White paper on Nutritional status in supporting a well-functioning immune system for optimal health with a recommendation for Switzerland

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A White Paper was developed by an Expert Panel («the Panel») in cooperation with the Swiss Society of Nutrition and Prof. Manfred Eggersdorfer to review the scientific evidence on the role of micronutrients in supporting a well-functioning immune system for optimal health, with special focus on viral infections.

1. Coronavirus pandemic: situation in Switzerland

The novel pandemic coronavirus (SARS-CoV-2) affected the Swiss population since the beginning of 2020. The virus leads to severe acute respiratory syndrome,[1] causes thrombotic events by affecting blood vessels[2] and has become a life threatening disease particularly in individuals with chronic diseases such as cardiovascular disease and older adults.[3] The COVID-19 pandemic affects more than 180 countries (https://covid19.who.int/) and in absence of a vaccine, there is no end in sight. Given that the virus is highly transmittable through droplets occurring when a person is in close contact with someone who has the infection or by indirect contact with surfaces contaminated with the virus, global public health bodies and governments have ignited strategies on social distancing, wearing masks, and practicing hygiene guidelines, and in severe cases, countries have also adopted «stay in place» or lockdown protocols to prevent COVID-19 spread.

In Switzerland 35,412 people have been infected and 1,707 people died as consequence of SARS-CoV-2 infection (status 02. August 2020). These numbers relate to an infection rate of 412.2 per 100.000 people and 198.7 deaths per 1.000.000 people. Switzerland has a similar infection rate like Italy and a higher rate compared to France, while the death rate per 1.000.000 people is two to three times lower compared to Italy, or France. However, when comparing Switzerland with Germany, Austria, Denmark, Norway or Finland the infection and mortality rate is about two to four times higher compared with these countries (WHO) which are neighboring countries or other European countries with comparable socio-economic status.

The role of nutrition, optimal micronutrient status and a well-functioning immune system as a modifiable factor to reduce risk of virus infections and its severity is highlighted in several recent scientific publications. These publications address the role of good nutritional status for a well-functioning immune system[4,5] and report a deficient or low status in some micronutrients, especially vitamin D, among COVID-19 patients.[6–10] Three meta-analyses have systematically reviewed randomized controlled trials that studied vitamin D supplementation and respiratory tract infections.[11–13] These systematic reviews showed a benefit of vitamin D supplementation for preventing lung tract infections among all age groups. Vitamin D supplementation, irrespective of dosing and schedule, reduced the probability for respiratory tract infections by 12%[14] in a meta-analysis of 25 randomized controlled trials (RCT) with 11321 participants, by 36%[11] in 11 RCTs with 5660 patients and 42%[12] in 5 RCTs, respectively. Among vitamin D deficient individuals (<25 nmol/L), the Vitamin D reduced the risk for acute respiratory tract infections in the meta-analysis by Martineau by 42%.[13]

Vitamin D acts on the immune system through various modes of action. Vitamin D plays a role in both innate and adaptive immune responses.[4] Vitamin D may play a role in the primary defense of lung barriers. In mice, a lack of vitamin D-receptors in the pulmonary epithelial barrier appeared to compromise its defense leading to more severe bacterial lipopolysaccharide-induced lung injury which was alleviated by vitamin D treatment.[15] Similarly in rats, pathological changes of bacterial lipopolysaccharide-induced lung injury were significantly milder in rats receiving vitamin D than those who did not.[16]

Based on observational studies, it has been suggested that low blood levels of vitamin D (25-hydroxyvitamin D) are associated with increased risk of COVID-19 infection.

In 20 European countries as of 20 May 2020,[17] a significant inverse correlation was observed between the population vitamin D status (measured in retrospect) and the national COVID-19 cases per one million population. A second observational study this time across 12 European countries in older adults reported a significant inverse relation between previously reported 25(OH)D levels and mortality from COVID-19 in the countries[18,19] found that COVID-19 mortality per million by country increases with northerly latitude suggesting a link with ultraviolet and vitamin D. Data from a retrospective cohort of 7,807 Israeli healthcare employees found a two-fold increase in the likelihood of COVID-19 infection in those with a low vitamin D level (75 nmol/L).[19–22] Smaller studies using hospital patient data (unpublished work or publications in press) in Germany, Indonesia[23] and Philippines[24] found that below normal Vitamin D levels were associated with increased odds of death.

