SYSTEMATIC REVIEW

Should zinc be used for COVID-19 prophylaxis or treatment? A rapid review [version 1; peer review: awaiting peer review]

Oghenekome A. Gbinigie1, Ralph K. Akyea2

1Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, OX2 6GG, UK
2Primary Care Stratified Medicine Research Group, University of Nottingham, Nottingham, NG7 2RD, UK

Abstract

Background: There have been intensive efforts worldwide to establish effective treatments for coronavirus disease 2019 (COVID-19), with recent interest in the use of zinc as a potential therapeutic agent. The aim of this rapid review was therefore to critically appraise and evaluate the evidence for using zinc as prophylaxis and/or treatment for COVID-19.

Methods: We conducted electronic searches on 20th and 21st May 2020 of PubMed, TRIP, EPPI COVID Living Map, MedRxiv, Google Scholar and Google. All searches were updated on 11th July 2020 to check for new relevant studies. We included in vivo studies assessing the safety and effectiveness of zinc, alone or combined with other interventions, as treatment or prophylaxis for COVID-19. Studies assessing the activity of zinc against SARS-CoV-2 in vitro were also included.

Results: We identified one observational study with a high risk of bias that was suitable for inclusion. The study authors found that treatment with a combination of zinc, azithromycin and hydroxychloroquine in patients hospitalised with COVID-19 resulted in increased odds of being discharged home (adjusted odds ratio (OR) 1.53; 95% CI 1.12 to 2.09; p = 0.008) and reduced odds of death or being transferred to a hospice (adjusted OR 0.559; 95% CI 0.385 to 0.811; p = 0.002), compared with treatment with hydroxychloroquine and azithromycin.

Conclusions: We identified extremely limited evidence from a study with methodological problems of an association between improvement in certain outcomes when COVID-19 patients are treated with a combination of zinc, hydroxychloroquine and azithromycin, compared with treatment with hydroxychloroquine and azithromycin. The results of randomised clinical trials in this area should provide robust evidence of the effectiveness of zinc as treatment/prophylaxis for COVID-19.

Keywords
COVID-19, coronavirus, zinc
This article is included in the Coronavirus (COVID-19) collection.

**Corresponding author:** Oghenekome A. Gbinigie (oghenekome.gbinigie@phc.ox.ac.uk)

**Author roles:** Gbinigie OA: Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; Akyea RK: Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Validation, Visualization, Writing – Review & Editing

**Competing interests:** OAG is in receipt of funding from the Wellcome Trust. RKA is in receipt of funding from the National Institute for Health Research School for Primary Care Research (NIHR SPCR).

**Grant information:** This work was supported by the Wellcome Trust through a Clinical PhD Fellowship to OAG [203921]. RKA is funded by a National Institute for Health Research School for Primary Care Research (NIHR SPCR) PhD Studentship award. The views expressed are those of the authors and not necessarily those of the NIHR, the NHS, or the Department of Health. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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**How to cite this article:** Gbinigie OA and Akyea RK. Should zinc be used for COVID-19 prophylaxis or treatment? A rapid review [version 1; peer review: awaiting peer review] Wellcome Open Research 2020, 5:188
https://doi.org/10.12688/wellcomeopenres.16173.1

**First published:** 07 Aug 2020, 5:188 https://doi.org/10.12688/wellcomeopenres.16173.1
Introduction

Whilst efforts to develop novel treatments for coronavirus disease 2019 (COVID-19), are ongoing, a number of existing treatments have been repurposed to try to treat this disease. One such candidate treatment is zinc.

Zinc is a micronutrient primarily obtained through dietary consumption. Rich sources of zinc include oysters, red meat, poultry, beans, nuts and fortified cereals. It is estimated that 20% of the population worldwide are at risk of zinc deficiency. Zinc has a number of functions including helping to maintain proper functioning of the immune system.

There is evidence that treatment with zinc may improve outcomes in some viral infections. In a meta-analysis of 12 studies of children aged under five years, the authors found that zinc supplementation for at least three months resulted in an 8% reduction in the incidence rate of respiratory illness compared with placebo (pooled rate ratio 0.92; 95% CI 0.85 to 0.99). When the results of eight trials of high dose zinc supplementation (greater than 75 mg zinc per day) were pooled in a systematic review by Hemila, there was a significant reduction in the duration of common colds, compared with placebo.

