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Study Protocol

Rapid review protocol: Zinc for the prevention or treatment of COVID-19 and other coronavirus-related respiratory tract infections

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ABSTRACT

Background: The global COVID-19 pandemic has prompted an urgent search for effective interventions. SARS-CoV-2 mortality/morbidity risk increases with age and for those chronic disease co-morbidities, both of which are associated with lower zinc status, as is the risk of infection.
Methods: Rapid review methods will be applied to a systematic review of zinc for the prevention or treatment of SARS-CoV-2 and viral respiratory tract infections in humans. Included are published studies reporting randomised and quasi-randomised controlled trials that compare zinc intervention to placebo and/or other comparator interventions. English and Chinese language databases will be searched for primary studies of viral respiratory tract infections and clinical trial registries for SARS-CoV-2 infections. Due to concerns about indirectness, studies evaluating non-SARS-CoV-2 coronavirus infections will be rated down by one level, and non-specific or confirmed non-coronavirus viral infections will be rated down by two levels. Review constraints include (1) using Google translate when screening articles published in languages other than English or Chinese and limited translation (2) following calibration, only one reviewer will screen articles, extract data, appraise quality and conduct the analysis, (3) prioritising data extraction and meta-analyses of SARS-CoV-2 studies and critical outcomes of other viral infections, followed by high risk groups and (4) reporting important preliminary findings prior to peer review if necessary.
Discussion: The application of these rapid review methods and broadening the inclusion criteria to include other coronavirus-related viral respiratory tract infections aims to enable a timely evidence appraisal of priority research questions and dissemination of results.
Study registration: PROSPERO CRD42020182044.

1. Background

1.1. Description of condition and setting

The global COVID-19 pandemic has prompted an urgent search for pharmaceutical and traditional, complementary and integrative medicine (TCIM) interventions to assist with prevention, treatment and recovery. Data from all countries indicate that the case fatality and morbidity rates from SARS-CoV-2 increases with age and for those with non-communicable chronic disease co-morbidities,[1–4] both of which are associated with lower zinc status.[5–7]

SARS-CoV-2 is a member of beta genus coronaviruses closely related to SARS-CoV. Currently, there is no specific antiviral treatment for SARS-CoV-2, nor for the other coronaviruses commonly associated with severe respiratory disease and mortality such as SARS-CoV and MERS-CoV.

Coronaviruses are responsible for up to 10% of upper respiratory tract infections.[8] Epidemiological surveillance suggests that coronavirus infections may be more common in adults and with co-infections. For instance, five-year surveillance data (2009–2014) in China of adult and paediatric populations with acute respiratory tract infections identified a viral cause in 48.2% of cases.[9] Of the 18 viral pathogens screened for, coronaviruses (HCoV OC43, 229E,

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NL63, HKU1) were the fourth most common (4.66%, $n = 582/12,502$) and were associated with the highest co-infection rate (47.07%, $n = 313/665$). Adults were significantly more likely than children to be infected with coronavirus. Rates of coronavirus infection in other populations and countries have ranged from 2% to 10%.[10–15]

1.2. Description of intervention

Zinc is a common nutritional supplement that is formulated as a stand-alone intervention or as a combination nutraceutical containing other vitamins, minerals and nutrient. Most zinc supplements are administered orally either as a single or divided dose, in the form of a lozenge, tablet, capsule or syrup. Some products are formulated for intramuscular or intravenous administration. The daily recommended dietary intake (RDI) of elemental zinc is around 2 mg for infants up to 6 months of age and gradually increases to 11 mg for males and 8 mg for females older than 13 years.[16] Tolerable upper limits for zinc are estimated to be 7 mg for children aged 1–3 years of age, increasing up to 25 mg for adults and females of any age who are pregnant or lactating. The no observed adverse effect level (NOAEL) for adults is around 50 mg/day.[17]

1.3. How the intervention might work

Through several mechanisms, zinc has the potential to reduce the risk of viral respiratory tract infections, including SARS-CoV-2, and shorten the duration and severity of illness. In vitro studies have demonstrated that zinc can inhibit the enzymatic activity and replication of SARS-CoV RNA polymerase and may inhibit angiotensin-converting enzyme 2 (ACE2) activity.[18–20]

