# Rachel Nicoll PhD – Written evidence (COV0049)

## Covid-19 in context

We will probably never be without COVID-19; indeed we are still living with two of the respiratory viruses from the three pandemics which have occurred in the previous 17 years (SARS, MERS and swine flu) [1]. Furthermore, we may never develop herd immunity or develop a safe and effective vaccine or drug for COVID-19 in time for winter; no drug or vaccine from the previous 3 pandemics has proved safe and effective or we would be using it now. With the winter COVID-19 second wave almost certainly on the way, not to mention the likelihood of future pandemics [2,3], it is imperative that we find a better way to protect ourselves.

## How COVID-19 affects the body

COVID-19 (or SARS CoV-2) is a multi-system inflammatory disease affecting principally the lungs, but can also target other organs. One of its main effects is to prevent red blood cells from carrying oxygen around the body, leading to dangerously low levels of oxygen, which cannot be resolved by ventilators, and the formation of blood clots. This leads on to lung tissue inflammation and pneumonia with acute respiratory distress syndrome (ARDS), while the blood clots damage the cardiovascular system. Death can occur not just from respiratory failure but also from sepsis and the excessive and uncontrolled inflammation, known as the 'cytokine storm'. [4-9]

Following COVID-19 infection, a person is most infectious/contagious during the first five days but symptoms, if any, tend to strike around the 10$^{th}$ day and sometimes as late as the 14$^{th}$ day [10]. This means that it is crucial to implement any protective measures well before we become symptomatic, when the disease is well entrenched in our body and we are likely to have already passed it on.

## Risk factors for severe COVID-19

The majority of cases of hospitalised COVID-19 are among the elderly; adults over 65 years of age represent 80% of hospitalisations and have a 23-fold greater risk of death than those under 65. Immune function declines with age, a condition known as immune senescence; for the same reason, vaccine responses are impaired in the elderly. Ageing also increases systemic inflammation, known as 'inflammaging'. [10-14]

The immune system is also impaired by the presence of other chronic diseases, particularly cardiovascular disease, obesity, type 2 diabetes, asthma, pulmonary disease, kidney disease and cancer, regardless of age [10,15-17]. These conditions are associated with a higher risk of severe COVID-19 and mortality and all are associated with increased inflammation, predisposing sufferers to the 'cytokine storm [18-22]. Researchers from Washington University School of Medicine, however, are finding that COVID-19 patients become seriously ill because their immune systems are under-functioning, while a joint US/Belgian study found that an immune-boosting drug restored inflammatory cells to a healthy level [23,24].

## The BAME community and COVID-19

Among ethnicities, the black, Asian and minority ethnic (BAME) communities suffer disproportionately from COVID-19 complications and mortality [25]. Many in this community are more prone to obesity, type 2 diabetes and cardiovascular disease, all risk factors for severe COVID-19. One explanation gaining traction is that the BAME community in the UK have much lower vitamin D levels, because

the screening effect of melanin pigment in darker skin means far stronger sunlight is required to make vitamin D from sun exposure [26,27].The Public Health England review into the reasons why the BAME community are disproportionately affected did not specifically review the role of diet and vitamin D, saying there was not enough evidence to support this. Similarly, the National Institute for Health and Care Excellence (NICE) recently published a review of vitamin D and COVID-19 and concluded that there was no evidence to support taking vitamin D supplements specifically to prevent or treat COVID-19. Although they recommend that the BAME community take 400IU/day vitamin D, this is for bone health and not for COVID-19 [28]. Several experts have taken issue with this approach, suggesting that boosting vitamin D levels is an obvious place to start [29,30]. Yet it now appears that 'UK scientists are to receive millions of pounds' to discover why the BAME community is at greater risk [31].

**The science so far ignored**

The Government, scientists and Public Health England have failed to mention that we have an immune system. Our immune systems have evolved highly effective mechanisms which, in a healthy state, can protect us from all viruses so far encountered; if this were not the case, the human race would now be extinct. Our immune system comprises the innate immune system, which carries out immune surveillance for pathogens and eliminates them using circulating macrophages, inflammatory cytokines and natural killer (NK) cells, and the adaptive immune system, which generates an immunological memory in the form of antibodies (immunoglobulins produced by B cells), memory T cells and NK cells [20,22,32].

Poor diet and lifestyle choices and lack of any effective advice or action from official sources have caused our immune systems to function sub-optimally, with increased susceptibility to all infections, particularly in those with COVID-19 risk factors. Other than to exercise and lose weight, there has been no recommendation on immune system support and no specific nutritional advice for those at risk. Yet there is evidence that patients with severe COVID-19 have depleted numbers of NK cells and other virus-attacking cells and their function is exhausted [33]. While a healthy diet and lifestyle might adequately support the immune system under normal conditions, it will be insufficient with the COVID-19 threat; supplementation will be required to increase blood levels of vital immune system micronutrients, particularly in the BAME community and those with COVID-19 risk factors. [10,20-22]

**What the science actually says**

There is a considerable volume of science showing how certain micronutrients, as well as dietary/lifestyle choices, can support the immune system and protect us from respiratory viruses in general [10,20]. The most essential of these micronutrients comprise vitamin C, vitamin D and zinc [34]; the first studies are now being published which suggest that these micronutrients could also protect us from COVID-19 or at least ensure that disease development does not progress to ARDS and the often fatal 'cytokine storm'. The European Food Safety Authority acknowledges these micronutrients are necessary for 'maintenance of functions of the immune system' [35]. The evidence for their protection against COVID-19 is set out in Annex A.