The mechanism by which zinc might inhibit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) activity is uncertain. In an in vitro study, Te Velthuis and colleagues assessed the activity of SARS-CoV in Vero-E6 cells, when the cells were treated with zinc and pyrithione. Pyrithione is a zinc ionophore, facilitating zinc ion transport across cell membranes into the intracellular space. The authors found that there was an additive inhibitory effect on SARS-CoV replication when Vero-E6 cells were treated with zinc combined with pyrithione, compared with treatment with either zinc or pyrithione alone. Furthermore, the authors found that the treatment of isolated SARS-CoV RNA-dependent RNA polymerase with zinc inhibited viral RNA synthesis in a dose-dependent fashion. Given that there is 79% genomic homology between SARS-CoV and SARS-CoV-2, it is possible that zinc may have a similar effect on SARS-CoV-2.

In vitro studies have shown that zinc deficiency is linked to an increase in levels of certain pro-inflammatory cytokines such as TNF-alpha and IL-8. It is, therefore, possible that zinc deficiency could exacerbate the cytokine storm seen in some cases of COVID-19, which can in turn trigger acute respiratory distress syndrome.

There are reports of clinicians using zinc as a treatment, combined with other drugs, for COVID-19. Donald Trump has also reported taking zinc as part of a COVID-19 prophylaxis regime. In light of this, it is important to establish whether there is evidence to support this approach. The aim of this review is to evaluate the evidence for the safety and effectiveness of zinc for COVID-19 treatment and/or prophylaxis.

Methods

Electronic database searches were conducted in PubMed, TRIP, MedRxiv and EPPI COVID Living Map on 20th May 2020. Additional searches were conducted in Google and Google Scholar on 21st May 2020 (see extended data for link to search strategy). All of the searches were re-run on 11th July 2020. We stopped searching Google and Google Scholar when we reached a page with no results relevant to this review. Searches were limited to studies published from 2019 onwards. The authors performed title and abstract screening and full text screening independently for separate sets of databases. The authors independently determined studies that were suitable for inclusion in the review, with disagreements resolved by discussion.

We included in vitro studies assessing the activity of zinc, alone or combined with other treatments, against SARS-CoV-2. We included in vivo studies assessing the safety and effectiveness of treatment or prophylaxis with zinc, alone or combined with other interventions, for COVID-19. We included studies that provided data to allow comparisons to be made between patients who did, and did not, receive zinc. We included participants of all ages and genders. No study setting or language restrictions were imposed. For inclusion, studies needed to report clinical and/or laboratory outcome data, such as time to recovery and viral load. Systematic reviews were used as a source of reference.

Forward citation and reference screening were performed on the included study. Both authors independently extracted data from the included study and performed a risk of bias assessment using the GRADE criteria, with disagreements resolved through discussion.

Results

Electronic database searches on 20th May 2020 identified 105 studies. The first seven pages (70 links) of Google Scholar were searched, and the first 25 pages of Google were searched (250 links). After title and abstract screening, 33 eligible studies were identified. Of these, one study was suitable for inclusion in this review. All searches were re-run on 11th July 2020, and no further studies suitable for inclusion were identified (see Figure 1 - flow diagram for study inclusion). The included study was rated as very low quality according to the GRADE criteria (see Table 1).

The study, conducted by Carlucci and colleagues, was a retrospective observational study assessing the clinical outcomes of patients hospitalised with COVID-19 in four New York hospitals (see Table 2). On 25th March 2020, clinicians in these hospitals added zinc to their usual treatment regime of hydroxychloroquine (HCQ) and azithromycin (AZT) for COVID-19 patients. The authors compared the outcomes of 411 patients receiving a combination of HCQ (400 mg OD followed by 200 mg BD orally for five days), AZT (500 mg OD orally, duration not reported) and zinc (220 mg BD orally for five days), with 521 patients receiving HCQ and AZT without zinc. The authors excluded patients who were additionally receiving other experimental COVID-19 treatments, such as lopinavir/ritonavir.

After adjusting their analyses for patient admission after 25th March 2020, the authors found that the addition of zinc to
HCQ and AZT resulted in significantly increased odds of being discharged home (adjusted odds ratio (OR) 1.53; 95% CI 1.12 to 2.09; p = 0.008) and reduced odds of death or being transferred to a hospice (adjusted OR 0.559; 95% CI 0.385 to 0.811; p = 0.002). However, they found that the addition of zinc did not significantly reduce the need for intensive care.
Table 2. Characteristics of included study.

