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Supplementation of the population during the COVID-19 pandemic with vitamins and micronutrients – how much evidence is needed?

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a global pandemic with severe respiratory disease and high morbidity and mortality [1]. In turn, there has been an unprecedented research effort to improve the understanding of pathophysiological mechanisms, risk factors, diagnostic tests, and measures for effective prevention and treatment of COVID-19. Age and age-related vulnerabilities – such as malnutrition and frailty – have emerged as the major risk factors for adverse clinical outcome and mortality in patients with COVID-19 [2]. Higher age is a general risk factor in most illnesses, but it is possible that the high fatality rate among the elderly frail population may be explained – at least in part – by deficiencies in specific vitamins and micronutrients, which are vital for a well-functioning immune system.

Over the last decades, many preclinical and observational studies have provided evidence that vitamins and micronutrients play an important role in the efficient functioning of the immune system. As a consequence, deficiencies in these vitamins and micronutrients may reduce the immune response of patients and increase their vulnerability to infections and to have more severe courses once infected. Vitamin C, for example, is an essential vitamin that cannot be synthesised by humans as a result of loss of a key enzyme in the biosynthetic pathway [3]. Severe vitamin C deficiency results in scurvy, which is characterised by weakening of collagenous structures, poor wound healing and impaired immunity with high susceptibility to fatal infections such as pneumonia [4]. Similarly, vitamin D has been shown to influence susceptibility to and severity of infection via multiple mechanisms with a direct impact on production of the antimicrobial peptide cathelicidin and different cytokines via the innate and adaptive immune system, as well as via the NFκB (nuclear factor kappa-light-chain-enhancer of activated B-cells) pathways [5].

One straight-forward "public health" approach would be to start vitamin and micronutrient supplementation of the entire population at risk to reduce the risk for deficiencies and thereby reduce vulnerabilities. Such an approach may be most suitable for interventions with high clinical efficacy, a high proportion of the population showing benefit, proof of safety and overall low treatment costs. Recently, several researchers from Switzerland have published a call for action to consider supplementation of high-risk groups with micronutrients and vitamins as a strategy to diminish adverse health consequences of COVID-19 in the Swiss population [6]. Clearly, supplements and vitamins are over-the-counter medications with excellent safety data and relatively low treatment costs. Still, to be a valuable public health strategy, evidence of clinical efficacy of broad vitamin and micronutrient supplementation of the population in question is needed. Whether this is the case for vitamins and micronutrients in the face of the COVID-19 pandemic needs further exploration and will be discussed in this brief review.

Deficiencies of specific micronutrients and risk of infections

There is evidence from preclinical and observational clinical studies that specific vitamins and micronutrients play a major role in immunity, and that deficiencies are related to higher risks for infection and adverse clinical outcomes [6]. Indeed, there is wide consensus about the importance of several vitamins (vitamins A, B_6, B_9, B_{12}, C, D and E), trace elements (zinc, iron, selenium and copper) and omega-3 long-chain polyunsaturated fatty acids (n-3 PUFA) for a well-functioning immune system [7]. As yet, these relationships are best documented for vitamin D and vitamin C [3–5]. Because deficiencies in vitamins and micronutrients are rarely isolated, but mostly in conjunction with general malnutrition and thus deficiencies in multiple nutrients, interpretation of studies regarding single compounds is challenging.

Vitamin D deficiencies in Switzerland

In Switzerland, there is a high number of patients with vitamin and micronutrient deficiencies, particularly among the elderly population. It has been estimated by the Swiss Federal Office of Public Health that large parts of the Swiss

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population have inadequate serum 25-hydroxy-vitamin D (25(OH)D) concentrations, particularly among the elderly, frail population. For example, a recent clinical multicentre study found that 60% of multimorbid medical inpatients had deficient vitamin D levels (<50 nmol/l) on admission and 25% were severely deficient (<25 nmol/l) [8]. In this study, vitamin D deficiency was associated with a 30% increase in mortality risk in a statistical regression model adjusted for demographics and comorbidities. Similar to other observational studies, however, the study could not allow causal inference and thus provide proof that supplementation with vitamin D would be effective in reducing excess mortality in patients with deficient levels. Several other studies have also confirmed that the vitamin D status of the Swiss population is inadequate for vulnerable populations groups (e.g., pregnant women, older adults, multimorbid patients), particularly during the winter season. For other vitamins and micronutrients, intake and levels in the general population have not been studied extensively recently.

