EVIDENCE SUMMARY

Should vitamin C be used as adjunctive treatment for COVID-19 infection in children?

Evidence Reviewers: Patricia C. Orduña, MD, DPPS, Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS; Ma. Lucila M. Perez, MD, MSc, FPPS

Recommendation

We suggest <u>against</u> the use of vitamin C as adjunctive treatment for COVID-19 infection in children.

Certainty of Evidence: Very Low
Strength of Recommendation: Weak

Consensus Issues
The recommendation was based on the evidence from eight (8) adult randomized controlled trials that showed no significant benefit and inconclusive results for length of hospital stay, length of ICU stay and need for mechanical ventilation. Although the panel deemed that the harm from the treatment was small, the benefits were uncertain when used as adjunctive treatment for COVID-19 infection. The uncertainty of the evidence coupled with the cost of the drug led the panel to vote against its use regardless of the route of administration. However, the panel agreed that vitamin C supplementation should still be given for those with low dietary vitamin C intake but not as a adjunctive treatment for COVID-19 infection. They also agreed that this recommendation is subject to change based on the availability of higher certainty of evidence.

Key Findings

We found no published studies on the role of Vitamin C as adjunct treatment in pediatric patients with COVID-19. Indirect evidence from eight (8) adult RCTs included in the Philippine COVID-19 Living Clinical Practice Guidelines [9] was reviewed. For the outcome of mortality, there was only a trend towards benefit with small negligible harm. There was no significant benefit and inconclusive results for length of hospital stay, length of ICU stay and need for mechanical ventilation. One study that used intravenous vitamin C reported no adverse events, while one that used oral preparation noted flushing, headache, vomiting and stomach pain. Overall certainty of evidence was very low because of indirectness, imprecision, and inconsistency.

Introduction

Vitamin C or ascorbic acid is an essential water-soluble vitamin that works as a co-factor for enzymes involved in biosynthesis of neurotransmitters, L-carnitine, and collagen among others. [1]. It plays a role in scavenging free oxygen radicals, reducing pro-inflammatory cytokines, promoting phagocytosis and chemotaxis of leukocytes and development and maturation of T-lymphocytes [2-5]. Vitamin C is widely promoted and used to treat respiratory infections. Some evidence supports its use in severe respiratory infections requiring ventilation [6] and in mitigating the duration and severity of common colds [7]. It has also been found to benefit children with viral myocarditis [8]. However, these studies have failed to show clinically significant benefit of vitamin

C in children with viral respiratory illness [6,7], and currently is not considered as standard-of-care.

Studies among Filipino children showed inadequate levels of Vitamin C intake in 35% of toddlers aged 24-35.9 months and in 60% of children aged 36-59.9 months old. [9] This finding was more apparent among Filipino school children and adolescents in the low socioeconomic status, with 68-96% reported to have inadequate vitamin C intake [10]. These children may benefit from adjunctive treatment with Vitamin C during COVID-19 illness. This systematic review seeks to determine the efficacy and safety of Vitamin C as adjunctive treatment in pediatric patients with COVID-19 infection.

Review Methods

We performed a comprehensive systematic search of related literature from MEDLINE via PubMed, Cochrane Library, ClinicalTrials.gov, MedRxIV.com, WHO COVID database, and HERDIN Plus. Freehand search using Google was also done. There was no limit in terms of date, language, and country of publication. The search was conducted using the following terms: COVID-19, SARS-CoV-2, nCOV-19, vitamin C, ascorbic acid and sodium ascorbate. Methodologies included randomized controlled trials, observational studies, case reports and case series, systematic reviews and meta-analyses. Our inclusion criteria for this review were as follows:

Table 1. PICO criteria for vitamin C and COVID-19.

Population	Children with COVID-19
Intervention/Exposure	Vitamin C or Sodium Ascorbate or Ascorbic Acid as adjunctive treatment
Comparison	Usual care, standard of care, placebo, any active control
Outcomes	Hospitalization, mortality, recovery, clinical improvement, need for mechanical ventilation, duration of hospital stay, duration of ICU stay, adverse events, negative viral conversion, adverse effects

Results

We found no published articles that matched our criteria. Results from the Philippine COVID-19 Living Clinical Practice Guidelines for adults were used as indirect evidence [11]. The guideline was appraised using AGREE II tool [Appendix 3].

