EVIDENCE SUMMARY

Should Zinc be used as an adjunctive treatment for COVID-19 in Children?

Evidence Review by: Joanna Marie Tan, MD DPPS, Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS, Ma. Lucila Perez MD MSc FPPS, Leonila F. Dans, MD, MSc, FPPS

Recommendation

We suggest <u>against</u> the use of zinc as adjunctive treatment of COVID-19 in children.

Certainty of Evidence: Low
Strength of Recommendation: Weak

Consensus Issues
The panel voted against the use of zinc as adjunctive treatment of COVID-19 in children based on the indirect evidence from six randomized controlled trials done in adults that showed inconclusive results in outcomes of in-hospital mortality, duration of recovery, length of hospital stay and hospitalization among ambulatory patients. The panel also agreed that there is a small to moderate potential for harm with moderate costs. However, the panel concurred that zinc treatment is important for those with documented zinc deficiency. They also agreed that this recommendation is subject to change until higher certainty of evidence is available.

Key Findings

Indirect evidence from 6 RCTs showed inconclusive results on the efficacy of zinc as adjunctive treatment, for the outcomes of in-hospital mortality, duration of recovery, length of hospital stay, and hospitalization among ambulatory patients. Adverse events were significantly higher in the group given zinc, and included local site irritation, metallic taste and GI intolerance.

Introduction

Zinc can inhibit the enzymatic activity and replication of SARS-CoV RNA polymerase through its effect on the virus attachment, infection, and uncoating. Zinc also stabilizes the cell membrane contributing to the prevention of virus entry into the cell. It was also demonstrated that Zinc may enzymatically inhibit viral replication through alteration of the proteolytic processing of replicase polyproteins and RNA-dependent RNA polymerase, potentially reducing the risk of viral respiratory tract infections, including SARS-CoV-2, and shorten the duration and severity of illness [1-3].

Zinc is also an essential co-factor element that may also modify the host's response to an infection. It has an essential role in immune and airway function, wound healing and tissue repair through protection from oxy-radicals which plays a vital role in the delay of recovery from viral respiratory illnesses [4]. It also plays a role in immunological response, through diminishing excessive inflammation and risk for cytokine storm by decreasing the activity of nuclear factor kappa B, through negative feedback mechanism [5].

Zinc deficiency is also often linked to impaired functions of all immune cells and is related to susceptibility by at least 16% to various respiratory infection worldwide, implying a crucial link

between zinc deficiency and the risk of infections, higher complication rates, prolonged hospital stay and higher mortality rate from COVID-19 hence suggesting the benefits of zinc supplementation [6].

The results of the studies regarding the utility of adjunctive zinc for children with pneumonia are conflicting, with several studies failing to show benefit of the use of adjunctive zinc supplementation on treatment failure or time to recovery [7,8]. A study in India of 700 infants (7 to 120 days old) with serious bacterial infections (pneumonia, sepsis, and diarrhea) suggested a beneficial effect of adjunctive zinc. Infants who were also treated with zinc (5 mg twice daily by mouth) had significantly less treatment failure (defined as a need to change antibiotics), as compared with those treated with placebo (10 versus 17) or a need for intensive care, or death at any time within 21 days. The absolute risk reduction for treatment failure was at 6.8 percent (95% CI 1.5-12.0) [9].

Five RCTs done among children with Lower Respiratory tract infection (ALRI) showed significant decrease on the hours of stay in the hospital among those treated with Zinc with a mean difference of -9.54 between Zinc and standard of care with 95% CI of -13.21 and -5.86 and a p value of <0.00001 [10-14]. Treatment failure was also evaluated wherein four RCTs showed that more patients on the standard of care compared to Zinc group necessitated change of antibiotics to a broader spectrum either due to lack of improvement or worsening of clinical status with an odds ratio of 0.81 with 95% CI of 0.38 and 2.24 but there was no noted statistical significance with a p value of 0.59 [17-18,21-22].

This review aims to determine the efficacy and safety of zinc as adjunctive treatment of COVID-19 among pediatric patients.

Review Methods

We comprehensively searched different electronic databases that included MEDLINE via PubMed, Cochrane Library, ClinicalTrials.gov, PubMed Clinical Queries, medRxIV, bioRxIV, WHO Clinical Trials Registry, WHO Therapeutics and COVID 19 Living Guidance, WHO Institutional Repository for Information Sharing and HERDIN Plus until January 7, 2022. Free search on Google was also performed. The following keywords were used: “zinc”, “zinc gluconate”, and “zinc sulfate” in free text and MeSH terms for “Zinc” and pediatric COVID-19 (Appendix 2). The table below shows our inclusion criteria.

