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# Pre-exposure and Post-exposure new prophylactic treatments against COVID-19 in healthcare workers

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## ABSTRACT

The Severe Acute Respiratory Syndrome-related Coronavirus 2 or novel coronavirus (COVID-19) infection pandemic continues to spread. Since the outbreak of the COVID-19 in Wuhan (China), healthcare workers have been infected and are considered at high risk of contamination. Moreover, in addition to the physical effects of COVID-19, the pandemic results in important mental health issues among healthcare workers such as anxiety, stress, depression, and further nervous or mental disorders. Despite the increasing number of clinical trials aiming to develop vaccines or test antiviral molecules, till now no efficient anti- SARS-CoV-2 drugs have been validated. The COVID-19 pandemic led us to call for an urgent nutritional intervention model that should be established to prevent and/or reduce the negative impact of COVID-19 on healthcare workers. In the present paper, we suggest a safe nutritional supplementation of Mg-Zn- B vitamins (B1, B6, B9, and B12) in healthcare workers as pre-exposure and post-exposure new prophylactic treatments. Furthermore, the paper reports the scientific arguments and the possible mechanisms by which the Mg-Zn- B vitamins supplementation may exert its beneficial effects in the healthcare workers facing the COVID-19 pandemic. Overall, the Mg-Zn- B vitamins supplementation would enhance the immune response against SARS-CoV2, prevent inflammatory processes and oxidative stress, fight or alleviate the COVID-19-related mental health issues, or even reduce the replication. Each element of the supplementation possesses important and promising effects contributing to the possible efficiency of the suggested Mg-Zn-B vitamins supplementation in healthcare workers.

Keywords: COVID-19, SARS-CoV-2, Supplementation, Zinc, Magnesium, Vitamins B.

## 1. INTRODUCTION

The Severe Acute Respiratory Syndrome-related Coronavirus 2 or novel coronavirus COVID-19 infection pandemic has affected 2 074 529 persons and resulted in 139 378 deaths in 213 countries (Figure 1) as of 17 of April [1]. Though several guidelines related to the post-exposure procedures regarding the healthcare workers have been established, lack of knowledge about the virus transmission and insufficient training seem to contribute to the spread of COVID-19 among healthcare staff [2]. According to the current guidelines, healthcare workers should benefit from the drastic protective measures applied for group A infections [3]. In fact, the pandemic has shown the need to identify all the possible resources and approaches to prevent infection of the healthcare workers by COVID-19 [4]. Moreover, to fight COVID-19 and its negative impacts on their physical and mental health, healthcare workers should adopt healthy behavior regarding physical activity and diet [5]. Nutrition is recognized as a part of the treatment approaches against several diseases. Actually, nutritional interventions have been shown to contribute to improving the prognosis of the Ebola outbreak in African populations [6]. Recently, it

has been advised to introduce nutritional intervention in the clinical care of COVID-19 patients, and assess malnutrition among them to improve their prognosis [7]. Thus, suggesting incorporation of nutritional supplementation in the treatment regimen of COVID-19 becomes an urgent and justified need.

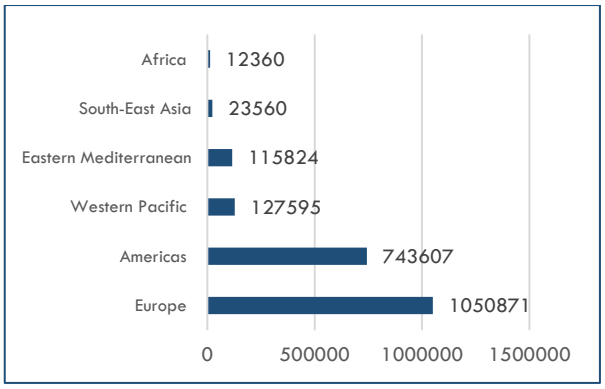


**Figure 1:** Confirmed COVID-2019 cases as of 17 April 2020 Based on WHO data (situation report n°87)

Increasing number of studies and clinical trials are attempting to find an efficient vaccine. Nevertheless, no vaccine for the prevention of COVID-19 exists, and vaccine candidates are being assessed regarding their efficiency and their effects on human health require longer follow up [8]. Likewise, despite several ongoing clinical trials, till now no effective treatments have been validated to be used against COVID-19.

