The results also showed no difference in the risk of small-for-gestational-age birth or of infant stunting at 1 year.  
  
Safety  
Daily intakes of up to 25 100 mcg (1,000 IU 4,000 IU) vitamin D, depending on age, in foods and dietary supplements are safe for infants and children, and up to 100 mcg (4,000 IU) is safe for adults, including those who are pregnant or lactating [78]. These ULs, however, do not apply to people taking vitamin D under the care of a physician.  
  
Higher intakes (usually from supplements) can lead to nausea, vomiting, muscle weakness, confusion, pain, loss of appetite, dehydration, excessive urination and thirst, and kidney stones. In extreme cases, vitamin D toxicity causes renal failure, calcification of soft tissues throughout the body (including in coronary vessels and heart valves), cardiac arrhythmias, and even death [117-119].  
  
Several types of medications might interact with vitamin D. For example, orlistat, statins, and steroids can reduce vitamin D levels [120,121]. In addition, taking vitamin D supplements with thiazide diuretics might lead to hypercalcemia [120].  
  
More information on vitamin D is available in the ODS health professional fact sheet on vitamin D.  
  
For information on vitamin D and COVID-19, please see the ODS health professional fact sheet, Dietary Supplements in the Time of COVID-19.  
  
Vitamin E  
Vitamin E, also called alpha-tocopherol, is an essential nutrient that is present in several foods, including nuts, seeds, vegetable oils, and green leafy vegetables. The RDA for vitamin E is 4 to 15 mg for infants and children, depending on age, and 15 to 19 mg for adults, including those who are pregnant or lactating [56].  
  
Vitamin E is an antioxidant that plays an important role in immune function by helping maintain cell membrane integrity and epithelial barriers and by enhancing antibody production, lymphocyte proliferation, and natural killer cell activity [4,5,15,17,25,58,79,122]. Vitamin E also limits inflammation by inhibiting the production of proinflammatory cytokines [123].  
  
Human and animal studies suggest that vitamin E deficiency impairs humoral and cell-mediated immunity, is associated with reduced natural killer cell activity, and increases susceptibility to infections [5,15-18,122]. High-dose vitamin E supplements (60 to 800 mg/day) for 1 to 8 months might enhance lymphocyte proliferation, interleukin-2 production, and natural killer cell activity and could increase antibody titers after hepatitis B and tetanus vaccines in adults age 60 or older [124-126].  
  
Frank vitamin E deficiency is rare, except in people with intestinal malabsorption disorders [56,79]. Research on the ability of vitamin E to improve immune function tends to use supplemental vitamin E rather than simply ensuring that study participants achieve adequate vitamin E status because it is thought that higher doses may be needed to achieve beneficial effects [122].  
  
Efficacy  
Pneumonia and other respiratory tract infections  
Because of vitamin E s effects on immune function, researchers have examined whether vitamin E supplementation can reduce the risk or severity of respiratory tract infections. However, study findings have been mixed. Some researchers suggest that differences among study findings may reflect differences in participants vitamin E status at baseline and differences in supplementation doses used in these studies [127].  
  
A prospective cohort study in 717 men and women age 65 years or older in Canada who were hospitalized with pneumonia found that those who took vitamin E supplements (doses not specified) were 63% less likely to be rehospitalized within 90 days than those who did not [128]. However, vitamin E supplementation did not affect the risk of death from pneumonia within 30 days of the initial hospitalization.  
  
A few clinical trials that have examined the effects of vitamin E supplementation on respiratory tract infections in infants and young children or in older adults suggest that vitamin E offers limited benefits and might even increase symptom severity. A clinical trial in a low-income urban area in India examined the effects of 200 mg alpha-tocopherol and 100 mg ascorbic acid twice daily or placebo for 5 days in 174 infants and young children age 2 to 35 months who were hospitalized with severe acute lower respiratory tract infections and receiving standard care [129]. Supplementation did not affect the time required to recover from illness.  
  
Another clinical trial in which 652 healthy men and women age 60 years or older took one of four different treatments daily for about 15 months identified no benefits and, in fact, found potential risks of vitamin E supplementation to prevent respiratory tract infections. The treatments were 200 mg vitamin E (as alpha-tocopheryl acetate), a multivitamin/mineral supplement (containing 10 mg vitamin E), a multivitamin/mineral and vitamin E, or placebo [130]. All but one of the participants had adequate vitamin E concentrations at the start of the study. The vitamin E supplements did not affect the incidence of acute respiratory tract infections throughout the trial. Moreover, participants who took the vitamin E supplement had longer durations of illness, more severe symptoms (including fever and activity restrictions), and greater numbers of symptoms than those who did not take vitamin E.  
  
Results were also negative in a similar trial in 617 adults age 65 or older living in nursing homes to determine whether daily supplementation with 200 IU vitamin E (91 mg, as dl-alpha-tocopherol) for 1 year reduced the risk of upper or lower respiratory tract infections [131]. Vitamin E supplementation did not affect the incidence of upper or lower respiratory tract infections or the total durations of the infections.  
  
Results were mixed in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study in 29,133 male smokers age 50 69 years who took 50 mg/day vitamin E (in the form of dl-alpha-tocopheryl acetate) with or without beta-carotene or placebo [132]. Vitamin E supplementation for a median of 6.1 years did not affect the risk of hospital-treated pneumonia. In contrast, a secondary analysis of data from this trial found that vitamin E supplementation reduced the risk of pneumonia by 69% among the 2,216 participants who started smoking at the age of 21 years or older, smoked 5 19 cigarettes per day, and exercised recreationally [133]. Among the 5,253 participants who smoked more than 19 cigarettes per day or did not exercise, however, vitamin E supplementation did not affect the risk of pneumonia.  
  
Safety  
All intake levels of vitamin E found naturally in foods are considered safe. Up to 200 mg to 800 mg/day supplemental vitamin E is safe for children, depending on age, and up to 1,000 mg/day is safe for adults, including those who are pregnant or lactating [56]. These ULs, however, do not apply to people taking vitamin E under the care of a physician. Higher vitamin E intakes can increase the risk of bleeding because of the vitamin s anticoagulant effect and can cause hemorrhagic stroke.  
  
Vitamin E supplementation might interact with certain medications, including anticoagulant and antiplatelet medications. It might also reduce the effectiveness of radiation therapy and chemotherapy by protecting tumor cells from the action of these agents [76,134,135].  
  
More information on vitamin E is available in the ODS health professional fact sheet on vitamin E.  
  
For information on vitamin E and COVID-19, please see the ODS health professional fact sheet, Dietary Supplements in the Time of COVID-19.  
  
Minerals  
Selenium  
Selenium is an essential mineral contained in many foods, including Brazil nuts, seafood, meat, poultry, eggs, and dairy products as well as bread, cereals, and other grain products. The RDA for selenium is 15 to 70 mcg for infants and children, depending on age, and 55 to 70 mcg for adults, including those who are pregnant or lactating [56].  
  
Human and animal studies suggest that selenium helps support both the innate and adaptive immune systems through its role in T-cell maturation and function and in natural killer cell activity [2,25,58,136-139]. It may also reduce the risk of infections [2,15,25,58,137-141]. As a component of enzymes that have antioxidant activities, selenium might help reduce the systemic inflammatory response that can lead to ARDS and organ failure [27,58,140,141].  
  
Low selenium status in humans has been associated with lower natural killer cell activity, increased risk of some bacterial infections, and increased virulence of certain viruses, including hepatitis B and C [2,5,10,15,27,137,142,143]. However, evidence is conflicting whether selenium supplementation enhances immunity against pathogens in humans [136]. Some research suggests that 100 to 300 mcg/day supplemental selenium improves immune function and that doses of 50 or 100 mcg/day enhance the immune response to poliovirus vaccine in adults with low selenium status [15]. However, a systematic review and meta-analysis of nine clinical trials in a total of 370 healthy men and women age 18 years or older found that 13 to 400 mcg/day supplemental selenium for 8 to 48 weeks did not affect immunoglobulin or white blood cell concentrations; the only beneficial effect was increased natural killer cell activity [136]. Studies have also examined whether intravenous selenium (which is classified as a drug in the United States) benefits adults with sepsis; those who are critically ill and requiring mechanical ventilation; adults who are undergoing elective major surgery; or those who are critically ill from burns, head injury, brain hemorrhage, or stroke [141,144,145]. The results of these studies provide no clear evidence of benefit.  
  
Selenium status varies by geographic region because of differences in the amounts of selenium in soil and in local foods consumed [56,146]. Selenium deficiency is very rare in the United States and Canada, but low selenium status is common in some areas of the world, such as parts of Europe and China [139,147].  
  
Efficacy  
HIV infection  
In children and adults with HIV, selenium deficiency is associated with a higher risk of morbidity and mortality [142]. However, studies that examined whether micronutrient supplementation, including selenium, affects risk of HIV transmission or disease outcomes in children and adults have had mixed results. An observational study in Thailand did not identify associations between selenium status in children with HIV and treatment outcomes [148]. This study included 141 boys and girls with HIV (median age 7.3 years), 97 of whom started ART over a period of 48 weeks. Baseline selenium levels (all of which were adequate) showed no associations with ART treatment outcomes.  
  
Clinical trials have found limited beneficial effects of selenium supplementation on immune function in people with HIV. A clinical trial in Rwanda examined the effects of selenium supplementation on CD4+ T-cell counts in 300 men and women 21 years of age or older with HIV. Participants had CD4+ T-cell counts between 400 and 650 cells/mcL, so they were not yet eligible for ART [149]. They took 200 mcg/day selenium or placebo for 24 months. During the trial, average CD4+ T-cell counts declined in both the treatment and placebo groups, but the rate of depletion was 43.8% lower in those who took selenium. However, selenium supplementation had no effect on the composite endpoint of a CD4+ count of less than 350 cells/mcL or initiation of ART.  
  
Selenium supplementation provided no benefits in another trial that randomized 146 men and women with HIV (mean age 38.6 years) in Iran who were receiving ART to take 50 mg/day zinc, 200 mcg/day selenium, or placebo for 6 months. The investigators then followed participants for another 3 months but found that selenium supplementation did not raise CD4+ T-cell counts [150].  
  
