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Journal of Trace Elements in Medicine and Biology 71 (2022) 126954

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb

Zinc augments the antiviral potential of HCQ/CQ and ivermectin to reduce the risks of more serious outcomes from COVID-19 infection

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ARTICLE INFO

Keywords:
COVID-19
Prophylaxis
Therapy
Zinc
Chloroquine
Hydroxychloroquine

ABSTRACT

Treatments do not replace vaccinations or restrictions, but are practical, effective, and safe means to help to reduce the fatality associated with COVID-19 infection. While no treatment is available and effective for all the current and future variants of COVID-19, treatments reduce the risk of COVID-19 becoming endemic and reduce mortality and collateral damages. The use of Zinc (Zn) for COVID-19 infection is here reviewed. Zn supplementation may help in prevention as well as during the administration of therapies. Zn supplementation reduces the risks of serious outcomes from Covid19 infection. Evidence also suggests that Zn helps in treatments of COVID-19 infection if taken in conjunction with antiviral drugs. The literature supports the use of Zn, with improvements towards a lower risk ranging from 37% in late treatment, RR 0.63 CI [0.53–0.74], to 78% in sufficiency, RR 0.22 CI [0.05–0.96].

1. Introduction

The COVID-19 pandemic is ongoing since December 2019, when the first cases were reported in Wuhan, China. So far, the outbreak has been more serious in western Europe, the United States, and South America, as shown by the total number of fatalities attributed to COVID-19 per million. The reliability of the data may differ considerably from one jurisdiction to the other. Opposite to South America, Africa is almost untouched by the pandemic, as almost untouched is China. There have been several waves and different variants of the virus.

1.1. Evolution of the pandemic

Fig. 1 is a summary of COVID-19 cases, fatalities, and vaccinations. Images are from ourworldindata.org. Countries such as Sweden that did not adopt any lockdown did better than countries such as the United Kingdom or Belgium that imposed a strict lockdown in the first wave of infection, and they did better also during the second and subsequent waves of infection when similarly, they are adopting less severe restrictions, indicating general lockdowns are not a correct measure to replace targeted protection of the vulnerable and are not sustainable [1–5].

The fatality of COVID-19 is much larger in Italy, Belgium, or the United Kingdom than in Sweden. The case fatality rates of 2020 and part of 2021, which do not factor vaccines and the latest much more infectious but apparently less-lethal Omnicron variant, were quite large for Italy, Belgium, or the United Kingdom at about 3%. These percentages were not accounting for the asymptomatic or mild that may have been undetected. About 20% of the total are mild or asymptomatic, the large majority of infections [2,3]. The fatalities are almost entirely within the risk categories of the compromised immune system [2–4].

Adopting antiviral therapies or negating their use made a substantial difference. Countries that practically do not use antivirals such as the United Kingdom, Italy, or Belgium, where drugs such as remdesivir, hydroxychloroquine, lopinavir/ritonavir, or interferon are discouraged following the advice by the world health organization [6], had case fatality rates till mid of 2021 up to 10 times larger than countries of similar quality health systems such as Qatar or the United Arab Emirates that routinely uses these antivirals as part of their Covid-19 protocols [7, 8]. The United Arab Emirates only has 0.3%, and Qatar 0.2%.

While the case fatality rate is certainly affected by many other factors, it is singular that those countries that do not use antivirals had one order of magnitude larger case fatality rates vs. those that kept using antivirals.

The course of the pandemic was ultimately changed by the introduction of the vaccines, starting from December 2020 in Israel. Vaccines have been effective to some extent, as the case fatality rate reduced in some countries such as the United Kingdom.

In the very last few weeks, the Omnicron variant has infected a huge number of people, with no difference between the vaccinated and the

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https://doi.org/10.1016/j.jtemb.2022.126954
Received 17 August 2021; Received in revised form 15 January 2022; Accepted 14 February 2022
Available online 17 February 2022
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non-vaccinated, but the case fatality rate dramatically dropped (the United Arab Emirates have 0.07%, the United Kingdom 0.15%), likely because of reducing the lethality.

This work aims to understand if there is any benefit from supplementation with Zinc in prophylaxis and therapy in conjunction with antivirals for COVID-19 infection.

1.2. Relevance of therapies

It is necessary to develop better therapies through existing or novel antivirals, and further study the role of supplements to reduce the consequences of the COVID-19 infection, as the solution of the COVID-19 emergency must encompass not only vaccines but also therapies and restrictions.