Zinc may also modify the host's response to an infection as it is an essential co-factor element with a broad range of functions in the body. Many of the beneficial effects of zinc appear to take place at the cell membrane.[8,21,22] Zinc (Zn2+) reduces the permeability of the cell membrane without penetration into or damage to the cell. Like other astringents, zinc alters the capillary epithelium, thus inhibiting transcapillary movement of plasma protein that in turn may reduce local oedema, inflammation, exudation, and mucus secretion.[21,22]

Zinc insufficiency/deficiency is known to diminish antibody and cell-mediated immunity in humans, is associated with an increased risk of infections, and may only become apparent upon immune system provocation.[23,24] Zinc has an essential role in immune and airways function, wound healing and tissue repair that in turn, may delay or prevent recovery from viral respiratory illnesses.[25–31] Other consequences of zinc deficiency include an increased risk of vitamin A deficiency that is also critical for immune function, due to carrier proteins and activation enzymes being dependant on sufficient zinc status.[32]

1.4. Why it is important to do this review

The potential role of zinc in preventing or treating SARS-CoV-2 infections is yet to be systematically evaluated and, along with other nutritional supplements, was not mentioned in a recent narrative review of TCIM for the treatment of coronavirus disease 2019 (COVID-19).[33] The findings of systematic reviews of related populations are promising; however, the reviews are limited by population, intervention, or are out of date. A 2016 Cochrane review that concluded zinc supplementation was effective for the prevention of pneumonia in children aged two to 59 months.[34] A 2017 systematic review of zinc lozenges found a 33% (95% CI: 21–45%) reduction in common cold duration compared to placebo.[35] The most recent 2013 Cochrane review of all types of zinc formulations for the common cold was later withdrawn due to methodological concerns that also applied to their earlier 2011 review,[36,37] leaving a 2000 review.[38] Also withdrawn from the Cochrane library is a 2017 protocol to update this review as it could not be completed within the editorial timeline.[39] Finally, zinc supplementation is not without potential safety concerns, that includes copper deficiency associated with higher doses and prolonged intake.[17]

1.5. Research question

The primary objective of this rapid review is to assess the effects of zinc on the incidence, duration and severity of acute upper or lower respiratory tract infections caused by SARS-CoV-2 infection in people of any age and of any zinc status when used as a preventive supplement or as a therapy.

The secondary objectives are to assess the effects of zinc on the incidence, duration and severity of acute upper or lower respiratory tract infections

1. caused by other coronavirus species, with a focus on SARS-CoV and MERS-CoV infections;
2. predominantly caused by viruses; and
3. in subgroups of populations at risk of zinc insufficiency/deficiency and those with a higher risk of severe acute respiratory syndrome (SARS) caused by SARS-CoV-2 infection.

2. Methods

2.1. Study design

A rapid review of primary studies with meta-analyses will commence at the end of April 2020 with the aim of completing the review by the end of June 2020. The rapid review methods applied were informed by leading methodologists,[40–44] including the most recent Interim Guidance from the Cochrane Rapid Reviews Methods Group, March 2020.[45]

Review constraints include (1) using Google translate when screening articles published in languages other than English or Chinese and limited translation (2) following calibration, only one reviewer will screens articles, extract data, appraise quality and conduct the analysis, (3) prioritising data extraction and meta-analyses of SARS-CoV-2 studies, followed by other coronavirus infections and high risk groups and (4) reporting important preliminary findings prior to peer review if necessary.

2.2. Protocol registration

This protocol was registered on 24 April 2020 with PROSPERO: CRD42020182044.[46] Minor edits have been made to improve the clarity of a priori registered statements. Other changes to the protocol are explicitly stated. This includes the decision to expand the inclusion criteria from only respiratory infections likely to be caused by a coronavirus to any viral infection and to tighten the exclusion criteria to respiratory illnesses that are almost always caused by a viral infection. All post hoc changes will be reported with the published results.

