COVID-19: Immune protection for the 2nd wave. An evidence-based guide

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Slides available on Coptic Medical Society website (https://copticmedical.com/)

Part I: Covid-19 in context

"We're not just fighting an epidemic; we're fighting an infodemic……This is a time for facts, not fear. This is a time for rationality, not rumours".

(Dr Tedros Adhanom Ghebreyesus, Director General, World Health Organisation)

Recent respiratory pandemics

- 1918 H1N1 virus, known as Spanish flu.
- 1957 H2N2 virus, known as Asian flu.
- 1968 H3N2 virus, still in circulation as a seasonal flu virus.
- 2003 Severe acute respiratory syndrome (SARS), also a coronavirus
- 2009 new H1N1 virus, known as Swine Flu originated in Mexico but spread globally. It contained a unique combination of influenza genes not previously identified in animals or people. Still in circulation as a seasonal flu virus.
- 2012 Middle East respiratory syndrome (MERS), also a coronavirus
- 2020 SARS CoV-2 (COVID-19)

Data extracted from the US CDC website https://www.cdc.gov/flu/pandemic-resources/basics/past-pandemics.html

An increasing number of viral pandemics in the future

- There is a roughly 650% annual increase in the number of epidemics in the last 20 years compared to the 200 prior years.
- The World Economic Forum predicts that epidemics will become more common with our increasingly connected age.
- The World Health Organisation (WHO) reports that there are 7,000 signals of potential viral outbreaks every month.
- The potential global hotspots are SE Asia, South America and West Africa. It is impossible to monitor all of these vast areas to a sufficient extent to halt the next pandemic in its tracks.
- It's a safe bet that we will have another viral pandemic fairly soon, possibly even before we have recovered from COVID-19.

(https://www.weforum.org/agenda/2020/03/coronavirus-global-epidemics-health-pandemic-covid-19/; Fan Y, Viruses, 2019; Wong ACP, Viruses, 2019; Song Z, Viruses, 2019; Dawson P, Vector Borne Zoonotic Dis, 2019)

‘Respiratory virus with human 'pandemic potential' found in pigs in China’

BBC News 30 June 2020 https://www.bbc.co.uk/news/health-53218704

Bubonic plague case: China takes precautions

(BBC News 6 July 2020 https://www.bbc.co.uk/news/world-asia-china-53303457)

We will have to live with COVID-19 and other viruses indefinitely

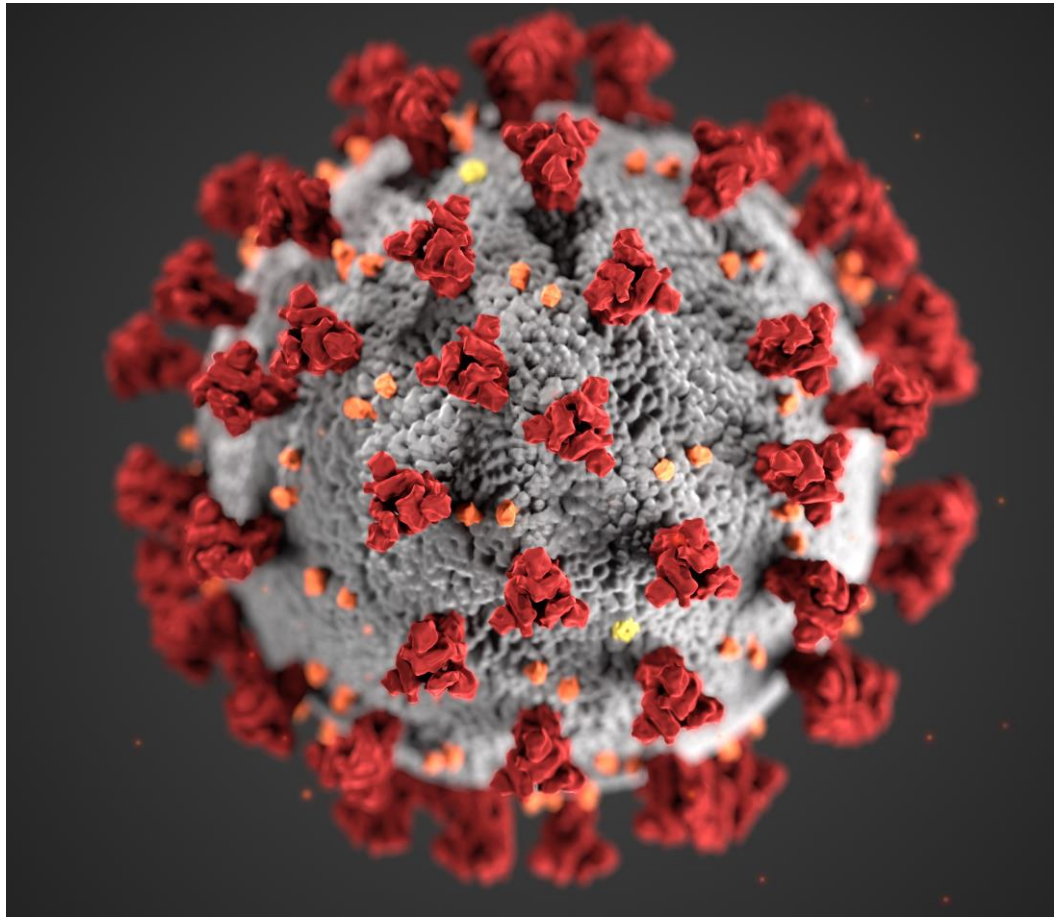
- A member of the UK government's Scientific Advisory Group for Emergencies (Sage) has said that COVID-19 will be present "forever in some form or another“ and that it would not be a disease like smallpox "which could be eradicated by vaccination".
- Scientists have consistently said that the total eradication of COVID-19 is technically impossible. We are still living with two of the respiratory viruses from the three pandemics which have occurred in the previous 17 years (MERS and swine flu).
- Many of these virus are still in circulation as seasonal flu; scientists seem to think this will be the case with COVID-19 as well.
- In Sir David Attenborough’s TV documentary, ‘Extinction: the facts’, a prominent scientist warned that there could be 5 new emerging diseases every year from places such as China.

(https://www.cdc.gov/flu/pandemic-resources/basics/past-pandemics.html; Sun H, Proc Natl Acad Sci U S A, 2020; BBC News 30 June 2020, https://www.bbc.co.uk/news/health-53218704).

And now we have COVID-19

- COVID-19 (or SARS CoV-2) is a type of coronavirus.
- Coronaviruses are so named for the appearance of spikes on the surface.
- There are many other types of coronavirus that can infect humans, including MERS, SARS and several varieties of common cold.

(https://www.cdc.gov/coronavirus/types.html)



Principal medical risk factors for COVID-19 or more severe COVID-19

- Age
- Asthma
- Pulmonary disease
- Smoking
- Cancer
- Obesity/metabolic syndrome
- Type 2 diabetes
- Cardiovascular disease, including hypertension
- Kidney disease

Most of these conditions are **inflammatory** and are **more prevalent with age**.

(Yannuck SF, Integr Med, 2020; Richardson S, JAMA, 2020; https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html;
Petrilli CM, https://www.medrxiv.org/content/10.1101/2020.04.08.20057794v1;

Other COVID-19 risk factors

- **The UK black, Asian and minority ethnic (BAME) community**: suffer disproportionately from COVID-19 complications and mortality. Many in this community are also more prone to obesity, type 2 diabetes and cardiovascular disease, all risk factors for severe COVID-19.
- Blood group: A Chinese study showed that blood group A was associated with a higher risk for acquiring COVID-19 compared with non-A blood groups, whereas blood group O was associated with a lower risk for the infection.
- Humidity: Dry air combined with cold temperature is known to enable viral transmission and is associated with impaired mucociliary clearance, innate antiviral defense and tissue repair function; viruses have greater stability at low temperatures. A US study showed that a drop in humidity in the prior weeks correlates most closely with the rise in influenza-related deaths.
- A US/Chinese study found that prior to lockdown, a one-degree Celsius increase in temperature reduces the R value by about 0.02 and a 1% relative humidity rise reduces the R value by about 0.008, i.e. high temperature and humidity reduce the transmission of COVID-19.

(Zhao J, https://www.medrxiv.org/content/10.1101/2020.03.11.20031096v2; Malhotra A, The Physician, 2020; Shaman J, PLoS Biology, 2020; Kudo E, PNAS, 2019 https://physicianjnl.net/index.php/phy/article/view/38Ho FK, https://www.medrxiv.org/content/10.1101/2020.04.28.20083295v1.full.pdf; Wang J, https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3551767; Herold T, https://www.medrxiv.org/content/10.1101/2020.04.01.20047381v2)

How COVID-19 affects the body in severe disease

- **Severe COVID-19 is a multi-system inflammatory disease.** It principally affects the lungs, but can also target the cardiovascular system, kidneys, skin and brain (bleeding, swelling). **Death can occur from acute respiratory distress syndrome (ARDS), sepsis and the excessive and uncontrolled inflammation, known as the 'cytokine storm'.**
- The virus 'spike' has an affinity for the angiotensin-converting enzyme (ACE) 2 receptor, present in lungs, blood vessels, gut and other organs, which it uses to gain entry to the body.
- In acute form COVID-19 presents as pneumonia with acute respiratory distress syndrome (ARDS) and possibly sepsis.
- Patients die of silent hypoxaemia (lack of blood oxygen) due to pulmonary perfusion, damaged haemoglobin and inhibition of haemoglobin transport; this means that red blood cells are prevented from carrying oxygen around the body, leading to dangerously low oxygen level, which cannot be resolved by ventilators.
- In addition there is abnormal coagulation, with microthrombi (tiny blood clots) damaging the cardiovascular system, kidneys, liver and gut. This leads on to lung tissue inflammation, which can lead to pneumonia and acute respiratory distress syndrome (ARDS).