Eight RCTs on adults were included in the updated guideline last November 2021 [Appendix 3]. Pooled analysis was done for 4 RCTs with hospitalized patients with moderate to severe COVID-19 as their inclusion population [12-15]**.** Vitamin C doses ranged from 50mg/kg/day to 24g/day and compared against standard of care or study-defined controls. Outcomes included mortality, length of hospital stay, length of ICU stay, need for mechanical ventilation, and adverse events. All four RCTs were used to determine outcomes on mortality rate and length of hospital stay.

Overall estimate on in-hospital mortality rate showed only a trend towards benefit with small negligible harm (RR 0.59; 95%CI 0.34 to 1.03). Overall estimate for length of hospital stay from the four pooled studies showed inconclusive results (MD -0.96, 95%CI -3.84 to 1.92). Two RCTs were pooled to determine outcome for length of ICU stay and showed inconclusive results (MD 1.35, 95%CI -0.12 to 2.83) [12,14]. Three RCTs were included to evaluate outcome of need for mechanical ventilation [12-14] and pooled estimates also showed inconclusive results (RR 0.93; 95% 0.60 to 1.44). Outcomes on adverse events were reported in only two RCTs [10, 14]. No adverse events were reported with use of intravenous vitamin C [12]. Meanwhile, adverse events such as flushing, headache, nausea and vomiting, stomach pain and diarrhea were reported

21.7% of patients who used high dose oral Vitamin C [16].

Three RCTs studied Vitamin C in conjunction with other adjunct treatments [17-19], while one study included adult COVID-19 patients managed as outpatient [16]. The study by Thomas et al. included adult patients with COVID-19 managed as outpatient [14]. They received either oral vitamin C, oral zinc gluconate, both agents or placebo. The study showed inconclusive results in terms of symptom reduction, hospitalization, mortality and adverse events, and was discontinued due to futility.

The studies of Darban et al. [17], Beigmohammadi et al. [18], and Hakamifard et al. [19] used vitamin C in combination with other adjunctive therapies. The study by Hakamifard et al. showed inconclusive results for the use of vitamins C and E in terms of mortality, length of hospitalization and improvement in clinical response [19]. The study by Darban et al. [17] did not show significant improvement in inflammatory markers and hypoxemia for adults given vitamin C, melatonin and zinc sulfate. Meanwhile, the study by Beigmohammadi et al. [18] showed significantly shorter duration of hospital stay, lower inflammatory markers and SOFA scores for patients given vitamin C in conjunction with vitamins A, B complex, D and E, but effect on mortality reduction was not significant.

The overall certainty of evidence from the studies included in the Philippine LCPG for adults was rated as low due to imprecision and inconsistency. For this review intended for the pediatric population, the overall certainty was further downgraded to very low because of indirectness. Evidence for vitamin C in COVID-19 was only found in adult studies.

Other Considerations (Evidence to Decision)

Intravenous vitamin C administration was the route used by majority of the studies included in this review. According to the search for pricing of available intravenous vitamin C in drugstores in the country, the cost is Php 110.00 for 10 ampules of 500mg/2ml [20], while price ranges from Php 85.00 to 300.00 per 10 ampules from various online sellers. According to the 2021 Philippine Drug Price Reference Index [21], the average cost is Php 28.19 per ampule.

No evidence was found in terms of cost-benefit use, patient's value or preferences and social impact, acceptability or compliance and feasibility in children.

Recommendations from Other Groups

The latest Pediatric Infectious Diseases Society of the Philippines (PIDSP) COVID-19 recommendations on multivitamins and minerals stated no evidence for or against its use in the treatment of COVID-19 in children. Nutritional support may be given upon the discretion of the attending physician with doses not exceeding the Recommended Dietary Allowance [22].

The Philippine Pediatric Society Parent's Guide on COVID-19 Infection in Children states that supplementation of nutrients (including vitamin C) may be beneficial to overall health but are not completely validated as preventive or therapeutic medications [23].

