



## EVIDENCE SUMMARY

### Should vitamin C be used as preventive measure 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 against the routine use of vitamin C for the prevention of COVID-19 infection in children.**

Certainty of Evidence: Very Low

Strength of Recommendation: Weak

#### Consensus Issues

This recommendation was made based on evidence from two adult observational studies. It revealed that vitamin C did not have significant benefit in preventing COVID-19 infection. Due to the uncertainty of the evidence, the panel opted to vote against the use of the drug specifically for the prevention of COVID-19. However, the panel agreed and strongly emphasized that when consumed within the proper dietary reference intake values, vitamin C is beneficial for the overall health of children. The panel 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 done on the role of Vitamin C as preventive measure for COVID-19 in pediatric patients. Indirect evidence from two observational studies in adults showed no significant benefit in using Vitamin C for the prevention of COVID-19 infection. Overall certainty of evidence was very low.

#### Introduction

Vitamin C or ascorbic acid is a water-soluble vitamin, which works as a co-factor for various enzymes processes [1]. It scavenges free radicals and reactive oxygen species which are products of physiological cell metabolism or associated with inflammatory diseases, and oxidative damage. It also decreases release of pro-inflammatory cytokines, supports phagocytosis and chemotaxis of leukocytes, enhances neutrophil clearance by macrophages, and promotes development and maturation of T-lymphocytes [2-8]. Various animal models have exhibited its immunomodulatory effects [9-10].

A Cochrane systematic review concluded that 1 to 2 g vitamin C per day is safe, inexpensive, and has a consistent effect on decreasing the duration and severity of the common cold [11]. This review, however, has not shown that regular intake of vitamin C decreases incidence of common colds among the general population [11], even at higher doses of  $\geq 1\text{g/day}$  [12].

A study done among Filipino children showed that mean intake of vitamin C was above adequate intake levels among 6-11.9 month-old infants, but inadequate in 35% of toddlers aged 24-35.9 months and in 60% of children aged 36-59.9 months old [13]. A more recent study done by



Angeles-Agdeppa et al. in 2019 among Filipino school children and adolescents in the low socioeconomic status found that 68-96% of the study population had inadequate vitamin C intake [14]. These children may benefit from additional supplementation. This review seeks to determine the efficacy and safety of vitamin C supplementation as prophylaxis for COVID-19 in the pediatric population.

## 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 PICO for this review was as follows:

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

<b>Population</b>	Children without COVID-19
<b>Intervention/Exposure</b>	Vitamin C or Sodium Ascorbate or Ascorbic Acid as prophylaxis or preventive treatment
<b>Comparison</b>	Usual care, standard of care, placebo, any active control
<b>Outcomes</b>	Incidence of COVID-19, forward transmission, viral load, adverse events

## Results

We found no published articles that directly matched our criteria. We found two studies in adults, included in this review as indirect evidence.

Two observational studies evaluated use of vitamin C as prophylaxis among adult outpatients. Behera et al. did a case-control study among 372 health care workers who were matched for profession, gender, age and date of diagnosis [15]. A total of 186 cases and 186 controls were asked if they took ivermectin, hydrochloroquine or vitamin C prior to testing. The study showed inconclusive results of vitamin C for the prevention of SARS CoV2 infection (OR 0.72; 95%CI 0.42, 1.27).

Louca et al. did an observational cross-sectional survey including 372,720 UK participants 16 to 90 years old who answered a self-reported questionnaire on COVID-19-related information through an app [16]. Exposure was self-reported, regular and constant dietary supplement usage in the previous 3 months during the first waves of the pandemic up to 31 July 2020, while outcome was incidence of SARS-CoV-2 infection before 31 July 2020. This study reported no significant association of vitamin C and COVID-19 infection for all participants (OR=1.02, 95%CI 0.99 to 1.06 p=0.197). Meanwhile, a positive association was found in men aged >60 years taking vitamin C supplements (OR=1.22, 95%CI 1.05 to 1.41, p=0.008) for testing positive for SARS-CoV-2.