Further, it was hypothesized that vitamin D supplementation may help reduce the severity of COVID-2019 infections.[24–28] A study in Indonesia including 212 patients, found that higher serum vitamin D levels were associated with less critical outcomes of COVID-19.[23] This may have clinical relevance especially in institutionalized older adults, who are at the higher risk for vitamin D deficiency[29] and severe COVID-19 infections.[3] Moreover, older adults are likely to suffer from multiple nutrient deficiencies.[30] Despite these emerging studies and well-established role of vitamin D in the immune defense of viral and bacterial infections,[4] the importance of optimal nutritional status for a well-functioning immune system, have not yet been broadly considered within prevention and treatment recommendations made by Public Health Policies with regard to COVID-19. Evidence exists for reduced risk for respiratory infection with vitamin D supplementation, however, a causal link between vitamin D and COVID-19 has not yet been established. Randomized controlled studies are underway investigating the effect of vitamin D supplementation on the outcomes and course of COVID-19 and its underlying mode of action. In the meanwhile, acknowledging low population vitamin D status is anyhow a problem, some countries already started to act and provide a vitamin D complement to elderly[31] and the National Health Service in England is advising the entire population to take a daily complement with vitamin D, not just at-risk groups.[32] Hence complementing a well-balanced diet with complements is a possible cost-effective approach to fill the nutritional gap.

In this context an expert panel meeting was initiated to summarize the role of micronutrients for a well-functioning immune system with the aim to develop a recommendation for Switzerland as an additional cost-effective supportive measure to help manage the current coronavirus pandemic and to influence Public Health Policy Makers to consider also nutritional guidance in addition to hygiene, distancing, drugs and vaccination.

2. Immune system as the «body's first line of defense» and role of lifestyle with focus on nutrition and especially micronutrients and omega-3 fatty acids

A well-functioning immune system is important to help reduce the risk of infections. Proper nutrition, including ensuring adequate micronutrient status, is one way to support effective immune function. Several vitamins and trace elements play important roles in supporting the cells and tissues of the immune system.4 Deficiencies or suboptimal status in these micronutrients have the potential to negatively affect immune function and may therefore decrease resistance and the effectiveness of the body's response to infections. Other nutrients such as omega-3 fatty acids also support an immune system to be effective. Optimal status with micronutrients and omega-3 fatty acids is considered to support optimal function of the immune system, with the potential to reduce the risk and consequences of infections, including viral respiratory infections.

Ideally adequate nutritional status should be achieved via a well-balanced diet. However, data indicate that this is not generally the case with the current lifestyle for a number of nutrients.[33] The nutritional status is even worse in older adults; with a considerable amount being deficient for several vitamins or at risk for vitamin deficiencies.[34] Hence enforcing a well-balanced diet, or if this is not possible, add nutritional supplements or functional foods enhanced with certain vitamin D is one possible cost effective option to fill the nutritional gap. If supplements are used this should be done within the framework of targeted nutritional strategies among at risk individuals and a well-balanced diet remains the primary goal. For supplements, the amounts need to fall within the recommendations and upper safety limits set by scientific expert bodies, such as in D-A-CH and by EFSA.

The importance of essential nutrients in maintaining a well-functioning immune system is well established as has been reviewed recently.[4,35,36] Particularly the roles of vitamins A, B6, B12, C, D, E and folate as well as the minerals zinc, iron, selenium and copper play important roles in supporting cells and tissues of the immune system. Indeed, with the exception of vitamin E, all of these micronutrients have been granted health claims in the European Union for contributing to the normal function of the immune system.37–45 Moreover, expert advice developed for the treatment of patients with COVID-19 have specifically stressed the importance of ensuring adequate intake of vitamin D. Additional benefits by omega-3 and trace elements may provide some additional benefit at levels of recommended daily intake to ensure a strong immune defense.[46,47]

In recent publications, recommendations were made for nutrients to support a well-functioning immune system in the general and healthy population.4

Vitamin D levels are frequently suboptimal, inadequate or deficient, likely due to reduced exposure to sunlight and synthesis in the skin. Vitamin D deficiency or inadequacy /suboptimal is associated with a general dysregulation of the innate and adaptive immune system as well as increased levels of inflammation.48–50 Vitamin D stimulates the antimicrobial defence and inhibits pathogens entry into tissues, it stimulates pathogen inhibition and elimination and regulates cytokines (IL-2, IL-6, IL-8, IL-12, IL-17, TNF-alpha, IFN-gamma, NFkBA).[51] A recent meta-analysis by Martineau and colleagues have reported that daily or weekly supplementation with vitamin D reduced the incidence of acute respiratory tract infections.[14] Since the coronavirus pandemic more than 1500 scientific papers have been published which address potential roles of vitamin D for the immune system in the context of SARS-CoV-2 infections. Currently more than 30 human studies with vitamin D are initiated to evaluate the benefit in the context of the coronavirus pandemic (www.clinicaltrials.gov).