(Li H, Lancet, 2020; Conti P, J Biol Regul Homeost Agents, 2020; Bellinvia S, Inflamm Res, 2020; Ragab D, Front Immunol, 2020; Cavezzi A, Clin Pract, 2020; Aygun H, Naunyn Schmiedebergs Arch Pharmacol, 2020)

Part 2: Our immune system

- Our immune systems have evolved highly effective mechanisms which, in a healthy state, can protect us from all the viruses we have so far encountered.
- If this were not the case, the human race would now be extinct.

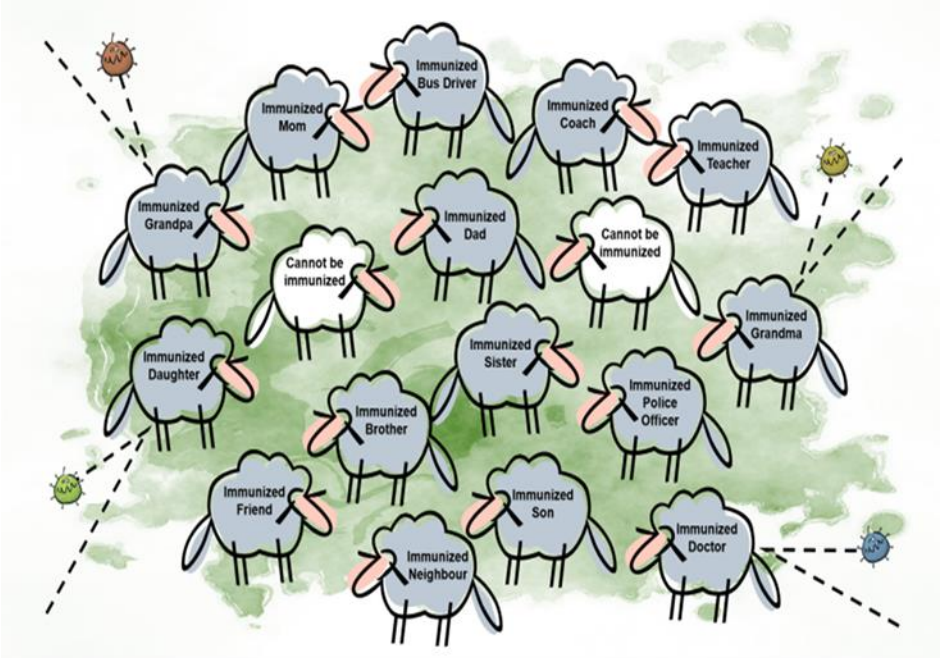
Immune system refresher

- The innate immune system carries out immune surveillance for pathogens and eliminates them using circulating macrophages, inflammatory cytokines and natural killer (NK) cells. Cytokines are cell signalling molecules, in this case encouraging inflammation.
- The adaptive immune system, which generates an immunological memory in the form of antibodies (immunoglobulins produced by B cells), macrophages, memory T cells and memory NK cells to every pathogen it encounters. This means that on detection of the same or a related pathogen, it can be destroyed quickly and effectively before it takes hold in the body.
- When the adaptive immune system is activated, antibodies mark the virus for destruction, macrophages destroy the virus in the circulation and T cells and NK cells destroy the virus within the cells in case the first two strategies have not worked.
- This is also the basis of vaccination, allowing a small amount of the virus to enter the body so that it's recognised as a pathogen and memory is formed by adaptive immune system cells.

(Calder P, BMJ Nutrition, Prevention & Health, 2020; Childs CE, Nutrients, 2019; Ratajczak W, Cent Eur J Immunol, 2018; Sun JC, Cold Spring Harb Perspect Biol, 2018; Vivier E, Science, 2011; Nikzad R, Sci Immunol, 2019)

Herd immunity

- Herd immunity occurs when a large portion of a community (the herd) becomes immune to a disease, making the spread of disease from person to person unlikely.
- As a result, the whole community becomes protected — not just those who are immune.
- The herd immunity threshold (HIT) is the proportion of the population that is capable of getting the disease in order for it to spread.
- Herd immunity is calculated using reproductive number (R), which is the estimated number of new infections that may occur from one infected person. R1 means that one person who's infected is expected to infect one other person; R <1 indicates that cases are declining while R >1 suggests that cases are on the rise.



How can we achieve herd immunity?

- Herd immunity can be achieved by vaccination or infection. However, there are huge uncertainties with both.
- Vaccines have successfully controlled deadly contagious diseases such as smallpox, polio, diphtheria, rubella and many others.
- Herd immunity can also be achieved by infection, when a sufficient number of people in the population have recovered from a disease and have developed antibodies and T cell immunity against future infection.

Part 3: So how can we protect ourselves?

Rachel Nicoll PhD, 2020

As he initiated lockdown, Boris Johnson said “We are shining the light of science on this invisible killer”.

What does the government's 'shining the light of science' actually entail?

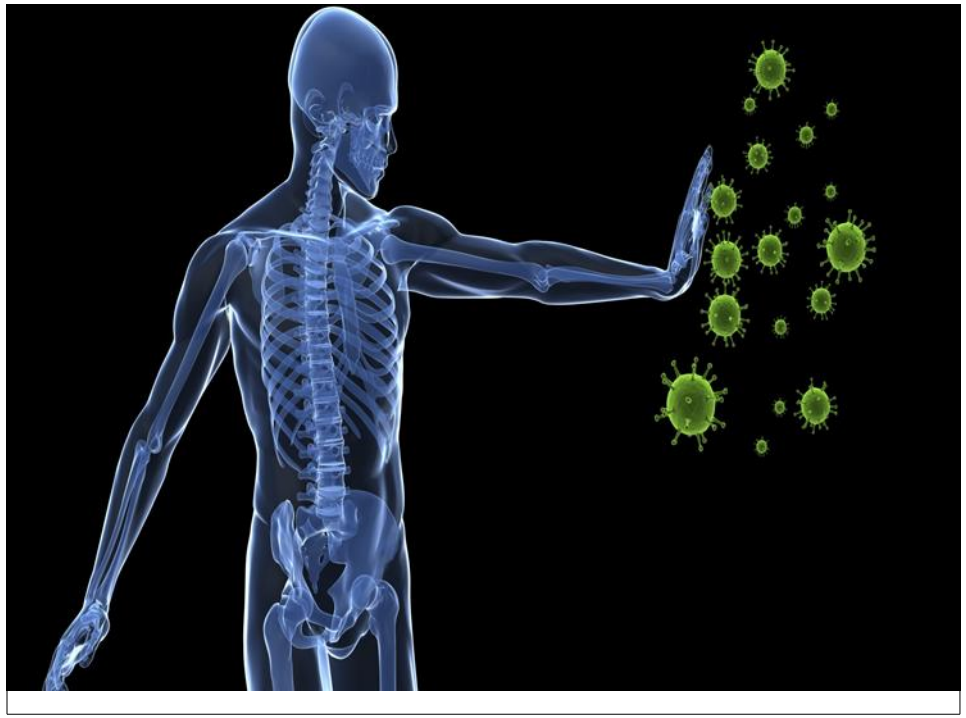
- So far, the protective measures recommended by all governments except Sweden include lockdown, self-isolation, quarantine, social distancing, masks, hand washing….
- And waiting for a safe and effective vaccine.
- Governments have no other strategy.

Can’t we just wait for a vaccine?

- We do not yet have a vaccine that is both safe and effective. We may never have one. No vaccine was ever successfully developed for any of the previous 21st century pandemics, such as SARS and MERS, because trials failed.
- Even if a vaccine is found to be both safe and effective, sufficient supplies will probably not be available until late 2021. We are not all miraculously going to be vaccinated on 1 March 2021 and life will return to normal.
- An expert group at the Royal Society has warned that even a safe and effective coronavirus vaccine will not return life to normal and we need to be realistic about what a vaccine can achieve.
- In any case, experts agree that vaccines on their own may not be enough to fight COVID-19. Just as not everyone is protected from the flu virus after vaccination, so not everyone may be protected from COVID-19.
- Furthermore, protection from some vaccines can wane over time. We don’t yet know whether 1 shot will be enough or whether boosters will be required.
- Vaccines typically have a poor response rate in the elderly, the group most at risk. Children can also have a paradoxical response.
- In any case, normal viral mutation will ensure that COVID-19 does not remain the same entity for long, rendering vaccines of less value over time unless they are continually updated.
- So there may be a safe and effective vaccine, but we shouldn’t count on it and we shouldn’t put our lives on hold waiting for it. And it likely won’t be sufficient to return life to normal.

