Foods to deliver immune-supporting nutrients

Philip C. Calder[1,2,*]

[1]School of Human Development and Health, Faculty of Medicine, University of Southampton, Southampton SO16 6YD, United Kingdom

[2]NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton SO16 6YD, United Kingdom

Abstract

Purpose of review: This article will briefly describe the role of specific dietary components, mainly micronutrients, in supporting the immune response and summarise the literature regarding foods and dietary patterns in the context of immunity and infectious illness. Literature on SARS-COV-2 infection and COVID-19 is referred to where appropriate.

Recent findings: Micronutrients, other nutrients and plant bioactives have roles in supporting the immune response. Low status of a number of micronutrients is associated with increased risk and severity of COVID-19. Recent studies report associations of plant-based diets with lower risk of, and less severe, COVID-19.

Summary: In order to support the immune response, sufficient amounts of a range of essential and non-essential nutrients and other bioactives, mainly from a plant-based diet should be consumed. Further research should define cause-and-effect relationships of intakes of individual dietary components and foods, and of dietary patterns with susceptibility to, and severity of, viral infections.

Key words: Immunity, Infection, Vitamin, Mineral, Microbiota, Food

Introduction and scope

Humans co-exist in an environment with other organisms including bacteria, viruses, fungi and parasites, some of which can be harmful, causing infectious disease. The social, economic and health consequences of infectious disease to humans are well known [1,2,3], but have been highlighted again over the last two years due to the emergence of severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) and the disease it causes, COVID-19. The SARS-CoV-2 pandemic has focused the attention of consumers, the health care sector, governments, regulators and industry on the importance of immune health and on the need to develop strategies to provide the population with the protection they require against harmful (i.e. pathogenic) organisms. The primary role of the immune system is to provide defense against harmful bacteria and viruses, which together are termed microorganisms or microbes, as well as fungi and parasites. Importantly, the immune system also provides immunologic tolerance to non-pathogenic organisms, to harmless environmental exposures (e.g. food) and to the individual themselves. In order to be effective against the wide array of possible threatening organisms, the human immune system has evolved to include many different cell types, many communicating molecules and multiple functional responses which are generally classified into innate and acquired immunity (Figure 1) [4*]. These functional responses may be divided into four general features:

- barrier function, preventing (micro)organisms from entering the body;
- recognition of (micro)organisms and identification of whether they are harmful or not;
- elimination of (micro)organisms identified as being harmful;
- generation of memory of immunological encounters.

These complex and sophisticated actions are achieved because the human immune system is comprised of many cell types, each with their own individual functional capabilities. These different cell types interact with one another as part of the immune response to assure effective protection from pathogens and effective tolerance to non-threatening exposures. There is variation in immune parameters among individuals [5] and many factors contribute to this variation (Figure 2) [4*,5]. These factors include genetics, infection history, vaccination history, illness, some medications, sex, and stage of the life course (e.g. pregnancy, infancy, old age). Lifestyle factors including stress, physical fitness and diet also have an influence (Figure 2). Diet is important because it provides the nutrients that have vital roles in supporting the immune response [6,7*], while other "non-nutrient" components of foods can also play roles in supporting the immune system. The diet provides:

- the fuels that provide energy for the immune system to function;
- the building blocks to support the high level of biosynthesis and cell replication required during the immune response;
- substrates for the production of some immune-active metabolites;
- many regulators of immune cell metabolism;
- agents with direct anti-microbial properties;
- anti-oxidants and anti-inflammatories providing the host with protection from the oxidative and inflammatory stress generated during the immune response;

- substrates for the development and maintenance of the intestinal microbiota which in turn modulates the immune system.

The aim of this article is to briefly describe the role of specific dietary components, mainly micronutrients, in supporting the immune response and to survey the literature regarding foods and diets/dietary patterns in the context of immunity and infectious illness. Literature that is relevant to SARS-COV-2 infection and COVID-19 will be referred to where appropriate.

Key immune-supporting nutrients

Multiple micronutrients play vital roles in supporting the immune response [7*,8,9,10**,11] (Table 1). The roles of vitamins A, C and D and zinc, copper and iron are well explored and fairly widely recognized, but B vitamins, vitamin E, vitamin K, selenium, magnesium and others also all have roles. Insufficient intake of several of these micronutrients impairs many aspects of both innate and acquired immunity and increases susceptibility to infections [7*,10**]. In many cases the immune impairments can be reversed by repletion and this reduces susceptibility to infection. Many micronutrients have been discussed in the context of infection with SARS-CoV-2 and COVID-19 but vitamins C [12,13*] and D [14*,15**] and zinc [16**,17*] have received the most attention.

Vitamin C

Vitamin C supports the activity of many cells of the immune system (Table 1) [18] and helps to control oxidative stress and inflammation. People deficient in vitamin C are susceptible to severe respiratory infections such as pneumonia and a meta-analysis reported a significant reduction in the risk of pneumonia with vitamin C supplementation, particularly in individuals with low dietary intakes [19]. Vitamin C supplementation has also been shown to decrease the duration and severity of upper respiratory tract infections, such as the common cold, especially in people under enhanced physical stress [20]. Multiple studies report an association between low vitamin C status and increased susceptibility to, and severity of, COVID-19 (e.g. [21]). Most studies investigating the ability of vitamin C to treat COVID-19 have focused on intravenous infusion rather than the oral route, as reviewed elsewhere [22].