Several clinical trials are currently focusing on evaluating the therapeutic and prophylaxis efficacy of minerals and vitamins supplements against COVID-19. COVIDAtoZ is a single-center, prospective, randomized clinical trial (NCT04342728) that examines the impact of ascorbic acid (vitamin c) and zinc gluconate in reducing the duration of symptoms in patients diagnosed with COVID-19.

Recently, HELPCOVID-19 Phase II interventional study (NCT04335084) has been initiated to evaluate the prophylactic effect of zinc-vitamins C and D supplements associated with Hydroxychloroquine, a medication used to treat malaria on healthcare workers who are exposed to COVID-19. Therefore, using a safe and efficient approach based on nutritional supplementation seems to be an intelligent alternative to prevent COVID-19 in healthcare workers.

In the present paper, we suggest using a safe nutritional supplementation of Mg-Zn- B vitamins (B1, B6, B9, and B12) in healthcare workers as a preventive treatment. Moreover, this supplementation could be combined with other anti- COVID-19 therapies in patients with mild to moderate symptoms. Here we provide the scientific basis of the possible effects attributed to the suggested supplementation.

## 2. COVID-19 AMONG HEALTH WORKERS

Healthcare professionals (medical and nonmedical staff) in contact with suspected COVID-19 patients are at high risk to be infected with SARS-CoV-2 [9]. In China, the first transmission of SARS-CoV-2 to healthcare workers was reported on 20$^{th}$ January. Among 44672 Chinese COVID-19 patients, 1716 (3.8%) were healthcare workers. Consequently, protecting healthcare workers constitutes a high priority to avoid a pandemic spread [10, 11].

As of 8 April 2020, COVID-19 has affected 22 073 health workers from 52 countries [12]. This situation is identical to that occurred during SARS and MERS outbreaks. Indeed, with the SARS-CoV-1 outbreak in 2003, it has been pointed out that healthcare workers were a vulnerable target of virus contamination. Among the SARS cases reported, healthcare workers represented 23% in the world, 41% in Singapore [13], and 21.1% in China [14]. The SARS outbreak caused the death of 1707 healthcare workers accounting for 21% of the total deaths recorded [15]. In line with this, MERS resulted in more than 18% of healthcare workers infected [16].

With the acceleration of the pandemic, health-care workers' involvement becomes crucial and access to protective equipment a major issue in most countries. Furthermore, stress, anxiety, infection risk, and physical and mental exhaustion of these individuals render them more vulnerable [17]. Likewise, anxiety, fear, stigmatization, and stress significantly affected healthcare workers during SARS and MERS outbreaks [18]. Nowadays, it is well admitted that besides the physical effects of COVID-19, the pandemic results in important mental health issues among patients and healthcare workers [19]. In China, 1563 medical healthcare workers have been investigated regarding the impact of COVID-19 on their mental health. The results of this recent multicenter survey have shown that stress-related symptoms were found to be the most frequent mental health problem occurring in 73.4% of the medical staff. Moreover, more than half of Chinese healthcare workers in the care of COVID-19 patients suffered from anxiety, 44.7% from depression, and 36.1% from insomnia [20].

Similarly, another cross-sectional study carried out in China evaluated the prevalence of mental health problems among 1257 healthcare workers in 34 hospitals. The survey found that 71.5% of the healthcare workers suffered from distress, 50.4% from depression, 44.6% from anxiety, and 34% from insomnia. Importantly, this study has revealed that women, nurses, and frontline medical staff

experienced more severe psychiatric disorders (anxiety and depression) [21].