Evidence from observational trials

In light of their important role regarding immune function, deficient levels of specific vitamins and micronutrients may increase the risk of acquiring an infection and of adverse outcome among infected patients. Most research looking at associations of vitamin and micronutrient deficiencies and clinical outcome was done in the years before COVID-19; however, today there are also several studies investigating levels of vitamins, mainly vitamins D and C, in COVID-19 patients. Table 1 provides an overview of currently published observational studies (upper part of the table) on the association of vitamin and micronutrient deficiencies and clinical outcomes in the population of patients with COVID-19. These studies, from several countries, suggest that for COVID-19 such associations are also present, particularly for vitamins D and C, although there is some heterogeneity among studies and some studies have not reported significant findings. This heterogeneity may be due to various reasons including differences in patient populations, differences in analytical methods, low number of patients in some studies (resulting in low power) and differences in outcomes assessed. As an important limitation of all observational research, levels of vitamins and micronutrients are strongly correlated with age, malnutrition and burden of chronic illnesses, and confounding is a major issue in this type of observational research.

Table 1: Overview of recent trials investigating the role of vitamins and other micronutrients in patients with COVID-19.

First author [Reference]	Study design	Sample size	Location	Investigated nutrient	Intervention	Treatment outcome
Arvinte [9]	Observational	21	USA	Vitamin C and vitamin D	None	↓serum levels of vitamin C and vitamin D in most critically ill patients. Older age and ↓vitamin C level appeared co-dependent risk factors for mortality
Ling [10]	Observational	444	UK	Vitamin D	None	Cholecalciferol booster therapy was associated with a reduced risk of COVID-19 mortality
Mendy [11]	Observational	689	USA	Vitamin D	None	Vitamin D deficiency was associated with hospitalisation and/or disease severity
Merzon [12]	Observational	782	Israel	Vitamin D	None	Low plasma 25(OH)D levels appeared to be an independent risk factor for COVID-19 infection and hospitalisation
Raisi-Estabragh [13]	Observational	1326	UK	Vitamin D	None	No important relation between the 25(OH)D status adjusted for the season and COVID-19 positivity
Chiscano-Camon [14]	Observational	18	Spain	Vitamin C	None	Undetectable vitamin C in more than 90% of the patients with ARDS
Hastie [15]	Observational	449	UK	Vitamin D	None	No potential link between vitamin D concentrations and risk of COVID-19 infection
Carpagnano [16]	Observational	42	Italy	Vitamin D	None	Significantly greater mortality risk due to COVID-19 in patients with severe vitamin D deficiency
Fasano [17]	Observational	105	Italy	Vitamin D	None	COVID-19 patients were more likely to be vitamin D non-supplemented than unaffected patients
Tan [18]	Observational	43	Singapore	Vitamin D, magnesium, vitamin B_{12}	None	A vitamin D / magnesium / vitamin B_{12} combination in older COVID-19 patients was associated with a significant reduction in the proportion of patients with clinical deterioration requiring oxygen
Jamali Moghadam Siahkali [19]	Randomised controlled trial	60	Iran	Vitamin C	1.5 g vitamin C intravenously every 6 h for 5 days vs placebo	No significantly better outcomes in high-dose vitamin C treated patients
Zhang [20]	Randomised controlled trial	54	China	Vitamin C	High-dose intravenous (24 g/d) vitamin C vs. placebo	No change in ventilation-free days; ↑PaO_2/FiO_2; ↓interleukin-6; ↓28-day mortality in patients with SOFA scores ≥3
Thomas [21]	Randomised-controlled trial	214	USA	Vitamin C and zinc	10 days of zinc gluconate (50 mg), ascorbic acid (8000 mg), both agents or standard of care	No difference in the duration of symptoms among the four groups
Entrenas Castillo [22]	Randomised-controlled trial	76	Spain	Vitamin D	Oral calcifediol at an initial dose of 0.532 mg, followed by 0.266 mg on days 3 and 7, and then weekly	Administration of a high dose of calcifediol or 25(OH)D significantly reduced the need of hospitalisation in patients with COVID-19
Murai [23]	Randomised-controlled trial	240	Brazil	Vitamin D	Single oral dose of 200,000 IU of vitamin D_3 vs placebo	A single high dose of vitamin D_3 did not significantly reduce hospital length of stay compared with placebo