So what about our immune system?

- Our immune system exists to protect us from all infectious organisms.
- There is an enormous amount of science showing that the immune system can be supported and boosted to protect against viral infections.
- The Government, scientists and Public Health England have completely failed to mention that we have an immune system which is capable of protecting us.
- So I am ‘shining the light of science’ on our wonderful virus-fighting immune system!



What can impair immune function?

- Diet (can also impact many COVID-19 risk factors): Too many carbohydrates and particularly too much sugar; not enough vegetables; not enough fibre; not enough quality protein; too many trans fats (in deep fried and processed foods); not enough healthy fats (omega-3s).
- Lifestyle: Smoking, excess alcohol, recreational drugs. Not enough exercise; but note that moderate exercise improves fitness and oxygen intake into the lungs, while intense exercise is pro-inflammatory.
- Poor sleep: Promotes inflammation and impairs T cell function.
- Chronic stress: An inflammatory condition
- Intestinal dysbiosis (too many pathogenic bacteria in the gut): It is thought that c70% of the immune system resides in the gut as gut-associated lymphoid tissue (GALT). Intestinal dysbiosis is always a source of inflammation.
- Sub-optimal intake of essential micronutrients: Vitamins A, B, C, D and E, zinc, magnesium, selenium, iron; omega-3 fats. Anyone eating a typical unhealthy Western diet can reasonably be assumed to have deficiencies in essential micronutrients!

(Calder P, BMJ Nutrition, Prevention & Health, 2020; Christ A, Immunity, 2019; Yannuck SF, Integrative Medicine, 2020; Wu HJ, Gut Microbes, 2012; Lazar V, Front Immmunol, 2018; Ibs KH, J Nutr, 2003; Childs CE, Nutrients, 2019; Wang T, J Immunol, 2004; Baeke F, Curr Opin Pharmacol, 2010)

So what can be done?

- Why do we need to support the immune system? Because there is evidence that patients with severe COVID-19 have depleted numbers of NK and other immune cells and their function is exhausted.
- However, most of the elements on the previous slide are under our control. We could all, even the elderly, have a healthy immune system if we paid attention to all the points on the slide.
- I'm focusing on the micronutrients vitamin C, vitamin D and zinc, which the European Food Safety Authority acknowledges are necessary for 'maintenance of functions of the immune system'.

(EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), Efsa J, 2016; Zheng M, Cell Mol Immunol, 2020).

Part 4: How to protect ourselves from COVID-19 (and what to do if infected)

- The first 5 days are when an affected person is most infectious; COVID-19 symptoms, if any, tend to strike around Day 10.
- By then the virus has gained a strong foothold in the body.
- This means that it is crucial to implement any protective measures well before we become symptomatic, when it may be too late.

Studies showing that vitamin C enhances the immune system

- Vitamin C has 11 antiviral mechanisms and should be the first line of defence against any viral disease. It affects the functions of phagocytes, production of interferon, replication of viruses and maturation of T-lymphocytes.
- It 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 little effect on the cold virus but these findings can generally be explained by the low vitamin C dose and the fact that requirement increases with infection; depletion of vitamin C levels in leucocytes is seen during colds and flu. Leukocytes normally have a more than 10-fold higher vitamin C requirement than other cells.
- 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. Vitamin C levels in coronavirus patients drop dramatically when they suffer sepsis. Furthermore, those with the highest vitamin C levels had a >40% lower risk of dying from respiratory disease, including pneumonia.
- A recent study showed depleted plasma vitamin C status (23 µmol/L) in 44 hospitalised patients with pneumonia, compared to healthy controls (56 µmol/L). The most severe patients in ICU had levels averaging 11 µmol/L, which is the level that defines scurvy.
- However, the dosage is 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).

(Yannuck SF, Integr Med, 2020; Hemila H,. Nutrients, 2017; Van Straten M, Adv Ther, 2002; Ran L, Biomed Res Int, 2018; Karlowski TR, JAMA, 1975; Hume R, Scott Med J, 1973; Anderson TW, Can Med Assoc J, 1974; Cathcart RF, Med Hypoth, 1971; Hemilä H, Nutrients, 2017; Carr AC, Nutrients, 2020 Myint PK, Eur J Clin Nutr, 2019; Deruelle F, J Altern Complement Med, 2008; Fujii T, JAMA, 2020; Fowler AA, JAMA, 2019; Kashiouris MG, Nutrients, 2020; Carr AC, Nutrients, 2017)

Low vitamin C levels in COVID-19-related ARDS and mortality

- A Spanish study found that in patients with COVID-19-related acute respiratory distress syndrome (ARDS), **vitamin C levels were undetectable in >90%** of the patients (Chiscano-Camon L, Crit Care, 2020).
- A US study found that among critically ill COVID-19 patients, **low vitamin C was a risk factor for mortality** (Arvinte C, Med Drug Discov, 2020).
- There have been suggestions that COVID-19 itself depletes vitamin C levels to induce **scurvy**. COVID-19 and scurvy have several common symptoms.

Studies showing that vitamin C is protective against any respiratory virus and pneumonia

- Vitamin C supplementation was effective in reducing pneumonia incidence, speeding up recovery and reducing mortality.
- An intake of 6 g/day has been shown to restore normal vitamin C levels in immune cells during colds, and studies have shown that the higher the dose, the greater the effect, with a 20% decrease in cold duration with 6 to 8 g/day. Furthermore, 46% of those taking 8 g/day in the first day of a cold report being symptom free after 24 hours.
- Meta-analyses show that in hospitalised patients, oral vitamin C can reduce the length of stay in intensive care 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'.
- Ideally, the dose should be titrated to 'bowel tolerance' levels. During a serious infection, most people can tolerate 1 g/hr without diarrhoea, giving a daily dose of >14 g/day.
- Studies are now showing that oral vitamin C can be used specifically in the prevention of COVID-19 and reviews are recommending vitamin C supplementation to protect against COVID-19.
- Oral vitamin C can suffer from poor absorption beyond a certain amount, but oral liposomal vitamin C is easily absorbed and can be taken in quantities approaching i/v vitamin C. Take in doses of at least 6g/day.

(Hemilä H, Nutrients, 2017; Jovic TH, Nutrients, 2020; Carr AC, Nutrients, 2020; Hemilä H, Nutrients, 2019; Hemilä H, J Intensive Car, 2020; Karlowski TR, JAMA, 1975; Hume R, Scott Med J, 1973; Anderson TW, Can Med Assoc J, 1974; Cathcart RF, Med Hypoth, 1971)

Studies showing the effectiveness of intravenous vitamin C treatment in reducing sepsis and mortality

- **Intravenous administration of vitamin C** helped reduce sepsis and reduce mortality (8.5% in those receiving vitamin C, compared with 40% of those who received no vitamin C).
- A meta-analysis of 12 trials with 1,766 patients in ICU found that vitamin C shortened ICU stay by 8%. Another meta-analysis of eight trials found that vitamin C shortened the duration of mechanical ventilation in critically ill patients.
- The mortality figure for those on ventilators released by the UK Intensive Care National Audit & Research Centre (ICNARC) recently puts it at 62%. Survival rates from sepsis in the acute and fatal phase of Covid-19 in both UK and New York Intensive Care Units run at a little over 50%.
- The use of intravenous vitamin C has proved to be so effective against COVID-19 in China and US hospitals that several clinical trials are now underway.

(Li R, Brief Bioinform, 2020; Colunga Biancatelli RML, Front Immunol, 2020; Liu F, BMJ Open, 2020; https://clinicaltrials.gov/ct2/show/NCT04264533; https://flccc.net/; https://www.evms.edu/covid-19/covid_care_for_clinicians/; https://www.evms.edu/media/evms_public/departments/internal_medicine/Marik-Covid-Protocol-Summary.pdf; Marik PE, Chest, 2017; Marik PE, Critical Care, 2018; Marik PE, World J Diabetes, 2020; Marik PE, J Thorac Dis, 2020)

Studies showing the effectiveness of i/v vitamin C as part of a protocol in treating COVID-19

- For hospitalised COVID-19 patients, the Frontline COVID-19 Critical Care Alliance (FLCCC) designed the **MATH+ Hospital Treatment Program**. They give 3,000 mg of intravenous vitamin C every 6 hours for up to 7 days, together with other drugs and micronutrients (further details after zinc). They have reported zero COVID-19 deaths in their ICUs in those without end-stage co-morbidities.
- Northwell Health in New York are now using intravenous vitamin C (1500 mg, 3-4 times daily) as a treatment for Covid-19 in addition to hydroxychloroquine, azithromycin and blood thinners. Early reports suggest that patients who received vitamin C did significantly better than those who did not receive vitamin C.
- A team at the Chelsea and Westminster Hospital added i/v vitamin C to the standard treatment package and reported a 21% lower mortality rate compared to the UK average of 40%, thus saving one in five lives; the study will be published soon (personal communication).
- Intravenous vitamin C is now included in the global REMAP-CAP study that is running controlled trials of possible treatments. The UK arm of the vitamin C trial is just getting underway at the Royal Surrey County Hospital. ICU patients (depending on their weight) will be getting around 3g intravenously four times a day for four days.