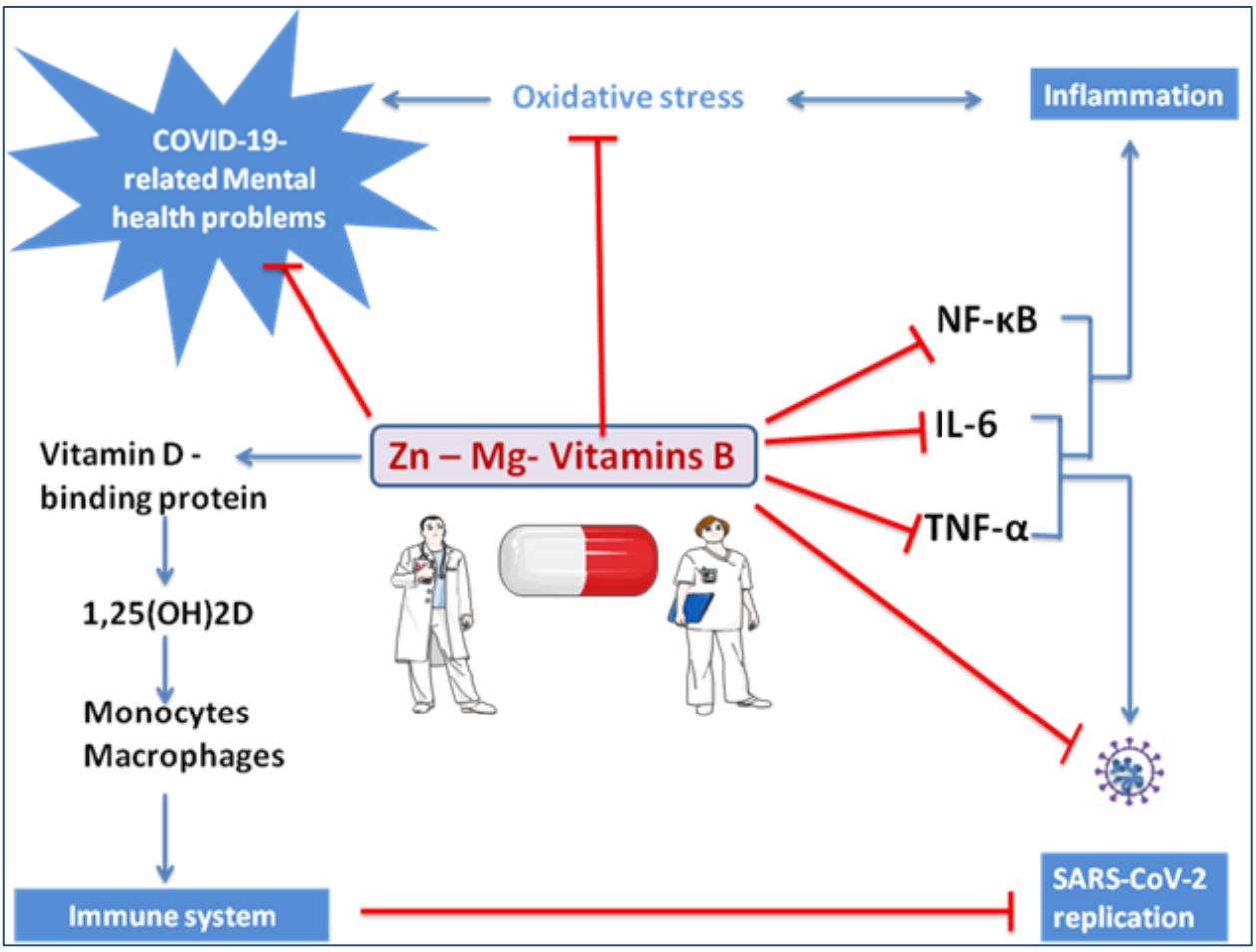


**Figure 2:** Summary of the possible effects and mechanisms of the Mg – Zn – Vitamin B supplementation against 2019-nCoV