<table>
<thead>
<tr>
<th>Authors (Year)</th>
<th>Carlucci et al., 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>USA</td>
</tr>
<tr>
<td>Setting</td>
<td>NYU Langone Health hospitals</td>
</tr>
<tr>
<td>Number of participants</td>
<td>932; with zinc (n=411); without zinc (n=521)</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>With zinc (63.19 ± 15.18); without zinc (61.83 ± 15.97)</td>
</tr>
<tr>
<td>Sex, Females</td>
<td>With zinc (n=147, 35.7%); without zinc (n=201, 38.6%)</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Patients who were admitted to the hospital with at least one positive test for COVID-19, received hydroxychloroquine and azithromycin, and were subsequently discharged from the hospital, transitioned to a hospice, or died</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Patients who were never admitted to hospital or receiving other investigational therapies for COVID-19</td>
</tr>
</tbody>
</table>
| Treatment      | • Hydroxychloroquine (400 mg once followed by 200 mg PO BID for five days) and azithromycin (500mg once daily) plus zinc sulphate (220 mg PO BID for five days) or  
|                | • Hydroxychloroquine (400 mg once followed by 200 mg PO BID for five days) and azithromycin (500mg once daily) |
| Findings       | Addition of zinc associated with:  
|                | • Increased odds of being discharged home  
|                | • Decreased odds of mortality/transfer to a hospice  
|                | Addition of zinc not associated with:  
|                | • Length of hospitalisation  
|                | • Duration of mechanical ventilation  
|                | • Need for invasive ventilation  
|                | • ICU duration  
|                | • Need for ICU |

Abbreviations: BID: bis in die; ICU: Intensive Care Unit; SD: standard deviation; USA: United States of America

(adjusted OR 0.733; 95% CI 0.471 to 1.14; p = 0.168) or the need for invasive ventilation (adjusted OR 0.804; 95% CI 0.487 to 1.33; p = 0.396). The addition of zinc to HCQ and AZT was also not associated with a change in the length of hospitalisation, the duration of mechanical ventilation nor the duration of time spent in the intensive care unit (p values of 0.646, 0.667 and 0.504, respectively). The authors conclude that the addition of zinc to HCQ and AZT may have some therapeutic benefit for COVID-19 patients.

There are, however, some important points that must be considered. The study design is observational; we cannot use these results to make causal inferences about the effect of zinc on outcomes in COVID-19 patients. The observed associations provide some information about zinc when combined with HCQ and AZT, but do not provide information about zinc as a standalone treatment. The authors do not report baseline levels of zinc in patients, hence, we cannot tell whether this might have influenced the observed associations.

The authors adjusted their analyses for date of admission to hospital. However, the baseline characteristics and hospital medications of the study participants show that there were some significant differences between the two groups that were not adjusted for in their analyses, including systolic blood pressure, troponin and lymphocyte count. It is possible that adjusting for these possible confounders may lead to different results. Propensity score matching of observational studies and randomisation of clinical trials are means of ensuring that baseline characteristics between groups are similar. We did not identify any clinical trials assessing the use of zinc as treatment or prophylaxis for COVID-19 that were suitable for inclusion. However, we have identified more than a dozen clinical trials registered to this purpose on the WHO International Clinical Trials Registry Platform (ICTRP) (see Table 3).