As demonstrated by the case of the Charles De Gaulle aircraft carrier

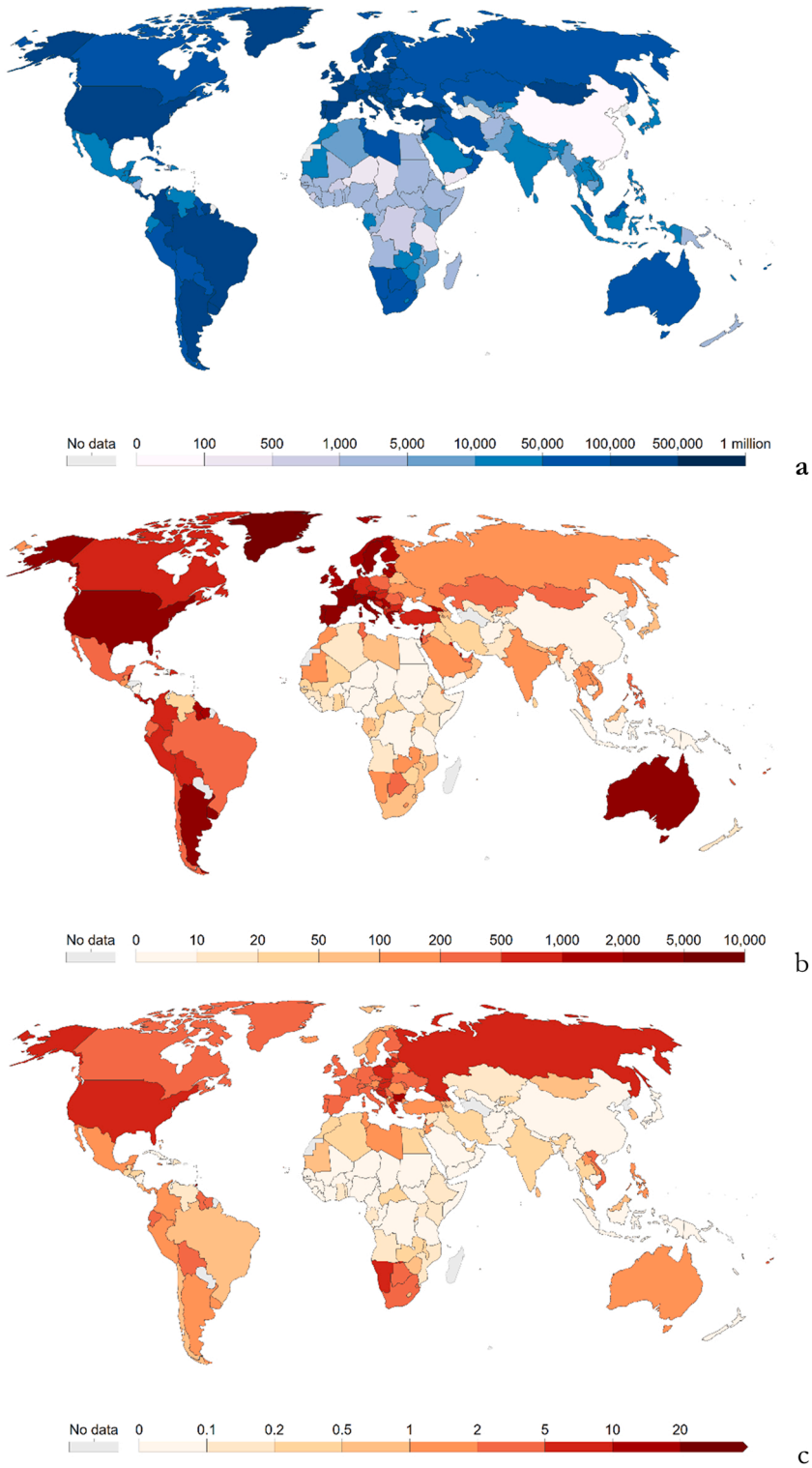

Fig. 1. Map of cumulative and latest 7-days moving average of cases (a, b), fatalities (c,d), and fully vaccinated (e). Images from ourworldindata.org. CC BY.

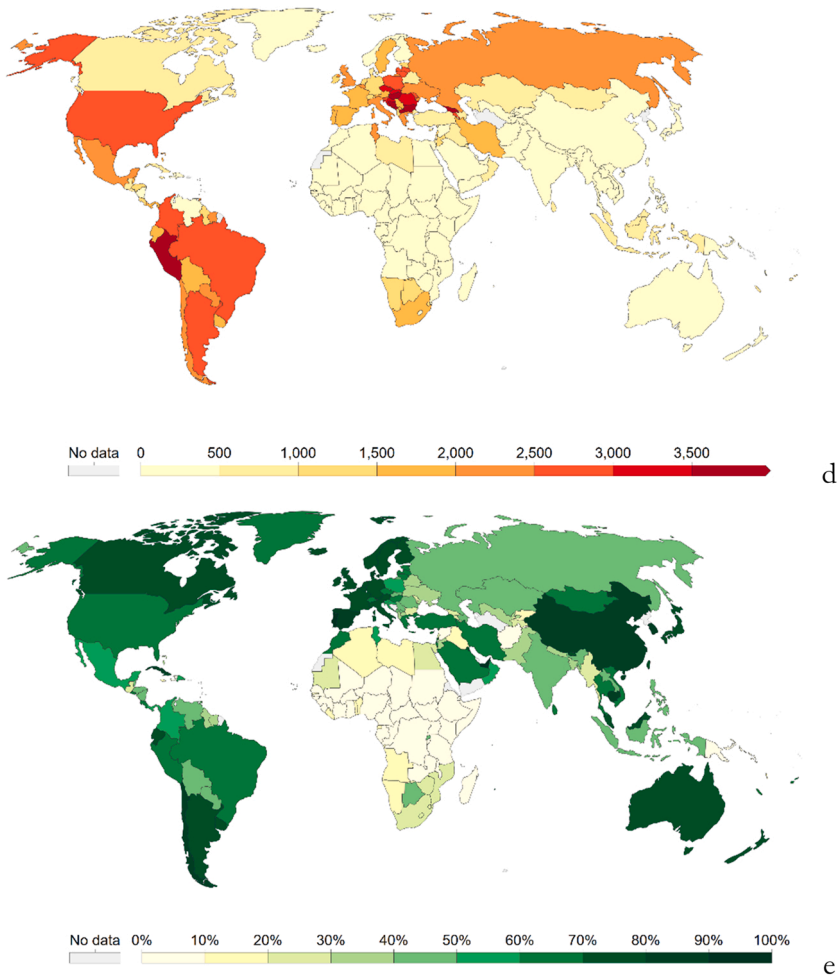

Fig. 1. (*continued*).

[9], of almost 2000 people, supposed to be healthy and with a strong immune system, who were all uniformly challenged by the virus, only 1081 were infected, and of the 1081, only 24 ended up in the hospital, with only 1 of them in need of intensive care [10]. After two weeks, there were only 2 still in the hospital, 1 of them needed intensive care [11]. After three weeks, only the 1 previously in intensive care was still hospitalized but out of the intensive care unit [12]. Thus, a strong immune system built through exercise, healthy food and nutrients, helps against COVID-19 infection [9].