Overall certainty of evidence was very low due to risk of bias, indirectness, and imprecision. Both studies enrolled adult populations primarily, and although Louca et al. also included adolescents aged 16-18 years old [16], the report did not quantify how many participants were in this adolescent age group. In addition, the study did not completely provide the raw numbers needed to compute the vitamin C supplementation of persons who tested positive and negative for SARS CoV2 across the UK, US and Sweden (reporting only the Odds Ratios for the UK component).



Both studies included intake of multiple prophylactic agents, thus the effect of vitamin C alone cannot be isolated from the results.

### Other Considerations (Evidence to Decision):

Vitamin C is widely available in all pharmacies and drugstores nationwide. According to the 2021 Philippine Drug Price Reference Index (DPRI), the mean prices for oral vitamin C syrup (100mg/5ml preparation) ranges from Php 17.50 for a 15ml bottle to Php 28.00 for a 120ml bottle. Meanwhile, ascorbic acid 500mg tablets costs Php 0.80 [17].

### Recommendations from Other Groups

The PPS parent guide [18] and PIDSP interim guidelines [19] have stated that nutritional support may be given at the attending physician's discretion as long as it does not exceed the recommended dietary allowance [20]. 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 [19].

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 [18].

### Research Gaps

There are no ongoing clinical trials on use of vitamin C as prophylaxis against COVID-19 in children. Further research is needed to evaluate its efficacy and safety in preventing COVID-19 infection among children..



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## Appendix 1. Search Yield and Results

Database	#	Keywords	Yield
<b>MEDLINE (Pubmed)</b>	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	(incidence of COVID-19) OR (forward transmission) OR (prevalence of COVID-19) OR ("viral conversion") OR (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)	5,437
	4	#1 AND #2 AND #3	97
	5	#1 AND #2 AND #3 AND Filters: Randomized Clinical Trial, Systematic Review, Meta-analysis	9
<b>Cochrane COVID-19 Study Register</b>	1	("vitamin C" or "sodium ascorbate" or "ascorbic acid" or "ascorbate" or "ascorbic") AND (incidence of COVID-19) OR (forward transmission) OR (prevalence of COVID-19) OR ("viral conversion") OR (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)	2,041
	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)	200
<b>WHO COVID Database</b>	1	("vitamin C" or "sodium ascorbate" or "ascorbic acid" or "ascorbate" or "ascorbic") AND (incidence of COVID-19) OR (forward transmission) OR (prevalence of COVID-19) OR ("viral conversion") OR (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) 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)	40
<b>clinicalTrials.gov</b>		"vitamin c" OR "sodium ascorbate" OR "ascorbic acid" AND "pediatric covid"	15
<b>MedRxiv</b>		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)	49
<b>HERDIN</b>		Vitamin c AND Pediatric COVID-19	0
<b>Google Scholar</b>		Vitamin c AND Pediatric COVID-19	8,740



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## Appendix 2. Characteristics of Included Studies

Author/ Year/ Study Design	Population	Intervention	Comparator	Outcome
Louca et al., 2021  Observational cross sectional survey	App users of self-reported Sarscov2 related information from UK (N=372,720), USA (N= 45,757), and Sweden (N= 27,373) aged 16 to 90 years old	Self-reported regular dietary supplement usage (constant use during previous 3 months) in the first waves of the pandemic up to 31 July 2020 among app users who had COVID-19 infection	No self-reported regular usage of dietary supplements in the first waves of the pandemic up to 31 July 2020 among app users who had COVID-19 infection	Outcome measure: SARS-CoV-2 infection before 31 July 2020.  No significant association of vitamin C and covid-19 infection for all participants (OR=1, p=1) Positive association in men aged >60 years taking vitamin C supplements (1.22, 95%CI 1.05 to 1.41, p=0.008) for testing positive for SARS-CoV-2.
Behera et al., 2021  Observational case control study	Healthcare workers matched for profession, gender, age and date of diagnosis (Case=covid positive, control=covid negative) (N=372)	Intake of ivermectin and/or hydroxychloroquine and/or vitamin-C and/or other prophylaxis for COVID-19 among HCW who tested positive for COVID-19 (case)	Intake of ivermectin and/or hydroxychloroquine and/or vitamin-C and/or other prophylaxis for COVID-19 among HCW who tested negative for COVID-19 (control)	Outcome measure: COVID-19 infection  Vitamin-C prophylaxis not associated with +/- SARS-CoV-2 infection (OR 0.72, 95%CI 0.42 to 1.27, p=0.23)