**Recommendations for the Government**

With no sign of a vaccine or drug solution in time for winter, I would propose:

1. That official guidance on personal immune system support is provided to the whole UK population, comprising, as a minimum, adequate supplementation with vitamins C and D and zinc.
2. To protect those at risk, including the BAME community and all healthcare workers, these key supplements are provided free of charge.

The organisation Frontline Immune Support for NHS Staff has crowdfunded the provision of key micronutrients, including liposomal vitamin C, vitamin D and zinc, to frontline NHS staff [36]. This level of support should be provided by government, not citizens' initiatives.

**Cost/benefit**
These micronutrients are very cheap. The cost of supplying them would be significantly lower than the cost of hospitalisation of further COVID-19 cases, particularly in intensive care. And it is impossible to put a price on the value of lives saved. The financial cost of the UK's vitamin D deficiency alone has been estimated at around £20 billion per annum, even prior to COVID-19.

At present, much of the UK population is in a state of fear and helplessness. These measures would foster a greater sense of safety and personal control among many, reducing mental health issues and giving people the confidence to venture out to resume normal life with the sense of optimism and positivity which is so badly needed to rebuild our economy.

## ANNEX A: Studies of micronutrients which can protect against COVID-19

### Vitamin C:

General immune protection:
Vitamin C has 11 antiviral mechanisms and should be the first line of defence against any viral disease, including COVID-19. Vitamin C enhances the immune system by stimulating leukocyte function, antimicrobial and natural killer cell activities and lymphocyte proliferation, thereby reducing replication of viruses and destroying them through generation of oxidative stress. Some trials show no effect on the cold virus but these findings can generally be explained by the low dose. Vitamin C deficiency is associated with increased susceptibility to infection but supplementation can reduce the severity of respiratory infections and help prevent ARDS and sepsis. Those with the highest vitamin C levels had a >40% lower risk of dying from respiratory disease, including pneumonia. However, the dose and delivery are important. The evidence for efficacy is greater and more consistent with an intake of at least 2g/day (the RDA is 400 mg/day, just enough to prevent scurvy). Prevention for COVID-19 will require a much higher dose, possibly up to 10g/day, which can enhance resistance to and improve recovery from more severe infectious diseases. [10,37-46]

COVID-19 protection and treatment:
Studies have shown that oral vitamin C can be used specifically in the prevention and treatment of COVID-19 [47,48]. Meta-analyses showed that oral vitamin C reduced the length of ICU stay and the duration on mechanical ventilation; the authors commented that given the insignificant cost of vitamin C, even a small reduction in ICU stay is worth exploring [49,50]. Oral liposomal vitamin C is best absorbed and should be taken in doses of at least 6g/day. The use of intravenous vitamin C has proved to be so effective against COVID-19 in China and US

hospitals that clinical trials are now underway [51,52]. For patients in critical care, the US Frontline COVID-19 Critical Care Alliance (FLCCC), designed the MATH+ Hospital Treatment Program, to treat COVID-19 patients in a state of hyperinflammation. They give 3g of intravenous vitamin C every 6 hours for up to 7 days, together with corticosteroids and anti-coagulants; they have reported zero COVID-19 deaths in their ICUs in those without end-stage co-morbidities [53-55].

**Vitamin D:**

General immune protection

Vitamin D can regulate both innate and adaptive immunity by stimulating dendritic cells (which detect the presence of viruses) and macrophages (which destroy pathogens) and aiding immune memory. It also regulates and suppresses the inflammatory cytokine response; this is particularly important for COVID-19, as the cytokine storm is a primary cause of death. A systematic review found that low vitamin D status was associated with increased risk of both upper and lower respiratory tract viral infections (COVID-19 is a lower respiratory tract infection), while a UK study found that Vitamin D deficiency is common in people who develop ARDS and appears to contribute to ARDS development. A 2019 meta-analysis of observational studies involving 20,966 patients found that those with vitamin D levels <50 nmol/l experienced a significantly increased risk of pneumonia and two further meta-analyses, the latest in 2017 comprising 25 trials and involving 11,321 subjects, found that vitamin D supplementation reduced the risk of acute respiratory tract infection, with improved results in those receiving daily or weekly oral vitamin D but not in those receiving infrequent very high doses. [10, 56-67]

