



Philippine Pediatric COVID-19 Living Clinical Practice Guidelines

In cooperation with the Pediatric Infectious Disease Society of the Philippines

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EVIDENCE SUMMARY

Should vitamin D be used as an adjunctive treatment and preventive measure for COVID-19 infection in children?

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Recommendations

We suggest against the use of vitamin D as adjunctive treatment for COVID-19 infection in children.

Certainty of Evidence: Very Low

Strength of Recommendation: Weak

We suggest against the routine use of vitamin D for the prevention of COVID-19 infection in children.

Certainty of Evidence: Very Low

Strength of Recommendation: Weak

Consensus Issues

Due to the uncertainty of the evidence as well as the cost and availability of the drug for the general population, the panel opted to vote against its use as an adjunctive treatment and preventive measure for COVID-19 in children. They also agreed that this recommendation is subject to change based on the availability of higher certainty of evidence. However, the panel strongly emphasized that vitamin D is necessary for those children with documented vitamin D deficiency.

Key Findings

Eight randomized controlled trials and one observational study, all done in the adult population, served as the evidence for treatment and prevention of COVID-19 in children, respectively. Indirect evidence from one observational study in adults suggests that vitamin D is not associated with reduced risk of SARS-CoV2 infection. Very low quality evidence from eight randomized controlled trials that compared vitamin D versus control in hospitalized adult patients with COVID-19 showed inconclusive results for the outcomes of mortality, ICU admission, need for mechanical ventilation, length of hospital stay, clinical improvement, and virologic clearance. The certainty of evidence was rated very low due to issues on risk of bias, indirectness, inconsistency and imprecision.

Introduction

Vitamin D is a fat-soluble vitamin essential in calcium and phosphorus homeostasis and in the maintenance of bone, skin, and tooth enamel. Receptors for vitamin D are nearly universally



expressed in human cells, including in cells of the immune system, and it can exhibit anti-inflammatory effects by modulating macrophage maturation, preventing excessive expression of antiviral cytokines, downregulating inflammatory T_H1 and T_H17 responses, and promoting regulatory T cell (T_{reg}) differentiation [1].

There are several studies that attempted to establish the link between respiratory illness and vitamin D deficiency. We identified two systematic reviews, done in the pre-pandemic period, that evaluated the efficacy of vitamin D supplementation as primary prevention of any respiratory tract infection in children, but these yielded inconsistent results. A meta-analysis of six studies in children showed inconclusive results for incidence of RTI with vitamin D supplementation (Intervention group: $N=3,400$; control group: $N=3,443$, RR 0.88, 95% CI 0.66–1.11, $I^2=80.4\%$, $p=.000$) [2]. However, evidence from another meta-analysis showed significant benefit of supplementation in trials where vitamin D was given to participants aged one year to less than 16 years old (IG=5994, CG=5877, OR 0.71, 95% CI 0.57-0.90, $I^2=46\%$, $P=0.027$) [3].

In relation to COVID-19, vitamin D deficiency is postulated to contribute to increased risk of COVID-19 infection and severity. A previously published meta-analysis of 23 studies in adults found a significant correlation between low serum vitamin D levels and COVID-19 infection (OR 3.3, 95% CI 2.5-4.3) as well as low serum vitamin D and severe COVID-19 (OR 5.1, 95% CI 2.6-10.3) [4]. Another meta-analysis of 13 studies in adults reported significantly higher levels of vitamin D in healthy patients compared to COVID-19 patients (MD = 3.93; 95% CI 2.84–5.02) [5]. A study involving hospitalized very elderly patients reported that bolus vitamin D supplementation was associated with decreased risk of severe COVID-19 and mortality [6]. Similar findings have also been reported in a meta-analysis of eight studies done in pediatric patients, showing significant correlation between vitamin D deficiency and severe COVID-19 (OR 5.5, 95% CI 1.560-19.515) [7]. These reports make vitamin D a supplement of interest for clinicians to prescribe in both prevention and treatment of COVID-19. This review seeks to determine the efficacy and safety of vitamin D as an adjunct for the prevention and treatment of COVID-19 in pediatric patients.

Review Methods

A database search of MEDLINE, the Cochrane COVID-19 Study Register, LitCOVID, the CADTH COVID-19 Evidence Portal, and the World Health Organization (WHO) COVID-19 database was done with a combination of free-text and MeSH terms including "COVID-19" and "vitamin D" was done to search for clinical practice guidelines (CPGs), randomized controlled trials (RCTs), cohort studies, case series, systematic reviews, and meta-analyses that report the effect of vitamin D compared to placebo or standard of care as prevention of COVID-19 in at-risk patients and as adjunct treatment in the management of COVID-19 patients. Preprints were obtained by searching the WHO COVID-19 database, which includes studies found in medRxiv. An additional search was done for CPGs using the CPG Infobase. Ongoing clinical trials were searched through the Cochrane COVID-19 Study Register and the WHO COVID-19 database, which includes trials from ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. The final search date was on January 12, 2022. Studies meeting the criteria described in Table 1 were included in the review.



Table 1. PICO criteria for Vitamin D and COVID-19.