2.3. Criteria for considering studies for this review

Studies. Included are randomised controlled trials and quasi-randomised controlled trials. Excluded are systematic reviews, non-randomised studies of interventions and studies without a concurrent control, such as case series and case reports.

Due to the need for expediency, review constraints include: studies reported only as an abstract (e.g. conference abstract), with incomplete outcome data or published in languages other than

English or Chinese will be included, however, the authors will not be contacted for further data nor clarification. Attempts will be made to translate studies published in languages other than English or Chinese, otherwise Google translate will be used to convert the text to English.

Population Included are people of any age, gender and zinc status who are (1) at risk of contracting an acute upper or lower viral respiratory tract infection, including healthy populations, (2) have a confirmed SARS-CoV-2 or other respiratory infection caused by a coronavirus species, including SARS-CoV and MERS-CoV, and/or (3) have either a laboratory confirmed viral respiratory tract infection (any virus) or an acute respiratory tract infection where the cause is most likely viral such as the common cold, non-seasonal rhino-sinusitis, laryngitis, flu-like illness, healthy people with acute bronchitis, or young children with pneumonia.

Excluded are people with respiratory tract infections or other upper/lower respiratory illnesses when the cause is confirmed not to be a viral infection, or a non-viral cause is common. This includes adolescents and adults with pneumonia, people of any age with bronchitis and a concurrent underlying health problem/comorbidity, and people of any age with otitis externa/media infections.[47] People with epiglottis or croup-like symptoms are also excluded.

Studies of eligible and ineligible participants will be included; however, the certainty of the evidence will be downgraded due to indirect/nonexclusive treatment effects on coronaviruses. If separate data are available for the eligible populations, only this information will be extracted for analysis.

Intervention/exposure. Included are any zinc conjugates such as salts or amino-chelates, either as a single ingredient, in any form (e.g. tablet, syrup, lozenge, spray, liquid), dose and duration, administered via oral, intranasal, sublingual, transdermal, intramuscular or intravenous routes.

Excluded are co-interventions and zinc administered alongside other nutraceuticals, herbs or pharmaceuticals unless both the intervention and control groups receive the intervention. The exception are co-ingredients where the primary purpose is to increase zinc's absorption or cellular retention and co-ingredients are unlikely to have any additional therapeutic effects on respiratory viral infections (e.g. chloroquine[48]). The a priori list of allowed co-ingredients are sulphur containing amino acids (e.g. histidine, methionine, cysteine, homocysteine, and taurine), low molecular weight acids (e.g. EDTA and citrate) and vitamin B12 (cobalamin, cyanocobalamin, methylcobalamin, adenosylcobalamin) for intestinal absorption of zinc,[49] and vitamin B6 (pyridoxine, pyridoxal, pyridoxamine and their 5′-phosphates) and magnesium for cellular retention of zinc.[50]

Comparators/control. Included are no zinc supplementation, placebo, another nutraceutical or usual care active treatment, and dose comparators with no control group.

Context/setting. There are no limits on the setting (home, community or hospital), location, nor the country in which the study was conducted. Studies in which the formulation of zinc was adapted to ensure its prophylactic or treatment mechanisms of effect will be included, providing the zinc intervention was intended to prevent and/or treat mechanisms of respiratory viral disease.[51] Studies investigating zinc for prophylaxis or treatment on mechanisms not associated with respiratory viral infections are excluded.

Outcome measures. Outcomes will not be used as a criterion for including nor excluding studies.[52] Studies reporting on at least one of the outcomes of interest rated as critically important or important, regardless of outcome priority in the primary study, may be included in the meta-analyses. The priority is to analyse critically important outcomes. If a study reports on other respiratory tract infection related outcomes that were not specified a priori as outcomes of interest for this review, the results will be noted in a narrative synthesis, but not necessarily pooled for meta-analyses nor reported in the summary of findings table.

As per the registered protocol, the outcome measures and their rating as critical, important and not important has been updated and informed by proposed core outcome sets for COVID-19[53,54] and other core outcome measures and sets published on the COMET Initiative database.[55,56] Any further changes will only be made prior to commencing the analysis and will be reported accordingly.