The lethality and infectivity of COVID-19 are much less than what has been portrayed [13]. As previously noticed, in countries with a good health system and proper use of antivirals (Qatar and the United Arab Emirates for example), the case fatality rate is 0.2–0.3%. Healthy and young people risk little from being challenged by the virus [13]. New variants are supposed to be more infective but less lethal, following the experience of the Spanish flu.

People previously infected by COVID-19 are not expected to get infected again within a short time frame [13]. Antibodies from prior infections and recovery [91,92] or vaccinations, should protect for about 7 months, even if the subject is highly controversial. Infection from new strains is possible, for those infected and recovered, as well as for those vaccinated. Vaccines' efficacy is fading with time and variants [93–95].

More or less severe containment measures have not produced any difference in the COVID-19 fatalities across Europe (see again the United Kingdom and Belgium compared to Sweden). Restrictions protecting the vulnerable must be kept in place for a long time [13]. They must also be made more sustainable for the general public. The solution of the COVID-19 emergency passes through vaccines, sustainable restrictions, and therapies.

There is an ongoing controversy about therapies and supplements, that includes also Zn. Mainstream media has proposed the view that COVID-19 has much greater infectivity and lethality than it does, and the only way to cease generalized lockdown is through vaccines. The role of supplements, and therapeutic agents, have been downplayed [7, 53]. No role is attributed to supplements such as Vitamin C, Multivitamin, Zinc, Vitamin D3, or repurposed antivirals such as CQ/HCQ, Ivermectin.

The use of intravenous Vitamin C is supported by many works, even if not specific to this coronavirus, some of them dating from the 1930 s, for example, [14–26]. This opportunity is limited to the phase of Acute Distress Respiratory Syndrome in some patients.

More general is the use of CQ/HCQ, supported by many specific works, for example, [27–58], mostly in prophylaxis and mild cases. Contrarian studies such as [47], despite being employed to call for an end to the use of CQ or HCQ for COVID-19 infection [48], do not change the positive outlook of CQ/HCQ. Apart from being flawed, marked by a conflict of interest, and now retracted, the study [47] does not affect the best uses of CQ/HCQ that are different from those considered, being prophylaxis, and mild or medium severity cases rather than severe cases. If the data could have been reliable, nevertheless the conclusions will not have been warranted. The resulting data was completely unreliable [49–51]. The paper [47] was eventually retracted because the tiny company claiming to have the world's largest database of COVID-19 infection would not allow the validity of the data (and code) unavailable for review to be independently validated. After the study [47]

flopped, another study was immediately latched out to maintain the ban on the use of CQ/HCQ. In the RECOVERY trial, patients were given very heavy doses of the drug at about 2400 mg in the first 24 h [52]. Giving severely infected patients 3x the usual dosage of most other studies also proves nothing about the safety and efficacy profile of CQ/HCQ for COVID-19 infection.

Similar to the case of the downplayed use of Intravenous Vitamin C, or CQ/HCQ, the role of many other drugs, and the role of supplements, to help with antivirals or simply make stronger the immune system, has been downplayed. Positive experiences have been made with many compounds, such as Fluvoxamine, Quercetin, Proxalutamide, iota-carrageenan, Molnupiravir, Povidore-Iodine, Curcumin, Ivermectin, Casirivimab/imdevimab, Sotrovimab, Bamlavinimab, Nitazoxanide, Budesonide, Vitamin D, Bromhexine, Colchicine, Aspirin, Favipiravir, CQ/HCQ, Remdesivir, Vitamin C and Zinc.

Vaccinations do not seem to reduce the number of infected, that must be treated. This is evidenced by comparing for example the time series of vaccinated, new cases, and new fatalities of neighboring countries such as Israel, Palestine, and Jordan having unequal shares of vaccinated. The highest peaks of infection were reached in Israel after vaccination. Israel is one of the leading countries for COVID-19 vaccinations. As of 23-May-2021, 62.87% of the population already received one vaccine dose, and 59.11% of the population was fully vaccinated, while 9.70% of the population was already infected and recovered. The Gross Domestic Product (GDP) per capita of Israel is $43,592, much larger than the $4405 in Jordan and $3562 in Palestine. The quality of the health care system may be considered proportional to the GDP per capita.

Despite claims of reducing cases in Israel following vaccinations, this does not seem the case. The peak of the latest outbreak of Sep. 14, 2021, was the highest on record, despite the higher percentage of previously infected and recovered, and the higher percentage of vaccinated, which could have reduced the spreading. Palestine and Jordan never reached similar peaks of infection. The comparison of the trajectories of new cases in the three countries does not support the claim that vaccines are effective in reducing infections, rather they prove the opposite. Vaccination reduces the number of fatalities more than the number of cases. The case fatality rate of Israel has been generally lower than Jordan (cumulative 0.61% vs. 1.29%) with the latest moving average of the case fatality rate of Israel reduced to 0.4% vs. the 0.9 of Jordan. Palestine has a cumulative case fatality rate of 1.02% and a latest moving average of the case fatality rate about the same as Israel.

Vaccines are important but are only a part of a more comprehensive approach. Vaccines do not prevent infection in every possible case. Not all vaccines are equal, especially against different strains. Other measures in addition to vaccines are relevant. All the available weapons, from sustainable restrictions, protecting the vulnerable, to effective contact tracing, from efficient therapeutic approaches based on antivirals, to vaccinations, from a healthy lifestyle to supplementation, are all needed to resolve the COVID-19 emergency.

As very well highlight in c19study [58], "*Treatments do not replace vaccines and other measures. All practical, effective, and safe means should be used. Elimination is a race against viral evolution. No treatment, vaccine, or intervention is 100% available and effective for all variants. Denying efficacy increases mortality, morbidity, collateral damage, and risk of endemic status*.".