25(OH)D = 25-hydroxy vitamin D; ARDS = acute respiratory distress syndrome; PaO_2/FiO_2 = ratio of arterial oxygen partial pressure to fractional inspired oxygen

Evidence from treatment trials

Clearly, observational studies are prone to bias, and interventional research is needed to understand clinical effects of vitamins and micronutrients – including the effect size and potential side effects. Among the different vitamins and micronutrients discussed, vitamin D and vitamin C had been studied most extensively regarding their role in the management of respiratory tract infections in the years before COVID-19 and generated the strongest evidence regarding efficacy and safety. A Cochrane meta-analysis focusing on the role of oral vitamin C for the prevention and treatment of common colds, which was updated in 2020 with a total of 30 randomised and nonrandomised trials, reported no consistent effect of daily supplementation with vitamin C in large doses to prevent colds, but modest benefits in reducing duration of cold symptoms [24]. The effect was more consistent in subjects on continuous supplementation and in those performing strenuous exercise. For vitamin D, a very recent updated systematic review and meta-analysis of individual participant data in 2021 investigated the effects of supplementation to prevent acute respiratory tract infections based on 43 eligible randomised controlled trials and a total of 48,488 participants [25]. According to the analysis, vitamin D supplementation reduced the relative risk of acute respiratory tract infection by about 8% (61.3% vs 62.3%) with the strongest effects in patients receiving daily or weekly boluses. There is also interventional research showing that a nutritional support strategy including micronutrients among other reduces adverse outcomes and mortality among malnourished patients [26], but it remains unclear whether micronutrients or support with protein and calories was the main driver of effects.

Most importantly, a number of randomised controlled trials have recently investigated effects of vitamin C and vitamin D supplementation and/or treatment on the risk for COVID-19 infection, as well as treatment courses of infected patients (table 1, lower part). These trials, however, ranging from 54 to 240 patients, did not report significant benefits except for one very small Spanish pilot study [22]. This parallel pilot randomised open-label, double-masked clinical trial found significant differences in the risk for intensive care unit (ICU) admission of patients receiving vitamin D vs not receiving vitamin D (50% vs 2%). None of these trials selected patients with deficient vitamin D levels before beginning the supplementation, the group of patients most likely to benefit from treatment.

Clearly, there are today insufficient data from randomised trials regarding the clinical benefits of vitamin and micronutrient supplementation overall, and more specifically regarding COVID-19. Importantly, however, when looking at the trial registration database (https://clinicaltrials.gov/), there is a high number of registered trials currently planned or ongoing (table 2), which will likely improve our understanding of the role of vitamins and micronutrients in the near future and provide more definite evidence regarding clinical benefits.

Conclusions and implications for patient care

Before answering the question regarding usefulness of supplementation of the population during a pandemic with vitamins and micronutrients as a public health strategy to reduce COVID-19 associated morbidity, it is important to define the level of evidence that is needed. Although there is evidence from preclinical and observational studies linking different vitamins and micronutrients to a well-functioning immune system, interventional research has been rather disappointing and/or lacking. A major problem is the fact that previous trials did not select patients according to the degree of deficiency, and a beneficial effect of supplementation in a person with normal or high levels cannot necessarily be expected. One could argue that it is reasonable to select an entire group of subjects at risk for acquiring severe COVID-19 for supplementation without knowing their level of deficiency, even if only those with deficiency would benefit – particularly if supplementation does not cause harm and is at low treatment cost. Many physicians would follow such a pragmatic view, whereas others prefer a more puristical attitude and would like to wait for more solid trial-based evidence. This dilemma cannot be resolved at the present time. It is not uncommon for public health measures that recommendations are based mainly on observational studies instead of randomised controlled trials, as such trials are challenging, expensive and time consuming. Examples are the recommended reduction of dietary salt or of added sugar. Such a strategy makes sense if most of the experimental and observational evidence points toward a beneficial effect, show little or no risk, low cost, and randomised intervention trials are not feasible in free-living populations. Such a strategy may also be appropriate during times of a pandemic where time is most precious.