The US-NIH COVID-19 Treatment Guidelines Panel also stated that there is insufficient evidence to recommend for or against the use of vitamin C for the treatment of COVID-19 in both non-critically ill and critically ill patients [24].

The Philippine COVID-19 LCPG (last updated December 2021) stated that there was insufficient evidence to recommend vitamin C as an adjunct treatment for adult patients with COVID-19.

Research Gaps

There are two ongoing studies on the efficacy of vitamin C as adjunctive treatment for COVID-19 that includes children in their population [Appendix 6]. Further research is needed to evaluate efficacy and safety of both oral and intravenous vitamin C in children with COVID-19, with stratification in terms of severity of illness.

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Appendix 1. Search Yield and Results

Database	#	Keywords	Yield
MEDLINE (Pubmed)	1	((("pediatric COVID-19" [Supplementary Concept] OR "COVID-19" [Supplementary Concept] "COVID-19 diagnostic testing" [Supplementary Concept] OR "COVID-19 drug treatment" [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 "coronavirus"[MeSH Terms] OR coronavirus*[all] OR corona-virus*[all] OR cov[tiab]) AND ((((((((((Vitamin C [tiab]) OR (sodium ascorbate [tiab])) OR (ascorbic acid [tiab])) OR (ascorbic [tiab])) OR (antioxidant [tiab])) OR (supplement [tiab])) OR (vitamin c* [tiab])) OR (vitamin C[MeSH Terms])) OR (ascorbic acid [MeSH Terms])) OR (sodium ascorbate [MeSH Terms])) OR (ascorbic [MeSH Terms])) OR (antioxidant[MeSH Terms])) OR (supplement[MeSH Terms] AND (pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens)	1,112
	2	"vitamin C" OR “ascorbic acid” OR “sodium ascorbate” OR "ascorbic" OR "ascorbate"	1,166
	3	(hospitalization OR hospitalized OR admission) OR (mortality OR death) OR (recovery OR remission OR improvement) OR ("mechanical ventilation" OR MV OR intubation) OR ("length of stay" OR "hospital stay" OR "length of admission" OR "time admitted" OR "time hospitalized") OR ("intensive care unit" OR ICU OR "ICU admission" OR "intensive care unit admission" OR "ICU stay") OR ("adverse event" OR "adverse events" OR complication OR complications) OR ("viral conversion" OR "negative viral conversion")	11,62 9,542
	4	#1 AND #2 AND #3	482
	5	#1 AND #2 AND #3 AND Filters: Randomized Clinical Trial, Systematic Review, Meta-analysis	31
Cochrane COVID-19 Study Register	1	("vitamin C" or “sodium ascorbate” or “ascorbic acid” or "ascorbate" or "ascorbic") AND (hospitalization OR hospitalized OR admission) or (mortality OR death) or (recovery OR remission OR improvement) or ("mechanical ventilation" OR MV OR intubation) or ("length of stay" OR "hospital stay" OR "length of admission" OR "time admitted" OR "time hospitalized") or ("intensive care unit" OR ICU OR "ICU admission" OR "intensive care unit admission" OR "ICU stay") or ("adverse event" OR "adverse events" OR complication OR complications) or ("viral conversion" OR "negative viral conversion")	5,907
	2	#1 AND (pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens)	543
WHO COVID Database	1	("vitamin C" or “sodium ascorbate” or “ascorbic acid” or "ascorbate" or "ascorbic") AND (hospitalization OR hospitalized OR admission) or (mortality OR death) or (recovery OR remission OR improvement) or ("mechanical ventilation" OR MV OR intubation) or ("length of stay" OR "hospital stay" OR "length of admission" OR "time admitted" OR "time hospitalized") or ("intensive care unit" OR ICU OR "ICU admission" OR "intensive care unit admission" OR "ICU stay") or ("adverse event" OR "adverse events" OR complication OR complications) or ("viral conversion" OR "negative viral conversion") AND (pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens)	781
clinicalTrials.gov		“vitamin c” OR “sodium ascorbate” OR “ascorbic acid” AND “pediatric covid”	31
MedRxiv		title "vitamin c" (match all words) and abstract or title "vitamin c" (match all words) and full text or abstract or title "vitamin c" (match whole all)	154
HERDIN		Vitamin c AND Pediatric COVID-19	0
Google Scholar		Vitamin c AND Pediatric COVID-19	1,300

