South African National Department of Health
Evidence summary
Component: COVID-19

EVIDENCE SUMMARY

Date: 23 September 2021

Research question: Should zinc be used in the management of COVID-19 patients?

Key findings

- This evidence summary evaluated the evidence base for the use of zinc for management of COVID-19.
- Two well reported trials were identified - One in hospitalized patients (n = 33) and one in outpatients (n = 108).
- The trials were underpowered to answer the question of whether zinc, when added to standard treatment, improves any of the important healthcare outcomes (e.g. mortality, clinical recovery, requirements for ventilation).
- The currently available evidence does not support the use of zinc except in a clinical trial setting.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: The Committee suggests that zinc supplements not be used for adults with COVID-19.
Eligible patients with COVID-19 in South Africa should be considered for enrolment in relevant therapeutic trials.
Rationale: The evidence of efficacy and safety is very uncertain at this point. Studies were underpowered to detect clinically relevant outcomes or improvement in clinical outcomes; and there is an uncertain risk of serious adverse effects.
Level of Evidence: Very low certainty evidence
Review indicator: Evidence of safety and/or efficacy that is sufficient to change the recommendation.

Therapeutic Guidelines Sub-Committee for COVID-19: Andy Parrish (chair), Gary Reubenson (vice-chair), Marc Blockman, Karen Cohen, Andy Gray, Tamara Kredo, Renee De Waal, Jeremy Nel, Helen Rees.

Note: Due to the continuous emergence of new evidence, the rapid review will be updated when more relevant evidence becomes available

Background: Following multiple queries from participants attending the COVID-19 rapid reviews webinar series by the National Department of Health, an evidence review was conducted for zinc in the management of COVID-19.

Zinc is an essential mineral[1] and zinc supplementation has been postulated to reduce mortality in severe pneumonia.[2 3] Zinc modulates antiviral[4] and antibacterial immunity[5] and participates in the inflammatory response, specifically regulating T-lymphocytes[6 7] that may reduce the cytokine storm in COVID-19. In vitro studies have shown that increased intracellular zinc concentrations impairs replication of a number of corona viruses[8], though not specifically SARS-CoV2. Therefore, there has been research interest to investigate whether zinc supplementation can improve clinical outcomes in COVID-19 with currently 26 clinical trials of zinc as mono- or adjuvant therapy registered on the International Clinical Trials Registry Platform.[9]

Zinc supplementation is associated with copper deficiency that may result in reversible hematologic defects[10] and potentially irreversible neurologic manifestations.[11] Common side-effects of zinc toxicity includes hypotension, pulmonary oedema, diarrhoea, vomiting, jaundice and oliguria.[12]

EVIDENCE REVIEW:

An evidence summary rather than a complete rapid review was conducted, as there is very limited randomised controlled trial data for zinc in the management of COVID-19.

Randomised-controlled trials:

A Cochrane supported meta-analysis[13]of two randomised controlled trials (RCTs)[14 15] showed that there remains significant uncertainty whether zinc is more effective and safer than standard care in treating patients COVID-19 (see Table 1 for summary of findings; and Table 2 for characteristics of the included studies).

Patel et al recruited 33 hospitalised participants[14], and Thomas et al enrolled 108 outpatients[15]. The trials compared zinc to placebo[15] or standard of care .[14] The mean age of the outpatient cohort was 45.2 years[15], and approximately 62 years in the trial of hospitalised patients.[14] The proportion of men ranged from 38% to 64% across the studies. The studies did not include adolescents, pregnant or breastfeeding women.

Outpatients were dosed daily with 50mg of zinc gluconate (7.15 mg of elemental zinc) for 10 days from confirmation of SARS-CoV2 infection; whilst hospitalised patients received high dose intravenous zinc chloride 0.5 mg/kg/day (equivalent to 0.24 mg/kg/day elemental zinc) for 7 days, or until hospital discharge or death.