(Carr AC, Crit Care, 2017; de Grooth HJ, Chest, 2018; Hemilä H, Nutrients, 2019; Hemilä H, J Intensive Care, 2020; https://healthinsightuk.org/2020/08/28/there-is-a-case-for-treating-virus-victims-with-vitamin-c-say-uk-intensive-care-experts/; https://covid19criticalcare.com)

Studies showing that vitamin D is essential for an appropriate immune response (1)

- Vitamin D can regulate both innate and adaptive immunity; it suppresses the excess inflammatory cytokine response. The vitamin D receptor is expressed on both innate and adaptive immune cells.
- Vitamin D can reduce infection risk by lowering viral replication rates through the induction of antimicrobial peptides.
- Moreover, vitamin D is a key modulator of the renin-angiotensin system and may counteract the alteration in angiotensin-converting enzyme 2 (ACE2) activity, seen when COVID-19 binds to ACE2 receptors.
- Many studies have shown that Vitamin D deficiency not only impairs immune function but also promotes excessive inflammatory reactions. Deficiency is most common in older adults, those with darker skins and those taking statins.
- 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 can manifest as both).
- 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. A UK study found that Vitamin D deficiency is common in people who develop acute respiratory distress syndrome (ARDS) and appears to contribute to ARDS development.

References on next slide.

Studies showing that vitamin D is essential for an appropriate immune response (2)

- Two 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. Patients not receiving bolus doses (but lower daily or weekly doses) and who were very vitamin D deficient experienced the most benefit; those with baseline 25(OH)D of >25 nmol/L receiving regular supplementary vitamin D experienced a 70% lower risk of ARI.
- Review articles have found that vitamin D deficiency is associated with impaired pulmonary function, acute lung injury, increased incidence of viral and bacterial infections and inflammatory disease including asthma and COPD, while supplementation decreases the risk of acute respiratory distress syndrome (ARDS).
- The former US CDC Chief, Dr Tom Frieden, has gone on record as saying “Vitamin D reduces the risk of respiratory infection, regulates cytokine production, and can limit the risk of other viruses…Adequate vitamin D may potentially provide some modest protection [against cytokine storms in the] vulnerable”.
- Supplementation is more effective in those deficient in vitamin D or with a vitamin D receptor polymorphism impairing vitamin D absorption and metabolism, which is surprisingly common.

Gatera VA, Adv Pharmacol Sci, 2018; Yannuck SF, Integr Med, 2020; Manson JE, Metab Clin Exp, 2020; Zhou YF, Medicine, 2019; Jolliffe DA, J Steroid Biochem Mol Biol, 2013; Wei R, Nutrients, 2015; Martineau AR, BMJ, 2017; Chang SH, J Biol Chem, 2010; Sassi F, Nutrients, 2018; Bergman P, PLoS One, 2013; Dancer RC, Thorax, 2015; Wang TT, J Immunol, 2004; Baeke F, Curr Opin Pharmacol, 2010; Aygun H, Naunyn Schmiedebergs Arch Pharmacol, 2020; Daneshkhah A, Preprint medRxiv, 2020; Monlezun DJ, Nutrients, 2015; Parekh D, Inflamm Allergy Drug Targets, 2013; Grant WB, Nutrients, 2020 preprint, https://www.preprints.org/manuscript/202003.0235/v1; Meltzer DO, https://www.medrxiv.org/content/10.1101/2020.05.08.20095893v1)

Relevance of blood levels of vitamin D (serum 25(OH)D levels)

Table 1: Vitamin D thresholds[1,5,6]	
Serum 25OHD levels (nmol/l)	**Vitamin D status**
<30	Deficient
30–50	Insufficient (may be inadequate in some people)
>50	Sufficient

(Lips P, Eur J Endocrinol, 2019; https://www.nhs.uk/conditions/rickets-and-osteomalacia/; Malhotra A, The Physician, 2020; Patel JV, Int J Cardiol, 2013; https://royalsociety.org/topics-policy/projects/set-c-science-in-emergencies-tasking-covid/; Vieth R, Am J Clin Nutr, 2001; Cashman KD, Eur J Nutr, 2019)

An international study showed that UK serum levels average only 50 nmol/l; since this is the average level, roughly 50% of the population will be below 50 nmol/l.

The Royal Society has recommended that since vitamin D has an important regulatory role in the human immune system, the government should provide a stronger public message about the importance of preventing Vitamin D deficiency.

- Although 50 nmol/l is a level necessary to prevent rickets, it is inadequate for immune system support; for this, experts believe that a level of 100-150 nmol/l is necessary.
- It is hardly surprising that rickets has re-appeared in the UK.

The inadequacy of the UK vitamin D recommended daily allowance (RDA)

- Current UK guidelines: supplement 400 IU/day in order to achieve a level of serum 25(OH)D of 50 nmol/l.
- Europe and the US recommend 600 IU/day, with 800 IU/day for those aged >70 years to achieve the same level of 25(OH)D. Why the difference? And why does the UK not recommend a higher level for the elderly?
- It was shown some years ago that UK vitamin D deficiency is more prevalent in the BAME community. But virtually nothing has been done to correct this or even to publicise it. Where are the recommendations for increased vitamin D intake in the BAME community?
- There is a persuasive argument that the European/US recommendation of 600 IU/day came about as a result of a statistical error and should in fact be considerably higher.
- 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.

(Veugelers PJ, Nutrients, 2014; Webster C, Ann Clin Biochem, 2013)

Studies showing vitamin D deficiency in COVID-19 (1)

- UK, US, Belgian, Irish and 2 Italian studies all found that testing positive for COVID-19, or developing acute respiratory distress syndrome (ARDS), were independently associated with lower serum vitamin D levels. 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 in COVID-19 patients.**
- Similarly, Israeli and US studies found that **vitamin D status was strongly inversely associated with COVID-19 incidence, hospitalisation, prevalence in intensive care and mortality**, respectively. US studies showed that testing positive for COVID-19 is strongly and inversely associated with vitamin D levels, irrespective of ethnicity, sex or age.
- In a **prospective study**, patients who had a vitamin D level measured in the year before COVID-19 testing, the relative risk of testing positive for COVID-19 was 1.77 times greater for patients with vitamin D deficiency compared with patients with vitamin D sufficiency, while those who were tested up to 10 years previously, a significant association was seen between low vitamin D levels and the risk of Covid-19, with the highest risk observed for severe vitamin D deficiency.
- 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.
- A German study found that vitamin D levels <30 nmol/L was associated with a high risk of invasive mechanical ventilation (HR 6.12) and/or death (HR 14.73).

(References on next slide)

Studies showing vitamin D deficiency in COVID-19 (2)

- An Iranian study showed that COVID-19 patients with serum 25(OH)D of ≥75 nmol/L showed a marked reduction in clinical severity, inpatient mortality and inflammation. Fewer than 10% of patients aged >40 with vitamin D levels ≥75 nmol/L died compared to 20% who had vitamin D levels <75nmol/L. Similarly, a UK Biobank study found that vitamin D levels were associated with COVID-19 infection in univariate, but not multivariate, analysis.
- Conversely, a Korean study found that subjects with COVID-19 showed significantly lower vitamin D values than the healthy control group.
- Several reviews reported that vitamin D deficiency can contribute to ARDS and was inversely correlated with CRP, the surrogate marker for the cytokine storm. They recommend supplementation, principally to reduce the inflammatory reaction.
- **Overall 13 studies found that low vitamin D levels were associated with COVID-19 incidence and severity, with 1 showing the opposite.**
- Studies also show that **poor vitamin D status is related to many of the COVID-19 risk factors** (obesity, type 2 diabetes, cardiovascular disease). One review talks about the 'fatal relationship' between vitamin D deficiency and comorbidities in COVID-19 patients.
- Several experts are becoming increasingly more vocal in suggesting that **boosting vitamin D levels is an obvious place to start to protect against COVID-19**.