Vitamin D

Vitamin D has pleiotropic actions within the immune system but does support the activity of several immune cell types [23]. Furthermore, some immune cells (e.g. dendritic cells, macrophages) can produce the active form of vitamin D suggesting it is important to immunity.

Vitamin D also promotes the production of antimicrobial proteins such as cathelicidin and β-defensins. Vitamin D deficiency impairs the response to the seasonal influenza vaccine [24] and meta-analyses of randomised controlled trials of vitamin D supplementation report reduced incidence of respiratory tract infections [25]. Vitamin D supplements seem most effective when given regularly, rather than as a bolus, and in individuals with low starting vitamin D status [25]. Multiple studies report an association between low vitamin D status and increased susceptibility to, and severity of, COVID-19 (e.g. [26]) and meta-analyses report that vitamin D deficiency increases risk of severe COVID-19, hospitalisation with COVID-19 and mortality from COVID-19 [27,28]. A study in an Italian residential care home reported that a bolus of vitamin D reduced mortality from COVID-19 [29]. Vitamin D supplementation in patients hospitalised with COVID-19 is reported to reduce COVID-19 severity (e.g. need for intensive care unit admission, mortality) [30,31].

Zinc

Zinc supports the activity of many cells of the immune system (Table 1) [32], helps to control oxidative stress and inflammation and has specific anti-viral actions [33] including inhibiting the replication of coronaviruses [34]. Zinc supplementation improves some markers of immunity especially in older people or those with low zinc intake [35] and improves vaccination responses [36] and meta-analyses of randomised controlled trials of zinc supplementation report reduced incidence of lower respiratory tract infections [37,38]. Multiple studies report an association between low zinc status and increased susceptibility to, and severity of, COVID-19 (e.g. [39]). Zinc supplementation in patients hospitalised with COVID-19 is reported to reduce risk of poor outcome including mortality [40,41].

Selenium

Selenium supports the function of many immune cell types (see Table 1) [42,43] and helps to control oxidative stress and inflammation. Extensive research in mice has shown that selenium deficiency impairs multiple immune responses and increases susceptibility to viral infection [44]. Furthermore, selenium deficiency in mice permits viral mutation, including of influenza viruses, so allowing normally weak viruses to become more virulent; research on selenium and viral infections has been comprehensively reviewed recently [44]. The permissive effect of selenium deficiency on viral mutation and virulence seems to relate the higher oxidative stress that exists in the absence of selenium. Selenium supplementation has been shown to enhance some markers of immunity in humans [45], although not all studies show this. Differences in the findings of different studies might relate to starting selenium status, and the selenium dose and the matrix used. Several studies report an association between low selenium status and increased susceptibility to, and severity of, COVID-19 (e.g. [39]). The potential for selenium to play a role in defence against SARS-CoV-2 and COVID-19 is nicely discussed elsewhere [46**,47**].

Amino acids and fatty acids

In addition to micronutrients, other essential nutrients, including amino acids and fatty acids, play important roles in supporting the immune system, and even non-essential amino acids and fatty acids seem important in this regard [48,49]. Both amino acids and fatty acids are important biosynthetic precursors (e.g. amino acids for proteins like antibodies and cytokines involved in the immune response and fatty acids for membrane lipid components to support production of new immune cells) and both give rise to specific immunologic mediators (e.g. arginine gives rise to nitric oxide which is toxic to bacteria and omega-6 and omega-3 polyunsaturated fatty acids give rise to lipid mediators that are important regulators of immunity and inflammation).

Important non-nutrient components of the diet

In addition to the "classic" nutrients described above, the diet also provides non-nutrients that are bioactive and some of these likely have a role in supporting the immune system to function and in helping to control oxidative and inflammatory stress. The effects of plant polyphenolic compounds in promoting resilience to infection have been discussed elsewhere recently [51**,52**,53*], as have the possibilities of these compounds to possess direct anti-viral activities [54,55]. Beta-glucans are another class of compounds of plant origin that have been demonstrated to have unique actions that result in immune training and immune support, as reviewed elsewhere recently [56,57*].

The importance of the gut microbiota to the immune system

Commensal bacteria within the gastrointestinal tract play a role in host immune defence by creating a barrier against entry of pathogens into the body and through the production of lactic acid and antimicrobial proteins which can directly inhibit the growth of pathogens. Commensal organisms also interact with the host's gut epithelium and gut-associated immune tissues [58]. These communications with the host occur through chemicals released from the bacteria (e.g. short chain fatty acids) or through direct cell-to-cell contact [58]. As a result of such actions, it likely that nutritional strategies that promote the growth of such commensal organisms will contribute to supporting the immune system. Some of the dietary components already mentioned, including vitamin D, omega-3 fatty acids, plant polyphenolics and beta-glucans, can influence the gut microbiota, but dietary fiber and prebiotic oligosaccharides have a much greater effect and typically promote the growth of lactobacilli and bifidobacteria that are considered to support immunity. In this regard, probiotic organisms are more widely studied and some lactobacilli and bifidobacteria have been shown to enhance some aspects of immunity including the response to vaccination [59,60,61,62]. These immune effects suggest that modifying the gut microbiota, particularly with probiotic organisms, could protect against infections. Systematic reviews and meta-analyses report that some probiotics can reduce the risk or duration of gastrointestinal infections (see [7*] for references), but there is also evidence that they reduce the incidence of respiratory infections and promote a better outcome, particularly in children [63,64,65,66,67,68,69]. This effect is likely due to the so-called gut-lung axis [70*], whereby altered gut microbiota affects cells that are part of the gut-associated immune system and these cells move to the lung-associated immune system to elicit beneficial actions.