	Vitamin D Prevention	Vitamin D Treatment
Population	Healthy children 18 years old and below without COVID-19	Children 18 years old and below with COVID-19
Intervention	Vitamin D	Vitamin D with standard of care
Comparison	No vitamin D	Placebo, standard of care, no vitamin D
Outcome	Incidence of COVID, forward transmission, viral load, adverse events	Hospitalization, mortality, recovery, clinical improvement, need for mechanical ventilation, duration of hospital stay, duration of ICU stay, adverse events, negative viral conversion

No restrictions on patient COVID-19 severity status, treatment outcome, or country were applied. Studies that were not original research, studies not in English, in-vitro studies, studies combining vitamin D with another drug, and those that compare vitamin D to treatments that are not placebo or standard of care were excluded.

The risk of bias of included studies was assessed using guide questions derived from Painless Evidence-Based Medicine [8] for RCTs. Certainty of evidence was assessed using the GRADE evidence profile [9]. Review Manager 5.4.1 was used for meta-analysis.

Results

A. Should vitamin D be used as a preventive measure for COVID-19 in children?

At this time, there is no direct evidence that answers our research question. A recently published observational study was done in the Catalonia region in Spain among individuals ≥ 18 years old, [10] which determined whether cholecalciferol or calcifediol supplementation achieving 25OHD levels ≥ 30 ng/ml offered protection against COVID-19. However, the overall certainty of evidence for this study was rated very low due to the observational study design and indirectness. (Appendix 4A).

Subgroup analyses of the cholecalciferol-supplemented and calcifediol-supplemented cohorts showed mixed results as follows: cholecalciferol was found to offer slight protection from SARS-CoV2 infection (n= 4352 [4.0%] vs 9142/216,686 [4.2%] in controls; HR 0.95, CI 95% 0.91–0.98, p=0.004); however, calcifediol did not confer protection (n = 5,662 [4.2%] vs 11,401 [4.2%] in controls; HR 0.99, CI 95% 0.96–1.03, p=0.646) (Appendix 3A). But overall effect, based on combined analysis of the two formulations, showed that vitamin D and control were equivalent for the outcome of SARS-CoV2 infection (RR 0.97, CI 95% 0.95-1.00) (Appendix 4A).



B. Should vitamin D be used as an adjunctive treatment for COVID-19 in children?

We found no RCTs, cohort studies, case series, systematic reviews, or meta-analyses that determined the effectiveness of vitamin D as an adjunct treatment for COVID-19 in pediatric patients, either exclusively or as a subgroup. The most recent CPG found that addressed vitamin D supplementation for COVID-19 treatment was that of the Philippine COVID-19 Living CPG, updated in December 2021 [11]. In this CPG, a systematic search was conducted with a final date of 14 November 2021 and eight RCTs (Appendix 3B) that used vitamin D as adjunct treatment for hospitalized adult patients were included. These studies enrolled a total sample size of 740 adults [12-19]. Subgroup analysis was done based on vitamin D status, with subgroups of four studies with low serum vitamin D and four studies with undetermined vitamin D status [14-15,17-18]. Outcomes considered for this review were: mortality, ICU admission, need for mechanical ventilation, length of hospital stay, clinical improvement, virologic clearance, and adverse effects. Certainty of evidence (Appendix 4B) was judged to be very low because of risk of bias, inconsistency, indirectness and imprecision. Pooled analysis (Appendices 4-5) showed inconclusive results for the outcomes of overall mortality (RR 0.73, 95% CI 0.38-1.40), ICU admission (RR 0.54, 95% CI 0.28-1.05), incidence of mechanical ventilation (RR 0.61, 95% CI 0.38-1.00), length of hospital stay (MD -0.48, 95% CI -1.91-0.94), clinical improvement (RR 0.58, 95% CI 0.28-1.18) and virologic clearance (RR 0.58, 95% CI 0.19-1.79). Subgroup analysis showed that mortality, ICU admission, mechanical ventilation, or hospital length of stay were not significantly affected by vitamin D supplementation for patients with undetermined and low baseline serum vitamin D. No adverse effects directly attributable to vitamin D supplementation were found in any of the RCTs. The CPG concluded that there was insufficient evidence to recommend the use of Vitamin D supplementation as an adjunct treatment for adult or pediatric patients with COVID-19 infection.

Other Considerations (Evidence to Decision)

Table 2. Evidence to Decision Considerations

<p>Cost</p>	<p>No evidence was found on the cost-effectivity of Vitamin D supplementation for COVID-19 in children.</p> <p>The approximate prices of vitamin D oral drops, syrup and capsule from local pharmacies are as follows: <i>Vitamin D3 100 IU/mL oral drops = Php 200.00 per 30 mL bottle</i> <i>Vitamin D3 200 IU/5 mL oral syrup = Php 250.00 per 250 ml bottle</i> <i>Vitamin D3 800 IU/capsule = Php 6.75 per capsule</i></p> <p>As per the the Interim Guidelines on COVID-19 from the Pediatric Infectious Disease Society of the Philippines (31 Aug 2020) [20], the recommended dose for vitamin D is as follows, to be given for 5 days: <i><2 years: 1,000 IU/day</i> <i>>2 years: 2,000 IU/day</i></p>
<p>Availability</p>	<p>Available as an over-the-counter medication in most local pharmacies.</p>
<p>Factors to Impact Acceptability or Compliance</p>	<p>The rationale of vitamin D supplementation in SARS-CoV-2 infection in children is based on the reduction of influenza A incidence with vitamin D supplementation [21].</p>



Recommendations from Other Groups

The recommendations of other groups on the use of vitamin D for the prevention or treatment of COVID-19 are summarized in the table below.

