



EVIDENCE SUMMARY

Should Zinc be used as a preventive measure for COVID-19 in children?

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

Recommendation

We suggest against the routine use of zinc for the prevention of COVID-19 in children.

Certainty of Evidence: Low

Strength of Recommendation: Weak

Consensus Issues

This recommendation is based on the evidence from one randomized controlled trial in adults. The indirectness of the population and the intervention (zinc + vitamin C versus zinc alone) as well as the uncertainty of the evidence led the panel to vote against the use of zinc as a preventive measure for COVID-19 in children and the panel pointed out that this might change until higher certainty of evidence is available. The panel also agreed that the drug may be too costly for those from low- to mid-income families and availability may be an issue in far-flung areas. However, the panel concurred that zinc treatment is important for those with documented zinc deficiency.

Key Findings

We found no direct evidence on the use of zinc for the prevention of COVID-19 in pediatric patients. We found only one randomized controlled trial that enrolled adults, which revealed that compared to control, there was significant benefit of zinc for the outcomes of laboratory-confirmed SARS CoV2 infection (both seropositivity for antibody and positive RT-PCR at Day 42), acute respiratory symptoms, and symptoms of COVID-19. No hospitalization nor death was observed in all treatment arms.

Introduction

Zinc has potent immunoregulatory and antiviral properties. It is postulated that Zinc may work for the treatment of SARS-CoV-2 because of its ability to modulate the viral entry, fusion, replication, viral protein translation and virus budding of respiratory viruses [1,2]. Zn²⁺ cations especially in combination with Zinc ionophore pyrithione were shown to inhibit SARS-coronavirus RNA polymerase (RNA dependent RNA polymerase, RdRp) activity by suppressing its replication [3].

Zinc deficiency is 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 and progression of the severity of COVID-19 hence suggesting the benefits of zinc supplementation [4].

Among children, the use of 10mg elemental zinc for ≤ 11 months and 20mg elemental zinc for > 11 months for longer than 3 months has been shown effective for preventing pneumonia. A



meta-analysis done in the pre-COVID time, among children ages two months and five years of age in resource-limited countries, showed that zinc significantly reduced the incidence of clinically confirmed pneumonia by approximately 20% (RR 0.79, 95% CI 0.71-0.88) [5,6]. The included studies were performed in Bangladesh, India, Peru, and South Africa. One study found a shorter course of pneumonia in children under five years of age in Mexico [7].

This review aims to determine the efficacy and safety of zinc in the prevention of COVID-19 among pediatric patients.

Review Methods

We performed a comprehensive systematic search of related literature from MEDLINE, MedRxiv.org, WHO Clinical Trials Registry, WHO Therapeutics and COVID 19 Living Guidance, WHO Institutional Repository for Information Sharing, HERDIN Plus, and clinicaltrials.gov. Freehand search using Google was also done. There was no limit as to date, language, and country of publication. Search was conducted using the following terms: Zinc, Zinc Deficiency, pediatric-COVID-19, Severe Acute Respiratory Syndrome Coronavirus 2, 2019-nCoV, viral illness, cough and diarrhea. The table below summarizes our inclusion criteria:

Table 1. Inclusion criteria for zinc for the prevention of COVID-19 among children

Population	Children without COVID-19
Intervention/Exposure	Zinc, zinc sulfate, zinc gluconate
Comparison	No zinc, placebo
Outcomes	Incidence of COVID, forward transmission, viral load, adverse events

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 was no direct evidence on the use of Zinc to prevent COVID-19 among pediatric patients. Only indirect evidence was available, wherein Zinc was used among adults for the prevention of COVID-19 infection.

One RCT was included in this review. The study of Seet et al. used four different arms to prevent COVID-19 among participants living in a dormitory: Zinc (40 mg) + vitamin C (250 mg) twice daily (total, zinc 80 mg and vitamin C 500 mg day), vitamin C (500 mg) once daily, hydroxychloroquine 400 mg (four tablets) once, followed by 200 mg (two tablets) daily, and ivermectin 12 mg/tab (1 tablet) daily given for 6 weeks [8]. For the analysis of this review, we compared the first two arms.