Vitamin C plays a key role in the immune defense as it is required by cells from the innate and the adaptive immune system and helps protect the body from damage as a consequence of excessive immune responses.52 Vitamin C deficiency increases the susceptibility to infections such as pneumonia and plasma levels decrease during an acute infection such as pneumonia.[53,54] Vitamin C levels decrease with stress and diseases. Therefore, ensuring adequate vitamin C intake is important.

Selenium influences the immune response largely through its action in selenoproteins that function as cellular antioxidants. Low selenium status levels are common in European countries, including Switzerland. Deficiency appears to enhance virulence or progression of some viral infections as evidenced by the relationship between Keshan disease, coxsackievirus B3 and influenza A,[55] all of those are exacerbated by low selenium status. Selenium also has an important role in the modulation of the inflammatory response and cytokine production. Supplementation of selenium improves the immune system response to viruses in deficient individuals.[56,57] COVID-19 patients with low selenium status have been shown to have higher mortality.[58]

Zinc is essential as approximately 10% of all human gene encoded proteins contain zinc.[59] Zinc affects both the innate and the adaptive immune systems as it regulates intracellular signaling pathways.60 Inadequate zinc status and/or deficiency is known to reduce the effectiveness of various immune cells,[61] resulting in thymic atrophy, lymphopenia, and impaired adaptive immunity.[62–64] It is also crucial in antiviral defense, by inhibiting the entry of viruses into the host cell through stabilization of the cell membrane, and interfering with their replication ability.[65] In institutionalized elderly, a low status (≥70 mg/dL vs. <70 mg/ dL) is associated with lower incidence of and faster recovery from pneumonia, and fewer antibiotic days.[66] Zinc deficiency further favors an inflammatory response and oxidative stress,[67] contributing to the negative effects of inflammaging.[68]

Prevalence of zinc inadequate/deficient status is close to 30% in older people living in care homes, compared to around 5% in their community-dwelling.[69] The risk increases with hospitalization and multiple comorbidities.[70] Several studies reported beneficial effects of zinc complements on immunity and infections in elderly people.[71] Given the potentially severe immunological impact of zinc deficiency, additional 10 mg/d of zinc are advised.

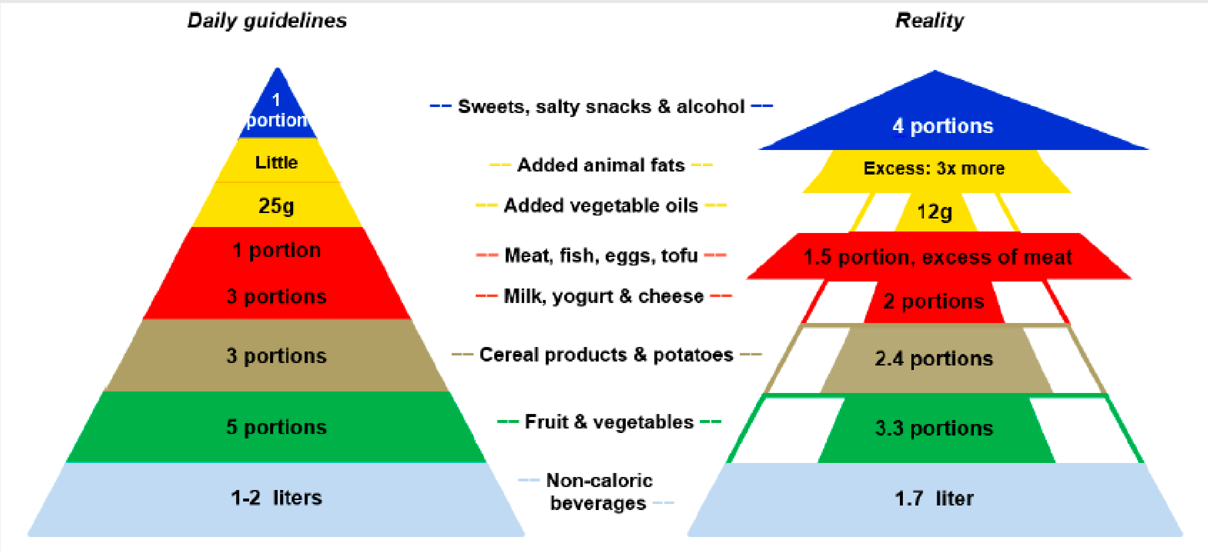
Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) with adequate intakes show a role in the mitigation of adverse effects of inflammation.[72] One of the most important discoveries relating to clinical nutrition is that both DHA and EPA are substrates for the synthesis of highly active lipid mediators important in regulating inflammatory processes and responses, including resolvins, protectins and maresins.[73,74] As a result, they support the resolution of inflammation and consequently support healing, which seems to be hampered in case of nutritional deficiencies of DHA and EPA.[75]