Table 3. Summary of recommendations from other groups.

Group	Recommendation
US NIH (April 2021) [23]	There is insufficient evidence to recommend either for or against the use of vitamin D for the treatment of COVID-19.
Australian COVID-19 Living CPG (December 2021) [24]	Do not use vitamin D analogues for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.
NICE COVID-19 rapid guideline: Vitamin D (December 2021) [25]	Do not offer a vitamin D supplement to people solely to prevent or to treat COVID-19, except as part of a clinical trial.
Cochrane: Vitamin D supplementation for the treatment of COVID-19: a living systematic review (March 2021) [26]	<p>There is insufficient evidence to determine the benefits and harms of vitamin D supplementation as a treatment of COVID-19.</p> <p>Moreover, we found only limited safety information, and were concerned about consistency in measurement and recording of these outcomes.</p>
Alberta Scientific Advisory Group: Vitamin D in the Treatment and Prevention of COVID-19 (7 Jan 2021) [27]	There is no high-quality evidence that suggests taking vitamin D supplements is specifically effective in the prevention or treatment of COVID-19.
Ontario COVID-19 Science Advisory Table (18 October 2021) [28]	Vitamin D is currently not recommended for the treatment of COVID-19.
Philippine COVID-19 Living CPG (18 March 2021) [11]	<p>We recommend against the use of Vitamin D supplementation to prevent COVID-19 Infection.</p> <p>There is insufficient evidence to recommend the use of Vitamin D supplementation as an adjunct treatment for patients with COVID-19 infection.</p>
Philippine Pediatric Society. A Parent's Guide on Covid-19 Infection in Children (December 2021) [29]	Supplementation of nutrients such as vitamin C, vitamin D, folate and omega fatty acids may be beneficial to overall health but are not completely validated as preventive or therapeutic medications.



Pediatric Infectious Disease Society of the Philippines. Interim Guidelines on Covid-19. (08 January 2022) [30]

There is no evidence for or against multivitamins and minerals as prevention or treatment of COVID-19 in children. Nutritional support may be given upon the attending physician's discretion with doses not exceeding the Recommended Dietary Allowance.

Research Gaps

There is a need for randomized controlled trials of vitamin D supplementation as a preventive and treatment measure against COVID-19 in children. These studies should aim to determine the optimal vitamin D doses to achieve benefit while balancing safety. As of January 2022, there is one ongoing pediatric clinical trial on vitamin D as adjunctive treatment of COVID-19 and one trial on vitamin D as COVID-19 prevention (Appendix 6).



References

- [1] Bahat G, Erbas Sacar D, Petrovic M. Vitamin D in patients with COVID-19: is there a room for it? *Acta Clin Belg.* 2021 Dec 20:1-7. doi: 10.1080/17843286.2021.2018832
- [2] Vlieg-Boerstra, B, de Jong N, Meyer R, et al. Nutrient supplementation for prevention of viral respiratory tract infections in healthy subjects: A systematic review and meta-analysis. *Allergy.* 2021;00:1–16. doi:10.1111/all.15136
- [3] Jolliffe DA, Camargo CA Jr, Sluyter JD, Aglipay M, Aloia JF, Ganmaa D, et al. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. *Lancet Diabetes Endocrinol.* 2021 May;9(5):276-292. doi: 10.1016/S2213-8587(21)00051-6
- [4] Ghasemian R, Shamshirian A, Heydari K, Malekan M, Alizadeh-Navaei R, Ebrahimzadeh MA, et al. The role of vitamin D in the age of COVID-19: A systematic review and meta-analysis. *Int J Clin Pract.* 2021 Nov;75(11):e14675. doi: 10.1111/ijcp.14675
- [5] Szarpak L, Rafique Z, Gasecka A, Chirico F, Gawel W, Hernik J, Kaminska H, Filipiak KJ, Jaguszewski MJ, Szarpak L. A systematic review and meta-analysis of effect of vitamin D levels on the incidence of COVID-19. *Cardiol J.* 2021;28(5):647-654. doi: 10.5603/CJ.a2021.0072.
- [6] Annweiler C, Hanotte B, Grandin de l'Eprevier C, Sabatier J-M, Lafaie L, C elarier T. Vitamin D and survival in COVID-19 patients: A quasi-experimental study. *J Steroid Biochem Mol Biol* 2020; 204: 105771
- [7] Shah K, Varna VP, Pandya A, Saxena D. Low vitamin D levels and prognosis in a COVID-19 pediatric population: a systematic review. *QJM.* 2021;114(7):447-453. doi:10.1093/qjmed/hcab202
- [8] Dans AL, Dans LF, Silvestre MAA. *Painless Evidence-Based Medicine.* 2nd ed. John Wiley & Sons; 2017.
- [9] GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2021. Available from gradepro.org.
- [10] Oristrell J, Oliva JC, Casado E, Subirana I, Dom nguez D, Toloba A, Balado A, Grau M. Vitamin D supplementation and COVID-19 risk: a population-based, cohort study. *J Endocrinol Invest.* 2022 Jan;45(1):167-179. doi: 10.1007/s40618-021-01639-9.
- [11] Joson MVASG, Tolosa MSS, Infantado MA. Among patients with COVID-19, should Vitamin D be used as adjunct treatment? Philippine COVID-19 Living Clinical Practice Guidelines. 2021.
- [12] Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CSC, et al. Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19: A Randomized Clinical Trial. *JAMA* 2021; 325: 1053–1060.
- [13] Castillo ME, Entrenas Costa LM, Vaquero Barrios JM, Alcal a D az JF, Miranda JL, Bouillon R, et al. 'Effect of Calcifediol Treatment and best Available Therapy versus best Available Therapy on Intensive Care Unit Admission and Mortality Among Patients Hospitalized for COVID-19: A Pilot Randomized Clinical study'. *J Steroid Biochem Mol Biol* 2020; 105751.
- [14] Rastogi A, Bhansali A, Khare N, Suri V, Yaddanapudi N, Sachdeva N, et al. Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study). *Postgrad Med J.* Epub ahead of print November 2020. DOI: 10.1136/postgradmedj-2020-139065.