For studies evaluating the prevention of respiratory tract infections, the critical outcomes of interest are the incidence and frequency of respiratory tract infections, and all-cause mortality. Important outcomes are the duration of illness and progression to more severe illness.

For studies evaluating the treatment of respiratory tract infections, the critical outcomes are the duration of illness, symptom severity, progression to more severe illness and all-cause mortality. Important outcomes are duration of respiratory support and adjunctive care (e.g. oxygen) and time taken for absorption/resolution of pulmonary infiltration.

For all studies, important outcomes also include health related quality of life and adverse events.

2.4. Search methods for identification of studies

The database search has been extended since protocol registration. Along with PubMed, selected EBSCO host databases (Academic Search Complete, Allied and Complementary Medicine Database (AMED), Alt Health Watch, CINAHL Plus with Full Text, Health Source, and PsycINFO) and the China Knowledge Resource Integrated Database (CNKI), Embase and Cochrane CENTRAL will also be searched and the inclusion criteria for CNKI will be extended from SARS-CoV-2 to that outlined in the population study types. Additionally, the U.S. National Library of Medicine Register of Clinical Trials (ClinicalTrials.gov); International Standard Randomised Controlled Trial Number Register (ISRCTN); World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP); Cochrane CENTRAL and Chinese Clinical Trial Registry will be searched for ongoing trials evaluating 2019-nCoV infections registered in 2019 or 2020. No other restrictions will be applied, including to publication date and language.

Review constraints include not systematically conducting bibliography searches of included articles and with the exception of clinical trials registries, not repeating the search prior to the final analysis. Minor adjustment to search terms may be made if the title and abstract screen reveals too few or excessive results. Prespecified terms will then be in/excluded to balance specificity and sensitivity of the search. Further details of the search strategy and terms are uploaded in a separate supplementary file.

2.5. Data collection and appraisal

Screening and data extraction. Review constraints include all reviewers screening the first 30–50 title/abstracts and 5–10 full papers for calibration and consistency, followed by only one experienced reviewer[44] independently screening the remaining titles/abstracts and full papers. To reduce the risk of missing eligible studies, a low threshold for inclusion will be applied to screening decisions and a second reviewer will check the studies excluded at full paper screen.

Additional constraints include:

- using Google Translate as needed to screen titles, abstracts and full papers not published in English or Chinese;

- only including potentially eligible trials published in languages other than English or Chinese if it is possible to translate and extract the data in a timely manner; and
- except for studies evaluating 2019-nCoV, the authors will not be contacted for further information.

Any potentially eligible studies where there is insufficient information to include them in the review, including those awaiting translation into English, will be moved to the 'Studies Awaiting Classification' table and noted in the PRISMA flow diagram.

EndNote[57] reference management software and electronic spreadsheets of piloted forms will be used for screening and data extraction. One reviewer will extract data about study design, participant number and characteristics, interventions, control/comparators, outcomes measures, effect size and direction.

Review constraints include all reviewers extracting 3–5 full papers for calibration and consistency, followed by data extraction by one reviewer only. For studies published in English, a second reviewer will check for errors. Attempts will be made to identify a second reviewer for studies published in languages other than English, otherwise Google translate will be used to convert the text to English. Any discrepancies will be resolved by consensus.

Risk of bias. The Cochrane RoB 2.0 tool,[58,59] will be used to appraise the risk of bias (RoB) of the outcomes in included studies that are critical outcomes of the review. For the remaining studies, the RoB 2.0 assessment will be applied to the study's primary outcome. Review constraints include all reviewers independently assessing the RoB of 3–5 studies for calibration and consistency, followed by only one reviewer assessing RoB for the remaining studies. For studies published in English, a second reviewer will verify the judgements and support statements. Attempts will be made to identify a second review for studies published in languages other than English. Any discrepancies will be resolved by consensus.