Discussion

We identified very limited evidence from a single observational study with a high risk of bias of an association between treatment with a combination of zinc, HCQ and AZT in hospitalised COVID-19 patients and increased odds of being discharged home and reduced odds of death or being transferred to a hospice, compared with treatment with a combination of HCQ and AZT. The study found no association between triple treatment with zinc, HCQ and AZT and reduced need for intensive care or invasive ventilation, compared with HCQ.
<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Scientific title</th>
<th>Recruitment Status</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTRN12620000454976</td>
<td>A prospective, single centre, randomized open labelled comparative clinical study to evaluate the effectiveness of Siddha medicine, Kabasura kudineer and vitamin c-zinc supplementation in the management of asymptomatic COVID 19 patients.</td>
<td>Not Recruiting</td>
<td>Australia</td>
</tr>
<tr>
<td>NCT04326725</td>
<td>A Randomised Controlled Trial of Early Intervention in Patients Hospitalised with COVID-19: Favipiravir versus Hydroxychloroquine &amp; Azithromycin &amp; Zinc vErsEs Standard CaRe - PIONEER</td>
<td>Recruiting</td>
<td>Turkey</td>
</tr>
<tr>
<td>NCT04351490</td>
<td>A randomized open labeled clinical study to compare the effectiveness of Kabasura kudineer and Vitamin-C Zinc supplementation in the management of asymptomatic SARS-CoV-2 patients</td>
<td>Not recruiting</td>
<td>France</td>
</tr>
<tr>
<td>EUCTR2020-001449-38-GB</td>
<td>A Randomized Study Evaluating the Safety and Efficacy of Hydroxychloroquine and Zinc in Combination With Either Azithromycin or Doxycycline for the Treatment of COVID-19 in the Outpatient Setting</td>
<td>Not recruiting</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>NCT04377646</td>
<td>A Randomized, Double-Blind, Placebo-Controlled Phase IIa Study of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the Prevention of COVID-19 Infection</td>
<td>Not recruiting</td>
<td>Tunisia</td>
</tr>
<tr>
<td>NCT04342728</td>
<td>A study on melatonin and Vitamin C and zinc efficacy in patients with COVID19 hospitalized in intensive care unit of Semnan Kowsar Hospital</td>
<td>Recruiting</td>
<td>United States</td>
</tr>
<tr>
<td>NCT04370782</td>
<td>Coronavirus Disease 2019- Using Ascorbic Acid and Zinc Supplementation (COVIDAt6Z) Research Study A Randomized, Open Label Single Center Study</td>
<td>Recruiting</td>
<td>United States</td>
</tr>
<tr>
<td>NCT04384458</td>
<td>COVID-19 Prophylaxis With Hydroxychloroquine Associated With Zinc For High-Risk Healthcare Workers Involved In Suspected, or Confirmed Cases of COVID-19.</td>
<td>Not recruiting</td>
<td>Brazil</td>
</tr>
<tr>
<td>IRCT20151228025732N52</td>
<td>COVID-19 Prophylaxis with hydroxychloroquine, Vitamin D, and Zinc supplementation in Danish nursing home residents - a randomized controlled trial - COVID-19 PREVENTION</td>
<td>Not Recruiting</td>
<td>Iran (Islamic Republic of)</td>
</tr>
<tr>
<td>NCT04407572</td>
<td>Does Zinc Supplementation Enhance the Clinical Efficacy of Chloroquine/Hydroxychloroquine in Treatment of COVID-19?</td>
<td>Not recruiting</td>
<td>Turkey</td>
</tr>
<tr>
<td>NCT04447534</td>
<td>Effect of a Combination of Nitazoxanide, Ribavirin and Ivermectin Plus Zinc Supplement on the Clearance of COVID-19: a Pilot Sequential Clinical Trial</td>
<td>Recruiting</td>
<td>Egypt</td>
</tr>
<tr>
<td>NCT04335084</td>
<td>Efficacy and safety of Hydroxychloroquine, Azithromycine and Zinc for the treatment of patients with SARS-Cov2 infection in Senegal: a dose ranging randomised trial. COVID-19</td>
<td>Recruiting</td>
<td>United States</td>
</tr>
<tr>
<td>PACTR202005622389003</td>
<td>Evaluating the immune boosting ability of a homeopathic therapeutic strategy involving a nosode Tuberculinum 1M, followed by Zincum Metallicum 6C, Chininum Arsenicosum 6C and Calc Phos 6x in asymptomatic novel corona virus disease (Covid-19 illness) vulnerable risk group.</td>
<td>Not Recruiting</td>
<td>Senegal</td>
</tr>
</tbody>
</table>
and AZT. Furthermore, there was no association with the treatment regime including zinc and a change in the length of hospitalisation, the duration of mechanical ventilation nor the duration spent in intensive care. We did not identify any studies evaluating the use of zinc as a standalone treatment for COVID-19, nor zinc (alone or in combination) as COVID-19 prophylaxis.