Ambulant patients reported on their symptoms and participants who received standard of care achieved a 50% reduction in their symptom severity scores at a mean of 6.7 days (SD 4.4 days) compared with 5.9 days (SD 4.9 days) for the zinc gluconate arm; whilst adverse effects occurred more frequently amongst participants on zinc supplementation compared to standard of care (18.5% vs 0%); with gastrointestinal events commonly reported.

The trial amongst hospitalised patients did not reach its target enrolment (due to stringent public health measures), and thus it could not be determined whether high-dose intravenous zinc improves clinical outcomes (increases oxygen saturation levels to reduce hospitalisation, oxygen supplementation or ventilation). No serious adverse events were reported, but three participants in the zinc cohort reported infusion site irritation.

The impact of zinc compared to no treatment for either hospitalised or outpatients with COVID-19 does not suggest benefit and does suggest gastrointestinal adverse effects are more common in the hospitalised cohort. However, this data is underpowered and therefore our level of confidence in these results is very low. There is uncertainty regarding the impact of zinc on clinically relevant patient outcomes (such as death, rate of hospitalisation, duration of hospital stay, need for oxygen supplementation or mechanical ventilation or clinical recovery) in the management of COVID-19. The certainty of the evidence is assessed as very low due to the small study numbers resulting in very serious imprecision. In addition, there were concerns with deviations from the intended intervention, missing data and measurement of adverse events in the open-label trial of ambulatory participants. One trial was conducted in a single institution that may limit generalisability; whilst results from the other multi-centre USA-based study may not be generalisable to the South African context.

Furthermore, there were insufficient data on the harms associated with high-dose zinc supplementation.

Guidelines:

1. *National Institutes of Health (USA)*[16] recommends against using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial (BIII).
2. *Australian guidelines for the clinical care of people with COVID-19*[17]*d*oes not recommend routine use of zinc for the treatment of COVID-19, outside of randomised trials with appropriate ethical approval.

Table 1: Summary of findings for zinc vs standard of care/placebo for mild/moderate/severe/critical/unclear COVID-19

Patient or population: Mild/Moderate/Severe/Critical/Unclear COVID-19
Setting: Worldwide
Intervention: Zinc
Comparison: Standard care/placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard care	Risk with Zinc				
Clinical improvement D28	833 per 1,000	**717 per 1,000** (458 to 1,000)	**RR 0.86** (0.55 to 1.32)	33 (1 RCT) [b]	⊕◯◯◯ VERY LOW [c,d,]	
WHO progression score (level 7 or above)D28	167 per 1,000	**133 per 1,000** (25 to 697)	**RR 0.8** (0.15 to 4.18)	33 (1 RCT) [b]	⊕◯◯◯ VERY LOW [c,d]	
All-cause mortality D28	167 per 1,000	**133 per 1,000** (25 to 697)	**RR 0.8** (0.15 to 4.18)	33 (1 RCT) [b]	⊕◯◯◯ VERY LOW [c,d]	
Serious adverse events	0 per 1,000	**0 per 1,000** (* to *)	**RR 18.15** (1.09 to 302.17)	108 (1 RCT) [e]	⊕◯◯◯ VERY LOW [f,g,h]	zero events in the control group

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Last update: 1 June, 2021
b. Patel O, 2020
c. Indirectness downgraded by 1 level: single study from a single institution, therefore results in this population might not be generalizable to other settings
d. Imprecision downgraded by 2 levels: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and very low number of participants
e. Thomas S, COVID A to Z, 2021
f. Risk of bias downgraded by 1 level: some concerns regarding deviations from the intervention, missing data, and outcome measurement
g. Indirectness downgraded by 1 level: We presume that the adverse event rates and the corresponding relative risks, are similar across diverse settings, therefore not downgraded for indirectness
h. Imprecision downgraded by 1 level: due to low number of participants

Source: Living mapping and living network meta-analysis of COVID-19 studies: Zinc vs standard of care/ placebo[13].