2.6. Data synthesis

Measures of effect. It is expected that studies will use different measurement tools and time points. Outcomes will be based on the number of participants, in preference to the number of events (e.g. number of people with an infection or event rather than the number of infections or events admissions per person). Outcome measures will be ranked according to their objectivity, validity, reliability and responsiveness to change. If multiple instruments are used to measure the same construct, attempts will be made to transform alternative instrument scores to the most common reference instrument score in order to improve clinician interpretability and precision.[60]

Time points will be grouped according to acute (less than 4 weeks), short-term (less than 3 months from randomisation or study enrolment), intermediate-term (more than 3 months but less than 1 year from randomisation or study enrolment), long-term (more than 1 year from randomisation or study enrolment), or not specified. Long-time points have greater importance for evaluating the prevention of illness; conversely, short-term time points are more important for evaluating the treatment of illness. The units of analyses in studies with multiple trial arms will be considered. Decisions to pool or split data for analyses will be guided by published recommendations.[51] If a study reports repeated observations not amenable to time to event analysis, a maximum of two time points per study will be extracted to minimise unit-of-analysis error. These will be selected based on those most clinically important.

As per the registered protocol, the measures of effect have been edited so they are more specific and more closely reflect published research on core outcome sets for COVID-19.[53,54] This includes only conducting a meta-analysis of critical outcomes rather than the previously stated maximum of 7 outcomes, and only reporting critical outcomes in the summary of findings table. Any further changes will only be made prior to starting the analysis and will be reported accordingly.

Critical outcomes for prevention of viral respiratory tract infections

1. Proportion of participants with one or more respiratory tract infections
2. Number of respiratory tract infections (episodes) per person
3. All-cause mortality rate

Important outcomes for prevention of viral respiratory tract infection

4. Number of symptomatic days per person
5. Number of symptomatic days per episode
6. Proportion of participants requiring hospital admission

Critical outcomes for treatment of mild to moderate viral respiratory tract infections

1. Symptomatic survival (i.e. remaining symptomatic) up to 14 days from onset of symptoms
2. Symptom severity score at the time when symptoms most commonly peak for the specific viral infection (e.g. day 3 of symptoms for common cold)
3. Total symptom severity score during the study period
4. Complication-free survival (not progressing to severe/critical illness or all-cause mortality) up to 60 days from onset of symptoms

Important outcomes for treatment of mild to moderate viral respiratory tract infections

5. Number of days from onset of symptoms to symptomatic recovery
6. Number of days from onset of symptoms to negative PCR result
7. Proportion of participants with complications (e.g. progressing to severe/critical or deceased from any cause) during the study period
8. Proportion of participants requiring hospital admission

Critical outcomes for treatment of severe to critical respiratory tract infections

1. Overall survival (all-cause mortality) up to 60 days from study enrolment
2. All-cause mortality rate up to 60 days during study period
3. Complication-free survival (not progressing from severe to critical, requiring mechanical ventilation, or all-cause mortality) up to 60 days from study enrolment
4. Proportion with complications (e.g. progressing from severe to critical, requiring mechanical ventilation, or deceased from any cause) during the study period
5. Symptomatic survival (i.e. remaining symptomatic) up to 6 weeks from onset of symptoms

Important outcomes for treatment of severe to critical respiratory tract infections

6. Number of days on mechanical ventilation
7. Number of days requiring critical/intensive care
8. Number of days from study enrolment to symptomatic recovery

9. Number of days from study enrolment to negative PCR
10. Number of days from study enrolment to absorption/resolution of pulmonary infiltration

For all studies other important outcomes are

1. Health-related quality of life score
2. Frequency of adverse events
3. Frequency of severe adverse events
4. Frequency of zinc withdrawal due to adverse reactions

Dichotomous outcomes will be presented as risk ratios (RR) in preference to odds ratios (OR). Time-to-event outcomes will be presented as hazard ratios (HR). Continuous data will be calculated as weighted mean differences (WMD) or standardised mean differences (SMD). Relevant 95% confidence intervals (CIs) will be calculated. The number needed to treat for additional benefit or harm (NNTB, NNTH) will be calculated as appropriate.