Two Cochrane Reviews also concluded that selenium supplements offer little, if any, benefit for people with HIV. The first review examined whether micronutrient supplementation reduces the burden of HIV infection in children, and it included three clinical trials that administered 30 or 60 mcg/day selenium as part of a multiple-micronutrient formulation in children with HIV who were living in South Africa or Uganda [45]. The authors found that evidence was insufficient to determine whether supplementation with selenium alone is beneficial. Similarly, the authors of a second Cochrane Review that included four clinical trials in a total of 1,187 adults with HIV concluded that 200 mcg/day selenium for 9 to 24 months may have little to no effect on CD4+ T-cell count and viral load and that evidence is insufficient to determine whether selenium supplementation affects the risk of hospital admission [46].  
  
Researchers have also examined whether blood selenium levels or selenium supplementation affect pregnancy outcomes in people with HIV. Findings from these studies suggest that low blood selenium levels are associated with a higher risk of preterm delivery and that selenium supplementation might reduce the risk of preterm delivery but has mixed effects on other outcomes. For example, a cross-sectional study in Nigeria of 113 pregnant individuals age 15 49 years with HIV found that those with a selenium deficiency (defined as blood selenium less than 0.89 mcmol/L) at 14 26 weeks of gestation were almost eight times as likely to have a preterm delivery as those with normal selenium levels [151]. Individuals with a low CD4+ T-cell count also had an eightfold higher risk of preterm delivery. In a clinical trial in Nigeria, researchers examined whether selenium supplementation affects pregnancy outcomes and disease progression in 90 pregnant individuals (mean age 29.7 years) with HIV at 14 to 27 weeks of gestation [152]. In this trial, participants took 200 mcg/day selenium or placebo between enrollment and delivery. Those who took selenium had a 68% lower risk of preterm delivery than those who took placebo, but the risk of low birthweight did not differ between the two groups. In addition, selenium supplementation did not affect the levels of HIV infection markers (CD4+ T-cell counts and viral load).  
  
Safety  
Up to 45 to 400 mcg/day selenium from foods and dietary supplements is safe for infants and children, depending on age, and up to 400 mcg/day is safe for adults, including those who are pregnant or lactating [56]. These ULs, however, do not apply to people taking selenium under the care of a physician.  
  
Higher intakes of selenium can cause a garlic odor in the breath and a metallic taste in the mouth as well as hair and nail loss or brittleness [56]. Other signs and symptoms of excess selenium intakes include nausea, diarrhea, skin rashes, mottled teeth, fatigue, irritability, and nervous system abnormalities.  
  
Cisplatin, a chemotherapy agent used to treat ovarian, bladder, lung, and other cancers, can reduce selenium levels in hair, plasma, and serum [153,154]. The evidence from studies examining whether selenium supplementation helps reduce the side effects of cisplatin and other chemotherapy agents is uncertain [154,155].  
  
More information on selenium is available in the ODS health professional fact sheet on selenium.  
  
For information on selenium and COVID-19, please see the ODS health professional fact sheet, Dietary Supplements in the Time of COVID-19.  
  
Zinc  
Zinc is an essential nutrient contained in a wide variety of foods, including oysters, crab, lobster, beef, pork, poultry, beans, nuts, whole grains, and dairy products. The RDA for zinc is 2 13 mg for infants and children, depending on age, and 8 12 mg for adults, including those who are pregnant or lactating [29].  
  
Zinc is involved in numerous aspects of cellular metabolism. It is necessary for the catalytic activity of approximately 100 enzymes and it plays a role in many body processes, including both the innate and adaptive immune systems [2,5,29,58,156-159]. Zinc also has antiviral and anti-inflammatory properties, and it helps maintain the integrity of tissue barriers, such as the respiratory epithelia [5,58,83,159-161].  
  
Zinc deficiency adversely affects immune function by impairing the formation, activation, and maturation of lymphocytes. In addition, zinc deficiency decreases ratios of helper to suppressor T cells, production of interleukin-2, and activity of natural killer cells and cytotoxic T cells [2,4,5,27,156,158,162]. Furthermore, zinc deficiency is associated with elevated levels of proinflammatory mediators [160]. These effects on immune response probably increase susceptibility to infections [163] and inflammatory diseases, especially those affecting the lungs [160].  
  
Studies have found associations between low zinc status and higher risk of viral infections [79], and people with zinc deficiency have a higher risk of diarrhea and respiratory diseases [2]. Poor zinc status is also common among people with HIV or hepatitis C and is a risk factor for pneumonia in older adults [27,58,161,164,165]. Some research suggests that zinc supplementation increases the number of T cells in the blood of older adults living in nursing homes [166].  
  
Although zinc deficiency is not common in the United States, 15% of the U.S. population might obtain marginal amounts of zinc [167]. Older adults are among the groups most likely to have low intakes.  
  
Efficacy  
Common cold  
Researchers have hypothesized that zinc could reduce the severity and duration of cold symptoms by directly inhibiting rhinovirus binding and replication in the nasal mucosa and suppressing inflammation [168,169]. In studies of the effects of zinc supplements on the common cold, zinc is usually administered in a lozenge or syrup that temporarily sticks to the mouth and throat, placing the zinc in contact with the rhinovirus in those areas.  
  
The results from clinical trials that have examined the effects of supplemental zinc on the common cold have been inconsistent. Overall, however, supplemental zinc in lozenge or syrup form appears to reduce the duration, but not the severity, of signs and symptoms of the common cold when taken shortly after a person develops a cold [170-173].  
  
In one clinical trial that found beneficial effects of zinc on the common cold, 50 adults took a zinc acetate lozenge (13.3 mg zinc) or placebo every 2 3 wakeful hours within 24 hours of developing the common cold for as long as they had cold symptoms. In comparison with placebo, the zinc lozenges reduced the duration of colds by 3 days and the severity of cold symptoms (cough, nasal discharge, and muscle aches) [174].  
  
Results were more mixed in another clinical trial in which 273 adults with experimentally induced colds took lozenges containing zinc gluconate (13.3 mg zinc) or zinc acetate (5.0 mg or 11.5 mg zinc) every 2 to 3 hours while awake, for a total of 6 lozenges per day, or placebo, for up to 14 days [175]. Illnesses lasted 1 day less with the zinc gluconate lozenges than with the placebo, but the lozenges had no effect on symptom severity. Furthermore, the 5.0 and 11.5 mg zinc acetate lozenges had no effect on cold duration or severity. In a second trial described in the same report, neither zinc gluconate nor zinc acetate lozenges affected the duration or severity of cold symptoms in comparison with placebo in 281 adults with colds [175].  
  
A 2021 systematic review and meta-analysis found that zinc appears to reduce the duration of the common cold but has mixed effects on the severity of signs and symptoms [170]. It included 28 clinical trials (including the three described above) with a total of 5,446 participants (mostly adults younger than 65 years) who had a community-acquired viral respiratory tract infection or were inoculated with a rhinovirus. Most trials provided zinc in the form of zinc acetate or gluconate lozenges with total daily zinc doses of 45 to 300 mg for up to 2 weeks, but some trials used nasal sprays or gels. In participants who used products containing zinc, symptoms resolved an average of 2 days earlier than in those who took a placebo. Zinc also reduced the severity of symptoms on the third day of illness. However, average daily symptom severity did not differ between those who were and were not treated with zinc supplements. In addition, zinc did not affect the risk of developing a cold after rhinovirus inoculation.  
  
Other recent systematic reviews and meta-analyses have also found that zinc shortens the duration of the signs and symptoms of colds but does not reduce the risk of colds [54,67,176]. The author of an earlier systematic review concluded that use of zinc lozenges at doses of over 75 mg/day reduced the duration of the common cold, whereas lower doses did not [172].  
  
Pneumonia in children  
In low-income countries, pneumonia is responsible for 15% of all deaths in children younger than 5 years and for 19% of all childhood deaths [177]. Poor zinc status is associated with greater susceptibility to pneumonia, more severe disease, and higher mortality risk in children [178-182].  
  
Several clinical trials have examined the effects of zinc supplementation on the incidence of pneumonia and as an adjunctive treatment for pneumonia. A 2016 Cochrane Review of six trials in low-income countries found that supplementation with 10 to 20 mg/day zinc for up to 20 months in a total of 5,193 children age 2 to 59 months resulted in lower incidence and prevalence of pneumonia than placebo [177].  
  
However, most research suggests that the adjunctive use of zinc supplements to treat pneumonia in children does not affect mortality or time to recovery. A 2020 systematic review and meta-analysis included 11 clinical trials in children age 2 to 60 months with mostly severe pneumonia in low- and middle-income countries [183]. Mortality rates from pneumonia and time to recovery from severe pneumonia did not differ between children treated with 10 to 20 mg/day supplemental zinc and those treated with placebo for 7 14 days or until discharge. Another meta-analysis of six placebo-controlled trials that included 2,216 children age 2 to 60 months found that zinc supplementation reduced mortality rates from severe pneumonia but not rates of treatment failure or changes in antibiotic therapy [184].  
  
Diarrhea and gastroenteritis in children  
Diarrhea is associated with high mortality rates among children in low-income countries, where it causes about 500,000 deaths annually [157,185]. Zinc supplementation may benefit children with acute diarrhea, especially in low-income countries, where zinc deficiency is common. Scientists believe that zinc s beneficial effects stem from its role in supporting adaptive immunity and maintaining the mucosal integrity of the gastrointestinal system [157].  
  
Clinical trials show that zinc supplementation helps shorten the duration of diarrhea in children in low-income countries. A 2016 Cochrane Review included 33 trials that compared the effects of zinc supplementation with those of placebo in 10,841 children age 1 month to 5 years who had acute or persistent diarrhea [186]. Most studies were conducted in Asian countries that had high rates of zinc deficiency. Zinc was administered in the form of zinc acetate, zinc gluconate, or zinc sulphate. The most common dose was 20 mg/day zinc, and about half the studies administered zinc for 2 weeks. The authors concluded, based on evidence of low to moderate certainty, that zinc supplementation shortens the duration of diarrhea by about half a day in children older than 6 months and reduces the likelihood that diarrhea will persist for at least 7 days by 27%. In addition, evidence that the authors deemed to have high certainty showed that zinc supplementation reduces the duration of diarrhea in children with signs of malnutrition by about a day. In children younger than 6 months, however, zinc supplementation did not affect mean duration of diarrhea or persistence of diarrhea for 7 days.  
  