The latest developments with the Omnicron variant appearing much more infective but much less lethal than the predecessors, with case fatality rate dramatically reduced (Australia 0.12%, United Kingdom 0.15%, United Arab Emirates 0.07% as per 12 January 2022), and affecting the vaccinated not less than the non-vaccinated (Sydney and Melbourne are experiencing 10,000 new daily cases per million mostly in between the vaccinated), demonstrate as a long-term vision is needed, to replace the short-term approach of forced vaccination and generalized lockdowns showing downfalls.

2. Materials and methods

The manuscript proposes a statistical analysis of the works with Zn for COVID-19 infection.

3. Results

CQ/HCQ is widely available and costs almost nothing being off-patent. Same as every other therapy affecting the reproduction cycle of SARS-CoV-2, it has been downplayed by those promoting lockdowns and vaccines as the only solution to COVID-19, negating the value of therapies. Therapies do not replace vaccines and lockdowns. They are practical, effective, and safe means which may help to win the race against SARS-CoV-2 evolution. No therapy, but also no vaccine, is 100% effective against all the variants. Denying the role of therapies increases the mortality, morbidity, and collateral damage of COVID-19 but makes society more reliant on vaccines and lockdowns. Since the very beginning, it has been virtually impossible, because of the conflicts of interest, to understand the best uses of CQ/HCQ (and other repurposed antivirals) for COVID-19 infection. Similarly, unclear is the possible use of Zn (and other supplements), in conjunction with CQ/HCQ or other drugs, or even alone. Here we summarize the evidence in terms of the percentage of scientific works supporting or negating a specific use. Treatments do not replace vaccinations or restrictions. Treatments are only practical, effective, and safe means to help to reduce the fatality associated with COVID-19 infection. While no treatment is available and effective for all the current and future variants of COVID-19, nevertheless treatments reduce the risk of COVID-19 becoming endemic and reduce mortality and collateral damages. While the CQ/HCQ controversy has been closed in the western countries (where the COVID-19 policies suffer most from political and economic biases), CQ/HCQ is still widely used in other countries of not certainly a larger case fatality rate. The countries where CQ/HCQ have limited use, have a total population of 0.9b. The countries where CQ/HCQ have widespread use have a total population of 4.9b. Mixed-use is proper to countries with a population of 1.1b. Unclear is the situation in the countries where the remaining 0.8b people live. There is a factor of 10 in between the case fatality rate of countries such as the United Kingdom which do not permit the use of CQ/HCQ (and almost every other antiviral) and countries such as the United Arab Emirates that permit to use of CQ/HCQ and many other antivirals.

3.1. CQ/HCQ

CQ/HCQ was first successfully used in China [30,41]. Despite the opposition in some specific sectors of the West to use CQ/HCQ for COVID-19, many countries have embraced this opportunity as their COVID-19 therapy of choice, but mostly in mild and medium severity cases, or even for prophylaxis.

Cell cultures and animal models identified that CQ/HCQ has antiviral properties [42,43] that are also specific to COVID-19 [44–46]. CQ/HCQ affects viral replication through the mechanism of infection.

CQ and more HCQ are generally safe, they are widely used worldwide, they have a low cost and wide availability, they have been helpful with prophylaxis as well as treatment of other infections.

Discovered in 1934 [59], CQ become popular after WWII. It was introduced into clinical practice in 1947 for the prophylactic treatment of malaria [60] and it has been widely used since then.

Certainly, CQ/HCQ are not drugs to be used ignoring the side effects as per every other drug, and there are certainly cases where the benefit to risk ratio is unfavorable. This does not affect the cases where conversely, the risk to benefit ratio is negligible.

Based on much more limited experience of COVID-19 infection at the beginning of this year, the Chinese panel [30] suggested the use of CQ/HCQ "*given that no contraindication applies*". Apart from comorbidities or risk factors, to be carefully considered on a case-by-case basis,

the panel also suggested avoiding simultaneous use with other medications.

CQ/HCQ has been used for COVID-19 treatment in many circumstances, showing promise, especially if used together with Azithromycin (AZM) [27–39].

It is also argued in [40–42] that prophylaxis with HCQ could prevent COVID-19 infection and improve viral shedding.

Every chemical compound may have toxicity and CQ/HCQ are no exception. The risk-to-benefit ratio of CQ/HCQ must certainly be considered in every case [54]. Especially if supplied with higher doses, the risk of using CQ certainly increases [55].

The contraindications of CQ are very well-known [56], and there is no need for experiments on COVID-19 patients who are already expected to suffer from severe side effects that are already indicated.

Independent studies in the west still find that HCQ helped hospitalized patients to better survive. A team at Henry Ford Health System in Southeast Michigan [57] published a study of 2541 hospitalized patients finding that given HCQ were less likely to die of COVID-19 infection. The overall fatality rate was 18.1% in the entire cohort, 13.5% in the HCQ group, 20.1% among those receiving HCQ plus azithromycin, 22.4% among those receiving azithromycin alone, and 26.4% for the control group.

The statistical analysis of published works of [58] includes all the published and pre-print works having as subject the use of CQ/HCQ against COVID-19. As very well summarized by c19study [58], Fig. 2, evidence from a total of 371 studies, 276 peer-reviewed, 305 comparing treatment and control groups, suggests CQ/HCQ has positive effects in most of the studies, in early treatment more than late studies. References details are given in c19study.com/hcqmeta.com. In early treatment, there is an average 64% of improvement (RR 0.36 CI [0.28–0.46]). In late treatment, there is more controversy, with still a 19% improvement, as toxicity effects are higher in very sick people, and COVID-19 is a race against the viral load build up extremely difficult to be a win at later stages.