In another recent study, Huang & Zhao [19] found that 35.1% of Chinese healthcare workers experienced generalized anxiety disorders, whereas 20.1% and 18.1% had depressive symptoms and sleep disorders, respectively. Interestingly, these mental disorders related to the COVID-19 were more pronounced in healthcare workers younger than 35 years. Tan *et al.* [22] evaluated the psychological consequences of the pandemic on 470 health workers in two tertiary centers in Singapore. Among them, 14.5% suffered from anxiety, 8.9% from depression, 7.7% from posttraumatic stress disorder, and 6.6% from stress. It should be noticed that this study has been carried out from 9 February to 13 March 2020 when Singapore recorded only 200 confirmed cases and 11 patients requiring critical care. In spite of that, the health care workers experienced important mental and nervous issues related to COVID-19. Surprisingly, the incidence of psychological impact was higher in nonmedical health care.

The different studies have shown that besides the risk of COVID-19 infection, anxiety, depression and other nervous or mental problems are the main impacts of the pandemic on healthcare workers. It is worth to notice that after wearing personal protection equipment, the healthcare workers cannot eat, drink, or even go to toilets. Furthermore, despite personal disinfection, these workers live with a major concern to transmit the disease to their family members. Such a situation is a natural source of anxiety and mental pressure [23]. Moreover, an increasing number of healthcare workers not specialized in infectious diseases is dispatched to COVID-19 care wards to support their colleagues. This situation may be a source of significant pressure and therefore several physical and mental impacts [24]. The COVID-19 pandemic led some scientists to require an "urgent psychological crisis intervention model" [25]. Likewise, we ask for an *urgent nutritional intervention model* that should be established to prevent and/or minimize the negative effects of COVID-19 on healthcare workers.

## 3. EXPECTED EFFECTS OF THE NUTRITIONAL SUPPLEMENTATION Mg-Zn-B VITAMINS

### 3.1. THE Mg-Zn-VITAMINS B CO-SUPPLEMENTATION AS A PREVENTIVE APPROACH THROUGH INHIBITION OR REDUCTION OF SARS-CoV-2 REPLICATION AND ENHANCING IMMUNE SYSTEM

Enhancing the immune function seems to be the first preventive and therapeutic strategies to adopt against COVID-19 in both healthcare workers and patients. Recently, the first case- report giving evidence that the immune response was responsible for the recovery of a COVID-19 patient in Australia has been published [26]. Decreased serum levels of magnesium have been reported in patients with SARS [27]. Similarly, zinc deficiency is usually associated with increased risk of human coronaviruses infections [28], impaired immunity [29], and altered the homeostasis of at least 16 minerals such as Mg, Se, Cu, K, and Fe [30]. On the other hand, Zn homeostasis plays a critical role in the immune response. Upon viral infection, plasma Zn levels decrease which in turn results in an important release of inflammatory Tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [31]. In COVID-19 patients, the worst outcome was observed in those developing the cytokine storm with an important production of TNF-α and ILs such as IL-6 leading to enhanced viral spread and fatal complications. In this context, it has been suggested that compounds able to inhibit or reduce IL-6 production may contribute to the protection against SARS-CoV-2- related pneumonia [32]. Interestingly, several studies have demonstrated that Mg-Zn co-supplementation caused a significant downregulation of both IL-1 and TNF-α expression [33]. In healthy young individuals, the Mg-supplementation caused a significant increase in adrenocorticotropic hormone (ACTH) concentrations leading to the reduction of IL-6 and cortisol levels [34].

Besides, Mg supplementation may enhance the immune system to fight SARS-CoV-2 through its action on vitamin D metabolism since renal and hepatic hydroxylation into its active form is Mg-dependent. Different studies have demonstrated that Mg-supplementation was able to correct vitamin D deficiency owing to its role as a co-factor for vitamin D–binding protein [35]. The action of vitamin D on the immune system during viral infections is exerted through modulation of monocytes and macrophages functions. In addition, vitamin D prevents inflammation by inhibiting maturation of dendritic cells, reducing the production of pro-inflammatory cytokines (TNF-α, IFN-γ, and IL-1β), and enhancing anti-inflammatory IL-10 [36, 37].