The overall certainty was low. Downgrading was done due risk of bias (due to lack of blinding and allocation concealment) and indirectness.



Seet et al. reported that there was a significantly lower proportion of persons who tested positive for SARS-Cov 2 on RT PCR within six weeks among those given zinc + vitamin C (50/634) than those given vitamin C alone (85/619) (RR 0.57; 95% CI 0.41; 0.80). Seropositivity to SARS-Cov 2 was also significantly lower among those given zinc + vitamin C (250/634) than those given with vitamin C alone (348/619) (RR 0.7; 95% CI 0.62; 0.79).

The study also reported that among those given zinc + vitamin C versus vitamin C alone, there was a significantly lower proportion of 1) persons who experienced acute respiratory symptoms (34/634 vs. 69/619) (RR 0.57; 95% CI 0.32; 0.71) and 2) persons who developed symptomatic COVID- 19 (33/634 vs. 64/619) (RR 0.50; 95% CI 0.34, 0.75).

This study reported no hospitalization or death due to COVID-19 within the six-week period, in any of the groups. [8]

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 [9,10]. 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 [11].

Zinc gluconate is also available in the market as a 70mg/tab chewable tablet P10.34 each containing 10mg of elemental Zinc per tablet [12]. No available data on the 2021 Philippine Drug Price Reference Index (DPRI).

Recommendations from Other Groups

Currently, there are no recommendations from NIH [13], CDC [14], WHO [15], and the American Pediatric Academy [16] on the use of zinc specifically in children, to prevent 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.



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Appendix 1. Search Yields and Results

Database	Search terms	Yield	Hits
PubMed	(((Zinc OR (Zinc Sulfate) OR (Zinc Gluconate) OR (integrative medicine[MeSH Terms])) OR (complementary medicine[MeSH Terms])) AND ("pediatric COVID-19" [Supplementary Concept] OR "COVID-19 prevention" [Supplementary Concept] OR "COVID-19 serotherapy" [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 (((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt])	3	0
PubMed	(((Zinc OR (Zinc Sulfate) OR (Zinc Gluconate) OR (integrative medicine[MeSH Terms])) OR (complementary medicine[MeSH Terms])) AND ("COVID-19" [Supplementary Concept] OR "COVID-19 prevention" [Supplementary Concept] OR "COVID-19 serotherapy" [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 (((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt])	75	1
Medrxiv	Zinc AND Prevention AND Pediatric COVID-19	52	0
Medrxiv	Zinc AND Prevention AND COVID-19	52	5
HERDIN	Zinc AND Prevention AND Pediatric COVID-19	0	0
Google Scholar	Zinc AND Prevention AND Pediatric COVID-19	16,600	1
Clinical Trial Registry	Zinc AND Prevention AND COVID-19	2	2



Appendix 2. Characteristics of Included Studies

Study author	Population	Intervention	Control	Outcome
Seet Open Label RCT Men Dormitory in Singapore 2021 Singapore	N=3037 Men mean age 33 Vitamin C + Zinc: 634 Vitamin C: 619 HCQ: 432 Ivermectin: 617 Povidone Throat Spray: 735	Zinc (40 mg) + Vitamin C (250 mg) twice daily (total, zinc 80 mg) for 6 weeks.	Vitamin C (500 mg day) administered once daily for 6 weeks	Positive serologic test within 6 weeks Positive RT PCR test within 6 weeks Acute respiratory symptoms Symptomatic COVID Incidence of hospitalization and death