Table 1. Inclusion criteria for zinc as adjunctive treatment of COVID-19 among pediatric patients

Population	Children with COVID-19
Intervention/Exposure	Zinc, zinc sulfate, zinc gluconate
Comparison	Standard of care
Outcomes	Need for hospitalization, mortality, recovery, clinical improvement, mechanical ventilation and duration of hospital and ICU stay

We searched for randomized controlled trials, observational studies, systematic reviews and meta-analyses.

The risk of bias of included studies was assessed using guide questions derived from Painless Evidence-Based Medicine for RCTs. Certainty of evidence was assessed using the GRADE evidence profile. Review Manager 5.4.1 was used for meta-analysis.

Results

There are no published studies on the use of Zinc among pediatric patients with Covid-19. This review uses indirect evidence from studies on adults with COVID-19 for the use of Zinc as adjunctive treatment.

We found a total of six RCTs wherein adult patients with COVID-19 were given zinc as an adjunct treatment for COVID-19. Among the six, four studies used zinc as the sole adjunctive treatment; the remaining two used it in combination with another adjunct. The studies were also done in different settings: two as outpatient and four in hospital settings and across all severities [15-20]. The overall certainty for each outcome was rated low. Downgrading occurred due to indirectness (from differences in population), and imprecision.

The studies of Abd Eisalam et al. [15] and Patel et al. [16] reported fewer mortalities among those given Zinc (7/111) than those who received standard of care (8/113). The study of Abd elsalam used Zinc with Hydroxychloroquine (control: hydroxychloroquine) while that of Patel used high dose zinc (control: placebo). The pooled result for the outcome of mortality yielded inconclusive results (RR 0.92; 95% CI o.35,2.44). The certainty of evidence was low because of indirectness (the studies enrolled adult patients) and imprecision.

The study of Thomas [17] and Kaplan [18] reported the outcome of hospitalization among ambulatory patients. The results were not pooled since the study by Kaplan et al. used other adjunctive agents in addition to zinc (i.e,. resveratrol). The said study reported one hospitalization from each study arm. In the study of Thomas, which used high dose Zinc versus standard of care, there were inconclusive results for the outcome of hospitalization (RR 1.44; 95% CI 0.36, 5.71).

The study of Patel [16] and Thomas [17] reported significantly more adverse events in the zinc group (13/73) compared to Standard of care (0/68) (RR 13.62 95%CI1.78, 104.43). The direct adverse effect noted on the study of Patel is infusion site irritation. In the study of Thomas there were ten noted adverse events in the Zinc group.

The study by Darban et al. [19] reported that there is no difference between the length of hospital stay among those given with high-dose vitamin C, melatonin, and zinc compared to standard of care in patients with severe COVID infection. (15 ± 3.3 days vs 14.1 ± 4.2 days; p= 0.7).

The study of Abdelmaksoud [20] reported that there is no difference in the duration of recovery among those who received zinc (MD 12 days, range = 8-17) and those who did not (MD 12 days, range = 8-20).

Other Considerations (Evidence to Decision)

Zinc Sulfate is available in drugstores and health outlets, as well as online shopping sites, which show one price at P101 for a 27.5mg/mL (10mg elemental zinc) per 15mL bottle and P107.5 per 60mL bottle. [21,22] The 2021 Philippine Drug Price Reference Index (DPRI) shows the mean price of P 34.75 for a 27.5mg/mL (10mg elemental zinc) 15ml oral drops and P 38.00 for a 55mg/5mL (20mg elemental zinc) 60mL syrup [23].

Zinc gluconate is also available in the market as a 70mg/tab chewable tablet P10.34 each containing 10mg of elemental Zinc per tablet [24]. No available data on the 2021 Philippine Drug Price Reference Index (DPRI).

Recommendations from Other Groups

The US-NIH COVID-19 Treatment Guidelines Panel recommends against using zinc supplementation due to insufficient evidence for or against the use of zinc for the treatment of COVID-19 [25]. Currently, there are no recommendations from CDC [26], WHO [27], and the American Pediatric Academy [28] on the use of zinc as an adjunct treatment in pediatric-COVID-19.

Research Gaps

As of January 2022, there are no ongoing trials investigating the effectiveness of zinc as adjunctive treatment for pediatric COVID-19. There are eight ongoing studies among adults.