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- [15] Lakkireddy M, Gadiga SG, Malathi RD, Karra ML, Raju ISSVPM, Ragini, et al. Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease. *Sci Rep* 2021; 11: 10641.
- [16] Elamir YM, Amir H, Lim S, Rana YP, Lopez CG, Feliciano NV, et al. A randomized pilot study using calcitriol in hospitalized COVID-19 patients. *Bone* 2021; 154: 116175.
- [17] Maghbooli Z, Sahraian MA, Jamalimoghadamsiahkali S, Asadi A, Zarei A, Zendeheel A, et al. Treatment With 25-Hydroxyvitamin D(3) (Calcifediol) Is Associated With a Reduction in the Blood Neutrophil-to-Lymphocyte Ratio Marker of Disease Severity in Hospitalized Patients With COVID-19: A Pilot Multicenter, Randomized, Placebo-Controlled, Double-. *Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol*. Epub ahead of print October 2021. DOI: 10.1016/j.eprac.2021.09.016.
- [18] Soliman AR, Abdelaziz TS, Fathy A. Impact of Vitamin D Therapy on the Progress COVID-19: Six Weeks Follow-Up Study of Vitamin D Deficient Elderly Diabetes Patients. *Proc Singapore Healthc* 2021; 20101058211041404.
- [19] Sánchez-Zuno GA, González-Estevez G, Matuz-Flores MG, Macedo-Ojeda G, Hernández-Bello J, Mora-Mora JC, et al. Vitamin D Levels in COVID-19 Outpatients from Western Mexico: Clinical Correlation and Effect of Its Supplementation. *J Clin Med*; 10. Epub ahead of print May 2021. DOI: 10.3390/jcm10112378.
- [20] Pediatric Infectious Disease Society of the Philippines. Interim Guidelines On The Screening, Assessment And Clinical Management Of Pediatric Patients With Suspected Or Confirmed Coronavirus Disease 2019 (Covid-19). 31 April 2020. Available from: <http://www.pidsphil.org/home/wp-content/uploads/2020/09/1598932106977519.pdf>
- [21] Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr*. (2010) 91:1255–60. doi: 10.3945/ajcn.2009.29094
- [22] Angeles-Agdeppa I, Tanda KV. Vitamin D status and usual nutrient intake of Filipino children aged 6–12 years in selected areas in the Philippines: A 2018 national nutrition survey. *Journal of Nutrition and Metabolism*. 2021;2021:1–9.
- [23] COVID-19 Treatment Guidelines Panel. *Coronavirus Disease 2019 (COVID-19) Treatment Guidelines*, <https://www.covid19treatmentguidelines.nih.gov/> (2021, accessed 12 January 2022).
- [24] National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical care of people with COVID-19. 2021 [version 48]. Available from: <https://covid19evidence.net.au/>
- [25] National Institute for Health and Care Excellence (2020, December). *Vitamin D for COVID-19 [A] evidence reviews for the use of vitamin D supplementation as prevention and treatment of COVID-19* (NICE guideline NG187). Retrieved from <https://www.nice.org.uk/guidance/ng187/>
- [26] Stroehlein JK, Wallqvist J, Iannizzi C, Mikolajewska A, Metzendorf M-I, Benstoem C, et al. Vitamin D supplementation for the treatment of COVID-19: a living systematic review. *Cochrane database Syst Rev*. 2021; 5: CD015043
- [27] Alberta Health Services, COVID-19 Scientific Advisory Group. Vitamin D in the Treatment and Prevention of COVID-19. 7 January 2021. Available from: <https://www.albertahealthservices.ca/assets/info/ppih/if-ppih-covid-19-sag-rapid-review-vitamin-d-treatment-and-prevention-covid-19.pdf>
- [28] Morris A, Andany N, Bobos P, Carlin S, Ciccotelli W, Graham C, et al. Evidence-based use of therapeutics for ambulatory patients with covid-19. COVID-19 Advisory for Ontario. 2021Oct18