The strongest evidence today is available for vitamin D, with large and high quality trials and meta-analyses from such trials proving effectiveness for prevention of respiratory infections, particularly in patients with deficient levels, receiving daily or weekly boluses. Whether these effects remain true for COVID-19 is currently uncertain. There is no evidence for harm when using vitamin D in doses up to 2000 units per day. For larger doses, however, an increase in falls and other adverse outcomes is possible. Importantly, a significant proportion of elderly patients in Switzerland and other countries do have deficient levels. And this group of subjects is also the one with the highest risk for a severe course of COVID-19.

One (theoretical) concern with improving immune function through supplementation of vitamins and micronutrients is a possible overstimulation of the inflammatory response, which has been shown to be a main driver for COVID-associated pneumonitis and associated mortality and morbidity. There is today, however, no data suggesting that micronutrients and vitamins would do any harm in COVID-19. Importantly, there are many trials currently planned and ongoing, which will increase our current understanding of the role of vitamins and micronutrients for prevention and treatment of COVID-19. Pending results of such trials, it would seem premature to strongly recommend multiple supplementations of high doses of different micronutrients and vitamins to the overall population. For vitamin D, however, the currently recommended supplementation of 800 units per day for the vulnerable population should be underscored, based on possible beneficial effect on COVID-19, besides its proven effects on

Table 2: Registered trials evaluating the possible role of vitamin D and other micronutrients in the COVID-19 pandemic.

Trial ID	Title	Status	Study design	Planned timeframe	Location
Vitamin D					
NCT04386044	*Investigating the Role of Vitamin D in the Morbidity of COVID-19 Patients*	Not yet recruiting	Observational trial	2020–2021	UK
NCT04628000	*Baseline Vitamin D Deficiency and COVID-19 Disease Severity*	Recruiting	Observational trial	2020–2022	USA
NCT04482673	*Vitamin D Supplementation in the Prevention and Mitigation of COVID-19 Infection*	Recruiting	Interventional randomised clinical trial	2020–2021	USA
NCT04407286	*Vitamin D Testing and Treatment for COVID 19*	Completed	Interventional clinical trial	2020	USA
NCT04535791	*Efficacy of Vitamin D Supplementation to Prevent the Risk of Acquiring COVID-19 in Healthcare Workers*	Recruiting	Interventional randomised clinical trial	2020–2021	Mexico
NCT04738760	*Clinical Outcomes of High Dose Vitamin D Versus Standard Dose in COVID-19 Egyptian Patients*	Recruiting	Observational trial	2020–2021	Egypt
NCT04449718	*Vitamin D Supplementation in Patients With COVID-19*	Completed	Interventional randomised clinical trial	2020	Brazil
NCT04370808	*VITACOV: Vitamin D Polymorphisms and Severity of COVID-19 Infection*	Not yet recruiting	Observational trial	2020–2021	Portugal
NCT04403932	*Increased Risk of Severe Coronavirus Disease 2019 in Patients With Vitamin D Deficiency*	Completed	Observational trial	2020	Spain
NCT04483635	*PRevention of COVID-19 With Oral Vitamin D Supplemental Therapy in Essential healthCare Teams*	Recruiting	Interventional randomised clinical trial	2021	Canada
NCT04363840	*The LEAD COVID-19 Trial: Low-risk, Early Aspirin and Vitamin D to Reduce COVID-19 Hospitalizations*	Not yet recruiting	Interventional randomised clinical trial	2020	
NCT04536298	*Vitamin D and COVID-19 Trial*	Recruiting	Interventional randomised clinical trial	2020–2021	USA
NCT04793243	*Vitamin D3 Levels in COVID-19 Outpatients From Western Mexico*	Completed	Interventional randomised clinical trial	2020	Mexico
NCT04487951	*N-terminal Pro B-type Natriuretic Peptide and Vitamin D Levels as Prognostic Markers in COVID-19 Pneumonia*	Recruiting	Observational trial	2020–2021	Egypt
NCT04334005	*Vitamin D on Prevention and Treatment of COVID-19*	Not yet recruiting	Interventional randomised clinical trial	2020	Spain
NCT04525820	*High Dose Vitamin-D Substitution in Patients With COVID-19: a Randomized Controlled, Multi Center Study*	Recruiting	Interventional randomised clinical trial	2020–2021	Switzerland
NCT04709744	*Impact of Vitamin D Level and Supplement on SLE Patients During COVID-19 Pandemic*	Completed	Observational trial	2020	Egypt
NCT04636086	*Effect of Vitamin D on Hospitalized Adults With COVID-19 Infection*	Recruiting	Interventional randomised clinical trial	2020–2021	Belgium
NCT04385940	*Vitamin D and COVID-19 Management*	Not yet recruiting	Interventional randomised clinical trial	2020	
NCT04459247	*Short Term, High Dose Vitamin D Supplementation for COVID-19*	Active, not recruiting	Interventional randomised clinical trial	2020	India
NCT04519034	*Vitamin D Status and Immune-inflammatory Status in Different UK Populations With COVID-19 Infection*	Not yet recruiting	Observational trial	2020	UK
NCT03188796	*The VITDALIZE Study: Effect of High-dose Vitamin D3 on 28-day Mortality in Adult Critically Ill Patients*	Recruiting	Interventional randomised clinical trial	October 10, 2017	Austria, Belgium
NCT04733625	*The Effect of Vitamin D Therapy on Morbidity and Mortality in Patients With SARS-CoV 2 Infection*	Completed	Interventional randomised clinical trial	2020	Egypt
NCT04394390	*Do Vitamin D Levels Really Correlated With Disease Severity in COVID-19 Patients?*	Enrolling by invitation	Observational trial	2020	Turkey
NCT04579640	*Trial of Vitamin D to Reduce Risk and Severity of COVID-19 and Other Acute Respiratory Infections*	Active, not recruiting	Interventional randomised clinical trial	2020–2021	UK
NCT04344041	*COvid-19 and Vitamin D Supplementation: a Multicenter Randomized Controlled Trial of High Dose Versus Standard Dose Vitamin D3 in High-risk COVID-19 Patients (CoVitTrial)*	Recruiting	Interventional randomised clinical trial	2020–2021	France
NCT04435119	*Covid-19 and Vitamin D in Nursing-home*	Completed	Observational trial	2020	France