There is overwhelming evidence that CQ and HCQ help considerably especially in the early treatment of COVID-19 infection. Mixed results are confined to cases of late treatment studies. In every other circumstance, the use of CQ/HCQ for COVID-19 infection is supported by the literature (see the list of works cited in [58]). Early treatment shows high efficacy, all the studies are positive, and 64% is the median

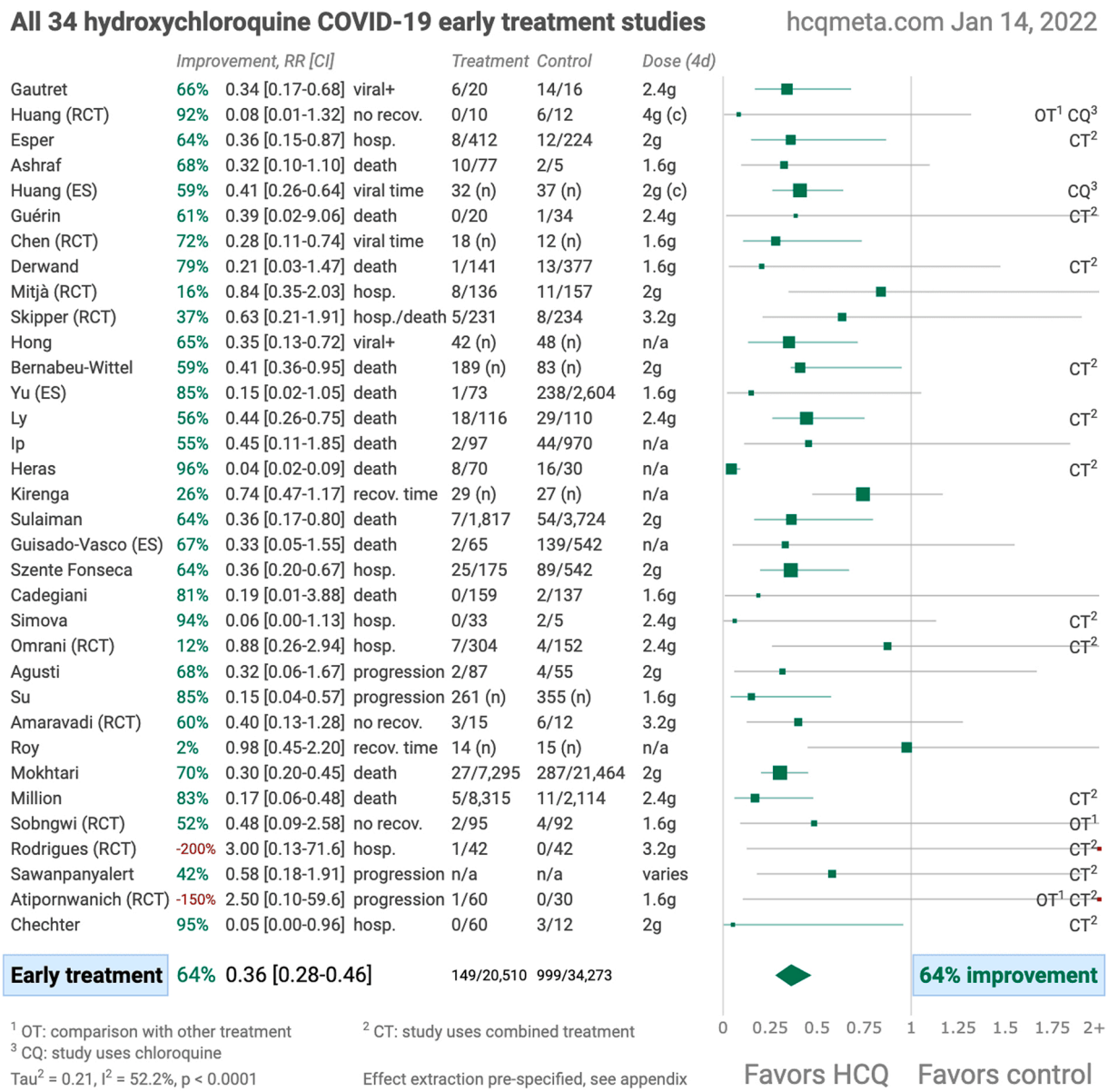

Fig. 2. Summary of CQ/HCQ studies. Images from c19study.com/hcqmeta.com. References details are given in c19study.com/hcqmeta.com.

improvement. CQ/HCQ are routinely used, for example in the United Arab Emirates [8], for high-risk asymptomatic, or mildly symptomatic. In this latter case, Favipiravir or Lopinavir-Ritonavir plus eventually Camostat are also alternatives being considered [8].

Research on the best uses of CQ/HCQ and the parameters for monitoring or controlling, for example, Zn, is important. Zn (and other parameters, such as vitamin C or vitamin D) do not have to be controlled only when CQ/HCQ is used, but always.

CQ/HCQ is a Zn ionophore pumping the mineral across cell membranes [61]. Intracellular Zn is identified as a possible anticancer and antiviral treatment. [61] investigated the interaction of Zn ions with chloroquine in a human ovarian cancer cell line (A2780). CQ enhanced Zn uptake. Free Zn ions were more concentrated in the lysosomes after the addition of chloroquine, which is consistent with previous reports showing that chloroquine inhibits lysosome function.

[62] demonstrated the virucidal activity of Zn for coronaviruses. The role of Zn in antiviral immunity is also discussed in [63]. [64] as well as [65] have proposed the use of Zn plus CQ in COVID-19 affected patients.

According to [65] CQ/HCQ inhibits pH-dependent steps of COVID-19 replication by increasing pH in intracellular vesicles and interfering with virus particle delivery into host cells. CQ/HCQ also targets extracellular Zn to intracellular lysosomes where it interferes with RNA-dependent RNA polymerase activity and COVID-19 replication. [65] hypothesize a Zn deficiency as a negative factor in the COVID-19 outbreak, and suggest the efficacy of CQ/HCQ plus Zn to be further explored in clinical trials.

[66] provides in vivo evidence that Zn sulfate in combination with HCQ may help with COVID-19. [67] suggests the use of Zn together with CQ against COVID-19. Zn may work as an antiviral through inhibition of COVID-19 RNA polymerase. This effect may improve the efficiency of CQ that is acting as a Zn ionophore. Zn may also reduce the activity of the angiotensin-converting enzyme 2 (ACE2), the receptor for COVID-19 [68]. Zn may also improve antiviral immunity acting on the interferon α production and increasing its antiviral activity [63]. Finally, Zn is anti-inflammatory by inhibiting NF-κB signaling and modulating the T-cell functions potentially limiting the cytokine storm in severe COVID-19 infections [69].