(Meltzer DO, https://www.medrxiv.org/content/10.1101/2020.05.08.20095893v1; Baktash V, Postgrad Med J, 2020; Carpagnano GE, J Endocrinol Invest, 2020; D'Avolio A, Nutrients, 2020; Meltzer DO, JAMA Netw Open, 2020; Hastie CE, Diabetes Metab Syndr, 2020; Kaufman HW, PLoS One, 2020; Im JH, Int J Infect Dis, 2020; De Smet D, https://www.medrxiv.org/content/10.1101/2020.05.01.20079376v2; Faul JL, Ir Med J, 2020; Ilie PC, Aging Clin Exp Res, 2020; Merzon E, FEBS J, 2020; Radujkovic A, Nutrients, 2020; Maghbooli Z, PLoS One, 2020; Danik JS, Curr Treat Options Cardiovasc Med, 2012; Vranic L, Medicina, 2019; Davies G, https://www.medrxiv.org/content/10.1101/2020.05.01.20087965v2.full.pdf; Grant WB, Nutrients, 2020; Arboleda JF, Front Immunol, 2020; Alipio M, https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3571484; Jovic TH, Nutrients, 2020; Afzal S, Lancet Diabetes Endocrinol, 2014; Daneshkhah A, https://www.medrxiv.org/content/10.1101/2020.04.08.20058578v4; Tang L, Sci Total Environ, 2021; Biesalski HK, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7276229/; Israel A, https://www.medrxiv.org/content/10.1101/2020.09.04.20188268v1?%253fcollection=; Brown RA, https://www.bmj.com/content/369/bmj.m2475/rapid-responses; Downing D, https://www.bmj.com/content/369/bmj.m2475/rr-11)

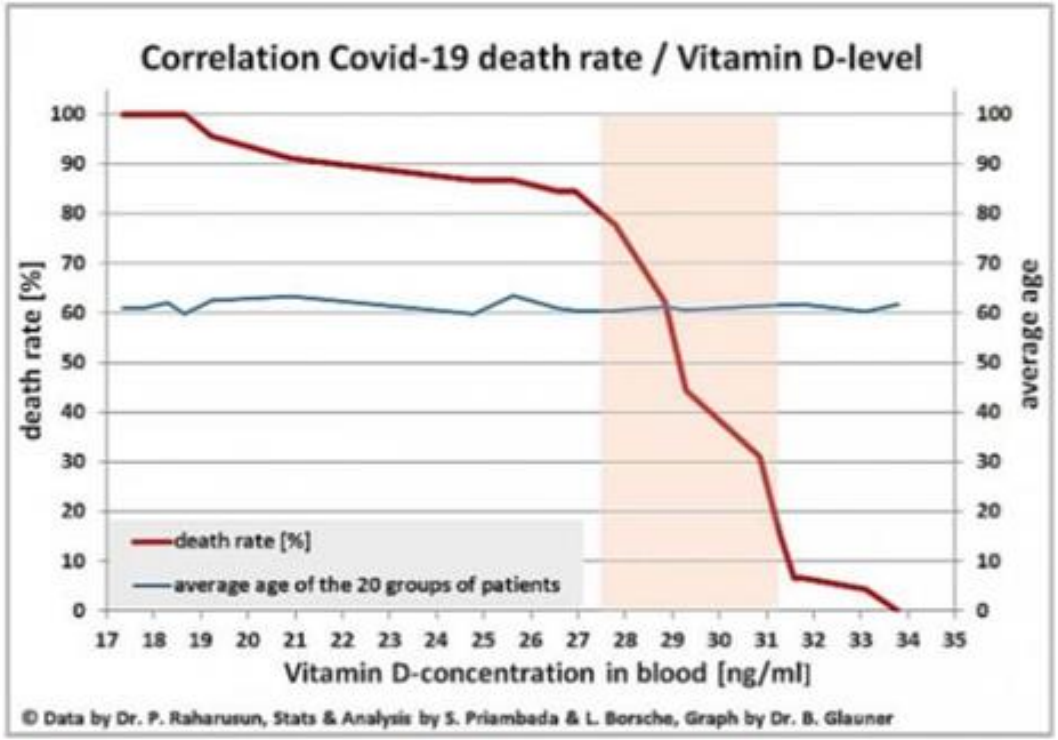
COVID-19 mortality and vitamin D status

An Indonesian study showed that:

- The majority of the COVID-19 cases with insufficient and deficient Vitamin D status died.
- The odds of death was higher in older and male cases with pre-existing condition and below normal Vitamin D levels.
- In multivariate analysis, Vitamin D status was strongly associated with COVID-19 mortality.
- Note that deaths start to reduce sharply at 27.5ng/ml (approx. 70nmol/L) but do not reach zero until around 35ng/ml (approx. 85nmol/L)

Similarly, an Italian study found that patients with severe vitamin D deficiency had a 50% mortality probability, while those with serum OH(25)D ≥25nmol/L had a 5% mortality risk.

(Raharusun P, https://emerginnova.com/patterns-of-covid19-mortality-and-vitamin-d-an-indonesian-study/; Carpagnano GE, J Endocrinol Invest, 2020)



Results of the age-adjusted clinical study by the working group of Dr. Prabowo Raharusun.

Vitamin D, COVID-19 and the BAME community

- The BAME community in the UK have much lower vitamin D levels, which is probably because the screening effect of melanin pigment in darker skin means far stronger sunlight is required to make vitamin D from sun exposure.
- The Public Health England recommendation is to take 400 IU/day vitamin D, but this is to avoid rickets and not for COVID-19.
- However, even if individuals in the BAME community take 400 IU/day vitamin D, they will fail to achieve even a blood level to avoid rickets.
- Yet it now appears that 'UK scientists are to receive millions of pounds' to discover why the BAME community is at greater risk.

(Grant WB, https://www.bmj.com/content/369/bmj.m1548/rr-22; Holick MF, Am J Clin Nutr, 2004; https://www.nice.org.uk/advice/es28/evidence/evidence-review-pdf-8777674477; https://www.bbc.co.uk/news/health-53565655)

Studies of COVID-19, vitamin D deficiency and the BAME community

- A study of UK NHS healthcare workers showed that those with vitamin D deficiency were significantly more likely to be from a BAME ethnic group. In multivariate analysis, **being a member of the BAME community was a significant independent predictor of vitamin D deficiency (OR 8·86; p<0·001).**
- All staff who had vitamin D deficiency were significantly more likely to experience symptoms of body aches and pains and vitamin D levels were also lower in those who had developed fever.
- Within the whole cohort there was an increase in COVID-19 antibodies (indicating prior infection) in those with vitamin D deficiency compared to those without vitamin D deficiency. Within the BAME male sub-group there was a significant increase in patients with antibodies in the vitamin D deficient group compared to the non-deficient group. This means that vitamin D deficiency is associated with prior COVID-19 infection and this is particularly marked in males from the BAME community with vitamin D deficiency, where 94% had antibodies compared to 52% in BAME males who were not vitamin D-deficient.
- Only vitamin D deficiency was a significant independent risk factor for developing COVID-19 antibodies (OR 2·6; p=0·002), i.e. a recent COVID-19 infection.
- Despite this, a UK Biobank study finding that ethnicity was only associated with COVID-19 infection in univariate, but not multivariate, analysis.

(Hastie CE, Diabetes Metab Syndr, 2020; Aduragbemi A Faniyi, https://www.medrxiv.org/content/10.1101/2020.10.05.20206706v1.article-metrics)

Vitamin D deficiency in severe COVID-19: what this means in terms of serum 25(OH)D levels

Table 1: Vitamin D thresholds[1,5,6]	
Serum 25OHD levels (nmol/l)	**Vitamin D status**
<30	Deficient
30–50	Insufficient (may be inadequate in some people)
>50	Sufficient

- A joint **US/Egyptian study** found that **mean serum vitamin D levels among COVID-19 patients was 22.9 nmol/L,** with lower levels correlating with a worse outcome (Munshi R, J Med Virol, 2020).

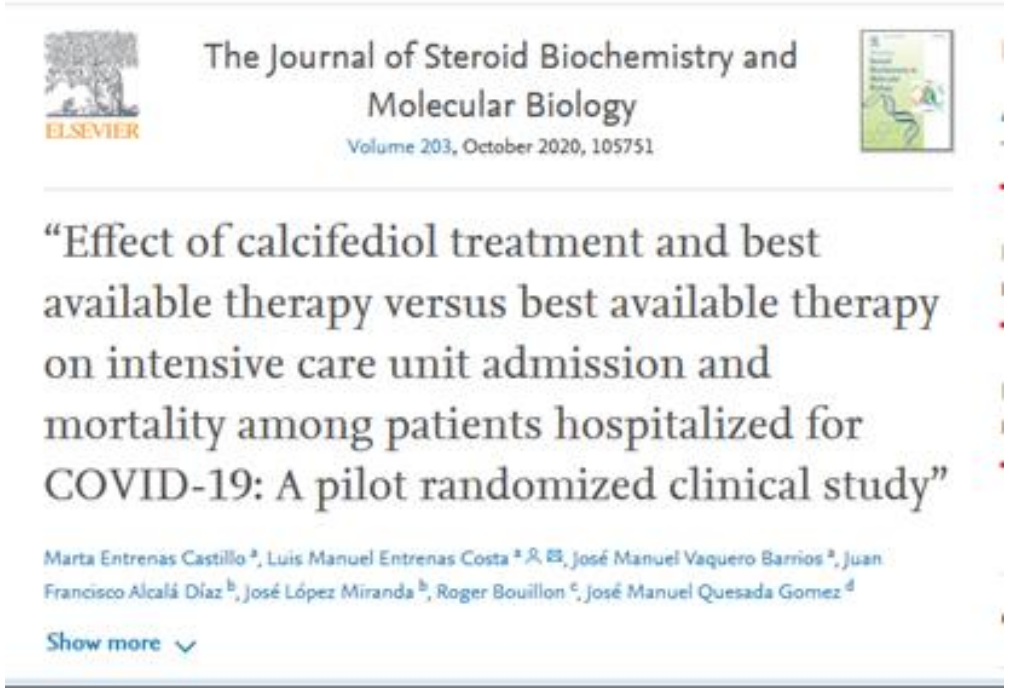
- A Irish study found that the patients who progressed to ARDS had a mean vitamin D level of 27 nmol/L, whereas those who did not progress to ARDS had a mean level of 41 nmol/L (Faul JL, Ir Med J, 2020).
- A US study found that vitamin D insufficiency prevalence in intensive care patients was 84.6%, vs. 57.1% in ward patients (https://www.medrxiv.org/content/10.1101/2020.04.24.20075838v1, Lau FH)
- A UK study found that the majority of COVID-19 inpatients had vitamin D insufficiency; 37% were deficient and 22% had severe deficiency (≤15 nmol/L). Only 19% of COVID-19 intensive care patients had vitamin D levels greater than 50 nmol/L, compared to >39% in ward patients. (Panagiotou G, Clin Endocrinol, 2020)