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- [29] Philippine Pediatric Society. A Parent's Guide on Covid-19 Infection in Children. 2021 December. Available from: <https://pps.org.ph/wp-content/uploads/2022/01/Parents-Guide-on-Covid-19-Infection-In-Children-1.pdf>
- [30] Pediatric Infectious Disease Society of the Philippines. Interim Guidelines On The Screening, Classification, and Management Of Pediatric Patients With Suspected Or Confirmed Coronavirus Disease 2019 (Covid-19). 08 January 2022. Available from: <http://www.pidsphil.org/home/wp-content/uploads/2022/01/1641793296797384.pdf>
- [31] Camargo CA Jr, Martineau AR. Vitamin D to prevent COVID-19: recommendations for the design of clinical trials. *FEBS J.* 2020;287(17):3689-3692. doi:10.1111/febs.15534



Appendix 1. Search Yield and Results

1. For Prevention

Database	#	Keywords/MeSH	Yield
MEDLINE (Pubmed)	1	((((("COVID-19" [Supplementary Concept] OR "COVID-19 drug treatment" [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 2019/12/1:3000/12/31[PDAT])) AND (((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])) OR (((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])) 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))((((("COVID-19" [Supplementary Concept] OR "COVID-19 drug treatment" [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 2019/12/1:3000/12/31[PDAT])) AND (((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])) OR (((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])) 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)	6,164
	2	"vitamin D" OR ergocalciferol OR cholecalciferol OR "vitamin D2" OR "vitamin D3" OR calcifediol OR calcidiol OR 25-hydroxycholecalciferol OR "25-hydroxyvitamin D ₃ " OR calcitriol OR "1,25-dihydroxycholecalciferol" OR "1,25-hydroxyvitamin D ₃ "	97,329
	3	((((((((("Incidence of COVID" OR "attack rate" OR "incidence rate" OR "incidence proportion") OR ("covid prevention" OR "forward transmission")) OR ("viral load" OR "virus titer" OR "viral burden")) OR ("adverse event" OR "adverse events"))	112,758
	4	#1 #2 #3 (all studies)	23



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	5	#1 #2 #3 (Meta-analysis, RCTs, Systematic reviews)	6
Cochrane Library	1	(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)	302,323
	2	"vitamin d" or ergocalciferol or cholecalciferol or "vitamin d2" or "vitamin d3" or calcifediol or calcidiol or calcitriol	15,755
	3	"Incidence of COVID" OR "attack rate" OR "incidence rate" OR "incidence proportion" OR "prevention" OR "forward transmission" OR "viral load" OR "virus titer" OR "viral burden" OR "adverse event"	234,422
	4	#1 #2 #3	6
	5	#1 #2 #3 (Interventional study)	5
	6	#1 #2 #3 (Rapid review)	1
LitCOVID	1	(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) AND ("vitamin D" or ergocalciferol or cholecalciferol or "vitamin D2" or "vitamin D3" or calcifediol or calcidiol or 25-hydroxycholecalciferol or "25-hydroxyvitamin D ₃ " or calcitriol or "1,25-dihydroxycholecalciferol" or "1,25-hydroxyvitamin D ₃ ") AND "Incidence of COVID" OR "attack rate" OR "incidence rate" OR "incidence proportion" OR "prevention" OR "forward transmission" OR "viral load" OR "virus titer" OR "viral burden" OR "adverse event"	13
	2	#1 AND <i>Chemicals: Vitamin D OR Cholecalciferol</i>	2
WHO COVID Database	1	(tw:(((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) AND ("vitamin D" or ergocalciferol or cholecalciferol or "vitamin D2" or "vitamin D3" or calcifediol or calcidiol or 25-hydroxycholecalciferol or "25-hydroxyvitamin D ₃ " or calcitriol or "1,25-dihydroxycholecalciferol" or "1,25-hydroxyvitamin D ₃ ") 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"))))	123
	2	#1 AND controlled clinical trial OR Systematic review OR Clinical Practice Guide OR Evidence synthesis	18

2. As Adjunct Treatment

Database	#	Keywords	Yield
MEDLINE (Pubmed)	1	(((((("COVID-19" [Supplementary Concept] OR "COVID-19 drug treatment" [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-	214,506



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		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 2019/12/1:3000/12/31[PDAT]))	
	2	"vitamin D" OR ergocalciferol OR cholecalciferol OR "vitamin D2" OR "vitamin D3" OR calcifediol OR calcidiol OR 25-hydroxycholecalciferol OR "25-hydroxyvitamin D ₃ " OR calcitriol OR "1,25-dihydroxycholecalciferol" OR "1,25-hydroxyvitamin D ₃ "	97,423
	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")	11,629,542
	4	(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)	4,835,990
	5	#1 AND #2 AND #3	763
	6	#1 AND #2 AND #3 AND Filters: Randomized Clinical Trial, Systematic Review, Meta-analysis	58
	7	#1 AND #2 AND #3 AND #4	103
Cochrane COVID-19 Study Register	1	("vitamin D" OR ergocalciferol OR cholecalciferol OR "vitamin D2" OR "vitamin D3" OR calcifediol OR calcidiol OR 25-hydroxycholecalciferol OR "25-hydroxyvitamin D ₃ " OR calcitriol OR "1,25-dihydroxycholecalciferol" OR "1,25-hydroxyvitamin D ₃ ") 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")	2,600
	2	#1 AND <i>Interventional</i> study type	289
	3	#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)	1,057
WHO COVID Database	1	("vitamin D" OR ergocalciferol OR cholecalciferol OR "vitamin D2" OR "vitamin D3" OR calcifediol OR calcidiol OR 25-hydroxycholecalciferol OR "25-hydroxyvitamin D ₃ " OR calcitriol OR "1,25-dihydroxycholecalciferol" OR "1,25-hydroxyvitamin D ₃ ") 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")	781
CPG Infobase	1	((("vitamin d") AND treatment AND la:en	1
	2	((("vitamin d") AND pedia OR children AND la:en	0