Appendix 2. AGREE II Appraisal of the Philippine COVID-19 Living CPG

Domain	Scope and Purpose	Stakeholder Involvement	Rigour of Development	Clarity of Presentation	Applica-bility	Editorial Indepen-dence	Overall quality of guideline
Assess-ment	89%	83%	88%	98%	85%	100%	83%

Appendix 3. Characteristics of Included Studies (from Tiu, Milan, Tolosa, and Infantado 2021 [9])

Author/Year/ Study Design	Population (N)	Intervention	Comparator	Outcomes
Jamalimoghadamsiahkali et al., 2021 **Open label RCT**	COVID-19 confirmed patients by RT-PCR or by clinical symptoms, Chest CT/HRCT, low oxygen saturation N=60	Vitamin C 1.5g Q6 x 5 days (6g/day) with lopinavir/ritonavir and HCQ	Lopinavir/ ritonavir and HCQ with no Vitamin C	No significant difference in terms of mortality (p>0.05), Patients on vitamin C: -Longer length of hospital stay (median 8.5 vs 6.5 days, p=0.028) -Higher SpO2 on 3rd day of admission (90.5% vs 88%; p=0.014)
Kumari et al. 2020	Severe COVID-19 patients (n=150)	50mg/kg/day intravenous vitamin C with standard Therapy	Standard therapy, no vitamin C	There were no statistically significant differences between the two groups in terms of mortality and need for mechanical ventilation. Patients on HDIVC group had earlier symptom free status (7.1 ± 1.8 vs 9.6 ± 2.1 days, p<0.001) and spent fewer days in the hospital (8.1±1.8 vs 10.7±2.2 days, p<0.0001) compared to patients without vitamin C
Zhang et al. 2021 Randomized placebo controlled	Severe COVID-19 confirmed patients N=56	Vitamin C 24g/day IV x 7 days (HDIVC)	No vitamin C	No statistically significant difference in terms of invasive mechanical ventilation-free days, 28-day mortality, 28-day mortality for severe (SOFA ≥3). Patients on HDIVC had higher P/F ratio, lower SOFA score The delta P/F from day 1 to 7 was (20±96.7 in HDIVC and -51.9±150.7 in the control group No study related adverse events in the trial.
Tehrani, et al., 2021 Single center clinical trial	Patients diagnosed with COVID-19 with moderate to severe symptoms (n=54)	Vitamin C 2g every 6 hours for 5 days in addition to standard treatment	Standard treatment (Hydroxicholoroquine, Kaletra and Interferon beta-1a	Oxygen saturation, respiratory rates, serum C- Reactive Protein (CRP) levels, lymphopenia and lung parenchymal involvement on CT, length of hospital stay, mortality Due to the effectiveness of high doses of intravenous vitamin C on reducing lung involvement and