A 2018 systematic review and meta-analysis had similar findings. It examined the use of zinc alone or in combination with other treatments for acute diarrhea and gastroenteritis in 174 studies in 32,430 children, mostly from low- and middle-income countries [187]. Analyses showed that zinc alone or in combination reduced the duration of diarrhea by about to 1 days. The authors concluded that zinc was one of the most effective interventions of those examined, especially when it was combined with Saccharomyces boulardii (a probiotic) or smectite (a natural clay that contains minerals), for reducing the duration of acute diarrhea and gastroenteritis in children.  
  
The WHO and UNICEF recommend supplementation with 20 mg zinc per day, or 10 mg for infants younger than 6 months, for 10 to 14 days to treat acute childhood diarrhea [185]. However, most trials of zinc supplementation for diarrhea have been conducted in low-income countries [157]. In well-nourished children, zinc supplements might have only a marginal effect on diarrhea duration.  
  
HIV infection  
HIV infection reduces the absorption and metabolism of zinc from foods [188]. In addition, people with HIV often have diarrhea, which can result in excessive losses of zinc. For these reasons, people with HIV often have low plasma or serum zinc levels.  
  
Several clinical trials have found some beneficial effects of zinc supplementation to manage the morbidity and mortality associated with HIV infection. In one trial, for example, 231 adults in the United States who had HIV infection and plasma zinc levels lower than 75 mcg/dL took supplemental zinc (12 mg/day for women or 15 mg/day for men) or placebo for 18 months [189]. The supplements reduced rates of immunological failure events (CD4+ T-cell counts less than 200 cells/mL) by 76% and rates of diarrhea by 60% but had no effect on mortality. Another trial in Iran randomized 146 adults with HIV to 50 mg/day zinc, 200 mcg/day selenium, or placebo for 6 months and then followed participants for another 3 months [150]. In this trial, the zinc supplements decreased rates of opportunistic infections but did not increase CD4+ T-cell counts.  
  
However, findings were less positive in two Cochrane Reviews and another trial (not included in either Cochrane Review) that assessed the potential benefits of supplementation with micronutrients, including zinc, or placebo in various populations with HIV. The first Cochrane Review, which focused on micronutrient supplementation for children with HIV, included two trials that administered 10 mg/day zinc with or without vitamin A for up to 15 months in a total of 128 children with HIV in South Africa [45]. One of these trials, which examined the risk of diarrhea or respiratory diseases, found that the combination of zinc and vitamin A supplementation did not benefit the children compared with vitamin A alone (the trial had no placebo group), whereas the other trial found that the risk of watery diarrhea was 49% lower with zinc supplements than with placebo. However, zinc supplementation did not affect viral load or mortality rates in this second trial. The second Cochrane Review evaluated micronutrient supplements for adults with HIV and included six clinical trials of zinc supplements (12 50 mg/day for 14 days to 18 months or 1 weekly 90 mg dose for 6 months) in a total of 826 participants [46]. The authors concluded that although zinc supplements might improve zinc status, the supplements appeared to have little if any effect on CD4+ T-cell counts or viral load and inconclusive effects on mortality and diarrhea frequency.  
  
In a placebo-controlled trial in 400 pregnant people with HIV in Tanzania, 25 mg/day zinc from 12 to 27 weeks gestation until 6 weeks after delivery had no effect on birth weight, duration of gestation, or rates of fetal mortality or early mother-to-child transmission of HIV [190,191]. In addition, zinc supplementation did not affect maternal viral load or CD4+, CD8+ or CD3+ T-cell counts. However, the supplements blunted the rise in hemoglobin concentrations between baseline and 6 weeks after delivery.  
  
Safety  
Intakes up to 4 34 mg/day zinc in foods and dietary supplements are safe for infants and children, depending on age, and up to 40 mg/day is safe for adults, including those who are pregnant or lactating [29]. These ULs, however, do not apply to people taking zinc under the care of a physician.  
  
Higher intakes can cause nausea, vomiting, loss of appetite, abdominal cramps, diarrhea, headaches, and a metallic taste in the mouth [29,32]. Chronic consumption of 150 450 mg/day zinc can cause low copper status, reduced immune function, and lower levels of high-density lipoproteins [192]. In clinical trials in children, zinc supplementation to treat diarrhea increased the risk of vomiting more than placebo [186,187].  
  
Zinc supplements might interact with several types of medications. For example, zinc can reduce the absorption of some types of antibiotics and penicillamine, a drug used to treat rheumatoid arthritis [193,194]. Other medications, such as thiazide diuretics and certain antibiotics, can reduce zinc absorption [195,196].  
  
More information on zinc is available in the ODS health professional fact sheet on zinc.  
  
For information on zinc and COVID-19, please see the ODS health professional fact sheet, Dietary Supplements in the Time of COVID-19.  
  
Botanicals  
Andrographis  
Andrographis paniculata, also known as Chu n X n Li n, is an herb that is native to subtropical and Southeast Asia [197]. Its leaves and other aerial (above-ground) parts are used in traditional Ayurvedic, Chinese, and Thai medicine for relieving symptoms of the common cold, influenza, and other respiratory tract infections [198-201]. The active constituents of andrographis are believed to be andrographolide and related compounds, which are diterpene lactones that might have antiviral, anti-inflammatory, and immune-stimulating effects [197,199,201-206].  
  
Efficacy  
Common cold, influenza, and other respiratory tract infections  
Results from several clinical trials suggest that andrographis might reduce the duration of upper respiratory tract infections and the severity of symptoms. One of these trials used a common andrographis preparation called Kan Jang. The trial included 50 men and women age 18 to 50 years with the common cold who took four tablets of Kan Jang (each containing 85 mg of an andrographis extract) three times daily for 5 days (1,020 mg total daily dose) or placebo within 3 days of developing cold symptoms [207]. Participants who took Kan Jang experienced milder symptoms, recovered sooner, and took fewer days of sick leave than those who took placebo. In another clinical trial, 223 men and women age 18 to 60 years with upper respiratory tract infections took either KalmCold containing 100 mg of an andrographis extract twice daily or placebo for 5 days [208]. The results showed no differences in symptom severity during days 1 to 3 of treatment. However, between days 3 and 5, participants who took KalmCold experienced milder symptoms including cough, nasal discharge, headache, fever, and sore throat (but not earache) than those who took placebo.  
  
Two systematic reviews and meta-analyses of clinical trials found that andrographis preparations had beneficial effects on symptoms and duration of the common cold. The more recent of these analyses, published in 2017, included 33 clinical trials (including the two described above) that evaluated the effects of andrographis alone or in combination with other herbs on symptoms of acute upper and lower respiratory tract infections in a total of 7,175 participants [199]. Treatment protocols varied widely, but typical daily doses ranged from 200 to 1,200 mg andrographis extract for 3 to 7 days; studies compared andrographis with placebo, usual care, or other herbal interventions. The analyses showed that andrographis significantly reduced the severity of cough, sore throat, and overall symptoms. However, the authors noted that the findings should be interpreted with caution because the studies were heterogenous and many were of poor quality.  
  
Similar findings were reported from a 2015 systematic review and meta-analysis [209]. It included six clinical trials (including the two described above) that administered Kan Jang or KalmCold (31.5 to 200 mg/day andrographis extract) for 3 to 10 days to treat cough symptoms resulting from the common cold or other upper respiratory tract infections in a total of 807 participants. All studies in this analysis compared andrographis with placebo, not usual care or other herbal interventions as in the 2017 meta-analysis described above. Andrographis reduced the frequency and severity of cough to a greater extent than placebo. Three earlier systematic reviews also showed that andrographis appears to alleviate symptoms of upper respiratory tract infections [200,201,210].  
  
Although these findings suggest that andrographis might be useful to manage the symptoms and reduce the duration of upper respiratory tract infections, the evidence has several weaknesses. For example, the studies used different andrographis formulations, and many of the clinical trials were conducted by investigators affiliated with the manufacturer of Kan Jang or KalmCold [200,201].  
  
Safety  
The safety of andrographis has not been well studied, but no safety concerns have been reported when typical doses of the herb (340 to 1,200 mg/day) were used for several days or weeks [200,201,211]. Clinical trials have found minor adverse effects, including nausea, vomiting, vertigo, skin rashes, diarrhea, and fatigue [199,201,209]. Allergic reactions might also occur [201,206]. Findings from some animal studies suggest that andrographis might adversely affect fertility, so experts recommend against its use by men and women during the preconception period and by people who are pregnant [198,200,201].  
  
According to animal and laboratory studies, andrographis might decrease blood pressure and inhibit platelet aggregation, so it could interact with antihypertensive and anticoagulant medications by enhancing their effects [211-213]. Because of its potential immune-stimulating effects, andrographis might also reduce the effectiveness of immunosuppressants [202,211].  
  
For information on andrographis and COVID-19, please see the ODS health professional fact sheet, Dietary Supplements in the Time of COVID-19.  
  
Echinacea  
Echinacea, commonly known as purple coneflower, is an herb that grows in North America and Europe [214]. Although the genus Echinacea has many species, extracts of E. purpurea, E. angustifolia, and E. pallida are the most frequently used in dietary supplements. The echinacea supplements on the market in the United States often contain extracts from multiple species and plant parts [215].  
  
Echinacea contains volatile terpenes, polysaccharides, polyacetylenes, alkamides, phenolic compounds, caffeic acid esters, and glycoproteins [214-216]. However, echinacea s purported active constituents are not well defined [216], and the chemical composition of various echinacea species differs [215].  
  
Echinacea might have antibacterial activities, stimulate monocytes and natural killer cells, and inhibit virus binding to host cells [3,214]. It might also reduce inflammation by inhibiting inflammatory cytokines [3]. Most studies of echinacea have assessed whether it helps prevent and treat the common cold and other upper respiratory illnesses, but it has also been used in traditional medicine to promote wound healing [214,216].  
  
Efficacy  
Common cold, influenza, and other respiratory tract infections  
Results from clinical trials examining the effects of echinacea for the common cold have been mixed. Overall, studies suggest echinacea might slightly reduce the risk of developing a cold but does not shorten the duration or severity of illness. For example, one clinical trial examined the effects of echinacea on the risk of the common cold in 755 men and women (mean age 23 years) [217]. Participants were healthy at the start of the 4-month study and took 2,400 mg/day of an E. purpurea extract (Echinaforce) or placebo; if participants came down with a cold during the study, they increased their dose to 4,000 mg per day. Participants taking echinacea had fewer colds and fewer days with cold symptoms than those taking a placebo. Another clinical trial examined whether echinacea helps treat the common cold in 713 male and female participants age 12 to 80 years who developed cold symptoms within 36 hours before enrollment [218]. Participants took E. purpurea and E. angustifolia extracts four times a day for a combined dose of 10,200 mg during the first 24 hours and then 5,100 mg for 4 days or placebo. Echinacea did not shorten illness duration or severity.  
  