Foods as sources of immune-supporting nutrients and non-nutrients

It is evident that a wide range of micronutrients (vitamins and minerals), amino acids, fatty acids and plant bioactives have roles in supporting the immune response, so contributing to host defence against pathogens, and in controlling oxidative and inflammatory stress, which are damaging to the individual. Therefore, in the interests of assuring the best possible immune response if an individual becomes infected, it would seem prudent to consume sufficient amounts of a broad range of essential and non-essential nutrients and other bioactives, although in most cases these amounts needed are not explicitly defined for the immune response [7*,11]. Many, although not all, of the important dietary components come from plant foods. Therefore, as stated elsewhere [7*] probably “the best diet to support the immune system is one with a diverse and varied intake of vegetables, fruits, berries, nuts, seeds, grains and pulses along with some meats, eggs, dairy products and oily fish to provide the nutrients that are hard to get enough of from plant-based foods.” This diet is consistent with those regarded as generally healthy [71], is consistent with current dietary guidelines [72] and would also promote a healthy gut microbiota [73], particularly if some fermented foods were included. Although a number of studies have examined the effects of individual foods and entire diets on inflammation, there are few such studies focussing on immune outcomes. However, in one randomised controlled trial researchers compared the effect of low ($\leq$ 2 servings per day) and high ($\geq$5 servings per day) intakes of fruits and vegetables on immune outcomes in older people [74]. After 12 weeks of the dietary intervention, the antibody response to the pneumococcal vaccine was higher in the group consuming the higher amount of fruits and vegetables [74]. This is good evidence that a diet richer in fruits and vegetables supports a stronger immune response, most likely because of the nutrients and bioactives that fruits and vegetables can deliver to the body. In this regard, studies of fruit juice and of an encapsulated concentrate of fruits and vegetables reported improvements in immune biomarkers [75,76,77] and a decrease in respiratory illness [77,78]. Recent studies have reported relationships between dietary patterns and susceptibility to, or severity of, COVID-19 [79*,80*].

Merino et al. [79*] used data from 592,571 users of a smartphone-based COVID-19 symptom app which also collected dietary information via a short food frequency questionnaire. The authors assessed diet quality using a "plant-based diet score", which emphasises healthy plant foods such as fruits and vegetables. 31,815 COVID-19 cases were reported. Compared with individuals in the lowest quartile of the diet score, high diet quality was associated with lower risk of COVID-19 (defied as a self-reported positive SARS-CoV-2 test) and severe COVID-19 (defined as self-reported hospitalisation with need for oxygen support): the hazards ratios for highest versus lowest quartile of diet quality were 0.91 (95% confidence interval (CI) 0.88 to 0.94) and 0.59 (95% CI 0.47 to 0.74). for infection and severity, respectively. The authors concluded that "a diet characterised by healthy plant-based foods was associated with lower risk and severity of COVID-19".

Kim et al. [80*] analysed data from a web-based survey of healthcare workers from six countries (France, Germany, Italy, Spain, UK, USA) who had substantial exposure to COVID-19 patients. There were 568 COVID-19 cases (138 moderate-to-severe and 430 mild-to-moderate) and 2,316 controls. Participants self-reported habitual consumption of one of eleven dietary types. These were then combined to create three different dietary patterns: plant-based, pescatarian, and low carbohydrate high protein. After adjusting for various confounders, participants who reported following 'plant-based diets' and 'plant-based diets or pescatarian diets' had lower odds ratios (0.27 (95% CI 0.10 to 0.81) and 0.41 (95% CI 0.17 to 0.99)) of moderate-to-severe COVID-19 compared with those who did not follow these diets. The authors concluded that "plant-based diets or pescatarian diets were associated with lower odds of moderate-to-severe COVID-19. These dietary patterns may be considered for protection against severe COVID-19".

Summary and perspectives

The existing evidence indicates that multiple micronutrients, other essential and non-essential nutrients, certain bioactives and also those dietary components that promote a diverse, healthy gut microbiota play vital roles in supporting all aspects of the immune response. Thus, the intake of these nutrients and non-nutrients needs to be considered in the context of susceptibility to viral (and other) infections and the subsequent severity of illness. The roles of specific nutrients including vitamin D and zinc in anti-viral immunity seem to be important. Amongst other micronutrients, selenium may be more important than is generally considered: the ability of selenium to prevent viral mutation is intriguing in the context of the emergence of SARS-CoV-2 variants. Furthermore, low intakes of several micronutrients impair vaccination responses [81*] and so intakes of these must be considered in the context of the current and future COVID-19 and other vaccination programmes. Although infection with SARS-CoV-2 and the resulting disease, COVID-19, have focussed attention on the need for individuals to have a sufficiently strong immune response to remain healthy, concern about "immune health" will remain relevant in the contexts of recovery from infection, emergence of new variants of viruses, vaccination and possible future pandemics.