Comparison with existing literature

There is some in vitro evidence that chloroquine and HCQ have anti-SARS-CoV-2 activity\(^{19-21}\). However, some believe that the primary function of these drugs in COVID-19 is to act as a portal of entry for zinc into cells, allowing zinc to inhibit SARS-CoV-2 activity\(^{22}\). Xue and colleagues report that chloroquine is a zinc ionophore in an in vitro study\(^{23}\). The authors added zinc alone, and zinc combined with chloroquine to the extracellular medium of A2780 cells (human ovarian cancer cell line). They found that there was significantly increased intra-cellular uptake of zinc when the A2780 cells were treated with zinc combined with chloroquine, compared with zinc alone. Moreover, they found that chloroquine encouraged accumulation of zinc in certain intracellular organelles such as lysosomes. The authors also found that chloroquine combined with zinc enhanced the ability of chloroquine to cause cell apoptosis, compared with chloroquine alone. These in vitro study findings provide support for the purported synergy between chloroquine (and its derivatives) and zinc, as suggested by Carlucci et al\(^{16}\). However, in vitro studies cannot fully replicate conditions inside the human body and we cannot infer that these findings would be replicated in vivo.

In a pre-print, Derwand and colleagues\(^{24}\) report the results of a retrospective case series of patients in the community in New York State who tested positive for COVID-19. In total, 141 consecutive patients - who were aged over 60 years, aged 60 years and below and experiencing breathlessness, or

<table>
<thead>
<tr>
<th>Trial ID</th>
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<th>Recruitment Status</th>
<th>Countries</th>
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<tbody>
<tr>
<td>CTRI/2020/05/025215</td>
<td>High-dose intravenous zinc (HDIVZn) as adjunctive therapy in COVID-19 positive critically ill patients: A pilot randomized controlled trial</td>
<td>Not Recruiting</td>
<td>India</td>
</tr>
<tr>
<td>CTRI/2020/07/026340</td>
<td>Impact of Zinc and Vitamin D3 Supplementation on the Survival of Institutionalized Aged Patients Infected With COVID-19</td>
<td>Not Recruiting</td>
<td>India</td>
</tr>
<tr>
<td>NCT04472585</td>
<td>Prospective study to assess therapeutic role of Zinc in COVID-19 patients</td>
<td>Recruiting</td>
<td>Pakistan</td>
</tr>
<tr>
<td>ACTRN12620000557932</td>
<td>Sub-cutaneous Ivermectin in Combination With and Without Oral Zinc and Nigella Sativa: a Placebo Randomized Control Trial on Mild to Moderate COVID-19 Patients</td>
<td>Not Recruiting</td>
<td>Australia; United States of America; Germany</td>
</tr>
<tr>
<td>NCT04392427</td>
<td>The effect of zinc on the treatment and clinical course of patients with SARS-cov2 (COVID-19)</td>
<td>Not recruiting</td>
<td>Egypt</td>
</tr>
<tr>
<td>NCT04395768</td>
<td>The Study of Quadruple Therapy Zinc, Quercetin, Bromelain and Vitamin C on the Clinical Outcomes of Patients Infected With COVID-19</td>
<td>Not recruiting</td>
<td>Australia</td>
</tr>
<tr>
<td>EUCTR2020-001363-85-DK</td>
<td>COVID-19 Prophylaxis with hydroxychloroquine, Vitamin D, and Zinc supplementation in Danish nursing home residents – a randomized controlled trial - COVID-19 PREVENTION</td>
<td>Not Recruiting</td>
<td>Denmark</td>
</tr>
<tr>
<td>CTRI/2020/06/025874</td>
<td>A randomized open labeled clinical study to compare the effectiveness of Kabasura kudineer and Vitamin-C Zinc supplementation in the management of asymptomatic SARS-CoV-2 patients</td>
<td>Not Recruiting</td>
<td>India</td>
</tr>
<tr>
<td>CTRI/2020/06/026045</td>
<td>Zinc Vitamin D and b12 Levels in the Covid-19 Positive Pregnant Women</td>
<td>Not Recruiting</td>
<td>India</td>
</tr>
</tbody>
</table>
were aged 60 years and below, were symptomatic and had at least one co-morbidity - received triple therapy with zinc sulfate 220 mg once a day, HCQ 200 mg twice a day and AZT 500 mg once a day. The control group comprised independent public reference data for 377 COVID-19 positive patients in the same community who received usual care. The authors found that triple therapy was associated with significantly reduced odds of hospitalization (OR 0.16; 95% CI 0.06 – 0.5; p < 0.001) and a non-significant reduction in all-cause mortality (OR 0.2; 95% CI 0.03 – 1.5; p = 0.16).