A 2019 systematic review and meta-analysis examined the effects of echinacea (E. purpurea, E angustifolia, E. pallida, or more than one form) to prevent upper respiratory tract infections or reduce the duration of illness [219]. Nine clinical trials (eight in adults and one in children) were included in the prevention meta-analysis portion of this analysis, and seven (all in adults) were included in the duration meta-analysis, including the two trials described above [217,218]. In comparison with placebo, echinacea reduced the risk of developing an upper respiratory infection by 22% but did not affect infection duration. A 2014 Cochrane Review of echinacea use for preventing and treating the common cold had similar results [220]. The review included 24 clinical trials with a total of 4,631 participants. Because of trial heterogeneity, the authors did not pool results for the main analyses, but they concluded that echinacea products might have a weak ability to reduce the risk of colds by about 10% to 20% but do not appear to help treat colds.  
  
Limited research has also examined whether echinacea is beneficial for influenza. One clinical trial found that echinacea had similar effects to oseltamivir (Tamiflu), a medication used to treat influenza. This trial included 473 male and female participants age 12 to 70 who had had influenza symptoms for up to 48 hours [221]. Participants took either E. purpurea extract (25 mL/day Echinaforce Hot Drink for 3 days and then 15 mL/day for 7 days) or oseltamivir for 5 days, followed by 5 days of placebo. The results showed no difference between E. Purpurea and oseltamivir followed by placebo in rapidity of recovery from influenza after 1 day, 5 days, or 10 days of treatment. In addition, participants taking echinacea experienced fewer adverse events, especially nausea and vomiting. Additional research is needed to confirm this finding.  
  
Safety  
Echinacea appears to be safe. The most common of echinacea s few adverse effects are gastrointestinal upset, such as diarrhea, sleeplessness, and skin rashes [32,216,217]. Isolated reports of elevated liver enzymes and liver injury have been associated with its use, but these events could have been caused by a contaminant or the product s preparation. In rare cases, echinacea can cause allergic reactions [216].  
  
The safety of echinacea during pregnancy is not known, so experts recommend against the use of echinacea supplements by people who are pregnant [222].  
  
Echinacea might interact with several medications. For example, echinacea might increase cytochrome P450 activity, thereby reducing levels of some drugs metabolized by these enzymes [223]. In addition, echinacea might reduce the effectiveness of immunosuppressants due to its potential immunostimulatory activity [224].  
  
For information on echinacea and COVID-19, please see the ODS health professional fact sheet, Dietary Supplements in the Time of COVID-19.  
  
Elderberry (European Elder)  
Elder berry (usually written elderberry ) is the fruit of a small deciduous tree, Sambucus nigra (also known as European elder or black elder), that grows in North America, Europe, and parts of Africa and Asia [225,226]. Elderberry contains many compounds including anthocyanins, flavonols, and phenolic acids that might have anti-inflammatory, antiviral, antimicrobial, and immune-stimulating effects [3,226-230]. Studies of the effects of elderberry have primarily used elderberry extracts, not the berries themselves [226].  
  
Efficacy  
Common cold, influenza, and other respiratory tract infections  
Components of elderberry might help prevent respiratory infections by inhibiting virus binding to host cells and by stimulating the immune system [226]. A few clinical trials have examined the effects of elderberry on the common cold and influenza. The results from these trials have been mixed. However, overall, they suggest that elderberry might help relieve symptoms of respiratory tract infections. One clinical trial examined whether elderberry extract helps prevent and treat the common cold [231]. In this trial, 312 men and women (mean age 50 years) took 600 mg/day elderberry extract or placebo for 10 days before traveling by air. They then took 900 mg/day elderberry extract or placebo during their air travel and for 4 to 5 days after the flight. Elderberry extract did not reduce the number of participants who developed a cold. However, among participants who did develop a cold, elderberry extract reduced cold duration by about 2 days and reduced the severity of symptoms.  
  
A 2019 meta-analysis included four clinical trials (including the trial described above) of the effects of elderberry supplementation on upper respiratory symptoms caused by the common cold or flu in a total of 180 participants age 5 to 59 years [227]. The analysis showed that elderberry supplementation reduced the duration of upper respiratory symptoms, and the effect was stronger for symptoms of influenza than for those caused by the common cold. A 2020 review included the same four trials as well as one that administered an herbal preparation containing both elderberry and Echinacea purpurea [228]. The results showed that elderberry might help relieve symptoms of the common cold and influenza when taken close to the onset of symptoms and for up to 2 weeks.  
  
In contrast, in a 2020 clinical trial, 87 male and female participants age 5 years and older with influenza for less than 48 hours took 15 ml (5,700 mg) elderberry extract (twice daily for ages 5 to 12 years and four times daily for ages 13 and older) or placebo for 5 days [232]. Elderberry had no effect on the duration or severity of illness.  
  
A 2021 systematic review of five clinical trials of elderberry to treat viral respiratory illnesses found beneficial effects on some, but not all, outcomes [233]. The results showed that elderberry supplementation for 2 to 16 days might reduce the severity and duration of the common cold and the duration of flu but does not appear to reduce the risk of the common cold. However, the authors noted that the studies were small, heterogeneous, and of poor quality.  
  
Safety  
Elderberry flowers and ripe fruit appear to be safe for consumption. However, the bark, leaves, seeds, and raw or unripe fruit of S. nigra contain a cyanogenic glycoside that is potentially toxic and can cause nausea, vomiting, diarrhea, dehydration due to diuresis, and cyanide poisoning [226,234,235]. The heat from cooking destroys this toxin, so cooked elderberry fruit and properly processed commercial products do not pose this safety concern [3,226,228,234,235]. Elderberry might affect insulin and glucose metabolism, so according to experts, people with diabetes should use it with caution [234]. The safety of elderberry during pregnancy is not known, so experts recommend against the use of elderberry supplements by people who are pregnant [222,226].  
  
Recent analyses suggest that some elderberry supplements are highly diluted or have been adulterated with a cheaper ingredient, such as black rice extract, instead of elderberry [225,236].  
  
Due to its potential immunostimulatory activity, elderberry might reduce the effectiveness of immunosuppressant medications [237].  
  
For information on elderberry and COVID-19, please see the ODS health professional fact sheet, Dietary Supplements in the Time of COVID-19.  
  
Garlic  
Garlic (Allium sativum) is a vegetable with a long history of culinary use. Garlic is also available as a dietary supplement in softgel, capsule, tablet, and liquid forms [238].  
  
Researchers have studied garlic mainly to determine whether it lowers blood pressure and cholesterol levels, but it might also have antiviral properties [32,239]. These properties are often attributed to two compounds in garlic allicin and ajoen [240]. Garlic might also have antimicrobial and antifungal activity [239].  
  
Some dietary supplements contain aged garlic extract, prepared from sliced garlic that is soaked in an aqueous ethanol solution for up to 20 months. The extract is then filtered and concentrated [241,242]. Aged garlic extract contains compounds, such as lectins, fructo-oligosaccharide, and N-alpha-fructosyl arginine, that might affect immune cell function [242]. It also contains S-allyl-L-cysteine and other compounds that might have antioxidant effects and reduce some inflammatory markers [242,243].  
  
Efficacy  
Common cold and influenza  
Only a few clinical trials have examined whether garlic supplements help prevent or treat the common cold or influenza, and results are inconclusive. One trial included 120 healthy men and women (mean age 26 years) who took 2.56 g/day aged garlic extract or placebo for 90 days during cold and flu season, February through May [244]. After 45 days, the researchers took blood samples from the participants and cultured the natural killer cells and gamma delta T cells. The natural killer cells and gamma delta T cells from participants who took the extract had a higher proliferation rate than those from participants who took placebo. After 90 days, the number of illnesses (colds and influenza) did not differ between groups, nor did the average number of symptoms per illness. However, participants who took aged garlic extract reported a smaller total number of symptoms during the study.  
  
Results were more positive in another trial, in which 146 men and women (mean age 53 years) took one capsule of a garlic supplement (dose not specified) or placebo daily for 12 weeks between November and February [240]. Participants who took garlic had fewer colds (24 among the full study population) during the study than those who took placebo (65 colds). In addition, colds lasted an average of only 1.52 days in the garlic group compared with 5.01 days in the placebo group.  
  
Safety  
Garlic is safely consumed worldwide as a culinary ingredient [239], and garlic and its derivatives are generally recognized as safe, according to the U.S. Food and Drug Administration (FDA) [245]. The adverse effects of garlic dietary supplements are minor and include bad breath, body odor, and skin rash [32,239,240].  
  
Garlic might interact with medications. For example, garlic might have anticoagulant effects, so it might interact with warfarin (Coumadin) and similar medications [239,246,247]. However, the findings from reported case studies on this interaction are inconclusive [239]. Garlic might also reduce blood pressure, so it might interact with antihypertensive medications [248-250].  
  
Ginseng  
Ginseng is the common name of several species of the genus Panax, most commonly Panax ginseng (also called Asian ginseng or Korean ginseng) and Panax quinquefolius (American ginseng) [251,252]. Asian ginseng is endemic to China and Korea, whereas American ginseng is endemic to the United States and Canada [251].  
  
Triterpene glycosides, also known as ginsenosides, are some of the main purported active constituents of ginseng [251,253]. Although ginseng contains numerous ginsenosides, research has focused on the Rb1 ginsenoside and compound K, a bioactive substance formed when the intestinal microbiota metabolize ginsenosides [251,253]. Both the product s preparation method and variations in people s intestinal microbiota can affect the type and quantity of ginseng s bioactive compounds in the body [253].  
  
Animal and laboratory studies suggest that ginseng stimulates B-lymphocyte proliferation and increases production of some interleukins and interferon-gamma [251]; these cytokines affect immune activation and modulation [1]. Ginseng might also inhibit virus replication and have anti-inflammatory activity. However, whether ginseng has a clinically meaningful effect on immune function in humans is not clear [251,254].  
  
Another botanical, eleuthero (Eleutherococus senticosus), is sometimes confused with true ginseng. Eleuthero used to be called Siberian ginseng, but it comes from the Eleutherococcus genus of plants, not the Panax genus, and it does not contain ginsenosides [251].  
  