References

[1] Kumar A, Kubota Y, Chernov M, Kasuya H. Potential role of Zinc supplementation in prophylaxis and treatment of COVID 19. Med Hypotheses.2020;10-11.

[2] Skalny AV, Rink L, Ajsuvakova OP, Aschner M, Gritsenko, Alekseenko SI, Svitunov AA, Petrakis D, Spandidos DA, Aaseth J. Zinc and respiratory tract infections: perspectives for COVID-19 (review) 2020; Int. J. MOl. Med.

[3] Han YS, Chang GG, Juo CG, Lee HJ, Yeh SH, Hsu JT, Chen X. Papain like protease 2 (PLP2) from severe acute respiratory syndrome coronavirus (SARS-CoV): express, purification, characterization and inhibition. Biochemistry. 2005;44(30):10349-103359.

[4] Arentz S, Hunter J, Guoyan Y, Goldenberg J, Beardsley J, Myers S, Metrz D, Leeder S. Zinc for the prevention and treatment of SARS-CoV2 and other acute viral respiratory infections:rapid review: Elsevier Public Health Emergency collectin. Advance Integrative Medicine 7(4):252-260. PMC7395818.

[5] Nabi-Afjadi M, Karami H, Goudarzi K et al. The effect of Vitamin D, magnesium and zinc supplements on interferon signaling pathways and their relationship to control SARS-CoV-2 infection. Clin Mol Allergy 19,21 (2021). https://doi.org//10.1186/s12948-021-00161-w.

[6] Jothimani D, Kailasam E, Danielraj S, Nallathambi B, Ramachandran H, Sekar P et al. COVID-19: Poor outcomes in patients with Zinc Deficiency. Int J Infect Dis, 2020Nov;100:343-349. Doi:10.1016/j.ijid.2020.09.014.Epub 2020 Sep10. PMID 32920234;PMCID:PMC7482607.

[7] Howie S, Bottomley C, Chimah O, Ideh R, Ebruke B, Okomo U, Onyeama C, Donkor S, Rodrigues O, Tapgun M, Janneh M, Oluwalana C, Kuti B, Enwere G, Esangbedo P, Doherty C, Mackenzie G, Greenwood B, Corrah T, Prentice A, Adegbola R, Zaman S. Zinc as an adjunct therapy in the management of severe pneumonia among Gambian children: randomized controlled trial. J Glob Health. 2018;8(1):010418.

[8] 8Sempértegui F, Estrella B, Rodríguez O, Gómez D, Cabezas M, Salgado G, Sabin LL, Hamer DH. Zinc as an adjunct to the treatment of severe pneumonia in Ecuadorian children: a randomized controlled trial. Am J Clin Nutr. 2014;99(3):497. Epub 2014 Jan 15.

[9] Bhatnagar S, Wadhwa N, Aneja S, Lodha R, Kabra SK, Natchu UC, Sommerfelt H, Dutta AK, Chandra J, Rath B, Sharma M, Sharma VK, Kumari M, Strand TA. Zinc as adjunct treatment in infants aged between 7 and 120 days with probable serious bacterial infection: a randomised, double-blind, placebo-controlled trial. Lancet. 2012 Jun;379(9831):2072-8.

[10] Bansal A, Parmar VR, Basu S et al. Zin supplementation in severe acute lower respiratory tract infection in children: A triple blind Randomized controlled placebo controlled trial. Indian J Pediatri2011;78:33-7.

[11] Bose A, Coles CL, Gunavathi et al. Efficacy of zinc in the treatment of severe pneumonia in hospitalized children <2yo. Am J Clin Nutr 2006;83:1089-96.

[12] Brooks WA, Yunus M, Santosham M et al. Zinc for severe pneumonia in very young children: double blind placebo-controlles trial. Lancet 2004;363:1683-8.

[13] Rerksuppaphol S, Rerksuppaphol L. A randomized controlled trial of zinc supplementation in the treatment of acute respiratory tract infection in Thai children. Pediatric Reports 2019; 11.7954.

[14] Valavi E, Hakimzadeh M, Shamsizadeh A, Aminzadeh M, Alghasi A. The efficacy of Zinc supplementation on outcome of children with severe pneumonia. A randomized double blind placebo controlled clinical trial. Indian J Pediatri 2011;78:1079-84.

[15] Abd-Elsalam S, Solima S, Esmail ES et al. Do zinc supplements enhance the clinical efficacy of hydroxychloroquine? A randomized, multicenter trial. Biol Trace Elem Res. 2021; 199:3642-3646.