Research published over the last two years has reported many times that low status of a number of vitamins and minerals is associated with increased risk and severity of COVID-19. It is important to keep in mind that such observations do not demonstrate cause-and-effect relationships. Furthermore, although some trials providing (often high doses of) specific micronutrients to patients with COVID-19 report benefits, many of these trials do not have an optimal design and not all trials do report benefit. It is also important to differentiate protective strategies from treatment strategies. Actions like wearing face masks, frequent hand washing and using hand sanitiser, social distancing and isolation limit exposure to pathogens and so they work to reduce infection risk. Having a strong immune response also reduces infection risk because it enables the individual to deal with the pathogens that they are exposed to, keeping them in check and even eliminating them. The result is that the individual will be infection free or have a low level of infection and remain asymptomatic or with low grade symptoms. Thus, strategies to support the immune system, including dietary strategies, can be an important contributor to prevention (and control) of infection. Once an individual has signs of significant infection and requires hospitalisation their immune system still requires support: it is well described that in individuals hospitalised with COVID-19, those with a weaker immune response and with exaggerated inflammation show a poorer outcome [82,83,84]. However, these individuals also show progressive impairments of other physiological systems [82]. Hence, where specific nutrients such as vitamin C [22], vitamin D [30,31], zinc [43,44] and omega-3 fatty acids [85] have been used therapeutically in patients hospitalised with COVID-19 it is unclear whether the benefits reported are due to effects on the immune system, on inflammation or on other systems in the body, or indeed on all of these.

Research in this field is important to help society deal with the continuing pandemic and to prepare for future pandemics. Further research is needed to define cause-and-effect relationships of intakes of individual nutrients, other dietary components and foods, and dietary patterns with susceptibility to, and severity of, viral infections. Even so, although many nutrients and bioactives are provided as part of a diverse, plant-based diet there is a question about whether sufficient amounts of some of the key immune active micronutrients (vitamin D, vitamin C, vitamin E, zinc, selenium), and perhaps some of the other bioactives, can be obtained from the diet [7*,11]. Thus, whether supplements are necessary to provide the relevant intakes of these components and whether immune-targeting functional foods with enriched levels of some of the key components can be developed are important questions.

Conclusions

Multiple micronutrients, other essential and non-essential nutrients, certain bioactives and also those dietary components that promote a diverse, healthy gut microbiota play important roles in supporting all aspects of the immune response. In order to support the immune response to help individuals deal effectively with pathogens should they become infected it would seem prudent to consume sufficient amounts of these nutrients and other bioactives, mainly from a plant-based diet. In support of this, recent studies report associations of plant-based diets with lower risk of, and less severe, COVID-19.

Funding

This research was not funded.

Conflicts of interest

PCC has research funding from Bayer Consumer Care; acts as an advisor/consultant to BASF AS, DSM, Cargill, Danone/Nutricia, Smartfish, Nutrileads, Bayer Consumer Care, GSK Consumer Healthcare, and Kemin; and has received speaking fees from BASF AS, DSM, Danone/Nutricia, Bayer Consumer Care, GSK Consumer Healthcare, Kremin and Proctor and Gamble. The University of Southampton previously received a writing fee from the European Fruit Juice Association.

References

1. Piret J, Boivin G: ***Pandemics throughout history***. *Front Microbiol* 2021, **11**:631736.
2. Mercer A: ***Protection against severe infectious disease in the past***. *Pathog Glob Health* 2021, **115**:151-167.
3. Janik E, Ceremuga M, Niemcewicz M, Bijak M: ***Dangerous pathogens as a potential problem for public health***. *Medicina (Kaunas)* 2020, **56**: 591.
4. Calder PC: ***Nutrition and immunity: lessons for COVID-19***. *Eur J Clin Nutr* 2021, **75**:1309-1318.

*An overview of the effects of ageing, frailty, obesity, selected micronutrients and the gut microbiota on the human immune response, including response to vaccination, and on susceptibility to respiratory infection, placing existing literature alongside newer COVID-19 related literature.

5. Calder PC, Kew S: ***The immune system: a target for functional foods?*** *Brit J Nutr* 2002, **88 Suppl 2**:S165-S177.
6. Calder PC: ***Feeding the immune system***. *Proc Nutr Soc* 2013, **72**:299-309.
7. Calder PC: ***Nutrition, immunity and COVID-19***. *BMJ Nutr Prev Health* 2020, **3**:74-92.

*A comprehensive review of the effects of ageing, frailty, obesity, many micronutrients and the gut microbiota on the human immune response, including response to vaccination, and on susceptibility to infection. Goes on to discuss the importance of a diverse plant-based diet to support the immune system.

8. Maggini S, Wintergerst ES, Beveridge S, Hornig DH: ***Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses***. *Brit J Nutr* 2007, **98 Suppl 1**:S29-S35.
9. Maggini S, Pierre A, Calder PC: ***Immune function and micronutrient requirements change over the life course***. *Nutrients* 2018, **10**:1531.
10. Gombart AF, Pierre A, Maggini S: ***A review of micronutrients and the immune system-working in harmony to reduce the risk of infection***. *Nutrients* 2020, **12**:236.

**Exceptional review of the roles of many micronutrients in the immune response and in promoting resistance to infection including the mechanisms involved.