Efficacy  
Common cold, influenza, and other respiratory tract infections  
Several clinical trials have examined whether ginseng helps prevent upper respiratory tract infections, such as the common cold and influenza. Although the evidence is limited, results from these trials suggest that ginseng might help reduce the risk of developing colds and other respiratory tract infections. However, its effects on symptom severity and duration are unclear.  
  
In one clinical trial, 100 healthy men and women age 30 to 70 years who had not received an influenza vaccine in the previous 6 months took 1 g Panax ginseng extract three times daily or placebo for 12 weeks [255]. Participants taking ginseng were less likely to develop an acute respiratory infection during the study period. However, for study participants who did develop an infection, symptom duration and severity did not differ between groups.  
  
A few clinical trials have examined the effects of CVT-E002 (COLD-fX), a patented ginseng extract that contains 200 mg Panax quinquefolius in each capsule. One of these trials included 323 men and women age 18 to 65 years with a history of at least two colds during the previous year who had not received an influenza vaccine in the past 6 months [256]. Participants took either two capsules per day of Cold-fX (for a daily dose of 400 mg ginseng) or placebo for 4 months starting in November. Participants who took ginseng developed fewer self-reported colds (mean 0.68 colds) during the study period than those who took placebo (mean 0.93 colds). In addition, ginseng reduced the total number of days with cold symptoms from a mean of 16.5 days to 10.8 days and reduced cold symptoms.  
  
A 2020 systematic review and meta-analysis of ginseng to prevent or treat acute upper respiratory tract infections included 10 clinical trials of Panax ginseng or Panax quinquefolius extracts (including those described above) in a total of 2,058 participants [253]. In all but one trial, ginseng was administered daily for 8 to 16 weeks, and the most common doses were 3 g/day Panax ginseng extract or 400 mg/day Panax quinquefolius extract. Ginseng reduced the risk of developing an upper respiratory tract infection by 31% but did not shorten symptom duration. The authors noted that the risk of bias was high to unclear for most trials and that the limitations of the evidence prevented them from drawing conclusions.  
  
Safety  
Ginseng appears to be safe. Most of its adverse effects, including headache, sleep difficulty, and gastrointestinal symptoms, are minor [253,254,257]. However, doses of more than 2.5 g/day might cause insomnia, tachyarrhythmias, hypertension, and nervousness [251,253].  
  
A few case reports of vaginal bleeding and mastalgia (breast pain) in the 1970s and 1980s from the use of ginseng preparations raised concerns about the safety of ginseng; as a result, some scientists concluded that ginseng has estrogenic effects [258-261]. However, one of these case reports involved use of Rumanian ginseng [260], and whether this was true ginseng is not clear. In addition, eleuthero was often referred to, incorrectly, as ginseng at that time because it was called Siberian ginseng. So, it is unclear whether these case reports reflected the effects of true ginseng. Nevertheless, some experts caution that ginseng might not be safe for use during pregnancy [253,262,263].  
  
Ginseng might interact with many medications. For example, it might increase the risk of hypoglycemia if taken with antidiabetes medications, increase the risk of adverse effects if taken with stimulants, and reduce the effectiveness of immunosuppressants [263,264].  
  
For information on ginseng and COVID-19, please see the ODS health professional fact sheet, Dietary Supplements in the Time of COVID-19.  
  
Tea and tea catechins  
Tea (Camellia sinensis) is a popular beverage around the world that has several purported health benefits. Tea is usually classified into one of three types green, black, and oolong according to the way in which the tea leaves are processed [265]. Green tea is made from dried and steamed tea leaves, whereas black and oolong teas are made from fermented tea leaves. Tea extracts are also available as dietary supplements. The purported health effects may vary by the type of tea as well as whether it is consumed as a beverage or dietary supplement.  
  
Tea is one of the richest sources of catechins, which are polyphenolic flavonoids, especially epigallocatechin gallate (EGCG) [266,267]. A typical 250 mL cup of brewed green tea contains 50 to 100 mg of catechins [268], whereas the same amount of brewed black tea contains about 14 to 88 mg of catechins [269]. Amounts vary, however, among tea samples and by brewing time. Studies are evaluating the potential health benefits of EGCG and other catechins, including their ability to modulate the immune system and their anti-inflammatory and antimicrobial properties [265,270]. Laboratory studies suggest that catechins might also have antiviral effects against the influenza A and B viruses [266].  
  
Efficacy  
Influenza and other respiratory tract infections  
Laboratory research suggests that tea and tea catechins might have antiviral activity. Researchers have therefore examined whether drinking tea or taking supplemental tea catechins affects the risk, duration, and severity of influenza or other respiratory tract infections. However, evidence from clinical trials is limited and mixed.  
  
Studies that found beneficial effects include a clinical trial that examined the effects of catechins and theanine (an amino acid in tea) on the risk of influenza in 197 male and female health care workers age 21 years or older in Japan [271]. Participants took 378 mg/day green tea catechins (including 270 mg EGCG) and 210 mg theanine or placebo for 5 months from November to April. Participants who took green tea catechins and theanine were 75% less likely to acquire clinically defined influenza (defined as the presence of fever and any two of the following symptoms: cough, sore throat, headache, or muscle pain) than those who took placebo. However, for laboratory-confirmed influenza, the incidence of influenza did not differ between groups.  
  
A 2021 systematic review and meta-analysis also showed that tea and tea catechins had some beneficial effects on the risk of influenza and other upper respiratory tract infections, although the evidence had some limitations [272]. The analysis included five prospective cohort studies and clinical trials that administered tea as a dietary supplement or beverage (including the trial described above) in a total of 1,948 participants. In the studies for which catechin doses were available, they ranged from 57 to 378 mg/day for 1 to 5 months. Consuming tea as a beverage or tea catechins as a dietary supplement reduced the risk of an upper respiratory tract infection by 32%, but several of the trials were of poor quality or had a high risk of bias.  
  
Results were also mixed in a 2022 clinical trial examining whether drinking 350 mL of a bottled beverage containing 490 mg of catechins for 12 weeks during the winter affected the duration and severity of upper respiratory tract infections in 109 healthy Japanese men and women (mean age 44.5 years) [273]. Catechins reduced the duration and severity of a runny nose, nasal congestion, and headache but did not affect other symptoms, including sore throat, cough, and fever.  
  
Safety  
Drinking moderate amounts of tea is safe. Green tea extract causes mostly mild to moderate adverse effects, including nausea, constipation, abdominal discomfort, and increased blood pressure [274].  
  
However, some green tea extracts might cause liver damage, especially when taken on an empty stomach [275,276]. Intakes of 800 mg EGCG/day or above increase levels of serum transaminases [276]. In addition, at least 50 case reports since 2006 have linked consumption of green tea extracts, primarily ethanolic extracts of green tea, with liver damage [277]. In a 2020 systematic review of the safety of green tea products, the U.S. Pharmacopeia (USP) evaluated 75 case reports of liver damage and animal pharmacological and toxicological information [278]. On the basis of the 35 case reports associated with supplements containing only green tea extract, the USP concluded that the consumption of green tea products definitely caused four cases of liver damage, probably or was highly likely to have caused 25 cases, and possibly caused five cases. The USP notes that problems are more likely when green tea extract is taken on an empty stomach and, therefore, advises taking green tea extracts with food to minimize the risk of liver damage [275,278].  
  
In addition, tea contains caffeine, which can cause sleep disturbances and feelings of nervousness, jitteriness, and shakiness [279]. For healthy adults, the FDA and the European Food Safety Authority (EFSA) state that up to 400 mg/day caffeine does not pose safety concerns [279,280], whereas the American Medical Association recommends a limit of 500 mg/day [281].  
  
These levels do not apply to people who are pregnant and may need to limit caffeine consumption further [280]. The American College of Obstetricians and Gynecologists notes that consuming less than 200 mg/day caffeine during pregnancy does not appear to affect the risk of miscarriage or preterm birth [282]. EFSA also states that up to 200 mg/day does not pose any safety concerns for the fetus [279]. However, some research suggests that even less than 200 mg/day caffeine is associated with decreased fetal growth [283].  
  
Caffeine can be toxic at 15 mg/kg (about 1,000 mg for a 150-lb adult) or more, causing nausea, vomiting, tachycardia, seizures, cerebral edema, and even death [284].  
  
Tea and its constituents might interact with certain medications. For example, green tea extract decreases plasma levels of atorvastatin, a statin medication [285]. In addition, combining caffeine from tea with other stimulants, such as bitter orange and ephedrine, can potentiate the caffeine s stimulant effects [279].  
  
Other Ingredients  
Glutamine  
Glutamine is an amino acid that is present in a wide variety of foods that contain protein, including beef, fish, poultry, soy and other beans, eggs, rice, corn and other grains, and milk and other dairy products [286-288]. The body also produces glutamine endogenously.  
  
Typical glutamine intakes in adults are about 5 g/day [289]. The adult human body contains about 70 to 80 g of glutamine, and more than 98% is contained in skeletal muscle cells [286,290].  
  
In normal conditions, the body can synthesize adequate amounts of glutamine to meet metabolic needs, so glutamine is not classified as an essential amino acid [291]. However, under extreme physiological stress, endogenous glutamine synthesis cannot keep up with metabolic need. Therefore, glutamine is classified as conditionally essential [291].  
  
In the immune system, glutamine is involved in lymphocyte proliferation and cytokine production as well as macrophage and neutrophil function [286]. Low glutamine levels are associated with poor immunologic function and an increased risk of mortality in patients in the ICU [292,293].  
  
Many patients who are critically ill or have undergone major surgery have low plasma and muscle glutamine levels [294]. Results from some studies suggest that glutamine reduces rates of infection and mortality in critically ill patients and reduces hospital length of stay and mortality in patients with burn injuries [292,294]. Clinical studies have administered glutamine both enterally and parenterally. When administered through these routes, glutamine is classified as a drug, not a dietary supplement, in the United States.  
  
Efficacy  
Critical illness (glutamine administered enterally or parenterally, not as a dietary supplement)  
Researchers have examined whether glutamine administration affects immune parameters and disease prognosis in critically ill patients. Typical glutamine doses are 20 to 35 g/day or 0.3 to 0.5 g per kg body weight for parenteral administration [286]. The evidence from these studies is limited and mixed.  
  