As shown in [70], based on a small but trustworthy trial (no conflict of interest) with a population of 141 confirmed COVID-19 patients in the treatment group and 377 confirmed COVID-19 patients of the same community in the untreated control group, Zn plus low dose HCQ and azithromycin helps with COVID-19 infection. After 4 days of onset of symptoms, 141 patients received triple therapy for 5 days. 4/141 treated patients were hospitalized against 58/377 untreated patients. 1/141 patients died in the treatment group versus 13/377 patients in the untreated group. No cardiac side effects were registered.

According to [71], unfortunately still a preprint (but is not the Ferguson paper [1] who drove the world to lockdown still only a flawed work only published as a preprint?), their retrospective analysis of 3473 hospitalized patients show 37% lower mortality with Zn and HCQ.

According to [72], their retrospective study of 932 COVID-19 patients shreds of evidence as Zn plus HCQ+AZ reduces mortality, ICU admission, and ventilation.

3.2. Ivermectin

COVID-19 treatment is a race against viral build-up that can be a win in many cases with the support of antiviral drugs slowing down the reproduction of Sars-Cov-2 in the early stages of infection. Several substances may help to reduce the Sars-Cov-2 reproduction in the early stages of infection, even if these substances are not a cure against COVID-19. c19study [58] summarizes the many substances which have helped to reduce the fatalities of COVID-19 infection. These substances are not 100% effective therapies (but nothing is 100% effective, vaccines included). But they help to reduce fatalities preventing viral load build-up as empirically verified in many works and consistently reported in the literature. CQ/HCQ was one of the first substances used for this purpose. Many others have followed, for example, ivermectin which is part of the very successful Uttar Pradesh home treatment kit.

In Uttar Pradesh, India's most populous state, a program sponsored by the local government and the World Health Organization (WHO) [87] had a significant positive impact on their recent COVID-19 outbreak, as also commented in the peer review [88,89]. The home treatment kit for those infected and isolated at home, of minimal cost 2.63$, included paracetamol tablets, Vitamin C, Multivitamin, Zinc, Vitamin D3, Ivermectin, and Doxycycline. Ivermectin as an antiviral is supported by many studies. The summary c19ivermectin.com [90] mentions 142 Ivermectin COVID-19 studies, 92 peer-reviewed, 75 with results comparing treatment and control groups. References details given in c19ivermectin.com.These studies show an average improvement in the prophylaxis of 83%, an average improvement in the early treatment of 66%, and an average improvement in late studies of 40%, Fig. 3.

Now, if the science of the not-for-profit organizations dislikes antivirals and only supports vaccines, and many countries in Europe and satellites states (such as Australia) prevent the use of practically every antiviral, not just CQ/HCQ or Ivermectin, this is an anomaly we only highlight here without any further comment. Zinc deficiencies have been associated with more serious consequences of COVID-19 infection in general, and reduced efficacy of antiviral therapies in many circumstances. The Uttar Pradesh kit also includes zinc (and vitamins and an antibacterial) in addition to Ivermectin.

3.3. Zn

The recent articles [73] and [74] summarize Zn effects on COVID-19 infection independent of the use of CQ/HCQ. Zn modulates antiviral and antibacterial immunity and regulates inflammatory response. In vitro experiments demonstrate that Zn possesses antiviral activity through inhibition of COVID-19 RNA polymerase. This may help the therapeutic efficiency of chloroquine that is a Zn ionophore. Zn may also decrease the activity of the COVID-19 receptor ACE2. Improved antiviral immunity by Zn may follow through up-regulation of interferon α production and increase its antiviral activity. Zn may have anti-inflammatory activity by inhibiting NF-κB signaling and modulation of regulatory T-cell functions that may limit the COVID-19 cytokine storm. Zn status may also reduce the risk of bacterial co-infection by improving mucociliary clearance and barrier function of the respiratory epithelium, as well as direct antibacterial effects against *S. pneumoniae*. Zn may also help with risk factors associated with COVID-19. However, these proposed supplementations of Zn against COVID-19 infection are not detailed and not proven by any trial.

Also according to [75], Zn may be used as a preventive and therapeutic agent alone or in combination with other strategies, but while data exists on the association of Zn with viral and respiratory tract infections, the evidence regarding COVID-19 infection is still missing.

[75] notes as most of the risk groups for COVID-19 infection experience Zn deficiency. They argue that Zn deficiency can predispose to infection and unfavorable progression of COVID-19 infection, as Zn is an antiviral and protects natural tissue barriers.

According to [76], a retrospective study of 120 hospitalized patients, Zinc and Vitamin A deficiency predisposes to the need for intubation and ICU admission in patients with COVID-19. According to [77], the status of Zn and Se transporter selenoprotein P (SELENOP), particularly low in COVID-19 patients, is important, suggesting correcting a deficit in Se and/or Zn by supplementation support convalescence. The preprint study [78] shows a correlation between low serum Zn levels and the outcome of COVID-19 infection.