11. Calder PC, Carr AC, Gombart AF, Eggersdorfer M: ***Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections***. *Nutrients* 2020, **12**:1181.
12. Carr AC, Rowe S: ***The emerging role of vitamin C in the prevention and treatment of COVID-19***. *Nutrients* 2020, **12**:3286.
13. Abobaker A, Alzwi A, Alraied AHA: ***Overview of the possible role of vitamin C in management of COVID-19***. *Pharmacol Rep* 2020, **72**:1517-1528.

*Comprehensive review of the roles of vitamin C in the immune response.

14. Mercola J, Grant WB, Wagner CL: ***Evidence regarding vitamin D and risk of COVID-19 and its severity***. *Nutrients* 2020, **12**:3361.

*Comprehensive review of the roles of vitamin D in antiviral immunity including in relation to SARS-CoV-2.

15. Griffin G, Hewison M, Hopkin J, Kenny R, Quinton R, Rhodes J, Subramanian S, Thickett D: ***Vitamin D and COVID-19: evidence and recommendations for supplementation***. *R Soc Open Sci* 2020, **7**:201912.

**Exceptional review of the roles of vitamin D in supporting the immune response and in protecting against respiratory illness. Covers SARS-CoV-2/COVID-19 literature. Discusses likely intakes of vitamin D required for immune health.

16. Wessels I, Rolles B, Rink L: ***The potential impact of zinc supplementation on COVID-19 pathogenesis***. *Front Immunol* 2020,**11**:1712.

**Comprehensive review of the roles of zinc in anti-viral immunity and protection against respiratory illness.

17. Pal A, Squitti R, Picozza M, Pawar A, Rongioletti M, Dutta AK, Sahoo S, Goswami K, Sharma P, Prasad R: ***Zinc and COVID-19: Basis of current clinical trials***. *Biol Trace Elem Res* 2021, **199**:2882-2892.

*Very good review of the roles of zinc in immunity put in the context of trials in COVID-19.

18. Carr AC, Maggini S: ***Vitamin C and immune function***. *Nutrients* 2017, **9**:1211.
19. Hemilä H, Louhiala P: ***Vitamin C for preventing and treating pneumonia***. *Cochrane Database Syst Rev* 2013, CD005532.
20. Hemilä H, Chalker E: ***Vitamin C for preventing and treating the common cold.*** *Cochrane Database Syst Rev* 2013, CD000980.
21. Chiscano-Camón L, Ruiz-Rodriguez JC, Ruiz-Sanmartin A, Roca O, Ferrer R: ***Vitamin C levels in patients with SARS-CoV-2-associated acute respiratory distress syndrome.*** *Crit Care* 2020, **24**:522.

22. Holford P, Carr AC, Jovic TH, Ali SR, Whitaker IS, Marik PE, Smith AD: ***Vitamin C-an adjunctive therapy for respiratory infection, sepsis and COVID-19.*** *Nutrients* 2020, **12**:3760.
23. Prietl B, Treiber G, Pieber TR, Amrein K: ***Vitamin D and immune function***. *Nutrients* 2013, **5**:2502-2521.
24. Lee MD, Lin CH, Lei WT, Chang HY, Lee HC, Yeung CY, Chiu NC, Chi H, Liu JM, Hsu RJ, Cheng YJ, Yeh TL, Lin CY: ***Does vitamin D deficiency affect the immunogenic responses to influenza vaccination? A systematic review and meta-analysis***. *Nutrients* 2018, **10**:409.
25. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, Esposito S, Ganmaa D, Ginde AA, Goodall EC, Grant CC, Griffiths CJ, Janssens W, Laaksi I, Manaseki-Holland S, Mauger D, Murdoch DR, Neale R, Rees JR, Simpson S Jr, Stelmach I, Kumar GT, Urashima M, Camargo CA Jr: ***Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data.*** *BMJ* 2017, **356**:i6583.
26. Merzon E, Tworowski D, Gorohovski A, Vinker S, Golan Cohen A, Green I, Frenkel-Morgenstern M: ***Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study***. *FEBS J* 2020, **287**:3693-3702.
27. Pereira M, Dantas Damascena A, Galvão Azevedo LM, de Almeida Oliveira T, da Mota Santana J: ***Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis.*** *Crit Rev Food Sci Nutr* 2020, in press.
28. Petrelli F, Luciani A, Perego G, Dognini G, Colombelli PL, Ghidini A: ***Therapeutic and prognostic role of vitamin D for COVID-19 infection: A systematic review and meta-analysis of 43 observational studies***. *J Steroid Biochem Mol Biol* 2021, **211**:105883.
29. Cangiano B, Fatti LM, Danesi L, Gazzano G, Croci M, Vitale G, Gilardini L, Bonadonna S, Chiodini I, Caparello CF, Conti A, Persani L, Stramba-Badiale M, Bonomi M: ***Mortality in an Italian nursing home during COVID-19 pandemic: correlation with gender, age, ADL, vitamin D supplementation, and limitations of the diagnostic tests.*** *Aging (Albany NY)* 2020, *12*:24522-24534.
30. Shah K, Saxena D, Mavalankar D: ***Vitamin D supplementation, COVID-19 and disease severity: a meta-analysis***. *QJM* 2021, **114**:175-181.