For example, a crossover trial examined the effects of enteral nutrition containing glutamine on immune function in moderately ill patients with systemic inflammatory response syndrome from a pulmonary infection in the ICU [295]. Thirty patients (age 30 to 92 years) received enteral nutrition containing 30 g added glutamine for 2 days followed by enteral nutrition containing 30 g added calcium caseinate for 2 days or the same formulations but in reverse order. A 1-day washout period with standard enteral nutrition separated each treatment period. Glutamine administration resulted in higher lymphocyte counts than calcium caseinate administration, suggesting enhanced immune function, but did not affect interleukin levels.  
  
Results from clinical trials in patients with critical illness have also been mixed. One trial in the United Kingdom included 84 men and women (mean age 65 to 66 years) in the ICU [296]. Patients received a standard parenteral formulation with or without 25 g added glutamine per day. Treatment duration was not specified, but administration continued until death or as long as clinically required. Patients who received the formulation with added glutamine had a lower risk of death during the subsequent 6 months than those who received the standard formulation.  
  
In another clinical trial in Scotland, 502 critically ill men and women (mean age 63 to 65 years) in the ICU received one of four parenteral treatments daily: standard formulation, standard formulation containing 20.2 g added glutamine, standard formulation containing 500 mcg added selenium, or standard formulation containing both glutamine and selenium for up to 7 days [297]. Glutamine did not affect the risk of new infections during the 14 days after randomization or mortality rates in the ICU or during the subsequent 6 months. It also had no effect on ICU or hospital length of stay, need for antibiotics, or rates of organ failure.  
  
Findings from a 2014 Cochrane Review suggest that glutamine may have beneficial effects on some but not all outcomes in patients who have critical illness or are recovering from major surgery. This review examined the effects of glutamine administration on various outcomes, including rates of infection and mortality, in adults who were critically ill or had undergone major surgery, such as abdominal or thoracic surgery [294]. It included 53 clinical trials (including the two described above) in a total of 4,671 participants that administered glutamine enterally or parenterally. Glutamine administration resulted in a 21% lower risk of in-hospital infectious complications than placebo. It also reduced the length of hospital stay by about 3.5 days and number of days on mechanical ventilation by about 0.7 days. However, glutamine did not affect mortality rates, and it prolonged ICU stays by about 0.2 days.  
  
The authors of a 2021 review that examined the effects of micronutrient supplementation, including glutamine, in adults with conditions or infections similar to COVID-19 concluded that evidence from human studies is very limited and that baseline nutrient status may affect study results [298]  
  
Safety  
Oral, enteral, and parenteral glutamine administration is considered safe [286,289,294]. Reported side effects are mainly gastrointestinal and include nausea, bloating, belching, pain, and flatulence [299].  
  
Oral doses used in clinical trials in adults ranging from 3 to 45 g/day for up to 10 weeks have had no major adverse effects [289]. Other research suggests that oral doses up to 0.9 g/kg are well tolerated, although doses higher than 0.6 g/kg are more likely to produce gastrointestinal symptoms [299]. Children age 4 to 18 years tolerate doses of 0.35 to 0.65 g/kg well, but higher doses may cause vomiting [300].  
  
The Food and Nutrition Board has not established a UL for glutamine [291]. The board notes that very few, if any, adverse effects have been reported from glutamine administration.  
  
No reports have described clinically relevant interactions between glutamine and medications.  
  
N-acetylcysteine and Glutathione  
N-acetylcysteine (NAC) is a derivative of the amino acid cysteine. NAC is an antioxidant that has mucolytic activity, so it helps reduce respiratory mucus levels [301-303]. NAC might improve immune system function and suppress viral replication [302,304,305]. NAC also appears to decrease levels of interleukin-6 and have other anti-inflammatory effects [301,303,306].  
  
Much of the research on NAC has used an inhaled, liquid form of this compound. This form which is classified as a drug in the United States, not a dietary supplement is approved by FDA as a mucolytic agent and for decreasing respiratory secretion viscosity [307]. NAC administered orally or intravenously also has FDA approval as a drug to treat acetaminophen poisoning [308,309]. Products containing NAC are also sold as dietary supplements [238].  
  
In addition to its direct effects in the body, NAC raises intracellular levels of glutathione, which is a tripeptide of glutamine, cysteine, and glycine [301,304,306,310,311]. Laboratory and animal studies suggest that glutathione has antioxidant activity and appears to have antiviral and antimicrobial effects and enhance natural killer cell and neutrophil activity [304,309,312,313]. Glutathione may also have anti-inflammatory effects via altered cytokine expression [309,310,314]. Adequate glutathione levels are needed for optimal innate and adaptive immune system function, including proper T-cell activation and differentiation [310,312,314].  
  
Most research indicates that oral glutathione supplementation does not raise intracellular glutathione levels because glutathione is hydrolyzed in the gastrointestinal tract [310]. As a result, NAC is often used in research studies because of its effects on intracellular glutathione levels.  
  
Efficacy  
HIV infection  
HIV infection appears to increase production of free radicals and deplete levels of free glutathione [315]. Therefore, people with HIV may have decreased intracellular levels of glutathione, which could increase their susceptibility to infectious diseases, such as tuberculosis [309]. Low glutathione levels have been associated with shorter survival in people with HIV [316], and NAC supplementation increases blood and T-cell levels of glutathione [317]. However, clinical research on the effects of NAC supplementation on the immune system in humans is very limited.  
  
In one clinical trial, researchers examined the effects of oral 600 to 6,000 mg NAC, depending on plasma glutamine levels, every other day for 7 months or placebo in 37 men and women with HIV who were taking ART [318]. An accompanying clinical trial (described in the same publication) evaluated the same treatment in 29 men and women with HIV who were not taking ART. NAC supplementation increased natural killer cell activity in both trials but did not affect CD4+ or CD8+ T-cell counts. In addition, NAC supplementation had inconsistent effects on viral load.  
  
Safety  
As an FDA-approved drug, the safety profile of NAC has been evaluated [307]. The American College of Chest Physicians and the Canadian Thoracic Society note that NAC has a low risk of adverse effects [319]. Typical doses are 600 mg/day, but up to 3,000 mg/day appears to be safe and well tolerated [320].  
  
Reported side effects of oral NAC include nausea, vomiting, abdominal pain, diarrhea, indigestion, and epigastric discomfort [309,321]. No safety concerns have been reported for products labeled as dietary supplements that contain NAC.  
  
NAC might have anticoagulant effects and reduce blood pressure, so it could have additive effects if taken with anticoagulants and antihypertensive medications [322]. The combination of NAC and nitroglycerine, used to treat angina, can cause hypotension and severe headaches [323,324].  
  
For information on NAC and COVID-19, please see the ODS health professional fact sheet, Dietary Supplements in the Time of COVID-19.  
  
Omega-3 fatty acids  
Omega-3 fatty acids (omega-3s) are polyunsaturated fatty acids (PUFAs) that are present in certain foods, such as flaxseed and fatty fish, as well as dietary supplements, such as those containing fish oil. Several omega-3s exist, including alpha linolenic acid (ALA), but most scientific research focuses on the long-chain omega-3s eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The main food sources of EPA and DHA are fatty fish and fish oil.  
  
The Food and Nutrition Board established an adequate intake (AI; intake assumed to ensure nutritional adequacy) for total omega-3s of 0.5 g per day for infants, and an AI for ALA of 0.7 to 1.6 g per day for children and teens age 1 and older and 1.1 to 1.6 g per day for adults, including those who are pregnant and lactating [291]. The Food and Nutrition Board did not establish intake recommendations for EPA and DHA in 2005 because, unlike ALA, EPA and DHA were not classified as essential. Although ALA can be converted to EPA and then to DHA, less than 1% of ALA is converted to DHA [325]. Therefore, consuming EPA and DHA directly from foods and/or dietary supplements is the only practical way to increase levels of these fatty acids in the body.  
  
Omega-3 fatty acids are components of the phospholipids that form the structures of cell membranes. Omega-3s also form eicosanoids, which are signaling molecules that affect the cardiovascular, pulmonary, immune, and endocrine systems [58,291,326].  
  
Omega-6 fatty acids, the other major class of PUFAs, also form eicosanoids, which tend to be more potent mediators of inflammation, vasoconstriction, and platelet aggregation than those made from omega-3s. Therefore, higher concentrations of omega-3s than of omega-6s tip the eicosanoid balance toward less inflammatory activity [124,327,328].  
  
Higher intakes and higher blood levels of EPA and DHA are associated with lower levels of inflammatory cytokines, such as interleukin-1 and interleukin-6 [311,327,329,330]. Immune system cells can easily incorporate EPA and DHA, which might also affect immune function by upregulating the activity of macrophages, neutrophils, T cells, B cells, natural killer cells, and other immune cells [2,327,331]. In addition, omega-3s may have antimicrobial and antiviral effects [58,332].  
  
Omega-3 deficiency can cause rough, scaly skin and dermatitis [291]. Almost everyone in the United States obtains sufficient ALA to avoid deficiency, but many people might benefit from higher intakes of EPA and DHA [333]. For example, immuno-inflammatory function may be impaired below certain blood levels of DHA and/or EPA [334,335].  
  
Efficacy  
Acute respiratory distress syndrome  
ARDS, a serious lung condition, is characterized by inflammation and multi-organ dysfunction that causes low blood oxygen levels. It usually results from another disease, such as COVID-19, or injury. ARDS has an in-hospital fatality rate of 27% to 45%, and survivors often have long-term physical, cognitive, and psychological impairments [336]. Because omega-3s can affect inflammation, researchers have hypothesized that these fatty acids might improve outcomes in patients with ARDS.  
  
Several clinical trials and meta-analyses have examined whether omega-3s, administered enterally or parenterally (which are not classified as dietary supplements in the United States), benefit patients with ARDS. The authors of meta-analyses published in 2008 and 2011 concluded that these treatments reduce the risk of mortality and organ failure, improve oxygenation status, and reduce the length of ICU stay and time on mechanical ventilation [337,338].  
  
However, more recent clinical trials and meta-analyses have yielded contrasting findings [336,339-342]. Some but not all findings were positive in one clinical trial with 58 men and women (mean age 63 to 64 years) who had mild to moderate ARDS, were on mechanical ventilation, and received a standard enteral formula that did or did not contain 720 mg omega-3s (including 360 mg EPA and 240 mg DHA) three times daily for 14 days [340]. Omega-3s improved some measures of oxygenation and lung function but did not affect number of ventilator-free days, length of ICU stay, 28-day mortality rates, or rates of multi-organ failure.  
  