Review constraints may include excluding underpowered outcomes of interest from the meta-analyses if there are at least two adequately powered studies reporting the same outcome.[61] Also, the study authors will not be contacted for missing data. The potential impact of attrition bias/missing outcome data on the outcome of interest will be evaluated in domain 3 of the Cochrane Risk of Bias 2.0 tool.[58]

Quantitative analysis. RevMan 5.3[62] and R software packages will be used for the meta-analyses. Review constraints include limiting the analysis to critical outcomes (the exception will be SARS-CoV-2 infections) and one researcher entering the data and conducting a meta-analysis for an outcome, with verification from a second reviewer. Any discrepancies will be resolved by discussion until a consensus is achieved. Any subgroup analysis will be prioritised according to directness of evidence and relevance to at risk populations and limited to a maximum of 3 outcomes.

Clinical methodology and statistical heterogeneity will be considered in our decisions to pool studies.[63] Statistical heterogeneity will be assessed using the I^2 statistic, and homogeneity assessed with the chi^2 test. I^2 statistics will be interpreted according to guidelines from the Cochrane Handbook[51] (0–40%: might not be important; 30–60%: may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity; 75–100%: considerable heterogeneity). If statistical heterogeneity is identified, we will explore possible explanations using a priori subgroups (listed below under Subgroups).

If data of ten or more RCTs can be combined, a funnel plot will be created to explore the potential for small study effects (such as publication bias). Funnel plots will be visually inspected and statistically analysed using Egger's regression for continuous outcomes and the Harbord score for dichotomous outcomes.[64]

The random-effects model will be used as it is assumed there will be clinical heterogeneity across the included studies. The inverse variance meta-analytic method will be used. Sensitivity analyses will be conducted by investigating the point estimate change if meta-analyses are limited to low RoB studies and by investigating the impact of outlier studies.

Missing data will not be imputed. The implications will be considered when appraising the risk of bias and interpreting the certainty of the evidence.

Sensitivity and subgroup analyses. Where possible, subgroup analysis of different zinc interventions according to dose, duration, formulation and administration and for the following discrete population groups will be conducted. We will use meta-regression to investigate dose effects.

The most important sub-group populations are those experiencing more severe illness and at a higher risk of mortality from COVID-19 infections and with a coinciding high risk for zinc deficiency/insufficiency. Known risk factors includes older adults,[5,6,65,66] people with chronic diseases,[3,67–69] residents of aged care facilities,[6,70] obesity[71,72] and possibly some CALD, socioeconomic or restrictive dietary groups.[5,73,74]

1. Age (e.g. infants, children, adults, older adults)
2. Country/ethnicity
3. Type of illness (e.g. common cold, pneumonia)
4. Cause of infection (e.g. SARS-CoV-2, SARS-CoV, MERS-CoV, any coronavirus, any presumed viral infection)
5. Severity (e.g. mild to moderate and managed at home; moderate to severe requiring hospital admission; critical requiring admission to intensive care)
6. COVID-19 risk factors (e.g. 60 years or older, chronic disease, obesity, health care worker, aged care resident)
7. Zinc status such as populations with confirmed zinc deficiency, people with insufficient dietary intake of zinc (e.g. people with limited access to animal foods,[75–77] consume plant based diets high in phytic acids e.g. cereals, starchy roots, tubers and legumes,[74] and older adults[6,7]) and people with increased biological need for zinc (e.g. pregnant and breastfeeding women,[74,78] early post-natal infants,[78,79] children,[80] people with chronic diseases, [67,81,82] and people with alcohol dependency[83]).

Grading evidence quality. One reviewer will assess the overall quality of evidence (certainty of effect estimates) for each of the critical and important outcomes by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, in which RCTs begin as high-quality evidence and are rated down by 1 or more of 5 categories of limitations according to risk of bias, inconsistency, indirectness, imprecision, and reporting bias.[84] A second reviewer will check for consistency and all authors will review and agree to the final GRADE ratings via consensus.