[16] Patel O, Chinni V, El-Khoury J, Perera M, Neto AS, McDonald C et a. A pilot double blind safety and feasibility randomized controlled trial of high dose intravenous zinc in hospitalized COVID-19 patients. (short communication) J Med Virol. 2021 May;93(5): 3261-3267. Doi: 10.1002/jmv.26895. Epub 2021 Mar 9. PMID: 33629384; PMCID: PMC8014767.

[17] Thomas S, Patel D, Bittel B et al. Effect of high dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial. JAMA Netw Open. 2021; 4: e210369.

[18] Kaplan HG, Wang K, Reeves KM, Scanlan JM, Nunn CC, Kieper DA et al. Resveratrol and zinc in the treatment of outpatients with covid-19 – the reszinate study – a phase ½ randomized clinical trial utilizing home patient obtained nasal and saliva viral sampling. SSRN. 2021 Oct; [cited 2021 Nov 20]. Available from: http://papers.ssrn.com/sol3/papers.cfm?abstract_id=3934228.

[19] Darban M, Malek F, Memarian M, Gohari A, Kiani A, Emadi A et al. Efficacy of high dose viamin c, melatonin and zinc in Iranian patients with Acute respiratory syndrome due to coronavirus infection: A pilot randomized trial. J cell Mol Anesth. 2021;6(2):164-7. DOI:http://doi.org/10.22037/jcma.v6i2.32182.

[20] Abdelmaksoud AA, Ghweil AA, Hassan MH et al. Olfactory disturbances as presenting manifestation among Egyptian patients wiyh COVID 19: possible role of Zinc. BIol Trace Elem Res 199, 4101-4108 (2021). Available from:https://doi.org/10.1007/s12011-020-02546-5.

[21] https://www.watsons.com.ph/drops-27.5mg-ml-15ml/p/BP10071791 Accessed: January 8, 2022 10:45.

[22] https://www.watsons.com.ph/zinc-sulfate-60ml/p/BP_10071790 Accessed: January 8, 2022 10:48.

[23] https://dpri.doh.gov.ph/download/2021-DPRI-As-of-October-5.pdf Accessed: January 8, 2022 10:50.

[24] https://www.mims.com/philippines/drug/info/zinbee?type=full Accessed: January 11, 2022 12:13.

[25] COVID-19 Treatment Guidelines Panel. Coronavirus diseases 2019 (COVID 19) Treatment Guidelines. National Institue of Health.2021 Accessed from https://www.covid19treatmentguidelines.nih.gov/ Accessed: January 8, 2022 11:00.

[26] https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html. Accessed Jan 31, 2022 16:00.

[27] World Health Organization. COVID-19 clinical management: living guidance (2021). https://apps.who.int/iris/handle/10665/338882.

[28] https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/outpatient-covid-19-management-strategies-in-children-and-adolescents/ Accessed Jan 31, 2022 16:10.