No benefits were found in another clinical trial in which 90 men and women (mean age 49 to 51 years) on mechanical ventilation who had acute lung injury, a mild form of ARDS, received either enteral fish oil containing 9,750 mg EPA and 6,750 mg DHA daily or placebo for 14 days [339]. Fish oil did not affect pulmonary or systematic inflammation, number of ventilator-free or ICU-free days, or rates of organ failure or 60-day mortality. Results were similar in a 2014 systematic review and meta-analysis that included seven clinical trials (one of which was the trial described above [339]) that compared enteral omega-3 supplementation with a control diet or placebo in a total of 955 adults with ARDS [341]. The most common omega-3s used were EPA and DHA, often in combination with gamma-linolenic acid (an omega-6 fatty acid); some studies also coadministered antioxidants. The results showed no differences in rates of 28-day all-cause mortality or numbers of ventilator-free days or ICU-free days, although omega-3 supplementation did improve oxygenation status at some time points.  
  
The evidence was inconclusive in a 2019 Cochrane Review of 10 clinical trials (including the two trials described above) that included a total of 1,015 adults in ICUs and examined the effects of immunonutrition for ARDS [336]. The treatments consisted of EPA with or without DHA and gamma-linolenic acid for up to 28 days. One study also administered antioxidants. The treatment was administered enterally in nine studies and parenterally in one study. The omega-3 treatments did not affect all-cause mortality rates, but the quality of this evidence was low. The authors were unable to determine whether the treatments affected ICU length of stay, number of days on a ventilator, or oxygenation because the evidence was of very low quality.  
  
In their guidelines on nutrition support therapy for adults who are critically ill, the Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition state that they cannot recommend routine use of enteral formulas that contain omega-3s (or other anti-inflammatory lipids) in patients with ARDS because the data are conflicting [343].  
  
Respiratory tract infections in infants and young children  
Immune system development begins before birth and continues for several months to a few years [344]. The membranes of immune system cells contain long-chain PUFAs including EPA, DHA, and the omega-6 fatty acid arachidonic acid (ARA) that play a role in immune system development [344]. For this reason, researchers have examined whether consumption of infant formula enriched with long-chain PUFAs during the first year of life has health benefits. Much of this research has focused on the effects of these infant formulas on allergic manifestations, including atopic dermatitis, food allergies, and asthma, in infants and young children. However, researchers have also examined whether these formulas affect the risk of respiratory infections.  
  
Several observational studies have examined whether infants who consume formula enriched with long-chain PUFAs during the first year of life have a lower risk of respiratory tract infections. Findings from these studies have been mixed, and some effects may depend on infant age and omega-3 dose. For example, an observational study analyzed data from 8,389 formula-fed infants born in France in 2011 [345]. At age 2 months, 26% of the infants consumed formula with added DHA and ARA only, and 11% consumed formula with added DHA, ARA, and EPA. The rest consumed unenriched formulas. Between age 2 months and 5.5 years, infants who consumed enriched formulas did not have a lower risk of upper or lower respiratory tract infections than those who consumed unenriched formulas. However, infants who consumed formulas containing 3.2 mg or more EPA per 100 kcal had a lower risk of lower respiratory tract infections than those who consumed unenriched formulas.  
  
Findings were also mixed in an observational study of 1,342 infants who consumed infant formulas containing 17 mg/100 kcal DHA and 34 mg/100 kcal ARA or formulas with no DHA and ARA or lower levels [346]. Infants who consumed enriched formulas had lower rates of bronchitis or bronchiolitis at age 5, 7, and 9 months than those who consumed unenriched formulas or formulas with low levels of DHA and ARA. At age 12 months, infants consuming enriched formulas also had a lower risk of upper airway infections. However, the incidence of all other respiratory illnesses at various ages was similar between groups. In another observational study of 233 infants who consumed infant formula containing 17 mg/100 kcal DHA and 34 mg/100 kcal ARA and 92 infants who consumed unenriched formula, the enriched formula group had lower risks of croup, bronchitis or bronchiolitis, nasal congestion, and cough during the first year of life [347].  
  
Very few clinical trials have examined the effects of infant formula containing added long-chain PUFAs on the risk of respiratory tract infections. A secondary analysis of two clinical trials included a total of 89 healthy formula-fed infants who received a standard infant formula with or without 17 mg/100 kcal DHA and 34 mg/100 kcal ARA for the first year of life [348]. Infants who received the formula containing DHA and ARA did not have a lower risk of nonallergic respiratory illnesses (e.g., upper respiratory infections, sinusitis, bronchitis, and pneumonia), but they did have a lower risk of common allergic diseases and symptoms, such as wheezing and asthma. In another clinical trial in Thailand, 180 healthy children age 9 to 12 years consumed milk containing fish oil (providing 200 mg EPA and 1,000 mg DHA per day) or placebo, 5 days per week for 6 months [349]. Only 54.3% of the children consuming fish oil became ill (mostly upper respiratory tract infections) compared with 67.4% of those who consumed placebo. Children consuming fish oil also had fewer episodes of illness and total days of illness. However, the percentage of children with fever did not differ between groups.  
  
Safety  
  
The Food and Nutrition Board did not establish a UL for omega-3s, although it noted that 900 mg/day EPA plus 600 mg/day DHA or more for several weeks might reduce immune function by suppressing inflammatory responses [291,350-354].  
  
Doses of 2 15 g/day EPA and/or DHA might also increase bleeding time by reducing platelet aggregation [291]. However, according to the EFSA, long-term consumption of a combined dose of EPA and DHA supplements of up to about 5 g/day appears to be safe for adults [355]. EFSA also notes that these doses have not been shown to cause bleeding problems or to adversely affect immune function, glucose homeostasis, or lipid peroxidation. FDA has also concluded that dietary supplements providing no more than 5 g/day EPA and DHA are safe when used as recommended [356].  
  
Commonly reported side effects of omega-3 supplements are usually mild and include unpleasant taste, bad breath, heartburn, nausea, gastrointestinal discomfort, diarrhea, headache, and odoriferous sweat [357,358]. Because of their antiplatelet effects, high doses of omega-3s might interact with anticoagulants [359]. However, according to the FDA-approved package inserts for omega-3 pharmaceutical preparations, studies have not found that these medications cause clinically significant bleeding episodes [360-362]. Omega-3s might also interact with other medications. For example, omega-3s might increase the risk of hypotension if taken with antihypertensive agents and might increase levels of cyclosporine, an immunosuppressant drug [363-365].  
  
More information on omega-3s is available in the ODS health professional fact sheet on omega-3s.  
  
For information on omega-3s and COVID-19, please see the ODS health professional fact sheet, Dietary Supplements in the Time of COVID-19.  
  
Probiotics  
Probiotics are live microorganisms that confer a health benefit on the host when administered in adequate amounts [366]. They include certain bacteria (e.g., Lactobacillus acidophilus, Lactobacillus rhamnosus, and Bifidobacterium longum) and yeasts (e.g., Saccharomyces boulardii). Probiotics are naturally present in some fermented foods, added to some food products, and available as dietary supplements.  
  
Probiotics are identified by their strain, which includes the genus, the species, the subspecies (if applicable), and an alphanumeric strain designation [367]. The units of measure for probiotics are colony-forming units (CFUs), which indicate the number of viable cells. Common amounts used in dietary supplements are 1 x 109 (1 billion CFU; commonly designated as 109 CFU) and 1 x 1010 (10 billion or 1010 CFU).  
  
Probiotics act mainly in the gastrointestinal tract [7]. They might improve immune function in several ways, including by enhancing gut barrier function, increasing immunoglobulin production, inhibiting viral replication, and enhancing the phagocytic activity of white blood cells. However, the mechanisms of their potential effects on immune function are unclear [7,368,369]. Some studies suggest that probiotics increase levels of natural killer cells, lymphocytes, and monocytes and that they decrease levels of proinflammatory cytokines, but other studies do not [370].  
  
Interpreting the results of probiotics research is especially challenging because findings for one probiotic strain cannot be extrapolated to others [7,371].  
  
Efficacy  
  
Acute infectious diarrhea in infants and children  
Probiotics might reduce the risk of infectious diarrhea and help manage its symptoms by stimulating the immune system and by secreting antimicrobial substances. In addition, they might limit the ability of pathogenic bacteria to colonize, adhere to, and invade the gut by competing for available nutrients and binding sites [372-374].  
  
Clinical trials have used a wide range of probiotic preparations, and results from these studies have been mixed. Several earlier clinical trials showed some beneficial effects of probiotics on acute infectious diarrhea in infants and children. In one of these trials, 64 indigenous children in Australia age 4 months to 2 years admitted to the hospital with acute diarrhea took 5 X 109 CFU Lactobacillus rhamnosus GG (LGG) three times per day or placebo for 3 days [375]. A smaller proportion of children who took LGG had diarrhea on day 2. However, probiotics did not affect the small intestine s functional absorptive capacity. In addition, the duration of diarrhea, total number of diarrhea stools, and diarrhea severity did not differ between groups. Another trial included 88 children in an urban middle-class population (country not specified) age 3 to 24 months who had acute mild to moderate diarrhea [376]. Infants younger than 1 year took 250 mg/day Saccharomyces boulardii, and older children took 500 mg/day or placebo for 6 days. Diarrhea duration was shorter (4.7 days) in children who took Saccharomyces boulardii than those who took placebo (6.2 days). Saccharomyces boulardii users also had fewer stools on the fourth day and were less likely to have persistent diarrhea for more than 7 days. In addition, subgroup analyses showed that the probiotic was more effective when administered within the first 48 hours of diarrhea onset.  
  
Findings were positive in a Cochrane Review of 63 clinical trials (including the two described above) in a total of 8,014 participants (primarily infants and children). Types of probiotics and treatment schedules varied widely, but 15 studies used more than 1 X 1010 CFU per day, 26 used 1 X 1010 CFU per day or less, and in 22 studies the dose was unclear. The results showed that single- and multi-strain probiotics shortened the duration of acute infectious diarrhea by about 25 hours [373]. The probiotics also decreased the risk that the diarrhea would last 4 or more days by 59% and led to approximately one less bowel movement on the second day in patients who received probiotics than in patients who did not.  
  