				improving clinical symptoms, further studies with a larger sample size are recommended to demonstrate the effects of this drug supplement.
Thomas et al, 2021 Open label RCT *study discontinued	COVID-19confirmed Patients treated as Outpatient N=214	Vitamin C 8,000mg/day Zinc gluconate 50mg; both zinc and vitamin c	Standard of care, no vitamin C	No significant difference among the 4 study groups in terms of days required to reach a 50% reduction in symptoms. No significant difference in any of the secondary outcomes.
Darban, et al, 2021 Randomized single center trial	Patients with severe COVID admitted to the ICU (n=20)	IV Vitamin C (2g q6hr), oral melatonin (6mg q6hr), oral zinc sulfate (220mg containing 50mg elemental zinc q6hr) for 10 days + standard of care	Standard of Care	High-dose vitamin C, melatonin and zinc added to standard of care is not associated with improvement in hypoxemia (PaO2/FiO2 ratio), and inflammatory markers including LDH, ESR, ferritin, CRP
Hakamifard, et al, 2021 RCT	Hospitalized non-severe COVID-19 patients (n=72)	Oral Vitamin C 1g daily and oral vitamin E 400IU daily + standard treatment	Standard treatment	Co-administration of Vitamin C and E did not have a improvement in clinical response of patients at the end of treatment (either cure, improvement, or failure), the duration of hospitalization, and the mortality rate
Beigmohammadi et al, 2021 RCT, single-blinded	ICU-admitted patients with COVID-19 (n=60)	25,000 IU daily of vitamins A, 600,000 IU once during the study of D, 300 IU twice daily of E, 500 mg four times daily of C, and one amp daily of B complex for 7 days.	No vitamins (placebo)	Significant changes were detected in serum levels of vitamins ($p < 0.001$ for all vitamins), ESR ($p < 0.001$), CRP ($p = 0.001$), IL6 ($p = 0.003$), TNF-a ($p = 0.001$), and SOFA score ($p < 0.001$) after intervention compared with the control group. The effect of vitamins on the mortality rate was not statistically Significant ($p=0.112$). The prolonged hospitalization rate to more than 7 days was

				significantly lower in the intervention group than the control group (p=0.001). Supplementation with vitamins A, B, C, D, and E could improve the inflammatory response and decrease the severity of disease in ICU-admitted patients with COVID-19.

Appendix 4. GRADE Evidence Profile

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Question: Vit C with standard treatment compared to standard treatment alone for adjunctive treatment of COVID-19 in children

Setting: Inpatient

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Mortality												
4	randomised trials	not serious	not serious	serious[a]	serious[b]	none	16/150 (10.7%)	29/160 (18.1%)	**RR 0.59** (0.34 to 1.03)	**74 fewer per 1,000** (from 120 fewer to 5 more)	⨁⨁◯◯ Low	CRITICAL
Length of hospital stay												
4	randomised trials	not serious	serious[c]	serious[a]	serious[b]	none	150	160	-	MD **0.96 higher** (3.84 lower to 1.92 higher)	⨁◯◯◯ Very low	CRITICAL
Length of ICU stay												
2	randomised trials	not serious	not serious	serious[a]	serious[b]	none	57	59	-	MD **1.35 higher** (0.12 lower to 2.83 higher)	⨁⨁◯◯ Low	CRITICAL
Need for mechanical ventilation												
3	randomised trials	not serious	not serious	serious[a]	serious[b]	none	28/132 (21.2%)	31/134 (23.1%)	**RR 0.93** (0.60 to 1.44)	**16 fewer per 1,000** (from 93 fewer to 102 more)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Adverse events												
2	randomised trials	not serious	serious[d]	serious[a]	serious[e]	none	17/78 (21.8%)	0/50 (0.0%)	**RR 36.43** (2.25 to 589.34)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Adult patients enrolled

b. Confidence interval crosses the null value

c. I2 = 71%

d. Variability in patient population: outpatient and severe

e. Wide confidence interval (all on the side of harm)

Appendix 5. Forest Plots (from Tiu, Milan, Tolosa, and Infantado 2021 [9])