31. Ghasemian R, Shamshirian A, Heydari K, Malekan M, Alizadeh-Navaei R, Ebrahimzadeh MA, Ebrahimi Warkiani M, Jafarpour H, Razavi Bazaz S, Rezaei Shahmirzadi A, Khodabandeh M, Seyfari B, Motamedzadeh A, Dadgostar E, Aalinezhad M, Sedaghat M, Razzaghi N, Zarandi B, Asadi A, Yaghoubi Naei V, Beheshti R, Hessami A, Azizi S, Mohseni AR, Shamshirian D: ***The role of vitamin D in the age of COVID-19: A systematic review and meta-analysis.*** *Int J Clin Pract* 2021, e14675.
32. Wessels I, Maywald M, Rink L: ***Zinc as a gatekeeper of immune function***. *Nutrients* 2017, **9**:1286.
33. Read SA, Obeid S, Ahlenstiel C, Ahlenstiel G: ***The role of zinc in antiviral immunity***. *Adv Nutr* 2019, **10**:696-710.
34. te Velthuis AJW, van den Worm SHE, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. ***Zn2+ inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture.*** *PLoS Pathol* 2010, **6**:e1001176.
35. Barnett JB, Dao MC, Hamer DH, Kandel R, Brandeis G, Wu D, Dallal GE, Jacques PF, Schreiber R, Kong E, Meydani SN: ***Effect of zinc supplementation on serum zinc concentration and T cell proliferation in nursing home elderly: a randomized, double-blind, placebo-controlled trial.*** *Am J Clin Nutr* 2016, **103**:942-951.
36. Karlsen TH, Sommerfelt H, Klomstad S, Kragh Andersen P, Strand TA, Ulvik RJ, Ahrén C, Grewal HM: ***Intestinal and systemic immune responses to an oral cholera toxoid B subunit whole-cell vaccine administered during zinc supplementation***. *Infect Immun* 2003, **71**:3909-3113.
37. Lassi ZS, Moin A, Bhutta ZA: ***Zinc supplementation for the prevention of pneumonia in children aged 2 months to 59 months.*** *Cochrane Database Syst Rev* 2016, **12**:CD005978.
38. Wang L, Song Y: ***Efficacy of zinc given as an adjunct to the treatment of severe pneumonia: a meta-analysis of randomized, double-blind and placebo-controlled trials.*** *Clin Respir J* 2018, **12**:857-864.
39. Heller RA, Sun Q, Hackler J, Seelig J, Seibert L, Cherkezov A, Minich WB, Seemann P, Diegmann J, Pilz M, Bachmann M, Ranjbar A, Moghaddam A, Schomburg L: ***Prediction of survival odds in COVID-19 by zinc, age and selenoprotein P as composite biomarker.*** *Redox Biol* 2021, **38**:101764.

40. Carlucci PM, Ahuja T, Petrilli C, Rajagopalan H, Jones S, Rahimian J: ***Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients.*** *J Med Microbiol* 2020, **69**:1228-1234.
41. Frontera JA, Rahimian JO, Yaghi S, Liu M, Lewis A, de Havenon A, Mainali S, Huang J, Scher E, Wisniewski T, Troxel AB, Meropol S, Balcer LJ, Galetta SL: ***Treatment with zinc is associated with reduced in-hospital mortality among COVID-19 patients: a multi-center cohort study.*** *Res Sq* 2020, rs.3.rs-94509.
42. Avery J, Hoffmann P: ***Selenium, selenoproteins, and immunity***. *Nutrients* 2018, **10**:1203.
43. Guillin OM, Vindry C, Ohlmann T, Chavatte L: ***Selenium, selenoproteins and viral infection***. *Nutrients* 2019, **11**:2101.
44. Beck M, Handy J, Levander O: ***Host nutritional status: the neglected virulence factor.*** *Trends Microbiol* 2004, **12**:417-423.
45. Broome CS, McArdle F, Kyle JA, Andrews F, Lowe NM, Hart CA, Arthur JR, Jackson MJ: ***An increase in selenium intake improves immune function and poliovirus handling in adults with marginal selenium status.*** *Am J Clin Nutr* 2004, **80**:154-162.
46. Zhang J, Saad R, Taylor EW, Rayman MP: ***Selenium and selenoproteins in viral infection with potential relevance to COVID-19.*** *Redox Biol* 2020, **37**:101715.

**Exceptional review of the roles of selenium in the immune response including in anti-viral immunity.

47. Hiffler L, Rakotoambinina B: ***Selenium and RNA virus interactions: potential implications for SARS-CoV-2 infection (COVID-19).*** *Front Nutr* 2020, **7**:164.

**Comprehensive review of the roles of selenium in anti-viral immunity.

48. Li P, Yin YL, Li D, Kim SW, Wu G: ***Amino acids and immune function***. *Brit J Nutr* 2007, **98**:237-252.
49. Gutiérrez S, Svahn SL, Johansson ME: ***Effects of omega-3 fatty acids on immune cells.*** *Int J Mol Sci* 2019, **20**:5028.
50. Doaei S, Gholami S, Rastgoo S, Gholamalizadeh M, Bourbour F, Bagheri SE, Samipoor F, Akbari ME, Shadnoush M, Ghorat F, Mosavi Jarrahi SA, Ashouri Mirsadeghi N, Hajipour A, Joola P, Moslem A, Goodarzi MO: ***The effect of omega-3 fatty acid supplementation on clinical and biochemical parameters of critically ill patients with COVID-19: a randomized clinical trial.*** *J Transl Med* 2021, **19**:128.