Appendix 3. Detailed Study Appraisal

Directness	Seet
	The population is Adult with COVID 19 instead of Pediatric, Intervention used was Vitamin C with Zinc instead of Zinc Alone. Outcome were the same.
Validity	
Randomly assigned to treatment groups	Yes
Allocation Concealment	No
Similar Baseline characteristic	Yes
Patient blinding and participants	This is an Open label, no blinding
Outcome assessor blinding	No blinding
Analyzed to group originally randomized	Yes
Adequate follow up	Yes
RESULTS	
Treatment Effect	3037 adult with mean age of 33years, VitC+Zn n 634 vs Vit C n 619 - Seropositivity: 250 vs 342 RR 0.7 (0.62,0.79) - RT pcr positivity: 50 vs 85 RR 0.57 (0.41, 0.8) - Acute Respiratory Syndrome: 34 vs 69 RR 0.48 (0.32, 0.71) - Symptomatic COVID 19: 33 vs 64 RR 0.5 (0.34, 0.75) - Hospitalization and Mortality: 0 vs 0
Precision	
APPLICABILITY	
Biologic Issues	None
Socioeconomic Issues	None

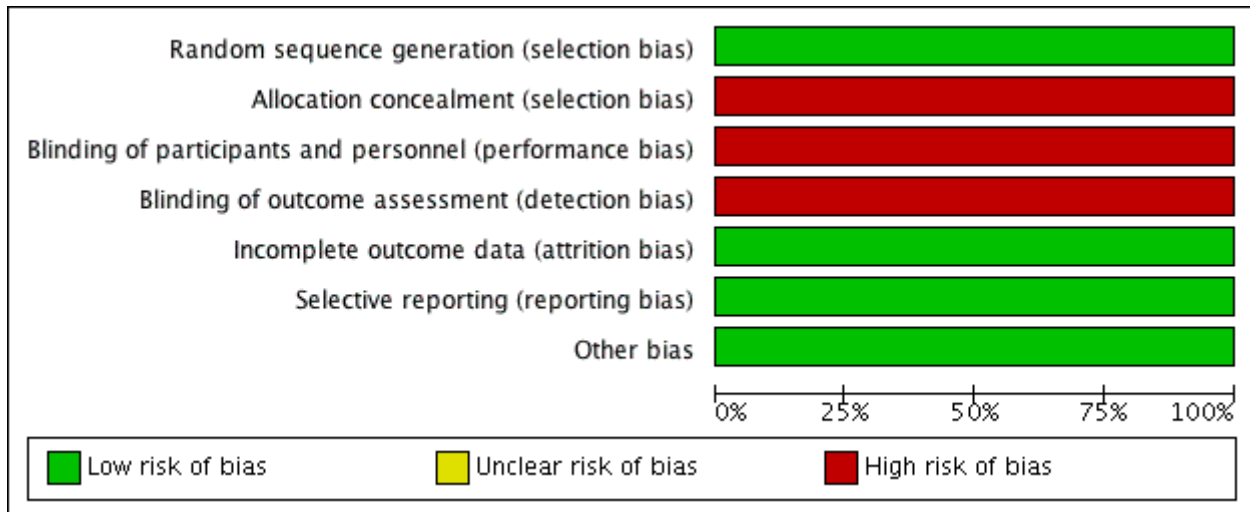
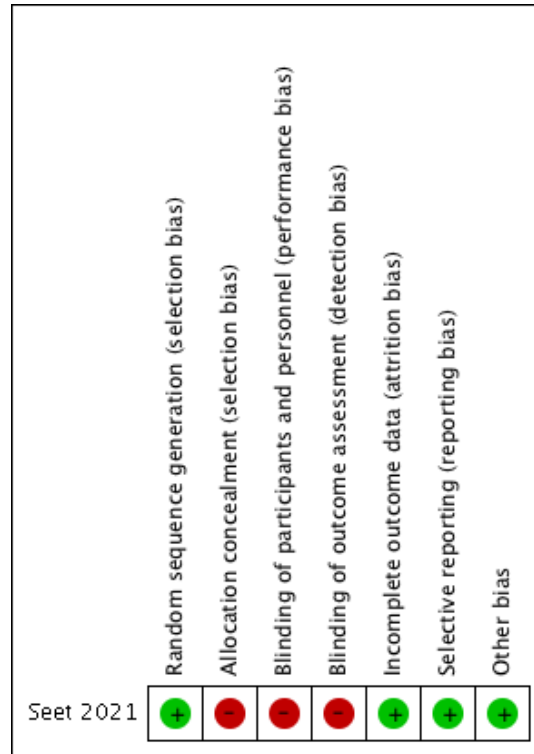