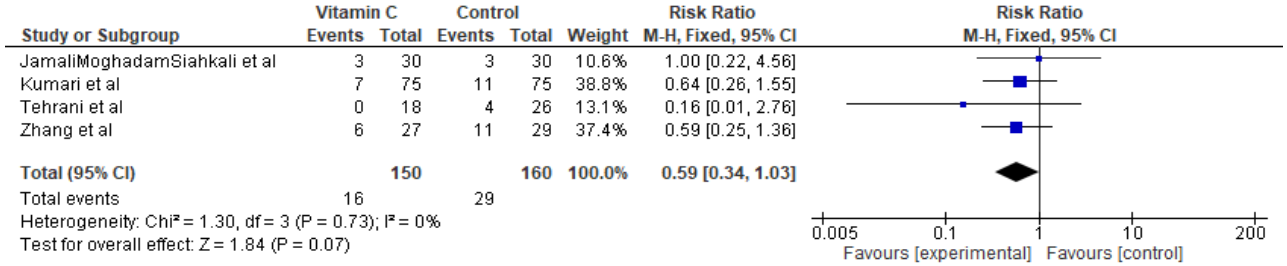

Figure 1. Mortality Outcome

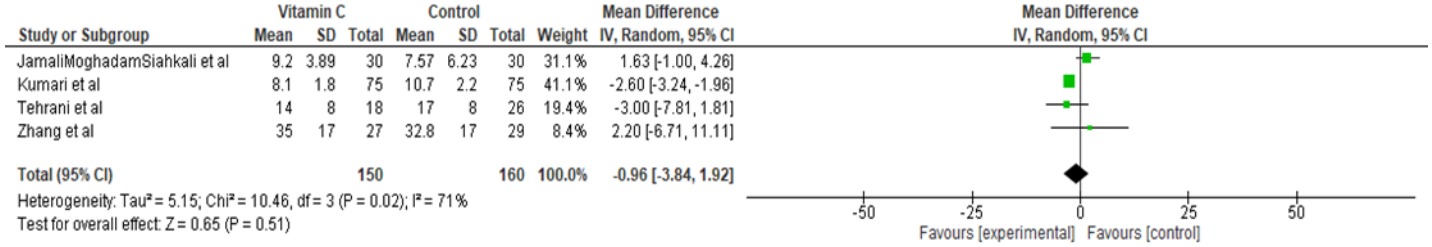

Figure 2. Length of hospital stay

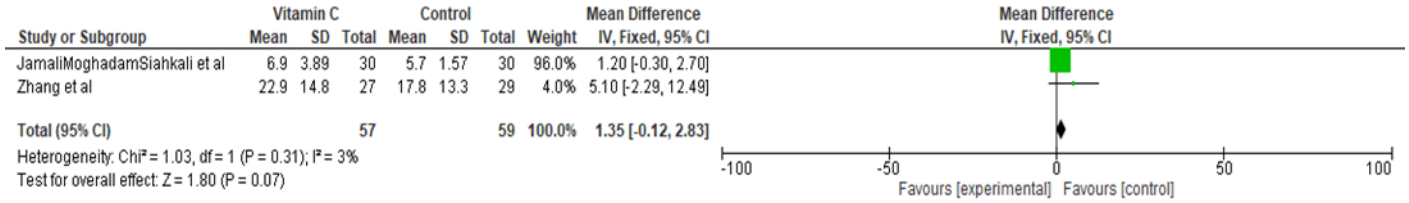

Figure 3. Length of ICU stay

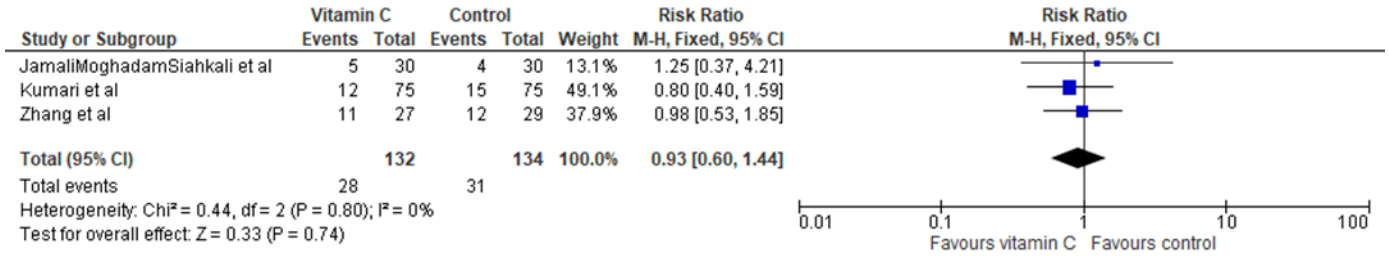

Figure 4. Need for mechanical ventilation

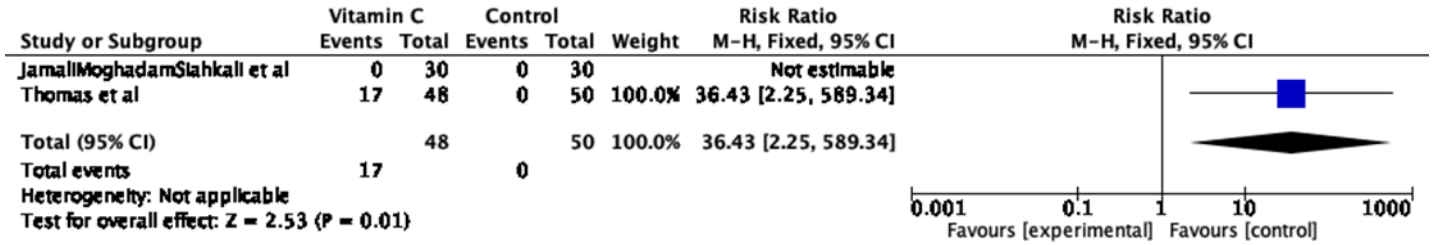

Figure 5. Adverse events

Appendix 6. Table of Ongoing Studies

Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
NCT04682574 Role of Mega Dose of Vitamin C in Critical COVID-19 Patients	Open label RCT	China	COVID-19 patients (children and adult)	Vitamin C 30g/day (10 grams TID) for 2 days with standard treatment	Primary Outcome: Partial pressure of Oxygen in arterial blood to fraction of inspired Oxygen (P/F ratio) Secondary Outcome: Duration of hospital stay	Jan 10, 2021 Status still recruiting
NCT04323514 Use of Ascorbic Acid in Patients With COVID 19	Single group assignment, open label	Italy	COVID-19 patients (children and adult)	Vitamin C 10g IV with conventional therapy	Primary Outcome: In-hospital Mortality Secondary Outcomes: PCR levels, lactate clearance, hospital stay, symptoms, positive swab, tomography imaging	Mar 13, 2021 Status still recruiting

Appendix 7. Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 10)

FACTORS	JUDGEMENT (N = 10)								RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No (1)	Yes (5)		Varies (2)		Uncertain (2)			
Benefits	Large	Moderate (1)	Small (2)	Trivial (1)	Varies (1)	Uncertain (5)			• Indirect evidence from adult studies show trend towards benefit in terms of mortality. • There was no significant benefit and inconclusive results for length of hospital stay, length of ICU stay and need for mechanical ventilation.