51. Stiller A, Garrison K, Gurdyumov K, Kenner J, Yasmin F, Yates P, Song BH: ***From fighting critters to saving lives: polyphenols in plant defense and human health***. *Int J Mol Sci* 2021, **22**:8995.

**Exceptional review of the role of polyphenols in both plant and human health including in anti-viral immunity.

52. Martín MÁ, Ramos S: ***Impact of dietary flavanols on microbiota, immunity and inflammation in metabolic diseases***. *Nutrients* 2021, **13**:850.

**Comprehensive review of the effects of flavanols on gut microbiota, immunity and inflammation, mainly in the context of metabolic diseases but the implications are broader.

53. Shakoor H, Feehan J, Apostolopoulos V, Platat C, Al Dhaheri AS, Ali HI, Ismail LC, Bosevski M, Stojanovska L: ***Immunomodulatory effects of dietary polyphenols.*** *Nutrients* 2021, **13**:728.

*Comprehensive review of polyphenols, immunity and inflammation including impact on inflammatory diseases.

54. Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, Wang Q, Xu Y, Li M, Li X, Zheng M, Chen L, Li H: ***Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods.*** *Acta Pharm Sin B* 2020, **10**:766-788.

55. Basu A, Sarkar A, Maulik U: ***Molecular docking study of potential phytochemicals and their effects on the complex of SARS-CoV2 spike protein and human ACE2***. *Sci Rep* 2020, **10**:17699.

56. Han B, Baruah K, Cox E, Vanrompay D, Bossier P: ***Structure-functional activity relationship of β-glucans from the perspective of immunomodulation: a mini-review***. *Front Immunol* 2020; **11**:658.

57. De Marco Castro E, Calder PC, Roche HM: ***β-1,3/1,6-glucans and immunity: state of the art and future directions.*** *Mol Nutr Food Res* 2021, **65**:1901071.

*Comprehensive review of the effects of β-1,3/1,6-glucans on immunity, inflammation and infectious disease including the mechanisms involved.

58. Verdu EF, Galipeau HJ, Jabri B: ***Novel players in coeliac disease pathogenesis: role of the gut microbiota***. *Nat Rev Gastroenterol Hepatol* 2015, **12**:497-506.

59. Lomax AL, Calder PC: ***Probiotics, immune function, infection and inflammation: a review of the evidence from studies conducted in humans.*** *Curr Pharm Des* 2009, **15**:1428-1518.

60. Maidens C, Childs C, Przemska A, Bin Dayel I, Yaqoob P: ***Modulation of vaccine response by concomitant probiotic administration***. *Brit J Clin Pharmacol* 2013, **75**:663-670.
61. Lei WT, Shih PC, Liu SJ, Lin CY, Yeh TL: ***Effect of probiotics and prebiotics on immune response to influenza vaccination in adults: a systematic review and meta-analysis of randomized controlled trials.*** *Nutrients* 2017, **9**:1175.
62. Yeh TL, Shih PC, Liu SJ, Lin CH, Liu JM, Lei WT, Lin CY: ***The influence of prebiotic or probiotic supplementation on antibody titers after influenza vaccination: a systematic review and meta-analysis of randomized controlled trials.*** *Drug Des Devel Ther* 2018, **12**:217-230.
63. Vouloumanou EK, Makris GC, Karageorgopoulos DE, Falagas ME: ***Probiotics for the prevention of respiratory tract infections: a systematic review.*** *Int J Antimicrob Agents* 2009, **34**:e1-197.
64. Liu S, Hu P, Du X, Zhou T, Pei X: ***Lactobacillus rhamnosus GG supplementation for preventing respiratory infections in children: a meta-analysis of randomized, placebo-controlled trials***. *Indian Pediatr* 2013, **50**:377-381.
65. King S, Glanville J, Sanders ME, Fitzgerald A, Varley D: ***Effectiveness of probiotics on the duration of illness in healthy children and adults who develop common acute respiratory infectious conditions: a systematic review and meta-analysis***. *Brit J Nutr* 2014, **112**:41-54.
66. Hao Q, Dong BR, Wu T: ***Probiotics for preventing acute upper respiratory tract infections.*** *Cochrane Database Syst Rev* 2015, CD006895.
67. Araujo GV, Oliveira Junior MH, Peixoto DM, Sarinho ES: ***Probiotics for the treatment of upper and lower respiratory-tract infections in children: systematic review based on randomized clinical trials***. *J Pediatr (Rio J)* 2015, **91**:413-427.
68. Wang Y, Li X, Ge T, Xiao Y, Liao Y, Cui Y, Zhang Y, Ho W, Yu G, Zhang T: ***Probiotics for prevention and treatment of respiratory tract infections in children: A systematic review and meta-analysis of randomized controlled trials***. *Medicine (Baltimore)* 2016, **95**:e4509.
69. Laursen RP, Hojsak I: ***Probiotics for respiratory tract infections in children attending day care centers—a systematic review.*** *Eur J Pediatr* 2018, **177**:979-994.
70. Willers M, Viemann D: ***Role of the gut microbiota in airway immunity and host defense against respiratory infections***. *Biol Chem* 2021, **402**:1481-1491.

*State-of-the-art discussion of the gut-lung axis.