3. Nutritional status of the Swiss population

Even in affluent countries, suboptimal, inadequate or even deficient status in a range of micronutrients affects a significant proportion of the population.[33] Until 2015, Switzerland had no national survey to assess food consumption and diet quality, such as adherence to food-based dietary guidelines (FBDG). Until then, scientists and policy makers relied on national agricultural statistics, regional epidemiological studies and assessment of single nutrition-related items in the Swiss Health Survey. The first national nutrition survey menuCH was conducted in 2014–2015 to fill this gap.[76] menuCH data indicated that the vast majority of the Swiss adult population poorly adhered to the national dietary recommendations. The survey showed that less than one out of five Swiss residents met the fruit and vegetable guidelines and that dietary behaviors in Switzerland were far from optimal. Despite these facts, Switzerland is one of the few high-income countries unable to base its nutrition policies on national representative data on food consumption and eating behaviors.[77] For some of the nutrients relevant for a well-functioning immune system data on intake and status are available for select regions and/or population groups.

Comparison of Swiss Dietary recommendations with the actual food consumption

The daily national food-based dietary recommendations (left) compared to the actual food consumption (right)[77]



Vitamin D status largely depends on sun-exposure while dietary intakes of vitamin D contribute little. Publications on vitamin D show for the regions Vaud, Fribourg, Ticino, and the cities Lausanne and Basel partly report status levels that are in the insufficient/deficient range. In a report by the Federal Office of Public Health it is estimated that in Switzerland 40–50% of the population is vitamin D deficient.[78] Another publication, including a representative sample of 3,191 Swiss adults of three cantons with mean age 47 years, found that 11% had levels below 25 nmol/mL, i.e. severely deficient.[79] The study found that per 10 ng/mL increase in 25(OH)D levels, mortality from all-causes decreased by 20%. In a recent paper the vitamin D status in first trimester pregnant women was evaluated and the majority (73%) of the population studied were found to have low serum levels of 25(OH)D <50 nmol/l.[80] More importantly, severe vitamin D deficiency defined as 25(OH)D levels below 25 nmol/l was present in one third (34.2%) of all pregnant women. The mean 25(OH)D level of all Swiss pregnant women was 37±20 nmol/l. The CoLaus cohort including 3,856 representative participants of Lausanne aged 51 years on average, demonstrated that mean 25(OH)D levels were insufficient; 46±23 and 50±23 nmol/L in those who did and did not develop insulin resistance, respectively.[81] In 428 Swiss hospitalized patients, aged 85 year on average, 25(OH)D levels were 32±25 nmol/L, and 55% of the hospitalized patients were vitamin D deficient (<25 nmol/L) and 23% insufficient (25-50 nmol/L).[82]

Representative, recent data for vitamin C status are not reported for Switzerland;[83] however, as vitamin C levels fall fast with stress, infections and diseases vitamin C is taken up as nutrient of concern.

Blood levels of EPA and DHA are highly related to intakes[84] and global mapping indicates low or even very low blood levels of omega-3 fatty acids in a large proportion of people for whom data are available.[85] For Switzerland, the data show that the omega-3 fatty acids status in the population is in the insufficient range;[86] this is in accordance with menuCH that fish intake, especially fatty fish intake is below recommendation.