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3. CADTH COVID-19 Evidence Portal

	Keywords	Yield
1	("vitamin d" OR ergocalciferol (D2) OR cholecalciferol (D3) OR Calcifediol OR 25-hydroxyvitamin D3 OR oral 25OHD OR Cholecalciferol OR vitamin D3 OR Ergocalciferol OR vitamin D2	0

4. COVID-Evidence medRxiv

	Keywords	Yield
1	"COVID 19" AND "Vitamin D"	15
2	"COVID 19" AND "Vitamin D" AND (Pedia OR Children)	0



Appendix 2. Characteristics of Included Studies

Table 2A. Characteristics of studies on Vitamin D as preventive measure for COVID-19 in adults.

	Author, Year, Title, Setting	Study Design	Population	Sample Size	Intervention	Comparator	Outcomes
1	Oristrell 2022 Vitamin D supplementation and COVID-19 risk: a population-based, cohort study Spain	Retrospective Cohort	≥ 18 years old supplemented with cholecalciferol or calcifediol	N=711,138	N=243,046 Cholecalciferol n = 108,343 Calcifediol use n = 134,703	N=468,092 Unsupplemented patients n=216,686 (Cholecalciferol group) n=269,406 (Calcifediol group)	- SARS-COV2 Infection - COVID-19 Mortality - Severe COVID

Table 2B. Characteristics of randomized controlled trials on vitamin D as adjunct COVID-19 treatment in adults (from Joson, Tolosa, and Infantado 2021)

	Clinical Trial ID/ Title	Population	Sample Size	Intervention	Comparator	Outcomes
1	Murai 2020 Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19 Brazil	Hospitalized patients with mild to severe COVID-19 Adults aged 18>yrs Positive for SARS-CoV-2 PCR or positive CT scan findings compatible with COVID-19	N=240	200,000 IU of vitamin D3 per orem given on day of admission (N=120)	Placebo (N=120)	Length of Hospital stay Mortality ICU admission Need for mechanical ventilator Duration of mechanical ventilator Serum vitamin D levels
2	Entrenas Castillo 2020 Effect of Calcifediol Treatment and best Available Therapy versus best Available Therapy on Intensive Care Unit Admission and Mortality Among Patients Hospitalized for COVID-19: A Pilot Randomized Clinical study Spain	Hospitalized patients with moderate to severe COVID-19 infection clinical picture of acute respiratory infection confirmed by a radiographic pattern of viral pneumonia positive SARS-CoV-2 PCR with CURB65 severity scale (recommending hospital admission in case of total score > 1).	N=76	Day of admission: 2 capsules of calcifediol (0.266 mg/cap). 1 capsule on days 3, 7, 14, 21, 28 until discharge or ICU admission. Plus standard of care (N=50)	Standard of care (N=26) defined as: 1) Hydroxychloroquine 400mg every 12 hours on first day and 200 mg every 12 hours for the following 5 days 2) Azithromycin 500 mg orally for 5 days,	ICU admission Mortality



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					3) For patients with pneumonia and NEWS score >5, Ceftriaxone 2 g intravenously every 24 hours was given for 5 days.	
3	<p>Rastogi 2020</p> <p>Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomized, placebo-controlled, study (SHADE study)</p> <p>India</p>	<p>Hospitalized patients with asymptomatic to mild COVID-19</p> <p>with or without co-morbidities (hypertension, diabetes mellitus, chronic obstructive airway disease, chronic liver disease, chronic kidney disease)</p> <p>with vitamin D deficiency defined as levels below 20 ng/ml</p>	N=40	<p>Daily 60,000 IU of cholecalciferol (5 ml oral solution in nano droplet form) for 7 days with the aim to achieve 25 (OH)D level >50 ng/ml (N=16)</p> <p>Subsequently, 25(OH)D levels were assessed at day 7 and a weekly supplementation of 60,000IU provided to those with 25(OH)D >50 ng/ml or else continued daily vitamin D 60,000 IU supplementation for another 7 days up until day-14 in participants with 25(OH)D <50 ng/ml</p> <p>Plus standard of care</p>	<p>Placebo (5 ml distilled water) (N=24)</p> <p>Plus standard of care</p>	<p>Proportion of participants who turn SARS-CoV-2 RNA negative at days 5, 7, 10, 14, 18 and 21 (real-time PCR, CFX-96 IVD, Bio-Rad)</p>
4	<p>Lakkireddy 2021</p> <p>Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease</p> <p>India</p>	<p>Hospitalized patients with mild to moderate COVID-19</p> <p>with vitamin D defined as levels below 30 ng/mL</p>	N=130	<p>60,000 IU of cholecalciferol (aqueol nano solution/Deksel) per orem daily for 8 days if with body mass index (BMI) between 18-25 and for 10 days if with BMI more than 25 (N=65)</p> <p>Plus standard of care</p>	<p>Standard of care (N=65)</p>	<p>Inflammatory markers and vitamin D levels before and after intervention (vitamin D levels, CRP, LDH, IL6, Ferritin, N/L ratio)</p> <p>Mortality</p> <p>ICU admission</p> <p>Mean hospital stay</p> <p>Adverse events</p>
5	<p>Elamir 2021</p> <p>A randomized pilot study using calcitriol in hospitalized COVID-19 patients</p> <p>USA</p>	<p>Hospitalized patients with COVID-19 with moderate to severe COVID-19</p>	N=50	<p>Calcitriol 0.5 ug daily for 14 days or discharge whichever came first.</p> <p>Plus standard of care: remdesivir (200 mg for one day followed by 100 mg for 4 days), dexamethasone (6 mg daily for 10</p>	<p>Standard of care</p> <p>Standard of care: remdesivir (200 mg for one day followed by 100 mg for 4 days), dexamethasone (6 mg daily for 10 days), or convalescent plasma</p>	<p>Oxygen requirements</p> <p>Length of hospital stay</p> <p>Need for ICU admission</p> <p>Mortality</p> <p>Readmission.</p>