Trial ID	Title	Status	Study design	Planned timeframe	Location
NCT04411446	*Cholecalciferol to Improve the Outcomes of COVID-19 Patients*	Recruiting	Interventional randomised clinical trial	2020	Argentina
NCT04552951	*Effect of Vitamin D on Morbidity and Mortality of the COVID-19*	Recruiting	Interventional randomised clinical trial	2020	Spain
NCT04621058	*Efficacy of Vitamin D Treatment in Mortality Reduction Due to COVID-19.*	Recruiting	Interventional randomised clinical trial	2020–2021	Spain
NCT04476680	*Reducing Asymptomatic Infection With Vitamin D in Coronavirus Disease*	Not yet recruiting	Interventional randomised clinical trial	2020–2021	UK
NCT04476745	*The Effect of D3 on Selected Cytokines Involved in Cytokine Storm in the Covid-19 Uninfected Jordanian People*	Enrolling by invitation	Interventional randomised clinical trial	2020–2021	Jordan
NCT04386850	*Oral 25-hydroxyvitamin D3 and COVID-19*	Recruiting	Interventional randomised clinical trial	2020–2021	Iran
Vitamin C					
NCT04401150	*Lessening Organ Dysfunction With VITamin C - COVID-19*	Recruiting	Interventional randomised clinical trial	2020–2022	Canada
NCT04664010	*Efficacy and Safety of High-dose Vitamin C Combined With Chinese Medicine Against Coronavirus Pneumonia (COVID-19)*	Active, not recruiting	Interventional randomised clinical trial	2020–2021	China
NCT04530539	*The Effect of Melatonin and Vitamin C on COVID-19*	Recruiting	Interventional randomised clinical trial	2020–2021	USA
NCT04363216	*Pharmacologic Ascorbic Acid as an Activator of Lymphocyte Signaling for COVID-19 Treatment*	Not yet recruiting	Interventional randomised clinical trial	2020–2021	
NCT04710329	*High-Dose Vitamin C Treatment in Critically Ill COVID-19 Patients*	Completed	Observational trial	2021	Turkey
NCT04357782	*Administration of Intravenous Vitamin C in Novel Coronavirus Infection (COVID-19) and Decreased Oxygenation*	Completed	Interventional clinical trial	2020	USA
NCT04323514	*Use of Ascorbic Acid in Patients With COVID 19*	Recruiting	Interventional clinical trial	2020–2021	Italy
NCT04682574	*Role of Mega Dose of Vitamin C in Critical COVID-19 Patients*	Recruiting	Interventional randomised clinical trial	2020–2021	Pakistan
NCT04344184	*SAFEty Study of Early Infusion of Vitamin C for Treatment of Novel Coronavirus Acute Lung Injury (SAFE EVICT CORONA-ALI)*	Recruiting	Interventional randomised clinical trial	2020–2021	USA
Zinc					
NCT04542993	*Can SARS-CoV-2 Viral Load and COVID-19 Disease Severity be Reduced by Resveratrol-assisted Zinc Therapy*	Active, not recruiting	Interventional randomised clinical trial	2020–2022	USA
NCT04621461	*Placebo Controlled Trial to Evaluate Zinc for the Treatment of COVID-19 in the Outpatient Setting*	Completed	Interventional randomised clinical trial	2020–2021	USA
NCT04551339	*Zinc Versus Multivitamin Micronutrient Supplementation in the Setting of COVID-19*	Enrolling by invitation	Interventional randomised clinical trial	2020–2021	USA
Omega-3					
NCT04647604	*Resolving Inflammatory Storm in COVID-19 Patients by Omega-3 Polyunsaturated Fatty Acids -*	Recruiting	Interventional randomised clinical trial	2020–2021	Sweden
NCT04553705	*Omega-3, Nigella Sativa, Indian Costus, Quinine, Anise Seed, Deglycyrrhizinated Licorice, Artemisinin, Febrifugine on Immunity of Patients With (COVID-19)*	Recruiting	Interventional randomised clinical trial	2020	Saudi Arabia
NCT04483271	*The Effect of Omega-3 on Selected Cytokines Involved in Cytokine Storm*	Enrolling by invitation	Interventional randomised clinical trial	2020–2021	Jordan
Different nutrients					
NCT04641195	*Vitamin D and Zinc Supplementation for Improving Treatment Outcomes Among COVID-19 Patients in India*	Not yet recruiting	Interventional randomised clinical trial	2021–2022	India
NCT04407572	*Evaluation of the Relationship Between Zinc Vitamin D and b12 Levels in the Covid-19 Positive Pregnant Women*	Completed	Observational trial	2020	Turkey
NCT04335084	*A Study of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the Prevention of COVID-19 Infection*	Recruiting	Interventional randomised clinical trial	2020–2021	USA
NCT04395768	*International ALLIANCE Study of Therapies to Prevent Progression of COVID-19*	Recruiting	Interventional randomised clinical trial	2020–2021	Australia