CONCLUSION:

. The currently available evidence does not support the use of zinc except in a clinical trial setting.

Reviewer(s): Ms TD Leong, Dr T Kredo

Declaration of interests: TDL (National Department of Health, Affordable Medicines Directorate, Essential Drugs Programme); TK (Cochrane South Africa, South African Medical Research Council; TK is partly supported by the Research, Evidence and Development Initiative (READ-It) - READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies); have no interests to declare in respect of zinc supplementation for COVID-19.

Table 2: Characteristics of completed RCTs

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
Patel O et al, 2021 (13) ACTRN12620000454976	RCT: quadruple blinding Single-centre in Australia Follow-up duration (days): 28 Funding: Australian Urologic Cancer Research Trust	n=33 Mean age: ±62 yrs 21 males Severity: Mild: n=15 / Moderate: n=13/ Severe: n=2 Critical: n=3 *Inclusion criteria:* Age ≥ 18 years; PCR-confirmed SARS-CoV-2 infection or by other laboratory assay; hospitalized SARS-CoV-2 infection of any duration; SaO2 ≤ 94% or Pao2: Fio2< 300 mg Hg; No chronic kidney disease *Exclusion criteria:* Age <18 or pregnant or lactating female; zinc allergy; Child C liver disease; eGFR ≤ 30 mL/min/1.73 m2; organ transplant which requires active immunosuppressive treatment which can interfere with kidney function; CPR within 14 days; DNR (do not resuscitate) DNI (do not intubate) orders; Death is deemed imminent or inevitable during this admission, and either the attending physician, patient or substitute decision-maker is not committed to active treatment; receiving dialysis or imminent need of dialysis; HIV infection; known/ suspected oxalate nephropathy or hyperoxaluria, scurvy, chronic iron overload, G-6PD deficiency; zinc for another indication; haemochromatosis	• Zinc, 0.5 mg/kg IV once a day over 3 hours [elemental zinc concentration 0.24 mg/kg/day] ***vs*** • Control Total duration of therapy: maximum of 7 days	*Primary outcomes:* • Level of oxygenation - oxygen flow (in litres/min) required to maintain blood oxygen levels > 94% and the worst (lowest) PaO2/FiO2 ratio in ventilated patients	*Primary outcomes:* • Not reported, as target sample size not reached. *Other outcomes:* (zinc vs control) • *Mean serum zinc on Day 6:* Zinc gp - increased serum zinc levels above the deficiency cutoff of 10.7 µmol/l, but not the control gp; (p < .001). • *Clinical improvement (Day 28):* 10/15 (67%) vs 14/18 (78%) • *WHO progression score (level 7 or above)D28:* 2/15 (14.3%) vs 3/18 (16.7%). • *Death (Day 28):* 2/15 (14.3%) vs 3/18 (16.7%). • *SAEs:* None • *Adverse events:* 3 three participants in the zinc group reported infusion site irritation.	• Pilot phase IIb study • Published article, the study registry, statistical analysis plan and protocol were available for data extraction and risk of bias assessment. • The study did not reach its target sample size due to reduction of eligible participants. Thus, several outcomes, including some primary outcomes, listed in the protocol and registry were not reported. Quote: "*Our study did not reach its target enrollment because stringent public health measures markedly reduced new patient presentations to zero. Consequently, we could not adequately assess the primary outcome of whether HDIVZn reduced the level of oxygenation in non-ventilated (Figure 3) or improved the PaO2/ FiO2 ratio in the four ventilated patients (data not shown) and other clinical efficacy outcomes (Table 2)*" • The study did not provide the proportion randomised per arm (only the overall number randomised). • ITT analysis **Overall judgement with regards to risk of bias:** ***"LOW RISK"***[13] • *Randomisation*: Allocation sequence random and allocation was concealed. **LOW RISK** • *Deviations from intervention:* Blinded study (participants and personnel/carers). ITT analysis. **LOW RISK** • *Missing outcome data: 39 participants randomized; 33 participants analyzed.- Risk assessed to be low for the outcomes: Mortality (D28). Clinical improvement (D28). WHO score 7 and above (D28).* **LOW RISK** • *Measurement of the outcome:* Blinded study (outcome assessor). **LOW RISK** • *Selection of the reported results:* Trial analysed as pre-specified for the outcomes collected. **LOW RISK**