Studies showing effectiveness of vitamin D as part of a protocol for treatment of COVID-19

- There are now numerous clinical trials of vitamin D administration for COVID-19 registered on various clinical trial websites. We do not yet have results for these.
- A Singapore trial 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%).
- Similarly, US researchers have successfully used several micronutrients for treatment, including vitamins C and D, while the MATH+ protocol, used in several US hospitals, includes 4000 IU/day vitamin D for both prevention and treatment.

(https://clinicaltrials.gov/ct2/results?cond=vitamin+D+and+Covid-19; http://www.chictr.org.cn/showprojen.aspx?proj=51390; Wen Tan CW, https://www.medrxiv.org/content/10.1101/2020.06.01.20112334v2; Brownstein D, https://cf5e727d-d02d-4d71-89ff-9fe2d3ad957f.filesusr.com/ugd/adf864_cc5004cfa84a46d3b1a0338d4308c42c.pdf; https://www.evms.edu/covid-19/covid_care_for_clinicians/; https://www.evms.edu/media/evms_public/departments/internal_medicine/Marik-Covid-Protocol-Summary.pdf)

The first vitamin D randomised controlled trial that persuaded Matt Hancock to think again



The Journal of Steroid Biochemistry and Molecular Biology

Volume 203, October 2020, 105751

"Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study"

Marta Entrenas Castillo [a], Luis Manuel Entrenas Costa [a], José Manuel Vaquero Barrios [a], Juan Francisco Alcalá Díaz [b], José López Miranda [b], Roger Bouillon [c], José Manuel Quesada Gomez [d]

Show more

Castillo ME, J Steroid Biochem Mol Biol, 2020

- In addition to normal standard care (hydroxychloroquine and azithromycin), patients were randomised to calcifediol (a vitamin D analogue) or placebo.
- Those receiving vitamin D were given 106,400 IUs on admission, 53,200 IUs twice over the next week and 53,200 IUs weekly.
- 2% of patients given vitamin D had to be transferred to ICU versus 50% for controls. None given vitamin D died versus 8% of controls.

Hancock orders review into use of vitamin D
(Daily Telegraph digital edition 16 October)

- As a result of the Spanish trial, Matt Hancock was persuaded to meet David Davis MP (Con) and Dr Rupa Huq MP (Lab), both strong advocates of vitamin D supplementation.
- He has now ordered a review into the use of vitamin D for preventing coronavirus and is advising the public to supplement.
- However, there is no indication of dosage and no interest in using vitamin D to treat COVID-19, which the Spanish trial showed was effective.
- Queen Mary University of London is now undertaking a 6 month vitamin D trial over the winter.

Vitamin D dosage to achieve an adequate serum level

- An adult will need to take 4000 IU/day of vitamin D3 for 3 months to reliably achieve a 75 nmol/L level; the BAME community may need twice as much.
- Several papers have suggested upper limits of daily dosage, citing the UK Scientific Advisory Committee on Nutrition **(SACN) 2016 report**, which set the recommended upper level of intakes at 2000 IU/day, citing a 2006 study by Vieth *et al* showing toxic effect.
- However the Veith *et al* study actually states that toxicity may occur at 25(OH)D concentrations beyond 500 nmol/L, so this warning has been misquoted and has given rise to a lot of pointless restriction of vitamin D intake.
- You would need to take more than 30,000 IU/day for three months to reach a blood level of 500 nmol/L of vitamin D!
- 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; infrequent very high doses are much less effective.

(Veith R, Am J Clin Nutr, 2001; Vieth R, J Nutr, 2006; Cashman KD, Eur J Nutr, 2019; UK Scientific Advisory Committee on Nutrition (SACN) (2016) Vitamin D and Health. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/537616/SACN_Vitamin_D_and_Health_report.pdf; European Food Safety Authority Panel, Scientific Opinion on the Tolerable Upper Level Intake Level of Vitamin D; EFSA J, 2012)

Studies showing the need for magnesium to activate vitamin D

- Magnesium assists in the activation of vitamin D; enzymes that synthesise and metabolise vitamin D are magnesium dependent. Deficiency in either of these nutrients is associated with numerous disorders and magnesium deficiency is almost as widespread as vitamin D deficiency.
- As many as 50% of those taking vitamin D supplements may not get significant benefit as the vitamin D simply gets stored in its inactive form, and the reason for this is because they have insufficient magnesium levels. Those who do not take supplemental magnesium need, on average, 146% more vitamin D per day to achieve a healthy blood level of 100 nmol/L, compared to those who take at least 400 mg/day of magnesium along with their vitamin D supplement.
- Magnesium supplementation increased serum levels of vitamin D when baseline concentrations were close to 75nmol/L, but decreased it when baseline concentrations were up to 125nmol/L.
- Similarly, in healthy postmenopausal women with vitamin D deficiency, administration of 500mg/day magnesium for 6 weeks resulted in significantly increased vitamin D levels.

(Uwitonze AM, J Am Osteopath Assoc, 2018; Vázquez-Lorente H, Nutrients, 2020; Dai Q, Am J Clin Nutr, 2018; https://www.grassrootshealth.net/project/our-scientists/; Cooper ID, Open Heart, 2020)

Studies showing the effectiveness of magnesium for COVID-19 prevention and treatment

- Magnesium assists in the activation of vitamin D; 400 mg/day should be taken with the vitamin D supplement.
- A Singapore study supplemented COVID-19 patients with 1000 IU/day vitamin D, 150 mg/day magnesium and vitamin 500 µg/day vitamin B12. Fewer patients required oxygen therapy or transfer to intensive care.
- Several researchers have recommended supplementing magnesium with vitamin D to combat COVID-19.

(Wallace TC, J Am Coll Nutr, 2010; Tang CF, Eur J Pharmacol, 2020; Tan CW, https://www.medrxiv.org/content/10.1101/2020.06.01.20112334v2) https://med.umn.edu/news-events/magnesium-could-help-covid-19-patients-pre-existing-heart-conditions; Iotti S, https://www.jle.com/en/revues/mrh/e-docs/the_covid_19_pandemic_is_there_a_role_for_magnesium_hypotheses_and_perspectives_317129/article.phtml)

Studies showing that zinc is necessary for a healthy immune response

- Zinc is a cofactor in 3,000 proteins and 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 infections.
- One of zinc's critical roles in immune function is its role in thymulin production and activity. Thymulin is involved in T-cell differentiation and enhancement of T and natural killer cell actions.
- It has a strong anti-viral role, preventing the binding of viruses to mucosal cells, can impair viral replication, functions as a signalling molecule for T-cells and acts as an antioxidant and anti-inflammatory agent; it was effective against the 2003 SARS coronavirus.
- **Zinc deficiency** is a common condition in elderly and individuals with chronic diseases, two groups with more severe COVID-19 outcomes. Furthermore, the **loss of taste and smell, commonly reported in COVID-19 patients, is a common symptom of zinc deficiency**.
- The body does not store zinc, so it is important to consume it every day to meet the body's requirements; low dietary consumption of zinc has been found in almost half the older population.