Fig. 4 from c19study.com/hcqmeta.com summarizes all the evidence in the literature for the use of Zn. There are 23 studies mentioned. References details are given in c19zinc.com. While the number of available studies is certainly limited, the evidence is overwhelmingly positive, improvements towards a lower risk ranging from 37% in late

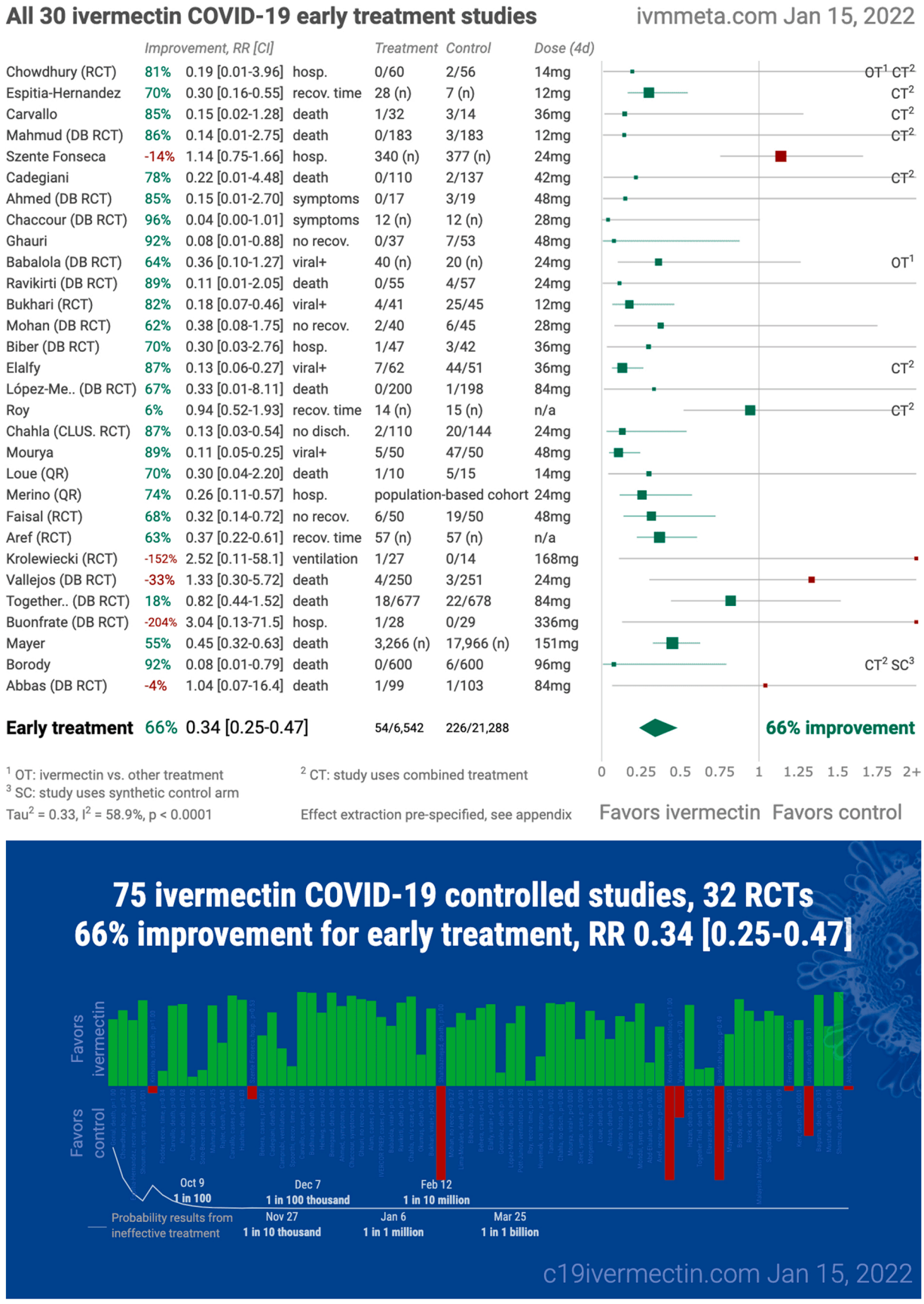

Fig. 3. Summary of Ivermectin studies. Images from c19ivermectin.com/. References details are given in c19ivermectin.com.