Mg – Zn - vitamins B co-supplementation may have direct inhibitory effects against the SARS-CoV-2 virus since several studies have demonstrated that these elements were able to effectively inhibit similar coronaviruses including SARS-CoV. Actually, it has been established that the replication of different RNA viruses including those responsible for respiratory diseases is inhibited by $Zn^{+2}$ [38, 39]. te Velthuis *et al.* [40] found that $Zn^{+2}$ at 2μM (with its ionophore pyrithione) was able to inhibit the replication of the SARS-CoV virus through inactivation of the RNA-synthesizing activity of the SARS-CoV- replication and transcription complex. Furthermore, $Zn^{2+}$ directly inhibited the activity of its RNA-dependent RNA polymerase. Similar results were obtained *in vivo* corroborating the antiviral effects of Zn supplementation [41]. Similar anti-SARS-CoV-2 effects are expected to be exerted by $Mg^{+2}$ since several studies have linked low $Mg^{2+}$plasma concentrations with elevated Epstein-Barr virus (EBV) levels, and showed that an $Mg^{2+}$ supplementation improves the EBV-related disease's outcome [42].

### 3.2. THE Zn-Mg-VITAMINS B CO-SUPPLEMENTATION MAY EXERT INDIRECT EFFECTS THROUGH ITS ANTI-INFLAMMATORY AND ANTIOXIDANT POTENTIALS

The Mg – Zn – vitamins B supplementation possesses important antioxidant and anti-inflammatory potentials. Indeed, it is thought that prolonged stressful situations as those the healthcare workers are experiencing nowadays result in a continuous release of cortisol leading to hyperactivation of neutrophils which in turn cause the generation of important amounts of oxidants [43]. Afshar-Ebrahimi *et al.* [44] investigated the impacts of magnesium oxide (250 mg) and zinc co-supplementation (220 mg) twice a day for 12 weeks in patients with polycystic ovary syndrome. The supplementation resulted in a significant decrease of inflammation as shown by the reduction of C-reactive protein (CRP) serum levels, and a significant increase in total antioxidant capacity. Furthermore, Mg-Zn co-supplementation caused a significant downregulation of both IL-1 and TNF-α expression. Mg and Zn supplementation were found to improve the anti-inflammatory and oxidative stress biomarkers, suggesting their effect as an anti-inflammatory and anti-oxidant agent [45, 46]. Moreover, promising anti-inflammatory effects were observed following Zn supplementation which upregulated the zinc transcription factor A20 able to inhibit the NF-κB signaling and therefore reduce cytokines release [33]. Bao *et al.* [47] found that daily supplementation of zinc (45mg/day) for 6 months, was able to significantly correct the zinc plasma concentrations and decrease those of CRP, IL-6, MDA, macrophage chemoattractant protein 1 (MCP-1), and secretory phospholipase A2. These results demonstrated the antioxidant and the anti-inflammatory

effects of Zn supplementation. Similar results were obtained in younger individuals [48]. Besides, the antioxidant effects of the supplementation may improve the COVID-19-related mental problems observed in healthcare workers. In fact, it has been demonstrated a significant association between both anxiety and depression symptoms and oxidative stress [49].

### 3.3. THE Mg – Zn - VITAMINS B CO-SUPPLEMENTATION COULD RELIEF THE COVID-19- RELATED MENTAL HEALTH PROBLEMS

The positive effects on the COVID-19-related mental health problems in healthcare workers may be attributed primarily to both vitamins B and Mg. Positive effects of $Mg^{2+}$ supplementation on mental health problems such as stress, insomnia, or anxiety have been demonstrated. Indeed, supplementation of $Mg^{2+}$ oxide (500mg/day/8 weeks) resulted in insomnia improvement and a significant reduction of stress levels in healthy individuals [50,51]. Recently, a co-supplementation of $Mg^{+2}$ (300 mg) – vitamins B (30 mg) and $Mg^{+2}$ alone was evaluated in 264 healthy persons with depression, anxiety, and stress symptoms. After 8 weeks, both supplementations resulted in a significant decrease in subjects with severe stress by 48% [52].