Research conducted through 2015 indicated that two strains LGG and Saccharomyces boulardii had the strongest evidence of efficacy [374]. A meta-analysis of 11 clinical trials with a total of 2,444 children showed that LGG reduced the duration of infectious diarrhea by about 1 day more than placebo or no treatment, and it was most effective at a daily dose of at least 1010 CFU [377]. Similarly, a review of 22 clinical trials with a total of 2,440 participants age 1 month to 15 years found that Saccharomyces boulardii (most commonly 109 to 1010 CFU/day for 5 10 days) reduced the duration of diarrhea by 19.7 hours, reduced stool frequency on days 2 and 3, and lowered the risk of diarrhea on days 3 and 4 [378].  
  
Using its requirement of at least two adequate and well-controlled studies each convincing on its own to establish an intervention s effectiveness, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) found that evidence supports the use of LGG (typically at least 1010 CFU/day for 5 7 days) and Saccharomyces boulardii (typically 250 750 mg/day [109 1010 CFU] for 5 7 days) in combination with rehydration for managing acute infectious diarrhea in pediatric patients [379].  
  
However, results from recent clinical trials have largely failed to show that probiotics benefit children with acute infectious diarrhea [380,381]. For example, a clinical trial in 971 participants age 3 months to 4 years with acute gastroenteritis presenting to U.S. pediatric emergency departments found that 1 x 1010 CFU LGG twice per day for 5 days was no better than placebo for improving outcomes [381]. In a similar trial, a combination probiotic containing 4 x 109 CFU L rhamnosus R0011 and L helveticus R0052 twice daily did not prevent the development of moderate to severe gastroenteritis within 14 days of enrollment compared with placebo in 886 Canadian children age 3 to 40 months with gastroenteritis [380]. Results were similar in a 2020 Cochrane Review of probiotics for treating acute infectious diarrhea that included 82 clinical trials in a total of 12,127 participants (mostly children younger than 18 years), and about two-thirds of the trials were conducted in countries with low or very low child and adult mortality rates [382]. The probiotics did not reduce the risk of diarrhea lasting 48 hours or longer. In addition, probiotics did not affect the duration of diarrhea, although this evidence was of very low certainty.  
  
In 2020, based on these and other more recent trials, ESPGHAN downgraded its recommendations from strong to weak for the use of LGG and Saccharomyces boulardii in infants and children with acute gastroenteritis [383]. ESPGHAN also made recommendations it characterized as weak for L reuteri DSM 179038 (1 x 108 to 4 x 108 CFU/day for 5 days) as well as L rhamnosus 19070-2 and L reuteri DSM 12246 (each 2 x 1010 CFU/day for 5 days) in combination with rehydration for managing acute gastroenteritis in pediatric patients.  
  
Common cold, influenza, and other respiratory tract infections  
Probiotics might reduce the risk of respiratory tract infections and shorten the duration of illness, possibly by stimulating the immune system and inhibiting viral replication [7].  
  
Most clinical trials that have examined whether probiotics reduce the risk of respiratory tract infections in infants, children, and adults have had positive findings. For example, one clinical trial assessed whether probiotics affect the incidence and duration of cold and flu-like symptoms in 326 healthy children age 3 to 5 years [384]. Participants took Lactobacillus acidophilus NCFM (1 x 1010 CFU total daily dose) twice daily, Lactobacillus acidophilus NCFM plus Bifidobacterium animalis subsp lactis Bi-07 (1 x 1010 CFU total daily dose), or placebo for 6 months from November to May. Lactobacillus acidophilus alone or in combination with Bifidobacterium animalis reduced the incidence and duration of fever and cough as well as the use of antibiotics. In addition, participants who took Lactobacillus acidophilus alone or with Bifidobacterium animalis had significantly fewer childcare absences than participants who took placebo. Findings were similar in a clinical trial in 898 healthy men and women age 18 to 70 years who took 1 x 109 CFU Lactiplantibacillus plantarum HEAL9 and Lacticaseibacillus paracasei 8700:2 or placebo daily for 12 weeks from October to February [385]. Among participants experiencing at least one cold, those who took probiotics had fewer colds (mean of 1.24 colds) than those who took placebo (mean of 1.36 colds), but symptom severity did not differ between groups.  
  
Systematic reviews and meta-analyses that have evaluated the use of probiotics to prevent or treat respiratory tract infections in children and adults have all found beneficial effects on some outcomes [386-390]. For example, a systematic review and meta-analysis included 20 clinical trials that examined the effects of Lactobacillus and Bifidobacterium on acute respiratory tract infections in children age 12 months to 12 years or adults [387]. Participants took Lactobacillus strains, Lactobacillus plus Bifidobacterium strains, or placebo for 3 weeks to 7 months, mostly during the winter. The probiotics had modest but statistically significant effects, reducing the number of days of illness per person by about a third of a day; shortening the duration of illness by almost a day; and reducing the number of days absent from day care, school, or work by about 4 hours in comparison with placebo.  
  
Probiotics were also found to be beneficial in a Cochrane Review of probiotic supplementation to prevent acute upper respiratory tract infections that combined findings from 12 clinical trials in a total of 3,720 children and adults [369]. The studies tested a wide variety of probiotics, including single and multiple strains, and most trials administered 109 to 1010 CFU/day for 3 months or longer. Probiotics reduced the risk of developing at least one acute upper respiratory tract infection by 47% and shortened the duration of illness by 1.89 days in comparison with placebo. However, the evidence was of low quality. The authors concluded that probiotics might help prevent acute upper respiratory tract infections.  
  
Results from a more recent meta-analysis also support the use of probiotics for respiratory tract infections. It included 39 studies in a total of 8,046 nonelderly, mostly healthy men and women that tested various probiotic strains, including Lactobacillus, Bifidobacterium, Enterococcus, and Lactococcus [386]. Probiotics reduced the risk of developing one or more respiratory tract infections by 9%, the duration of illness by 0.23 days, and the severity of symptoms.  
  
One challenge with evaluating the findings of clinical trials of probiotics is that the effects of probiotics appear to vary by strain. This is illustrated by a cohort study in France that followed 8,389 children from birth until age 5.5 years [391]. At age 2 months, 57.4% of the children consumed infant formula enriched with various probiotic strains, and 42.6% consumed formula without probiotics. Children who consumed formula containing Bifidobacterium lactis (BB12) at age 2 months had a 16% lower risk of lower respiratory tract infections until at least age 5.5 years than those who consumed formula not containing probiotics. However, consumption of formula with other strains of Bifidobacterium or with Lactobacillus or Streptococcus did not affect the risk of lower respiratory tract infections. In addition, the results showed no correlations between consumption of formula containing any of the probiotic strains at age 2 months and risk of upper respiratory tract infections.  
  
Another challenge is that more than 200 types of viruses can cause respiratory infections, and the effects of probiotics may vary by virus [7]. Research in free-living participants cannot be constrained to a preselected virus, so some researchers have addressed this issue by experimentally inducing respiratory tract infections caused by a single virus. One of these studies examined the effects of Bifidobacterium animalis subspecies lactis B1-04 in 152 healthy young men and women (mean age 22 to 23 years) who were exposed to rhinovirus (RV)-A39 [392]. Participants took 2 x 109 CFU daily of the probiotic or placebo for 28 days before the RV-A39 challenge and for 5 days afterward. Probiotic supplements reduced the chemokine ligand 8 response to the rhinovirus infection, suggesting less severe symptoms. The supplementation also reduced the virus titer and proportion of participants shedding virus in their nasal secretions. However, the probiotic did not affect symptom scores, infection rates, or levels of lower respiratory inflammation.  
  
Ventilator-associated pneumonia  
Studies examining whether probiotics reduce the risk of ventilator-associated pneumonia (VAP) in people who are critically ill have had inconsistent findings.  
  
Some findings were positive in a 2010 trial that randomized 146 male and female patients, mean age 53 to 55 years, on mechanical ventilation to placebo or enteral 2 x 109 CFU LGG twice daily until extubation, tracheostomy placement, or death [393]. Only 19.1% of the LGG group developed VAP, whereas the rate was 40.0% in those treated with placebo. In contrast, enteral LGG (1 x 1010 CFUs twice daily for a median of 9 days) did not reduce the risk of VAP in another clinical trial in 2,653 critically ill patients (mean age 59.8 years) in the ICU [394].  
  
A 2022 systematic review and meta-analysis also had mixed findings. It included 18 clinical trials (including the two trials described above) in a total of 4,893 adult patients on mechanical ventilation in the ICU [395]. Twelve of the trials used probiotic supplementation (mostly Lactobacillus), and six used synbiotics (combinations of probiotics and prebiotics). Evidence of low certainty showed that probiotics reduced the incidence of VAP by 32%. However, the effect was not statistically significant in double-blind studies or in studies with a low risk of bias. According to evidence of moderate certainty, probiotics also reduced the length of ICU stay by about 2.2 days.  
  
Similar findings were reported in a 2014 Cochrane Review that included eight clinical trials in a total of 1,083 participants [396]. These trials examined the effects of various strains of probiotics, including Lactobacillus, Bifidobacterium, and Streptococcus. The probiotics decreased the incidence of VAP by 30%. However, the authors noted that the quality of this evidence was low. Furthermore, probiotics did not affect rates of ICU mortality or in-hospital mortality, incidence of diarrhea, length of ICU stay, or duration of mechanical ventilation, according to evidence of very low quality.  
  
Other reviews have had mixed findings [397-400], and many review authors have noted that significant trial heterogeneity, risk of bias, or both hinder evaluation of the available evidence [395,397,399].  
  
Safety  
Probiotics, such as strains of Lactobacillus, Bifidobacterium, and Propionibacterium, have a long history of use in foods and are often present in the normal gastrointestinal microbiota, indicating that probiotic supplements are safe for most people [368]. Side effects, which are usually minor, include gastrointestinal symptoms, such as gas [7,369]. However, potential safety concerns can include systemic infections, especially in people who are immunocompromised [368]. For example, in a few cases, mainly in people who were severely ill or immunocompromised, the use of probiotics was linked to bacteremia, fungemia (fungi in the blood), or infections that resulted in severe illness [401,402].  
  
Probiotics are not known to interact with medications. However, antibiotic and antifungal medications might decrease the effectiveness of some probiotics [403,404].  
  
More information on probiotics is available in the ODS health professional fact sheet on probiotics.  
  
For information on probiotics and COVID-19, please see the ODS health professional fact sheet, Dietary Supplements in the Time of COVID-19.  
  
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