Appendix 1. Search Yields and Results

Database	Search terms	Yield	Hits
Pubmed	((("pediatric COVID-19" [Supplementary Concept] OR "COVID-19" [Supplementary Concept] "COVID-19 diagnostic testing" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [Supplementary Concept] OR "COVID-19 vaccine" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR "2019-nCoV" OR "2019nCoV" OR "cov 2" OR "Covid-19" OR "sars coronavirus 2" OR "sars cov 2" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus 2" OR "COVID 19" OR "COVID-19" OR "2019 ncov" OR "2019nCoV" OR "corona virus disease 2019" OR "cov2" OR "COVID-19" OR "COVID19" OR "nCov 2019" OR "nCoV" OR "new corona virus" OR "new coronaviruses" OR "novel corona virus" OR "novel coronaviruses" OR "SARS Coronavirus 2" OR "SARS2" OR "SARS-COV-2" OR "Severe Acute Respiratory Syndrome Coronavirus 2") OR ((19[tiab] OR 2019[tiab] OR "2019-nCoV" OR "Beijing" OR "China" OR "Covid-19" OR epidem*[tiab] OR epidemic* OR epidemy OR new[tiab] OR "novel"[tiab] OR "outbreak" OR pandem* OR "SARS-CoV-2" OR "Shanghai" OR "Wuhan") AND ("Coronavirus Infections"[Mesh] OR "coronavirus"[MeSH Terms] OR coronavirus*[all] OR corona-virus*[all] OR cov[tiab] OR pneumonia-virus*[tiab]))) AND ((((((((((zinc [tiab]) OR (zinc gluconate [tiab])) OR (zinc sulfate [tiab])) OR (zinc supplement [tiab])) OR (antioxidant [tiab])) OR (supplement [tiab])) OR (zinc* [tiab])) OR (zinc[MeSH Terms])) OR (zinc gluconate [MeSH Terms])) OR (zinc sulfate [MeSH Terms])) OR (Zinc supplement [MeSH Terms])) OR (antioxidant[MeSH Terms])) OR (supplement[MeSH Terms]	1735	6
Cochrane	((zinc):ti,ab,kw OR Zinc* OR MeSH descriptor: [Zinc] explode all trees) AND (COVID-19 OR SARS-CoV-2 OR MeSH descriptor: [COVID-19] explode all trees)	120	4
	((zinc):ti,ab,kw OR Zinc* OR MeSH descriptor: [Zinc] explode all trees) AND (pediatric COVID-19 OR SARS-CoV-2 OR MeSH descriptor: [COVID-19] explode all trees)	120	0
clinicalTrials.gov	“zinc” and “pediatric covid”	55	0
	“zinc” and “covid”	55	0
MedRxiv	title "zinc" (match all words) and abstract or title "zinc" (match all words) and full text or abstract or title "zinc" (match whole all)	265	0
CovidNMA	Zinc	3	3
WHO International Clinical TRials Registry platform	“Zinc” and “pediatric COVID 19”	0	0
HERDIN	“Zinc” and “pediatric COVID 19”	0	0
Google Scholar	“Zinc” and “pediatric COVID 19”	16,600	1
China Knowledge Resource integrated database	“Zinc” and “pediatric COVID 19”	48	0

Appendix 2. Characteristic of Included Studies: Randomized Control Trials

Study author	Population	Intervention	Control	Outcome
Abd-Elsalam 3 tertiary care centers in Assiut, Tanta and Cairo EGYPT	N= 191 Confirmed RT-PCR positive in three egyptian tertiary care centers from June 23 to August 23,2020 Divided into mild, moderate, severe and critical based on WHO classification	Zinc sulfate 220mg (elemental zinc 50mg) BID HCQ (400mg BID D1, then 200mg BID x 4 days) Standard of care	HCQ (400mg BID D1, then 200mg BID x 5 days) Standard of care	Recovery within 28 days Death Need for mechanical ventilation Duration of Hospital stay (days)
Thomas Multiple outpatient settings in Ohio and Florida USA	N=214 Patients > 18 years old who were newly diagnosed by RT-PCR in an outpatient setting From April 27 to October 14, 2020	Zinc gluconate (50mg OD at bedtime) x 10 days n=58 (20 did not complete follow-up: 11 lost, 9 discontinued intervention) *58 zinc + ascorbic acid x 10 days (11 did not complete: 3 lost, 8 discontinued)	Standard of care only (n=50) *ascorbic acid (8000mg over 2-3x/day) N=48 (14 did not complete, 7 lost, 7 discontinued)	Days required to reach 50% reduction in symptoms Death Hospitalization Serious Adverse Events
Kaplan (Lancet Preprint: no peer review) Outpatient Phase ½ clinical trial USA	N=30 Mild to Moderate COVID	Zinc methionine/ cysteine (Life Extension) 150 mg daily total (50 mg capsules orally three times daily and resveratrol (Mega Resveratrol) 2000 mg orally twice daily for five days.	Placebo Capsule	Primary outcome: Reduction in viral shedding Secondary outcomes: - Reduction of symptoms - Adverse events - Incidence of hospitalization - Length of hospitalization - Days on ventilator support - Time until the 4-symptom score is zero - Composite score at Day 5 - Hospitalization - Deaths
Patel et al In Hospital setting AUSTRALIA	N=33 Hospitalized patients -severe -critical 2021	Zinc Chloride IV at 0.5mkd (elemental Zn 0.24mkd)	Placebo	Death Continuing Hospitalization