Results of Selenium status studies in Europe suggest suboptimal concentrations for populations in most of this region if 90 µg of Selenium/L of plasma.[87] Overall, the results indicate that 98.7 µg/L of Selenium in plasma or serum are required to optimize glutathione peroxidase (GPX) activity. A monitoring study of serum selenium concentration in the Swiss population was carried out on healthy blood donors from different regions of Switzerland. With a mean serum concentration of 98 µg /L the Selenium status of the healthy adults was in this range however with the lowest measured concentration of 62 µg /L this showed a large variation in Selenium levels.[88] A low level is a risk factor as higher Selenium status has been linked to enhanced immune competence with better outcomes for viral infections. These publications and data should probably be considered for Public Health strategies (enriching fertilization with Selenium)[89] although such measures are slow and need years to succeed; alternatively nutritional strategies may be proposed like the use of complements to support the population's health in the time of the coronavirus pandemic.

4. Recommendation of the expert panel for a well-balanced diet and suggestion for an optimal nutrient status

The Panel was clear that we are presently in a special and urgent situation because of the coronavirus pandemic. Data indicate that the Swiss population and in particular adults age 65 and older are at risk for suboptimal, inadequate or even deficient status for a number of nutrients that support our immune response, especially vitamin D, omega-3 fatty acids and selenium. The «crisis» requires prompt action to secure adequate nutrient status and replenish nutrient stores fast, which can only be achieved by complementing a well-balanced diet.

Given the importance of adequate supply with micronutrients as well as omega-3 fatty acids, the following recommendations to support the immune system were made:

- **Recommendation for a well-balanced diet**
  The Panel agreed to stress the recommendation to follow a well-balanced diet; this should be the first recommendation. However, to change nutritional habits on a population level is a difficult and long lasting endeavor and does not correspond to the urgency of a pandemic. Furthermore an optimal nutritional status is often not achieved without a complement. Therefore the Panel recommends a complement that should be added to the diet and fill the nutrient gap for the general population and especially for the adults age 65 and older. This complement is targeted to strengthen the immune system and has the following nutrients composition:

- **Vitamin C:** Supplementation with 200 mg/day is recommended.

- **Vitamin D:** 2000 IU (50 µg) per person and day; this is higher than the daily recommended intake (DRI = 800 IU) because this dose has demonstrated to reduce risk for respiratory tract infections (Martineau 2019). The dose is well within the safety range as the Upper Limit (UL) for vitamin D is 4000 IU/day and person.

- **DHA and EPA:** recommendation is 500 mg DHA and EPA per person and day to reduce inflammation risks.

- **Selenium:** 50 -100 µg per person and day as the Swiss population is low in selenium alike other European populations.

- **Zinc:** 10 mg per person and day as the Swiss population is low in zinc

5. A comprehensive approach for health in the Swiss population

This overview indicates that an optimal intake and status of micronutrients is a contributor to a well-functioning immune system. The data are not all very strong, but quality is sufficient to support conclusions by EFSA that some micronutrients matter to immunity. While vaccinations, treatments and social behavior rules are very important in dealing with the pandemic of SARS-CoV-2 they are either not yet existing or as a standalone approach insufficient. This is why public health risk assessments and management strategies are crucial. A possible risk management strategy is to strengthen efforts for a well-balanced and diverse diet. This long-lasting effort will not deliver fast results. This is why these efforts need to be complemented with a complement that ensures optimal intake of all these nutrients. A complement is a safe, effective and potential cost-effective way to fill the nutrient gap.

In view of the risk for a prolonged pandemic or a second wave of the coronavirus pandemic in fall or winter next to additional viral infection risks like common cold, flu and others, there is a responsibility for the individual but also for policy makers, Public Health and Nutrition authorities to act based upon the learnings from the current coronavirus pandemic and the science published. Therefore we recommend a nutrition policy approach as a management strategy for the COVID-19 pandemic while providing a complement to the entire population as an effective strategy to support a well-functioning immune system, and further protect the health of individuals and the society overall.

This **White Paper** is a short report on the role of nutrition and optimal nutritional status for a well-functioning immune system for communication to a broader audience and to stimulate actions by authorities; we note however that due to the recent onset of the pandemic, there is currently no clinical trial evidence available of the role of the nutrients with regard to COVID-19. However a scientific paper summarizing the referenced studies will follow as next step.

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Impressum

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