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Appendix 4. Risk of Bias





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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 FPDS

Question: Should Zinc be used as a preventive measure for COVID-19 in children?

Setting: General pediatric population

Bibliography: Seet, et al. 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)		
Serologic Positivity												
1	randomised trials	serious ^a	not serious	serious ^b	not serious	none	250/634 (39.4%)	348/619 (56.2%)	RR 0.70 (0.62 to 0.79)	169 fewer per 1,000 (from 214 fewer to 118 fewer)	⊕⊕○○ Low	CRITICAL
RT PCR Positivity												
1	randomised trials	serious ^a	not serious	serious ^b	not serious	none	50/634 (7.9%)	85/619 (13.7%)	RR 0.57 (0.41 to 0.80)	59 fewer per 1,000 (from 81 fewer to 27 fewer)	⊕⊕○○ Low	CRITICAL
Acute Respiratory Syndrome												
1	randomised trials	serious ^a	not serious	serious ^b	not serious	none	34/634 (5.4%)	69/619 (11.1%)	RR 0.48 (0.32 to 0.71)	58 fewer per 1,000 (from 76 fewer to 32 fewer)	⊕⊕○○ Low	CRITICAL
Symptomatic COVID 19												
1	randomised trials	serious ^a	not serious	serious ^b	not serious	none	33/634 (5.2%)	64/619 (10.3%)	RR 0.50 (0.34 to 0.75)	52 fewer per 1,000 (from 68 fewer to 26 fewer)	⊕⊕○○ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. the study of Seet is not blinded and had no allocation concealment

b. the study of Seet used Adult COVID 19 patients and used Vitamin C with Zinc vs Vitamin C