Harm	Large	Moderate	Small (6)	Trivial	Varies (1)	Uncertain (3)			• No adverse events from intravenous vitamin C [12] • Adverse events noted with oral preparation: flushing, headache, vomiting, stomach pain [16]
Certainty of evidence	High	Moderate		Low (1)		Very low (9)			• Rated very low due to imprecision, inconsistency and indirectness
Balance of effects	Favors drug	Probably favors drug (1)	Does not favor drug or no drug (2)	Probably favors no drug	Favors no drug	Varies (3)	Uncertain (4)		
Values	Important uncertainty or variability	Possibly important uncertainty or variability (2)		Probably no important uncertainty or variability (5)		No important uncertainty or variability (3)			
Resources required	Uncertain (1)	Varies (2)	Large costs	Moderate costs (6)	Negligible costs or savings	Moderate savings	Large savings (1)		• IV vitamin C: Php 110.00/10 ampules of 500mg/2mL • Pp 28.19/amp
Certainty of evidence of resources required	No included studies		Very low (8)	Low (2)	Moderate	High			
Cost-effectiveness	No included studies (8)	Varies (1)	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 (7)	Varies	Reduced (1)	Probably reduced	Probably no impact (2)	Probably increased	Increased		
Acceptability	Uncertain (5)	Varies (1)	No	Probably no	Probably yes (4)	Yes			
Feasibility	Uncertain (5)	Varies (1)	No	Probably no	Probably yes (4)	Yes			

Additional Comments

- Most Filipino children have low dietary vitamin C intake and would need supplementation for this reason.
  Availability and accessibility in far-flung areas needs to be considered since the route of administration discussed in the evidence is intravenous.