71. Cena H, Calder PC: ***Defining a healthy diet: evidence for the role of contemporary dietary patterns in health and disease***. *Nutrients* 2020, **12**:334.
72. US Department of Health and Human Services and US Department of Agriculture: 2015–2020 Dietary Guidelines for Americans, 8th Edition. 2015. Available at: http:// health.gov/dietaryguidelines/2015/guidelines/.
73. Singh RK, Chang HW, Yan D, Lee KM, Ucmak D, Wong K, Abrouk M, Farahnik B, Nakamura M, Zhu TH, Bhutani T, Liao W: ***Influence of diet on the gut microbiome and implications for human health.*** *J Transl Med* 2017, **15**:73.
74. Gibson A, Edgar JD, Neville CE, Gilchrist SE, McKinley MC, Patterson CC, Young IS, Woodside JV: ***Effect of fruit and vegetable consumption on immune function in older people: a randomized controlled trial.*** *Am J Clin Nutr* 2012, **96**:1429-1436.
75. Bub A, Watzl B, Blockhaus M, Briviba K, Liegibel U, Müller H, Pool-Zobel BL, Rechkemmer G: ***Fruit juice consumption modulates antioxidative status, immune status and DNA damage.*** *J Nutr Biochem* 2003, **14**:90-98.
76. Inserra PF, Jiang S, Solkoff D, Lee J, Zhang Z, Xu M, Hesslink Jr R, Wise J, Watson RR: ***Immune function in elderly smokers and nonsmokers improves during supplementation with fruit and vegetable extracts***. *Integr Med* 1999, **2**:3-10.
77. Nantz MP, Rowe CA, Nieves C Jr, Percival SS: ***Immunity and antioxidant capacity in humans is enhanced by consumption of a dried, encapsulated fruit and vegetable juice concentrate***. *J Nutr* 2006, *136*:2606-2610.
78. Lamprecht M, Oettl K, Schwaberger G, Hofmann P, Greilberger JF: ***Several indicators of oxidative stress, immunity, and illness improved in trained men consuming an encapsulated juice powder concentrate for 28 weeks***. *J Nutr* 2007, **137**:2737-2741.
79. Merino J, Joshi AD, Nguyen LH, Leeming ER, Mazidi M, Drew DA, Gibson R, Graham MS, Lo CH, Capdevila J, Murray B, Hu C, Selvachandran S, Hammers A, Bhupathiraju SN, Sharma SV, Sudre C, Astley CM, Chavarro JE, Kwon S, Ma W, Menni C, Willett WC, Ourselin S, Steves CJ, Wolf J, Franks PW, Spector TD, Berry S, Chan AT: ***Diet quality and risk and severity of COVID-19: a prospective cohort study***. *Gut* 2021, **70**:2096-2104.

*Used data from 592,571 users of a COVID-19 symptom app to relate dietary quality to risk and severity of COVID-19. High diet quality was associated with lower risk of COVID-19 and of severe COVID-19. The authors concluded that “a diet characterised by healthy plant-based foods was associated with lower risk and severity of COVID-19”.

80. Kim H, Rebholz CM, Hegde S, LaFiura C, Raghavan M, Lloyd JF, Cheng S, Seidelmann SB: ***Plant-based diets, pescatarian diets and COVID-19 severity: a population-based case-control study in six countries***. *BMJ Nutr Prev Health* 2021, **4**:257-266.

*Analysed data from a web-based survey of healthcare workers from six countries who had substantial exposure to COVID-19 patients. Participants self-reported habitual consumption of one of eleven dietary types, which were then combined to create three different dietary patterns: plant-based, pescatarian, and low carbohydrate high protein. Participants who reported following 'plant-based diets' and 'plant-based diets or pescatarian diets' had lower risk of moderate-to-severe COVID-19 compared with those who did not follow these diets. The authors concluded that "plant-based diets or pescatarian diets were associated with lower odds of moderate-to-severe COVID-19. These dietary patterns may be considered for protection against severe COVID-19".

81. Rayman MP, Calder PC: ***Optimising COVID-19 vaccine efficacy by ensuring nutritional adequacy.*** *Brit J Nutr* 2021, **126**:1919-1920.

82. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B: ***Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study***. *Lancet* 2020, **395**:1054-1062.

83. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, Zhang X, Zhang M, Wu S, Song J, Chen T, Han M, Li S, Luo X, Zhao J, Ning Q: ***Clinical and immunological features of severe and moderate coronavirus disease 2019.*** *J Clin Invest* 2020, **130**:2620-2629.

84. Ruan Q, Yang K, Wang W, Jiang L, Song J: ***Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China***. *Intens Care Med* 2020, **46**:846-848.

85. Doaei S, Gholami S, Rastgoo S, Gholamalizadeh M, Bourbour F, Bagheri SE, Samipoor F, Akbari ME, Shadnoush M, Ghorat F, Mosavi Jarrahi SA, Ashouri Mirsadeghi N, Hajipour A, Joola P, Moslem A, Goodarzi MO: ***The effect of omega-3 fatty acid supplementation on clinical and biochemical parameters of critically ill patients with COVID-19: a randomized clinical trial.*** *J Transl Med* 2021, **19**:128.

Figure legends

Figure 1. The components of the immune system and their division into innate and acquired immunity. IFN, interferon; IL, interleukin; ILCs, innate lymphoid cells; MAIT, mucosal associated invariant T; TGF, transforming growth factor; TNF, tumor necrosis factor. Taken from [4*].

Figure 2. Factors that influence the immune response. Note that the listing is not exclusive. Taken from [4*].