bone and muscle. Such a recommendation has clearly more upsides than downsides and may alleviate the heavy burden of this devastating disease [27]. In addition, it is time to conduct high-quality trials to better understand whether and which supplementation for which group of subjects is indeed effective in improving immune defence and thereby lowering the burden of COVID-19. Specifically, this includes observational studies looking at the level of different vitamins and micronutrients in different populations to better understand at-risk groups, as well as interventional research to understand which vitamins and micronutrients (in what doses) provide most benefits. Only time will tell whether early implementation of such a public health strategy, as promoted by Berger and colleagues [6], will in the end save lives, and to what costs.

Potential competing interests

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Trial ID	Title	Status	Study design	Planned timeframe	Location
NCT04780061	*Dietary Supplements for COVID-19*	Not yet recruiting	Interventional randomised clinical trial	Jul 05	Canada
NCT04468139	*The Study of Quadruple Therapy Zinc, Quercetin, Bromelain and Vitamin C on the Clinical Outcomes of Patients Infected With COVID-19*	Recruiting	Interventional clinical trial	2020	Saudi Arabia
NCT04558424	*RCT, Double Blind, Placebo to Evaluate the Effect of Zinc and Ascorbic Acid Supplementation in COVID-19 Positive Hospitalized Patients in BSMMU*	Not yet recruiting	Interventional randomised clinical trial	2020–2021	Bangladesh
NCT04342728	*Coronavirus 2019 (COVID-19)- Using Ascorbic Acid and Zinc Supplementation*	Completed	Interventional randomised clinical trial	2020–2021	USA

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