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Appendix 6. Forest Plots

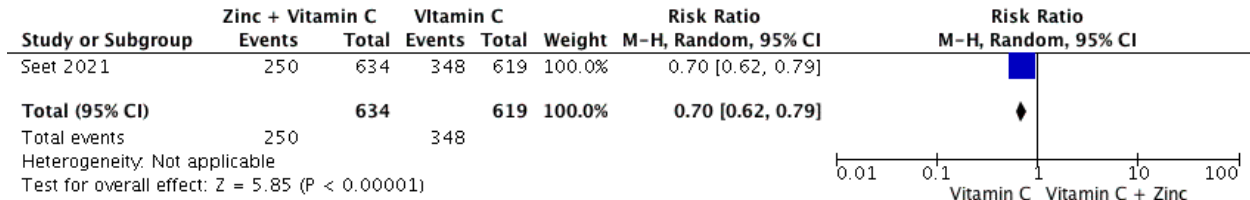


Figure 1. Positivity of serology

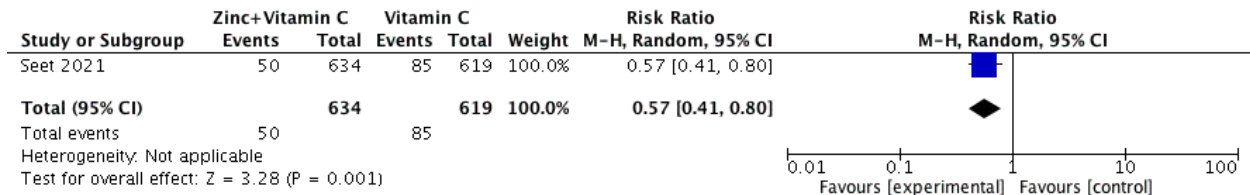


Figure 2. Positivity of RT-PCR

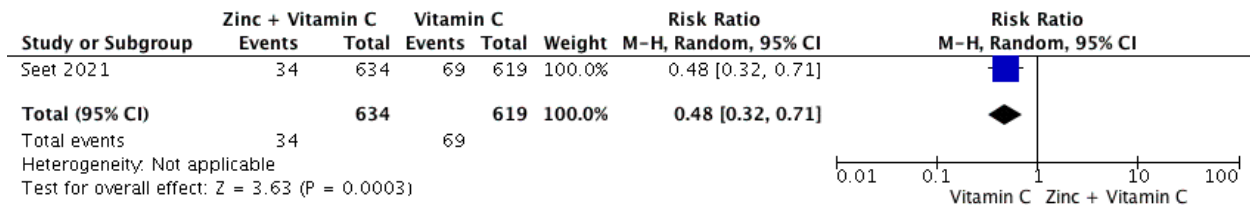


Figure 3. Acute respiratory syndrome

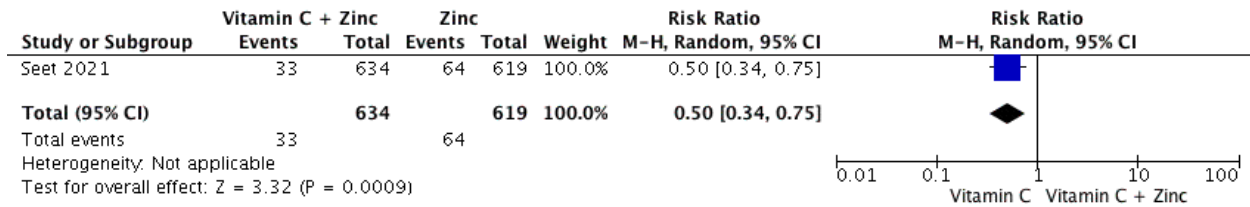


Figure 4. Symptomatic COVID-19



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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 (8)	Small	Trivial (1)	Varies	Uncertain (2)		<ul style="list-style-type: none"> Indirect evidence showed significant benefit of zinc + vit C for lab-confirmed COVID, acute respiratory symptoms and symptoms of COVID-19
Harm	Large	Moderate (1)	Small (2)	Trivial (4)	Varies	Uncertain (4)		<ul style="list-style-type: none"> No significant adverse events
Certainty of evidence	High	Moderate		Low (11)		Very low		<ul style="list-style-type: none"> Rated low due to indirectness, risk of bias
Balance of effects	Favors drug (6)	Probably favors drug (4)	Does not favor drug or no drug	Probably favors no drug	Favors no drug	Varies	Uncertain (1)	
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (1)		Probably no important uncertainty or variability (7)		No important uncertainty or variability (1)		
Resources required	Uncertain (1)	Varies	Large costs	Moderate costs (5)	Negligible costs or savings (3)	Moderate savings (2)	Large savings	<ul style="list-style-type: none"> 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	Low (1)	Moderate (6)	High		
Cost-effectiveness	No included studies (9)	Varies	Favors the comparison	Probably favors the comparison (1)	Does not favor the comparison or the intervention (1)	Probably favors the intervention (1)	Favors the intervention	
Equity	Uncertain (6)	Varies	Reduced (1)	Probably reduced (1)	Probably no impact (1)	Probably increased (2)	Increased	
Acceptability	Uncertain (4)	Varies	No	Probably no	Probably yes (7)	Yes		
Feasibility	Uncertain (3)	Varies	No (1)	Probably no	Probably yes (6)	Yes (1)		

Additional Comments

- Low levels of zinc in the Filipino children is a factor to consider in preventive care.