However, no demographic data, clinical characteristics or co-morbidities were available for the control group; it is therefore not possible to tell whether the treated group and controls were comparable. Furthermore, the authors report that triple therapy was ‘well tolerated,’ yet 21% of treated patients (30/141) reported adverse events, including weakness, gastrointestinal side effects and rashes. No safety data was available for the control group. Of note, this study provides some information about zinc in combination with HCQ and AZT. It does not, however, provide information about zinc as a standalone therapy, nor does it tell us whether the addition of zinc to HCQ and AZT has an additive benefit compared with dual treatment with HCQ and AZT.

Strengths and limitations
We believe that there are considerable strengths to this rapid review. We conducted the review quickly to facilitate timely dissemination of the findings, with less than a week between the searches being updated and the review being submitted for publication. We used a broad search strategy to maximise capture of relevant studies. We also searched pre-print servers and Google/Google Scholar to increase our chances of capturing grey literature.

However, we recognise the limitations of this rapid review. Given the rapid pace at which COVID-19 studies are being published, it is possible that we may have missed studies relevant to this review, particularly studies not published in English. We tried to minimise this risk by not applying any language restrictions to our eligibility criteria. Furthermore, whilst we adhered closely to the methods used in a systematic review (see reporting guidelines for link to PRISMA checklist25), we did not perform dual screening at the title and abstract or full-text screening stages.

We also recognise significant limitations of the identified evidence. We identified a single study, with high risk of bias, assessing the use of zinc as a treatment in combination with other interventions for COVID-19. We cannot use this data to make any assertions about zinc as a standalone treatment, nor as prophylaxis for COVID-19. The study data came from four hospitals in New York; we do not know whether the observed associations are generalizable to other populations. The authors did not report baseline levels of zinc. If zinc does have favourable effects in COVID-19, this benefit may be influenced by the zinc status of the individual, with zinc replete patients benefiting less from zinc supplementation. Finally, the study was published as a pre-print and has not been formally peer-reviewed.

Implications for clinical practice and research
In light of the extremely limited evidence identified, and the methodological flaws outlined above, there is insufficient evidence to recommend that clinicians prescribe zinc for COVID-19 treatment or prophylaxis outside of clinical trials. The included study used secondary care data, thus, we did not identify any evidence for the use of zinc in primary care settings. We are aware of 24 studies, mostly clinical trials, which have been registered to investigate the effectiveness of zinc as COVID-19 treatment/prophylaxis. Some of these studies are being conducted in primary care settings. The results of well-conducted, randomised, adequately powered clinical trials should provide primary and secondary care clinicians with definitive evidence for the effectiveness of zinc as a COVID-19 therapeutic/prophylactic agent. It is critically important that these clinical trials report safety data. Zinc supplementation can cause gastrointestinal side effects such as nausea and vomiting, diarrhoea, gastritis, and dysgeusia26,27.

Conclusion
There is extremely limited evidence of poor quality that treatment of hospitalised COVID-19 patients with a combination of zinc, HCQ and AZT is associated with increased odds of being discharged home and reduced odds of death or being transferred to a hospice, compared with treatment with HCQ and AZT combined. We did not identify any evidence for the use of zinc as prophylaxis for COVID-19, nor as a standalone treatment. The results of clinical trials including zinc in the intervention regimens should provide definitive evidence of the effectiveness and safety of this treatment in the context of COVID-19.

Data availability
Underlying data
All data underlying the results are available as part of the article and no additional source data are required.

Extended data
Figshare: Search strategy - “Should zinc be used for COVID-19 prophylaxis or treatment? A rapid review”. https://doi.org/10.6084/m9.figshare.12728432.v114

This project contains the following extended data:
- Appendix_1_zinc_search_strategy_Wellcome_Open_Research.docx (Study search strategy)

Reporting guidelines
Figshare: PRISMA checklist for ‘Should zinc be used for COVID-19 prophylaxis or treatment? A rapid review’ https://doi.org/10.6084/m9.figshare.12730532.v115

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Acknowledgments:
We would like to thank Nia Roberts (Specialist Librarian) for her help with search terms for the database searches.
References