COVID-19 protection and treatment

Several reports show that vitamin D deficiency is related to COVID-19 incidence, as well as mortality and severe disease. US, Belgian, Italian and Irish studies all found that testing positive for COVID-19, or developing ARDS, were independently associated with lower vitamin D levels [68-71]. A recent study of 20 European countries by Queen Elizabeth Hospital Foundation Trust found a correlation between level of vitamin D deficiency and COVID-19 related deaths and cases; the UK was among those countries with the greatest mean vitamin D deficiency [72]. Similarly, Israeli, US and Indonesian studies found that vitamin D status was strongly inversely associated with COVID-19 incidence, hospitalisation, prevalence in intensive care and mortality, respectively [73-76]. A US study found that vitamin D insufficiency prevalence in intensive care patients was 84.6%, vs. 57.1% in ward patients [74], while a UK study found that only 19% of intensive care patients had 25(OH)D levels greater than 50 nmol/L, compared to >39% in ward patients [77]. A joint US/Egyptian study found that mean serum vitamin D levels among COVID-19 patients was 22.9 nmol/L, well below the level required to avoid rickets, with lower levels correlating with a worse outcome [78], while a study from the Philippines showed that for each standard deviation increase in serum vitamin D levels, the odds of experiencing only mild COVID-19 rather than severe illness was 7.94 times greater and the odds of having a mild clinical outcome rather than a critical outcome was as high as 19.61 times greater [79]. Two reviews reported that vitamin D deficiency had been found to contribute to ARDS and was inversely correlated with CRP, the surrogate marker for the cytokine storm [80,81]; the authors recommended that at-risk individuals took 10,000 IU/day for a few weeks to raise vitamin D levels rapidly, followed by 5,000 IU/day, with the objective of raising vitamin D concentrations above 100-150 nmol/L. Two further

reviews confirmed that poor vitamin D status is also related to COVID-19 risk factors and complications [82] and recommend supplementation, principally to reduce the inflammatory reaction [83].

As at 3 August 2020, there were 23 vitamin D and COVID-19 studies registered on the US Clinical Trials website [84] and >10 Chinese clinical trials in progress on the use of vitamin D in COVID-19 [85]. One trial from Singapore, gave 1000 IU/day oral vitamin D3, 150mg/day magnesium and 500µg/day vitamin B12 to COVID-19 patients aged ≥50 who did not require oxygen on admission; in multivariate analysis, supplementation was associated with a significant reduction in the proportion of patients with clinical deterioration requiring oxygen support and/or intensive care support (17.6% versus 61.5%) [86]. Similarly, US researchers have successfully used several micronutrients for treatment, including vitamins C and D [87], while the MATH+ protocol, used in several US hospitals, includes 4000 IU/day vitamin D for both prevention and treatment [88,89].

A Dutch study [90] showed that UK serum levels average only 50nmol/l; since this is the average level, roughly 50% of the population will be below 50nmol/l. Although 50nmol/l is a level necessary to prevent rickets and osteomalacia, it is inadequate for immune system support; for this, experts believe that a level of 100-150nmol/l is necessary. It is hardly surprising that rickets has re-appeared in the UK [91]. Furthermore, the majority of those of South Asian or black ethnicity in the UK are either deficient or severely deficient [25,92]. The Dutch findings were confirmed by the Royal Society, which recommended that since vitamin D has an important regulatory role in the human immune system, the government provide a stronger public message about the importance of preventing Vitamin D deficiency and that hospitals consider assaying serum vitamin D levels in COVID-19 patients [93].

Current UK guidelines recommend supplementing 400 IU/day of vitamin D, whereas Europe and the US recommend 600 IU/day, with 800 IU/day for those aged >70 years, to achieve a 25(OH)D level of 50 nmol/l. There is a persuasive argument that the US recommendation of 600 IU/day came about as a result of a statistical error and should in fact be closer to 9000 IU/day [94]. Since many experts believe that 75 nmol/l is the minimum level for immune support, this makes the UK recommendation of 400 IU/day all the more inadequate, particularly for the BAME community. The recommendation for optimum immune support is 4,000 IU/day for adults to achieve a 75 nmol/l level, with the BAME community needing twice as much [95,96]. Daily doses of 10,000 IU and even 30,000 IU have been demonstrated to be perfectly safe by the European Food Safety Authority Panel [97]; infrequent very high doses are much less effective.

**Zinc:**

General immune protection

Zinc plays a crucial role in the function of all immune cells, with even a mild deficiency inducing cell-mediated immune dysfunction, decreasing immune response and increasing susceptibility to many infections. It has a strong anti-viral role and can impair viral replication, prevents the virus binding to mucosal cells and acts as an antioxidant and anti-inflammatory agent; it was effective against the 2003 SARS coronavirus [98]. Furthermore, the loss of taste and smell, commonly reported in COVID-19 patients, is a common symptom of zinc deficiency. Low dietary consumption of zinc has been found in almost half the older population. [10,98-101]

COVID-19 protection and treatment

One of the reasons for the potential success of hydroxychloroquine in treating COVID-19 is the fact that it is a zinc ionophore, i.e. a zinc transport molecule that helps zinc enter immune cells [102,103]. A trial of zinc, low dose hydroxychloroquine and azithromycin found that significantly fewer COVID-19 patients were hospitalised or died compared to an untreated group [104], while the addition of zinc to hydroxychloroquine and azithromycin resulted in increased frequency of being discharged home and reduction in mortality or transfer to hospice compared to no zinc [105]. The MATH+ protocol includes up to 100 mg/day of zinc for prevention and treatment [88,89].

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