Study author	Population	Intervention	Control	Outcome
Darban Single center active controlled open label parallel grou setting IRAN	N=20 Severe COVID 2021	Oral zinc sulfate (220 mg containing 50 mg elemental zinc, q6hr) for 10 days (5-7) IV vitamin C (2g, q6hr), oral melatonin (6 mg, q6hr) plus standard of care	Standard cares were azithromycin (250 mg/day), lopinavir/ritonavir (100mg/25mg/day), glucocorticoids and necessary oxygen	Primary outcome: changes in severity pf hypoxemia (PaO2/ FiO2 ratio) Other outcomes included inflammatory markers (LDH, ESR, ferritin, CRP at baseline, days 5 and 10 after treatment initiation)
Abdelmaksoud Quaratine department hospitals EGYPT	N = 134 2021	Zinc therapy (220 mg zinc sulfate equivocal to 50 mg elemental zinc twice daily [33]) plus the Egyptian protocol of treatment of COVID-19	Egyptian protocol of COVID- 19 treatment without zinc therapy	Mean serum zinc levels, median duration of recovery of gustatory/ olfactory function, median duration of complete recovery among those who had anosmia/hyposmia

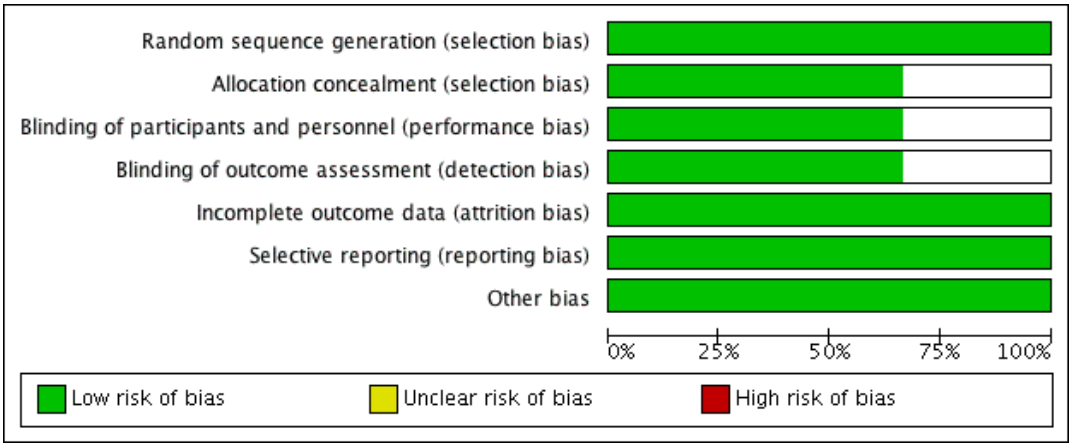
Appendix 3. Detailed Study Appraisal

Directness	Abd-Elsalam	Thomas	Kaplan	Patel	Darban	Abdelmaksoud
	Yes, it had similar outcomes, but different population (adult) and interventions (Zinc as add on to HCQ vs HCQ, which is not standard of care currently) P= Patients with COVID (mild, moderate, severity) I=Zinc+HCQ vs HCQ O=Duration of hospital stay, recovery	Yes, similar intervention and outcome but different population P= Adults diagnosed with COVID I= Zinc, ascorbic acid, ascorbic acid with zinc, standard of care O= Reduction in severity or duration of symptoms	Yes similar outcomes but population is similar Adult COVID patients, but the intervention (Zinc + resveratrol) and primary outcomes are different (reduction in viral shedding)	Yes similar outcome but the population, intervention(high-dose IV Zinc) and primary outcome are different (lowest oxygen saturation for non-ventilated and worst PaO2/ FiO2 for ventilated)	Yes similar outcome but different population (Adult COVID severe), intervention (standard of care vs standard of care with oral melatonin, oral zinc, IV vit C), and different outcome (changes in hypoxemia	Yes, similar intervention (zinc) and outcome but different population (Adult Patients with COVID of various severities), similar
Validity						
Randomly assigned to treatment groups	Yes RCT	Yes RCT Open label trial	Yes RCT	Yes RCT	Yes RCT	Yes RCT
Allocation Concealment	Not mentioned	No Open label	Yes	Yes	No	Not mentioned
Similar Baseline characteristic	Yes No significant difference	Yes No significant difference	Yes	Yes	Yes	Yes
Patient blinding	Not mentioned	No	Yes	Yes	No	Not mentioned
Caregiver blinding	Not mentioned	No	Yes	Yes	No	Not mentioned