Vitamins B play important roles, as a coenzyme, in both the central and the peripheral nervous systems. Since mammals cannot synthesize them, vitamins B supplementation has been demonstrated to result in synergistic beneficial effects in different nervous problems such as anxiety, depression, and stress-related disorders [53]. Vitamin B complex (B1, B2, B3, B5, B6, B9, and B12) has been shown to play critical roles to prevent, improve or even treat mental health disorders such as anxiety, stress, or depression [54]. In their meta-analysis, Young *et al.* [55] reviewed and analyzed 18 studies regarding the effects of vitamins B supplementation on mental issues in healthy or at-risk individuals. The authors found that the vitamins B supplementation was significantly associated with reduced stress symptoms (SMD = 0.23, 95% CI: 0.02 - 0.45, $p$ = 0.03). Interestingly, it has been demonstrated that the co-supplementation of Mg (200mg) and vitamin B6 (50mg) for 1 month synergistically relieved anxiety [56].

On the other hand, Zn is related to the activity of 200 enzymes and was found to be involved in neurological functions. Several studies have demonstrated that zinc supplementation improved different mental health problems such as anxiety [57, 58].

## 4. THE Mg – Zn – VITAMINS B SUPPLEMENTATION

Based on those previous literature data, we suggest an alternative nutritional supplementation of Mg – Zn – vitamins B as a preventive intervention against COVID-19 in healthcare workers. Furthermore, this supplementation may be useful when combined with other anti- COVID-19 therapies in patients with mild to moderate symptoms.

Overall, we suggest using the following nutritional supplementation in healthcare workers during the COVID-19 pandemic.

### 4.1. PROPHYLAXIS TREATMENT FOR COVID-19

- Zinc supplementation: 50- 75 mg of zinc gluconate to be taken daily at bedtime (Zinc should not be taken for more than 2 months);
- Magnesium supplementation: Daily dose of 1500 mg of magnesium pidolate for 4 weeks;
- B1-B6 supplementation: 1:1 of vitamin B1–vitamin B6 combination; daily dose 250 mg and 250 mg, respectively for 4 weeks;
- B9 supplementation: 5 mg of folic acid to be taken daily for 4 weeks;
- B12 supplementation: 1 mg of vitamin B12 to be taken monthly for 4 months.

### 4.2. THERAPEUTIC APPROACH FOR MILDLY AND MODERATE-SYMPTOMATIC PATIENTS WITH COVID-19

- 75-100 mg/day of zinc gluconate for 5 days;
- 4500 mg of magnesium pidolate divided into 3 daily doses for 10 days;
- 1:1 of vitamin B1–vitamin B6 combination; daily dose 750 mg and 750 mg, respectively divided into 3 *daily doses* for 10 days;
- 15 mg of folic acid to be taken daily divided into 3 *daily doses* for 10 days;
- 1 mg of vitamin B12 to be taken daily for 10 days.

## 5. CONCLUSION

The outbreak of the severe Acute Respiratory Syndrome-related Coronavirus 2 (COVID-19) infection pandemic has led the scientific community to adopt various strategies to treat it. Nonetheless, till now no efficient drugs or vaccines have been made available in spite of the important number of ongoing clinical trials. Healthcare workers are considered a vulnerable group at high risk of contamination and psychological issues. In this paper, we suggested a safe nutritional supplementation of Mg – Zn - B vitamins (B1, B6, B9, and B12) as pre-exposure and post-exposure new prophylactic treatments. Owing to the important beneficial properties of its components (Mg, Zn, and B vitamins), the supplementation could be a promising alternative preventive or even therapeutic approach in patients with mild or moderate symptoms. Further clinical investigations of the suggested supplementation, the doses and treatment durations should be undertaken.

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