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				days), or convalescent plasma		
6	<p>Maghbooli 2021</p> <p>Treatment With 25-Hydroxyvitamin D3 (Calcifediol) Is Associated With a Reduction in the Blood Neutrophil-to-Lymphocyte Ratio Marker of Disease Severity in Hospitalized Patients With COVID-19: A Pilot Multicenter, Randomized, Placebo-Controlled, Double-Blinded Clinical Trial</p> <p>Iran</p>	Hospitalized patients with moderate to severe COVID-19	N=106	<p>Calcifediol 25 mcg per orem once daily for 30 days</p> <p>Plus standard of care: a combination of hydroxychloroquine, azithromycin, and ceftriaxone for patients with pneumonia</p>	<p>Placebo</p> <p>Plus standard of care: a combination of hydroxychloroquine, azithromycin, and ceftriaxone for patients with pneumonia</p>	<p>Length of Stay</p> <p>Need for Mechanical Ventilation</p> <p>Mortality</p> <p>ADE</p> <p>Admission to ICU</p>
7	<p>Soliman 2021</p> <p>Impact of Vitamin D Therapy on the Progress COVID-19: Six Weeks Follow-Up Study of Vitamin D Deficient Elderly Diabetes Patients</p> <p>Egypt</p>	Hospitalized elderly diabetes patients with SARS-CoV-2 with vitamin D deficiency.	N=56	200,000 units of high dose cholecalciferol single dose IM	Placebo	<p>Mortality</p> <p>Need for Mechanical Ventilation</p>
8	<p>Sánchez-Zuno 2021</p> <p>Vitamin D Levels in COVID-19 Outpatients from Western Mexico: Clinical Correlation and Effect of Its Supplementation</p> <p>Mexico</p>	Outpatient adults with mild COVID-19	N=42	10,000 IU daily of vitamin D3 in soft capsule form for 14 days	Standard of care	<p>Clinical Improvement (D7)</p> <p>Virologic Clearance (D14)</p>



Appendix 3: Grade Evidence Profile

3A. Grade Evidence Profile: Vitamin D for Prevention of COVID-19 in Children

Author(s): Buban, Racoma, Tolosa, and Perez

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

Bibliography: Oristrell 2022

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	no Vitamin D	Relative (95% CI)	Absolute (95% CI)		

SARS-Cov2 Infection

1	observational studies	serious ^a	not serious	serious ^b	not serious	none	10014/243046 (4.1%)	20543/468092 (4.4%)	RR 0.97 (0.95 to 1.00)	1 fewer per 1,000 (from 2 fewer to 0 fewer)	⊕○○○ Very low	CRITICAL
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CI: confidence interval; RR: risk ratio

Explanations

a. Retrospective review of records and absence of blinding

b. Population studied included adults ≥ 18 years old with different vitamin D dose recommendations from children



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3B. Grade Evidence Profile For Treatment (updated for pediatric patients; from Joson, Tolosa, and Infantado 2021)

Question: Should Vitamin D supplements compared to placebo be used as adjunct treatment for COVID-19?

Bibliography: Murai, Entrenas-Castillo, Rastogi, Lakkireddy, Elamir, Maghbooli, and Soliman

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D supplements	Placebo/Standard of Care	Relative (95% CI)	Absolute (95% CI)		
Mortality (ITT) (follow-up: range 30 days to 60 days)												
6 ^a	randomised trials	serious ^b	serious ^c	serious ⁱ	serious ^d	none	21/353 (5.9%)	24/305 (7.9%)	RR 0.73 (0.38 to 1.40)	21 fewer per 1,000 (from 49 fewer to 31 more)	⊕○○○ Very low	CRITICAL
ICU admission (ITT) (follow-up: range 30 days to 60 days)												
5	randomised trials	serious ^e	serious ^{c,f}	serious ⁱ	serious ^g	none	35/313 (11.2%)	61/289 (21.1%)	RR 0.54 (0.28 to 1.05)	97 fewer per 1,000 (from 152 fewer to 11 more)	⊕○○○ Very low	CRITICAL
Need for Mechanical Ventilation (ITT) (follow-up: range 30 days to 60 days)												
4	randomised trials	not serious	serious ^{a,c}	serious ⁱ	serious ^g	none	25/238 (10.5%)	31/214 (14.5%)	RR 0.61 (0.38 to 1.00)	56 fewer per 1,000 (from 90 fewer to 0 fewer)	⊕○○○ Very low	CRITICAL
Hospital length of stay												
3	randomised trials	not serious	serious ^c	serious ⁱ	serious ^d	none	210	210	-	MD 0.48 days lower (1.91 lower to 0.94 higher)	⊕○○○ Very low	CRITICAL