Outcome assessor blinding	Not mentioned	No	Yes	Yes	No	Not mentioned
Analyzed to group originally randomized	Yes	Yes	Yes	Yes	Yes	Yes
Adequate follow up	Yes	Yes	Yes	Yes	Yes	Yes
RESULTS						
Treatment Effect	**Mean Hospital Stay** Zinc:13.51 ± 5.34 days Zinc + HCQ**:** 14.01 ± 6.26 days *p=0.553* **Hospital mortality**, Risk difference:n 0.05 (-0.06, 0.06)	**50% reduction of symptoms**, Zinc: 5.9 (4.9) days Std: 6.7 (4.4) days *p=0.38*	**Reduction in viral shedding** -no statistically significant difference (p=0.7) **In-hospital mortality:** Zinc: 0/14 Placebo: 0/16 2 were admitted-one each for the interventions. **LOS** Zn: 46-day LOS with 30 days in the ICU Placebo: 11-day LOS with 5 days in the ICU	**In-hospital mortality (28-day outcome):** Zinc: 2/ 15 (14.3%) Control: 3/18 (16.7%)	**PaO2/FiO2 at day 10** Placebo: 222.2 ± 65 Zn: 230.1 ± 59.1, p=0.2 **Length of ICU stay**: Placebo: 15 ± 3.3 days Zn: 14.1 ± 4.2 days p = 0.3	**Serum zinc level:** Mild: 0.67 ± 0.18 Common: 0.62 ± 0.14 Severe: 0.73 ± 0.18 Extremely severe: 0.72 ± 0.22 p= 0.084 **Mean duration of recovery of olfaction:** Zinc arm: 7 days (range 5-9 days) Control: 18 days (range 14-22 days) **Duration of complete recovery** Zinc arm: Median 12 (range 8–17 days) Control: Median 12 (range 8–20 days)
Precision	**Length of hospital stay:** Zn: 13.51, 5.34 days 95% CI: 12.47 to 14.594 Zn+HCQ: 14.01, 6.26 days *95% CI: 12.734 to 15.286 days* *MD: 0.500 (-1.16, 2.16), p=0.55*	Zn: 95% CI: 0.40 (−1.77 to 2.58) AA: 95% CI 0.40 (−1.99 to 2.80) Zn+AA: 95% CI: 0.07 (−1.94 to 2.09)	N/a	N/a		

	In-hospital mortality Zinc: 5/96 (5.21%) HCQ: 5/95 (5.26%) *Risk difference: 0.05 (-0.06, 0.06)* *NS*					
APPLICABILITY						
Biologic Issues	None	None	None	None	None	None
Socioeconomic Issues	None	None	None	None	None	None

Appendix 4. Risk of Bias



Appendix 5. GRADE Evidence Profile

Author(s): Joanna Marie Tan, MD DPPS, Maria Teresa Tolosa, MD D Clin Epi, FPDS , Ma. Lucila Perez MD MSc FPPS
Question: Should Zinc be used as an adjunctive treatment for COVID-19 in children?
Setting: General pediatric population, in-patient and out-patient
Bibliography: Abd Eisalam 2020, Patel 2021, Thomas 2020, Darban 2021, Abdelmaksoud 2021

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zinc	Standard of care	Relative (95% CI)	Absolute (95% CI)		
In Hospital Mortality												
2	randomised trials	not serious	not serious	serious[a]	serious[b]	none	7/111 (6.3%) 8/113 (7.1%)	8/113 (7.1%)	**RR 0.92** (0.35 to 2.44)	**5 fewer per 1,000** (from 41 fewer to 91 more)	⨁⨁◯◯ Low	CRITICAL
Hospitalization among Ambulatory patients												
1	randomised trials	not serious	not serious	serious[c]	serious[b]	none	5/58 (8.6%)	3/50 (6.0%)	**RR 1.44** (0.36 to 5.71)	**26 more per 1,000** (from 38 fewer to 283 more)	⨁⨁◯◯ Low	CRITICAL
Adverse Events												
2	randomised trials	not serious	not serious	serious[c]	serious[d]	none	13/73 (17.8%)	0/68 (0.0%)	**RR 13.62** (1.78 to104.43)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL
Length of Hospitalization												
1	randomised trials	not serious	not serious	serious[c]	serious[b]	none	In the study of Darban the use of High dose Vitamin C+Melatonin and Zinc (15 days) compared to Standard of Care (14.1 days) showed no significant difference in the length of hospital stay.				⨁⨁◯◯ Low	CRITICAL
Duration of Recovery												
1	randomised trials	not serious	not serious	serious[c]	serious[b]	none	In the study of Abdelmaksoud there is no difference in the duration of activity among those who received Zinc (12 days) compared to those who received standard of care (12 days).				⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio
Explanations
a. studies used Adult patients with COVID-19
b. the confidence interval crossed the line of unity
c. study used was done among Adult patients with COVID-19
d. the confidence interval is wide