Thomas S et al, 2021 (14) NCT04342728	Open-label RCT Multi-centre in USA Follow-up duration (days): 28 Funding: not reported	n=108 4 treatment arms – vitamin C (n1=48); standard of care (n2=50); zinc (n3=58); zinc+vitamin C (n4=58) **NB: This review focused on zinc (n=58) vs standard of care (n=50)** Mean age : 45.2 years 82 males Severity : Unclear *Inclusion criteria:* New diagnosis in an outpatient setting; Aged ≥18 years; menstrual period within the past 30 days or previous sterilization; Negative pregnancy test *Exclusion criteria:* Hospitalized; Resided outside of Ohio or Florida; pregnant; Actively lactating; advanced chronic kidney disease; Liver disease awaiting transplantation; History of calcium oxalate kidney stones.	Zinc gluconate 50mg/day (7.15 mg of elemental zinc) for 10 days ***vs*** Standard care (SOC)	*Primary outcomes:* Number of days required to reach a 50% reduction in symptom severity score from peak symptom score.	**Zinc group vs control group** *Primary outcomes:* • **Days to reach a 50% reduction in symptom severity score:** ○ **SOC: 6.7 days (SD 4.4 days)** ○ **Zinc: 5.9 days (SD 4.9 days)** ○ Vitamin C: 5.5 days (SD 3.7 days) ○ Zinc+vitamin C: 5.5 days (SD 3.4 days); (overall p = 0.45). *Other outcomes:* • **Non-serious adverse effects:** ○ **Zinc: 18.5%** ○ **SOC: 0%** ○ Vitamin C: 39.5% ○ Zinc+vitamin C: 32.1%; (overall P < 0.001) GIT events were most commonly reported.	• Open-label RCT using an ITT analysis. • Primary outcomes were reported in the report but not prespecified in the trial registr – e.g. mortality.. • Some outcomes from the registry were omitted in the publication (e.g., period of mechanical ventilation). • Secondary outcomes (e.g., number of patients with specific symptoms) were reported in the publication, but not pre-specified in the trial registry. • The study was terminated early due to futility, and target sample size not reached Quote: "*Due to slower than expected enrollment, an interim analysis was conducted at approximately 40% of expected enrollment (214 of 520 patients). Stopping for superiority would only be considered if any treatment group achieved P < .001 compared with placebo. Stopping for futility would be considered if the conditional power was less than 30% for any (or all) treatment groups compared with placebo…The OSMB met on October 23, 2020, and recommended stopping the study for futility. The futility criteria was met for the 3 active treatment groups compared with the usual care group.*" • Patient-reported symptoms to determine symptom severity scores. **Overall judgement with regards to risk of bias:** "*MODERATE RISK*"[13] • *Randomisation*: Allocation sequence random and allocation was concealed. **LOW RISK** • *Deviations from intervention:* Unblinded study. No information on concomitant antivirals and biologics. **MODERATE RISK** • *No missing outcome data:* 214 participants randomized; 214 participants analyzed for mortality outcome; 196 patients analyzed for adverse events. Risk assessed to be some concerns for the outcome: Adverse events. **MODERATE RISK** • *Measurement of the outcome:* Unblinded study (outcome assessor). Risk assessed to be some

						concerns for the outcome: Adverse events. **MODERATE RISK** • *Selection of the reported results:* Adverse events were pre-specified. Mortality outcome was not pre-specified, Risk assessed to be low for the outcomes: Mortality. Adverse events. **MODERATE RISK**

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