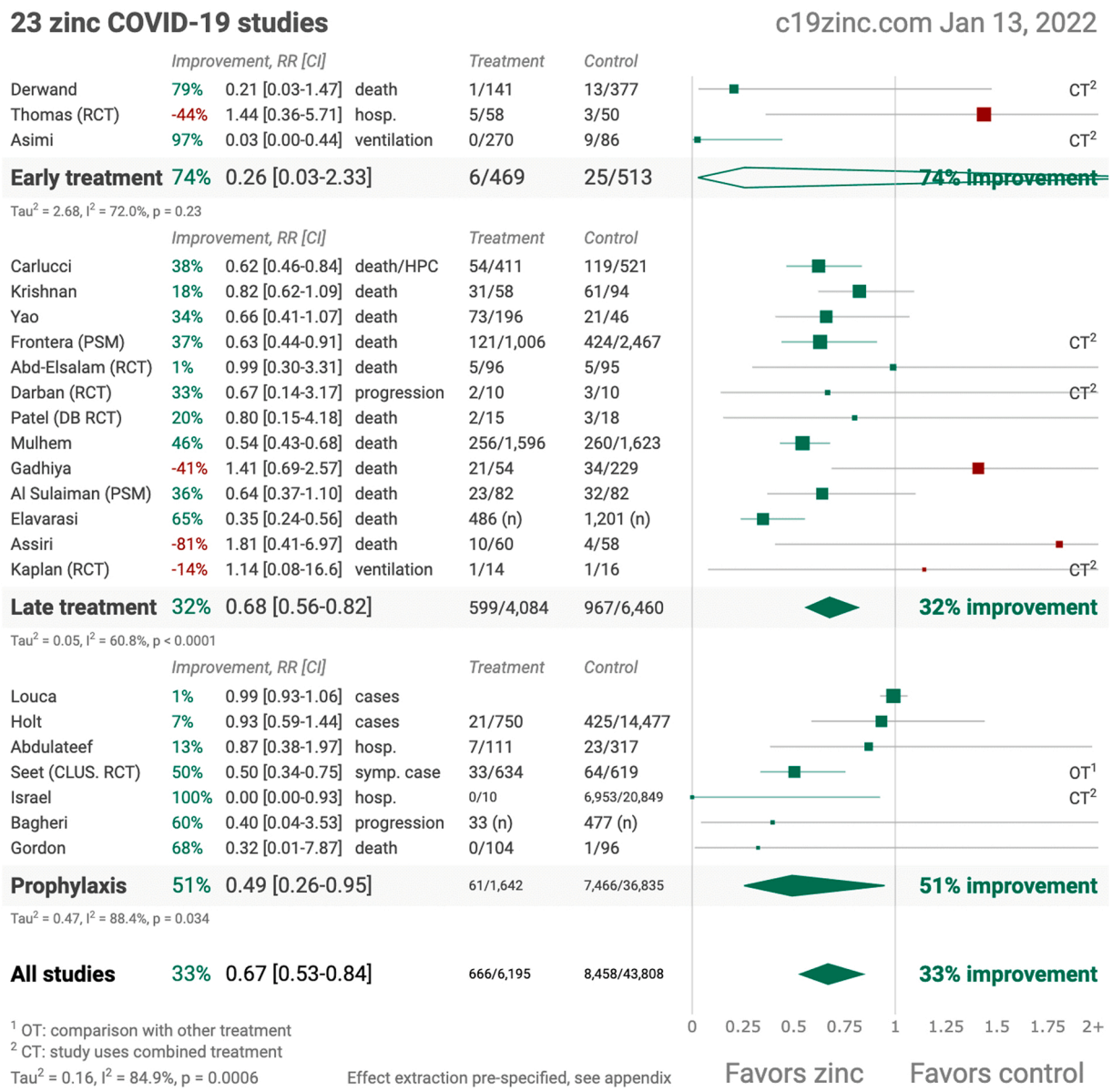

Fig. 4. Summary of Zn studies. Images from c19zinc.com/. References details are given in c19zinc.com.

treatment, RR 0.63 CI [0.53–0.74], to 78% in sufficiency, RR 0.22 CI [0.05–0.96].

Fig. 4 only reports about supplementation during treatments. Supplementation is also relevant in prophylaxis. It is of paramount importance to reduce the risk of being severely infected by COVID-19, and supplements are an important ingredient of a stronger immune system. It is wrong to argue that a strong immune system induces autoimmunity, allergies, or in the case of COVID-19 a cytokine storm and leads to death, and thus a strong immune system is as problematic as a weak one. The fatalities of COVID-19 are almost entirely limited to those with a weak immune system. An immune system must certainly be balanced, strong enough for the defense of infections and tumors, but not too strong to have unwanted or overreactions. To make the immune system strong enough for the defense of infections is the goal of nutrition plus a healthy lifestyle and appropriate food intake. The importance of nutrition and supplements is also stressed in [79–85]. Dietary changes during the COVID-19 pandemic are supported in [86].

There are many seminal reviews available in the literature on Zn use, including RCT, in silico studies, various other compounds additional to those mentioned with Zn ionophore activity excluded for the limit of space. The molecular mechanisms of Zn in immunity are similarly excluded. The reader may find this information – if interested - in [99–103].

Likewise, no mention is made of more than 50 clinical trials going on of Zn with other drugs/nutritional supplements. Zn supplementation may induce Zn toxicity. Zn toxicity levels have been seen to occur at ingestion of greater than 50 mg of Zn [96]. However, Zn has been used therapeutically at 150 mg/day for months or even years [97,98]. Specific experience with COVID-19 is missing.

4. Discussion and conclusions

The paper has summarized empirical evidence in favor of using Zn in combination with antiviral drugs against COVID-19 infection. The paper has discussed Zn, CQ/HCQ, Ivermectin, and other products that are part of the COVID-19 therapies, in terms of their statistical efficacy against COVID-19, without entering into the details of the specific mechanisms of action. While Zn alone is not a cure for COVID-19, Zn administered together with antivirals in comprehensive therapies works quite well especially in the early stages of infection, see the Uttar Pradesh

experience or the many works cited. In addition to the listed references, the work refers to the databases of c19study, including 371 studies on CQ/HCQ, 23 studies with Zn, and 142 studies with Ivermectin. Some of the studies on CQ/HCQ and Ivermectin also mention Zn. Details of the works in these databases appearing in Figs. 2 to 4 are in these databases.

Zn supplementation for COVID-19 infection is a subject of controversy, as is the case for almost every therapy or supplement suggested for COVID-19. Some studies are supporting supplementation, in prophylaxis as well as treatment in conjunction with antiviral drugs. However, contrarian studies also exist, often biased by a conflict of interest.

Secure appropriate levels of vitamins and minerals in general, and Zn in particular, is important in prophylaxis. Levels of vitamins and minerals in general, and Zn in particular, are important also during treatment with antivirals.

There are countries where, following the WHO advice, the use of antivirals, in general, is prevented (for example Belgium, the UK, or France). Then there are countries where the same antivirals, lopinavir/ritonavir, CQ/HCQ, remdesivir, etc etc are used (for example UAE, Bahrein, Qatar). The case fatality rate is certainly not only dependent on therapies. However, countries using antivirals have lower case fatality rates than countries that do not use antivirals (a factor of 10 difference).

In particular, CQ/HCQ, when not used in the most severe cases of COVID-19 infection, with dosage largely more than the one needed for mild cases, and over a much longer period, as it was done in the WHO solidarity trial, are beneficial. To check for deficiency of Zinc is also important, and if care is taken to ensure that there is no deficiency in Zinc, there is no contraindication. Thus, we may conclude that taking care of Zinc levels is sufficient, is generally positive in COVID-19 infection, with or without CQ/HCQ, in prophylaxis as well as treatment. This is also the outcome of a subdivision of literature works in positive and negative for different severity of the infection.

The work has important real-world implications for today's epidemic, with the real risk of COVID-19 becoming endemic, if only focusing on vaccines while neglecting antivirals.

Conflict of interest

The author received no funding and has no conflict of interest to declare.

Authors contribution

Single author manuscript.

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