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## Appendix 3. GRADE Evidence Profile

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin C intake	No Vitamin C Intake	Relative (95% CI)	Absolute (95% CI)		
<b>COVID-19 Infection</b>												
1	case control	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	29/67 (43.3%)	157/305 (51.5%)	<b>OR 0.72</b> (0.42 to 1.23)	<b>82 fewer per 1,000</b> (from 207 fewer to 51 more)	⊕○○○ Very Low	CRITICAL
1	cross sectional	very serious <sup>a,d</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	-	-	<b>OR 1.02</b> (0.99 to 1.06)	Not estimatable	⊕○○○ Very low	CRITICAL

CI: confidence interval; OR: odds ratio

### Explanations

- a. Included intake of multiple prophylactic agents; effect of Vitamin C alone cannot be isolated from results
- b. Adult patients enrolled
- c. Confidence interval crosses the null value
- d. Reported findings from UK data only (did not include findings from USA, Sweden)



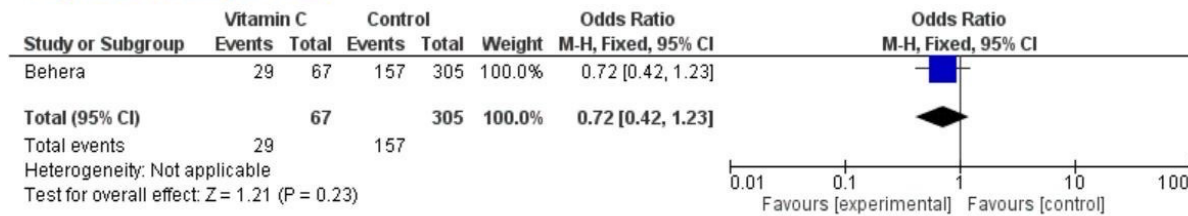


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## Appendix 4. Forest Plots



**Figure 1.** Intake of vitamin C and COVID-19 infection



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## Appendix 5. 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	
	No (2)	Yes (6)		Varies (2)		Uncertain (1)	
<b>Problem</b>	No (2)	Yes (6)		Varies (2)		Uncertain (1)	
<b>Benefits</b>	Large	Moderate (1)	Small	Trivial (3)	Varies	Uncertain (7)	
<b>Harm</b>	Large	Moderate	Small	Trivial (4)	Varies	Uncertain (7)	
<b>Certainty of evidence</b>	High	Moderate		Low (1)		Very low (10)	
<b>Balance of effects</b>	Favors drug	Probably favors drug (2)	Does not favor drug or no drug (3)	Probably favors no drug	Favors no drug	Varies	Uncertain (6)
<b>Values</b>	Important uncertainty or variability	Possibly important uncertainty or variability (4)		Probably no important uncertainty or variability (4)		No important uncertainty or variability (3)	
<b>Resources required</b>	Uncertain (1)	Varies	Large costs	Moderate costs (5)	Negligible costs or savings (4)	Moderate savings	Large savings (1)
<b>Certainty of evidence of resources required</b>	No included studies (10)		Very low (1)	Low	Moderate	High	
<b>Cost-effectiveness</b>	No included studies (11)	Varies	Favors the comparison	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention	Favors the intervention
<b>Equity</b>	Uncertain (7)	Varies (2)	Reduced	Probably reduced	Probably no impact (2)	Probably increased	Increased
<b>Acceptability</b>	Uncertain (5)	Varies	No	Probably no	Probably yes (5)	Yes (1)	
<b>Feasibility</b>	Uncertain (4)	Varies (1)	No	Probably no	Probably yes (5)	Yes (1)	

### Additional Comments

- It may be cost-beneficial to those with low vitamin C intake.