Appendix 6. Forest Plots

Study or Subgroup	Zinc Events	Zinc Total	Standard of Care Events	Standard of Care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abd Elsalam 2020	5	96	5	95	64.8%	0.99 [0.30, 3.31]
Patel 2021	2	15	3	18	35.2%	0.80 [0.15, 4.18]
Total (95% CI)		**111**		**113**	**100.0%**	**0.92 [0.35, 2.44]**
Total events	7		8			

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)

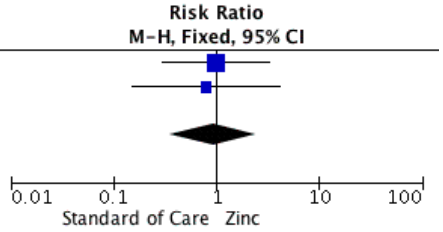


Figure 1. In-hospital mortality

Study or Subgroup	Zinc Events	Zinc Total	Standard of care Events	Standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI
Thomas 2020	5	58	3	50	100.0%	1.44 [0.36, 5.71]
Total (95% CI)		**58**		**50**	**100.0%**	**1.44 [0.36, 5.71]**
Total events	5		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.51 (P = 0.61)

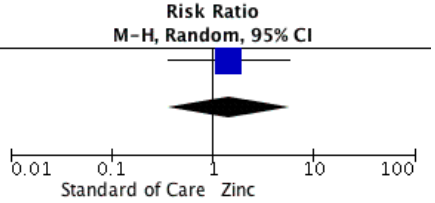


Figure 2. Hospitalization among ambulatory patients

Study or Subgroup	Zinc Events	Zinc Total	Standard of Care Events	Standard of Care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Patel 2021	3	15	0	18	46.0%	8.31 [0.46, 149.21]
Thomas 2020	10	58	0	50	54.0%	18.15 [1.09, 302.17]
Total (95% CI)		**73**		**68**	**100.0%**	**13.62 [1.78, 104.43]**
Total events	13		0			

Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 2.51 (P = 0.01)

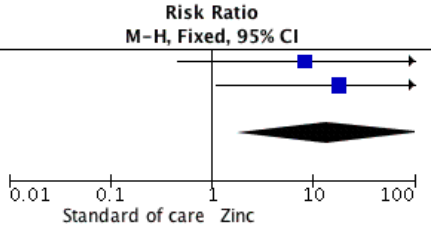


Figure 3. Adverse events

Appendix 7. Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 11)

FACTORS	JUDGEMENT (N = 11)							RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (10)		Varies		Uncertain (1)		
Benefits	Large	Moderate	Small (2)	Trivial	Varies (1)	Uncertain (8)		• Inconclusive results for in-hospital mortality, duration of recovery, length of hospital stay, hospitalization among ambulatory patients
Harm	Large	Moderate (4)	Small (4)	Trivial	Varies (2)	Uncertain (1)		• Adverse events significantly higher in the intervention group compared to control
Certainty of evidence	High	Moderate		Low (11)		Very low		• Rated low due to indirectness, risk of bias, imprecision
Balance of effects	Favors drug	Probably favors drug	Does not favor drug or no drug (2)	Probably favors no drug (5)	Favors no drug (2)	Varies	Uncertain (2)	
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (4)		Probably no important uncertainty or variability (5)		No important uncertainty or variability (1)		
Resources required	Uncertain (1)	Varies (1)	Large costs	Moderate costs (5)	Negligible costs or savings (3)	Moderate savings (1)	Large savings	• Zinc sulfate 27.5mg/mL: Php 101.00/15mL bottle • Zinc sulfate 27.5mg/mL: Php 107.50/60mL bottle • Zinc gluconate 70mg/tab: Php 10.34/tab
Certainty of evidence of resources required	No included studies (4)		Very low (1)	Low (2)	Moderate (4)	High		
Cost-effectiveness	No included studies (10)	Varies	Favors the comparison	Probably favors the comparison	Does not favor the comparison or the intervention (1)	Probably favors the intervention	Favors the intervention	
Equity	Uncertain (8)	Varies (1)	Reduced (1)	Probably reduced	Probably no impact (1)	Probably increased	Increased	
Acceptability	Uncertain (7)	Varies	No	Probably no (1)	Probably yes (3)	Yes		
Feasibility	Uncertain (6)	Varies	No (1)	Probably no (1)	Probably yes (2)	Yes (1)		

Additional Comments

- Zinc treatment may be beneficial to Filipino children who are zinc-deficient.