(Yannuck SF, Integr Med, 2020; te Velthuis AJ, PLoS Pathog, 2010; Prasad AS. Adv Nutr, 2013; Ibs KH, J Nutr. 2003; Yu M, J Exp Med, 2011; Vogel M, https://www.medrxiv.org/content/10.1101/2020.10.07.20208645v1?%253fcollection=; https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional; https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=19&contentid=Zinc)

Studies showing the efficacy of zinc for COVID-19 prevention 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. Zinc is in fact largely insoluble and cannot easily enter through the cell wall, so a zinc ionophore is very helpful.
- Zinc is also critical to prevent against sepsis. During sepsis, zinc homeostasis is profoundly altered with zinc moving from the serum into the liver. Persistent low serum zinc is associated with recurrent sepsis in chronically ill patients
- It has been suggested that serum zinc could be useful as a diagnostic marker for evaluating the severity and predicting the outcome of sepsis.
- A Spanish study demonstrates that serum zinc levels <50 µ/dl at admission correlating with worse clinical presentation, longer time to reach stability and higher mortality.
- A trial found that 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.
- A US study found that the addition of 220 mg zinc sulphate (containing 50 mg elemental zinc) twice daily to hydroxychloroquine and azithromycin for five days gave COVID-19 patients a >50% increased frequency of being discharged home.
- The MATH+ protocol includes up to 100 mg/day of zinc for prevention and treatment.
- Note that zinc deficiency frequently occurs in elderly patients and in those with cardiovascular disease, chronic pulmonary disease or diabetes, all risk factors for COVID-19 and more severe COVID-19.

(Childs CE, Nutrients, 2019; Alker W, Nutrients, 2018; Hoeger J, PLoS One, 2017; Derwand R, Med Hypoth, 2020; https://www.evms.edu/covid-19/covid_care_for_clinicians/; te Velthuis AJ, PLoS Pathog, 2010; Carlucci PM, Preprint, 2020; https://www.evms.edu/media/evms_public/departments/internal_medicine/Marik-Covid-Protocol-Summary.pdf; Xue J, PLoS One, 2014; Scholz M, https://www.preprints.org/manuscript/202007.0025/v1; Carlucci P, https://www.medrxiv.org/content/10.1101/2020.05.02.20080036v1; https://www.sciencedirect.com/science/article/pii/S0306987720306435; Vogel M, https://www.medrxiv.org/content/10.1101/2020.10.07.20208645v1?%253fcollection=)

Quercetin: an alternative zinc ionophore with many anti-viral properties

- Quercetin is a plant flavonoid found mainly in fruits and vegetables. Anyone eating a typical Western diet will not be consuming much quercetin! It is a safe zinc ionophore, proven in many studies. It is currently being trialled as an alternative for hydroxychloroquine for COVID-19.
- Quercetin is also a potent antiviral and anti-inflammatory in its own right, inhibiting the release of pro-inflammatory cytokines. During the 2003 SARS outbreak, it was effective in blocking entry to the cells.
- Quercetin can also inhibit the proteolytic activity of the main protease found in coronaviruses; this has long been considered a potential treatment target but no drug has yet been developed to achieve this.
- Quercetin's antiviral capacity has been attributed to six main mechanisms of action:
  - Inhibiting the virus' ability to infect cells by transporting zinc across cellular membranes
  - Inhibiting viral replication in already infected cells
  - Reducing infected cells' resistance to treatment with antiviral medication
  - Inhibiting platelet aggregation (many COVID-19 patients suffer abnormal blood clotting)
  - Inhibiting excessive inflammation
  - Promoting action of interferons
- Quercetin is available in all health food stores and on line. 500-1000mg/day is safe and effective.

(References on next slide)

Studies showing the efficacy of quercetin for COVID-19 and other viruses

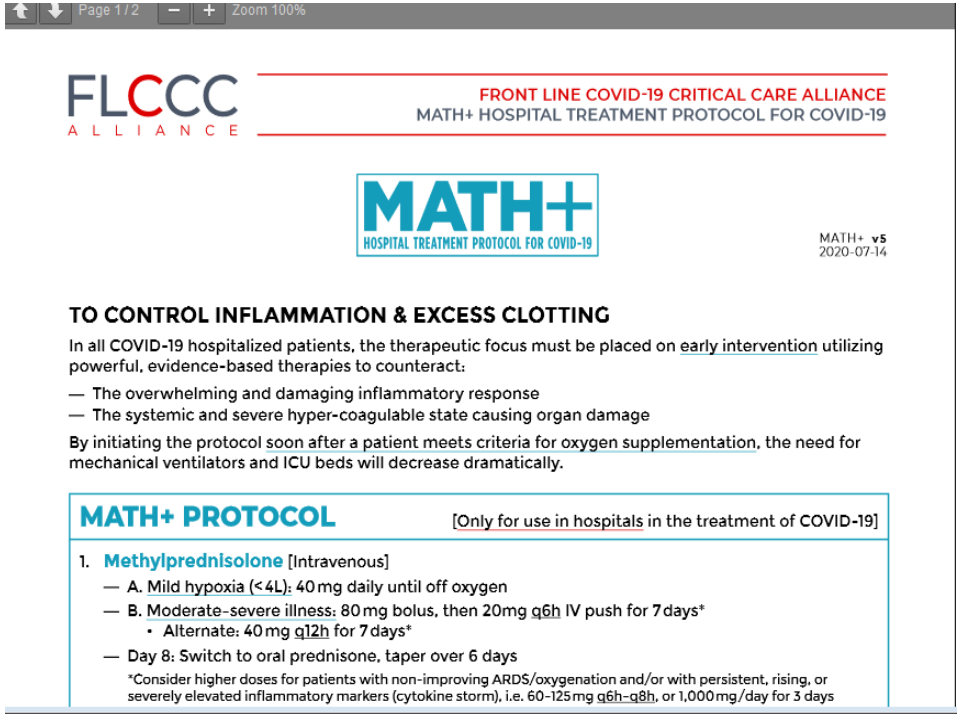
- A computer modelling study looked at small molecules capable of binding either to the COVID-19 spike protein or the ACE2 receptor to prevent the virus entering the cells. They found that quercetin was one of the most effective natural products.
- Numerous studies show its anti-viral properties through blocking entry of the virus into the body or inhibiting viral replication enzymes.
- Quercetin and vitamin C co-administration has a synergistic effect due to overlapping antiviral and immunomodulatory properties and the capacity of vitamin C to recycle quercetin, increasing its efficacy. Both are recommended in the FLCCC protocol.
- The Swiss Policy Research protocol effectively combines vitamins C and D, zinc and quercetin.

(Dabbagh-Bazarbachi H, J Agric Food Chem, 2014; Ryu YB, Bioorg Med Chem, 2010; Nguyen TT, Biotechnol Lett, 2012; Li Y, Nutrients, 2016; Tyzsér J, Mediat Inflamm, 2016; Yi L, J Virol, 2004; Khaerunnisa S, https://www.preprints.org/manuscript/202003.0226/v1; Smith M, https://s3-eu-west-1.amazonaws.com/itempdf74155353254prod/11871402/Repurposing_Therapeutics_for_COVID-19__Supercomputer-Based_Docking_to_the_SARS-CoV-2_Viral_Spike_Protein_and_Viral_Spike_v4.pdf; Yi L, J Virol, 2004; Chen L, Bioorg Med Chem, 2006; Chiow KH, Asian Pac J Trop Med, 2016; Colunga Biancatelli RML, Front Immunol, 2020; Nicolantonio JJ, Med Hypoth, 2020; https://swprs.org/a-covid-19-strategy/)

Frontline COVID-19 Critical Care Alliance (FLCCC)

- Developed by the Front Line COVID-19 Critical Care Working Group led by Dr. Paul Marik, chief of the Division of Pulmonary & Critical Care Medicine at Eastern Virginia Medical School Norfolk.
- The full protocol is found at https://covid19criticalcare.com
- The FLCCC protocol had a zero death rate in all patients without end-stage co-morbidities.

(Marik P, Expert Rev Anti Infect Ther, 2020; https://www.evms.edu/media/evms_public/departments/internal_medicine/Marik-Covid-Protocol-Summary.pdf)



Page 1 / 2 Zoom 100%

FLCCC ALLIANCE

FRONT LINE COVID-19 CRITICAL CARE ALLIANCE
MATH+ HOSPITAL TREATMENT PROTOCOL FOR COVID-19

MATH+
HOSPITAL TREATMENT PROTOCOL FOR COVID-19

MATH+ v5
2020-07-14

TO CONTROL INFLAMMATION & EXCESS CLOTTING

In all COVID-19 hospitalized patients, the therapeutic focus must be placed on early intervention utilizing powerful, evidence-based therapies to counteract:

— The overwhelming and damaging inflammatory response
— The systemic and severe hyper-coagulable state causing organ damage

By initiating the protocol soon after a patient meets criteria for oxygen supplementation, the need for mechanical ventilators and ICU beds will decrease dramatically.