It is anticipated that due to the recent emergence of the COVID-19 pandemic, direct evidence for COVID-19 will be sparse. For this reason, evidence from studies evaluating respiratory tract infections caused by other viruses including heterogenous populations were the vast majority of infections are likely to be viral are included. This will necessarily lead to important indirectness issues. To address this, we plan to rate down once for estimates deriving from populations with non-2019nCoV coronaviruses (e.g. MERS-CoV, SARS-CoV and HCoV OC43, 229E, NL63, HKU1) and twice for heterogeneous viral populations (e.g. studies on the "common cold", childhood pneumonia) or confirmed non-coronavirus infections (e.g. rhinovirus, influenza).

Data synthesis The findings will be structured around the condition (e.g. pathogen, type/severity of illness), outcome measures (critical, important, other), risk of bias assessment for critical outcomes and primary study outcomes, characteristics of the intervention (dose, duration, formulation, administration etc.), control (placebo or comparative intervention) and study characteristics (study design, participants, context, funding source). A summary of findings table will be limited to the critical outcomes and up to 3 critical or important outcomes for any subgroup analyses. Studies only reporting important outcomes will be narrated only. Other outcomes reported will be noted, however, the results will not be reported. Relevant results from clinical trials registries will be narrated.

2.7. Reporting and dissemination of results

Due to the urgency of disseminating evidence-based information, review findings will be reported as they become available and in the following order of priority, that begins with studies of populations with SARS-CoV-2 infection, followed by SARS-CoV

and MERS-CoV infections, and then populations with higher risk of SARS-CoV-2 infections and/or increased morbidity/mortality. Dissemination may include the use of medRxiv.org for example, as "preprints" of review findings prior to formal peer review.

3. Discussion

Rapid reviews respond to time and resource constraints that legitimately prevent the full application of the recommended methods for a high-quality systematic review.[45] Notwithstanding all efforts should be made to optimise the rigour, transparency and reproducibility of a rapid review, beginning with a protocol whenever possible.[45]

The decision to apply rapid review methods was made in response to a call from the World Naturopathic Federation (WNF) for researchers to quickly generate robust evidence summaries abour the potential role of commonly used naturopathic interventions.[85] The rapid review method constraints outlined in this protocol align with in the recently released *Interim Guidance from the Cochrane Rapid Reviews Methods Group*.[45] Constraints include not systematically searching the bibliography of all included articles, not contacting the authors for further information, using automated translation for studies published in languages other than English or Chinese, a single reviewer screening the majority of titles, abstracts and full-text articles, a single reviewer appraising the risk of bias and extracting data for analysis, and a staged approach, as needed, to the analysis and reporting of results. Steps have been implemented to optimise consistency and verify accuracy, as there are risks when only one reviewer screens, extracts and appraises the studies.[86] Other acceptable rapid review constraints that were not applied include the decision to conduct meta-analyses when possible, not to restrict the search by date or language, and to search more databases than the minimum three databases recommended by the Cochrane Rapid Reviews Methods Group (i.e. MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL)).[45] The decisions to extend the database search and include a reviewer fluent in Chinese aligns with recent recommendations for rapid reviews of TCIM.

Systematic reviews are time and resource intensive,[87] particularly when the number of included studies are large, as is likely to be the case for zinc for the prevention or treatment of any viral respiratory infection. The application of the rapid review methods outlined in this protocol has therefore made it feasible to broaden the inclusion criteria to include other coronavirus-related viral respiratory tract infections. In doing so, whilst the evidence is less direct and will be downgraded, an empty review is avoided. As Petitti et al. from the US Preventative Task Force once said:

> "Decision makers do not have the luxury of waiting for certain evidence. Even though evidence is insufficient, the clinician must still provide advice, patients must make choices, and policy makers must establish policies".[88]

The application of these rapid review methods and broadening the inclusion criteria to include other coronavirus-related viral respiratory tract infections should enable a timely evidence appraisal of priority research questions and dissemination of results.

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Author contributions

Conceptualization: SA. Methodology: JH, SA, JG, JB, GY. Writing – Original Draft: JH, SA, JG. Writing – Review & Editing: GY, JB, DM, SL.

Conflict of interest

This review was not undertaken as part of a contractual relationship with any donor or sponsor.

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Ethical statement

This research did not require an ethical approval as it does not involve any human or animal experiment.

Data availability

The data will be made available upon request.

Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.imr.2020.100457.

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