MATH+ PROTOCOL [Only for use in hospitals in the treatment of COVID-19]

1. **Methylprednisolone** [Intravenous]
   — A. Mild hypoxia (<4L): 40 mg daily until off oxygen
   — B. Moderate-severe illness: 80 mg bolus, then 20mg q6h IV push for 7 days*
      • Alternate: 40 mg q12h for 7 days*
   — Day 8: Switch to oral prednisone, taper over 6 days

*Consider higher doses for patients with non-improving ARDS/oxygenation and/or with persistent, rising, or severely elevated inflammatory markers (cytokine storm), i.e. 60-125 mg q6h-q8h, or 1,000 mg/day for 3 days

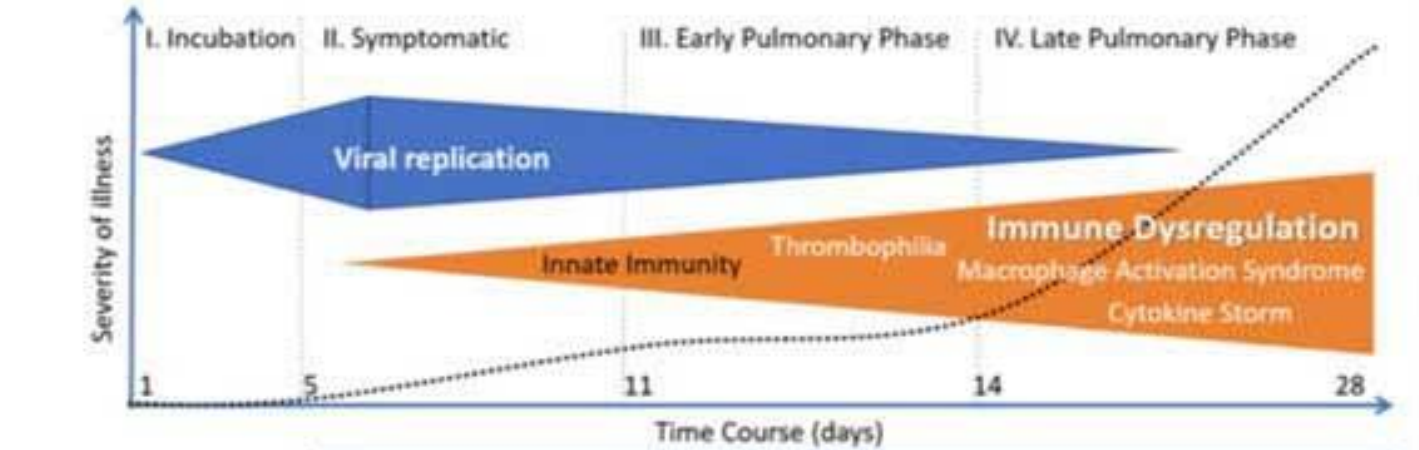
Principles underlying the MATH+ protocol

Recognition that a COVID-19 infection comes in two stages, each of which needs a different approach.

- Stage 1: The virus enters the body via the upper part of the throat (nasopharynx) where it starts multiplying rapidly; peak viral replication takes place at the earliest signs of symptoms. At this time, the focus should be on antiviral therapies and anti-inflammatories should be avoided. In this stage the immune system is under-functioning.
- Stage 2: Once oxygen saturation starts to decline, the disease has entered the stage where hyperinflammatory immune responses become apparent. At this point, anti-inflammatories are definitely required. In this stage the immune system is over-functioning.

Diagram taken from the FLCCC protocol https://covid19criticalcare.com

Figure 1. The course of COVID-19 and General Approach to treatment



Ground-glass infiltrates	+	++	+++ ++++
Clinical Symptoms	Fever, malaise, cough, headache, diarrhea	SOB – Mild hypoxia ≤4 L/min N/C & aSat < 94%	Progressive hypoxia
Treatment approach	Antiviral Rx	Anti-inflammatory: Immune Suppressive Rx	
Potential therapies	? Ivermectin	Methylprednisolone 40mg q 12 inc. to 80 mg q 12 if reqd.	
		Enoxaparin 60 mg/day	Enoxaparin 1mg/kg s/c q 12
	? Remdesivir (IV)		
	Vitamin C 500mg PO BID	Vit C 500mg PO q 6	Vitamin C 3g IV q 6

THIS IS A STEROID RESPONSIVE DISEASE:
HOWEVER, TIMING IS CRITICAL

The MATH+ protocol

- The MATH+ Protocol is designed to treat Stage 2 of COVID-19 infection —when the hyperinflammatory immune response sets in - but for best results, it must be administered early.
- There are several versions of the protocol as the team refined their understanding of COVID-19. This is the comprehensive version.
- Within 6 hours of hospital admission:
  - Intravenous methylprednisolone, to suppress the immune system and prevent organ damage from cytokine storms. For mild hypoxia, 40 milligrams (mg) daily until off oxygen; moderate to severe illness, 80 mg bolus followed by 20 mg per day for seven days. On Day 8, switch to oral prednisone and taper down over the next six days.
  - High-flow nasal oxygen to avoid mechanical ventilation that can damage the lungs.
  - Subcutaneous heparin (enoxaparin), to thin the blood and prevent blood clots. Give 40-60 mg daily until discharged.
  - **Intravenous vitamin C to control inflammation and prevent the development of leaky blood vessels in the lungs. Give 3g/100ml every six hours for up to seven days.**
  - **Zinc: 75-100 mg/day**
  - **Vitamin D3 20,000 – 60,000 IU single oral dose, followed by 20,000IU D3 weekly until discharged from hospital.**
  - **I/v Magnesium: 2g. Keep between 2.0 and 2.4 mmol/l. Prevent hypomagnesaemia (which increases the cytokine storm)**
  - Thiamine (vitamin B1) 200mg IV every 12 hours
  - Melatonin 6-12 mg at night
  - Famotidine (an antacid) 40mg/day (reduce dose with renal impairment)
  - Atorvastatin 80mg/day
  - Optional: Remdesivir, 200 mg IV loading dose D1, followed by 100mg day IV for 9 days
  - Broad-spectrum antibiotics if superadded bacterial pneumonia is suspected based on procalcitonin levels and resp. culture
  - Early noradrenaline for hypotension.

The FLCCC COVID-19 'At Home' protocol for mildly symptomatic patients (Stage 1)

- The 'At Home' protocol comprises:
  - Vitamin C — 500 mg/day
  - Zinc — 75-100 mg/day (acetate, gluconate or picolinate). After one month, reduce the dose to 30-50 mg/day
  - Quercetin — 250 mg/day to 500 mg/day
  - Melatonin (slow release) — Build up to 6-12mg at night
  - Vitamin D3 — 2,000 to 4,000 IU/day
- There are also some optional drugs, including aspirin: 20-40 mg/day.
- If treating COVID-19 at home, it is important to measure **oxygen saturation** regularly. If it drops to <94% when sitting or walking, it's time to go to the hospital.

(https://www.evms.edu/media/evms_public/departments/internal_medicine/Marik-Covid-Protocol-Summary.pdf)

Swiss Policy Research protocol

Prevention

Zinc: 50-100 mg/day

Quercetin: 500-1000 mg/day

Bromhexine (a mucolytic): 25-50 mg/day

Vitamin C: 1000 mg/day

Vitamin D: 2000 IU/day

Early treatment

Zinc: 75-150 mg/day

Quercetin: 500-1500 mg/day

Bromhexine: 50-75 mg/day

Vitamin C: 1000mg/day

Vitamin D: 4000 IU/day

Hospital treatment

Hydroxychloroquine: 400 mg/day

High-dose vitamin D (1 x 100,000 IU)

Azithromycin (up to 500 mg/day)

Heparin (usual dosage)

https://swprs.org/on-the-treatment-of-covid-19/

‘President Trump well enough to return to work’

The President's treatment protocol has reportedly included vitamin D and zinc.

Frontline Immune Support for NHS Staff

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 (www.frontlineimmunesupport.com).

Conclusion (1)

- We may never develop herd immunity or develop a safe and effective vaccine for COVID-19, at least for some considerable time. It will take a very long time to vaccinate everyone and it won't work for everyone (including the elderly, who are most at risk) and may wear off over time.
- With the prospect of further lockdown, it is imperative that we find a better way to protect ourselves.
- We will have to live with COVID-19 indefinitely, as we have had to live with many other viruses. This will be the case even if a safe and effective vaccine is found. Even when the COVID-19 pandemic passes, it is certain that there will be other viral epidemics in the near future.
- Scientific, medical and government advice has completely ignored our immune system, which is highly effective at protecting us from viruses, provided it is functioning optimally.
- Immune function can be impaired by 21st century lifestyles and particularly lack of the essential micronutrients vitamins C and D and zinc. These micronutrients, with the addition of quercetin and magnesium, are highly effective in protecting against and treating COVID-19.

Conclusion (2)

- The BAME community is particularly at risk for COVID-19.
- My recommendations to the House of Lords Science and Technology Committee were:
  - 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.
  - To protect those at risk, including the BAME community and all healthcare workers, these key supplements should be provided free of charge. Key micronutrients, as provided by Frontline Immune Support for NHS Staff should be given out by government, not citizens' initiatives.
- 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.

Summary of supplement recommendations for COVID-19 prevention and initial treatment

- Vitamin C: Minimum 2g/day, increasing with symptoms to 'bowel tolerance' until symptoms disappear. Liposomal vitamin C is much better absorbed and approximates to the effect of intravenous vitamin C.
- Vitamin D: Minimum 4000 IU/day, increase with symptoms. Smaller daily doses are more effective that weekly very high doses.
- Zinc: Minimum 30mg/day, increasing with symptoms up to 100mg/day.
- Magnesium: 400 mg/day.
- Quercetin: 500-1000 mg/day increasing to 1500 mg/day with symptoms.