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Clinical Improvement (follow-up: mean 7 days)

1	randomised trials	very serious ^h	not serious	serious ⁱ	serious ^a	none	7/21 (33.3%)	11/19 (57.9%)	RR 0.58 (0.28 to 1.18)	243 fewer per 1,000 (from 417 fewer to 104 more)	⊕○○○ Very low	CRITICAL
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Virologic Clearance (follow-up: range 14 days to 21 days)

2	randomised trials	serious ⁱ	not serious	serious ⁱ	serious ^a	none	7/38 (18.4%)	19/44 (43.2%)	RR 0.58 (0.19 to 1.79)	181 fewer per 1,000 (from 350 fewer to 341 more)	⊕○○○ Very low	IMPORTANT
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CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

- Serious inconsistency due to different direction of effect by one study Murai which contributed to 32.7% of the over all effect and with risk of bias rated as not serious.
- serious risk of bias due to high drop out rate in the study of Murai, Lakkireddy and Maghbooli which contributed to 66.8% of the overall treatment effect
- Serious inconsistency due to differences in dosage and formulation of vitamin D.
- serious imprecision due to wide confidence interval
- serious risk of bias due to high drop out rate in the study of Murai, Lakkireddy and Maghbooli which contributed to 69.7% of the overall treatment effect
- serious risk for inconsistency; high heterogeneity I²=55%
- Imprecision downgraded by 1 level: due to low number of event rate and wide confidence interval.
- serious risk of bias due to unblinded patients and outcome assessors which may have affected how symptoms were reported
- Risk of bias downgraded by 1 level: some concerns due to unclear randomization and allocation concealment, and lack of blinding in participants and personnel.
- Serious indirectness as studies recruited adults exclusively.

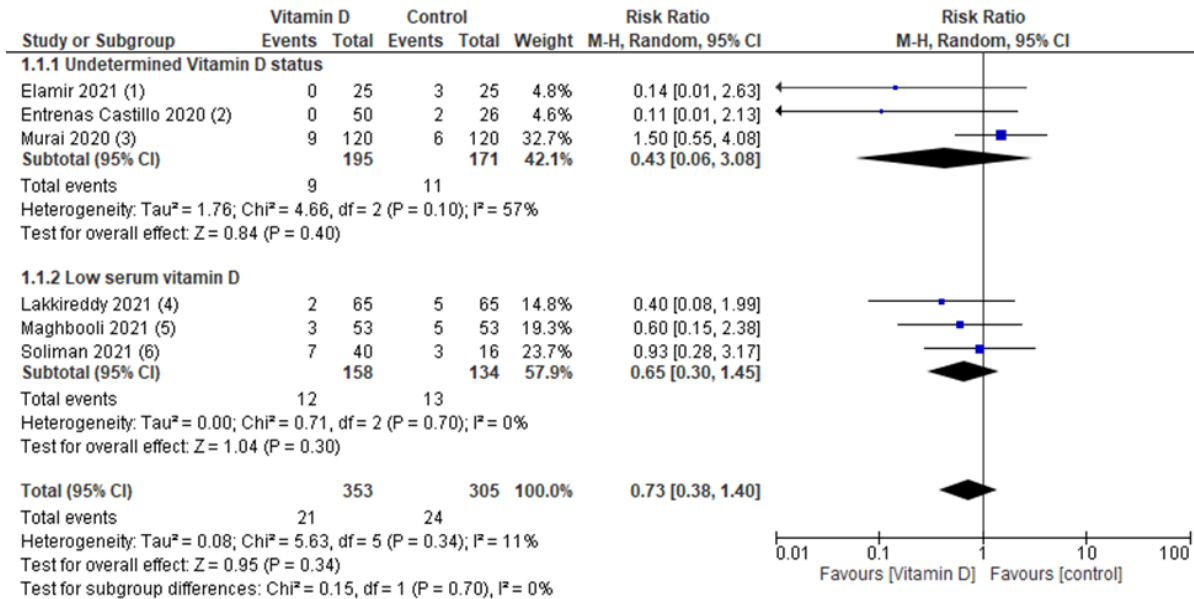


Appendix 4A: Forest Plots from Included Studies (Prevention, January 27, 2022)



Figure 1.1. Prevention

Appendix 4B: Forest Plots from Included Studies (from Joson, Tolosa, and Infantado 2021)



Footnotes

- (1) moderate to severe
- (2) moderate to severe
- (3) mild to severe; vitamin D group (mean 21.2 ng/mL; SD 10.1); control group (mean 20.6 ng/mL; SD 8.1)
- (4) mild to moderate; vitamin D <30 ng/mL
- (5) moderate to severe; vitamin D <30 ng/mL
- (6) severity not stated; vitamin D <20 ng/mL

Figure 1.2. Mortality, overall (ITT).

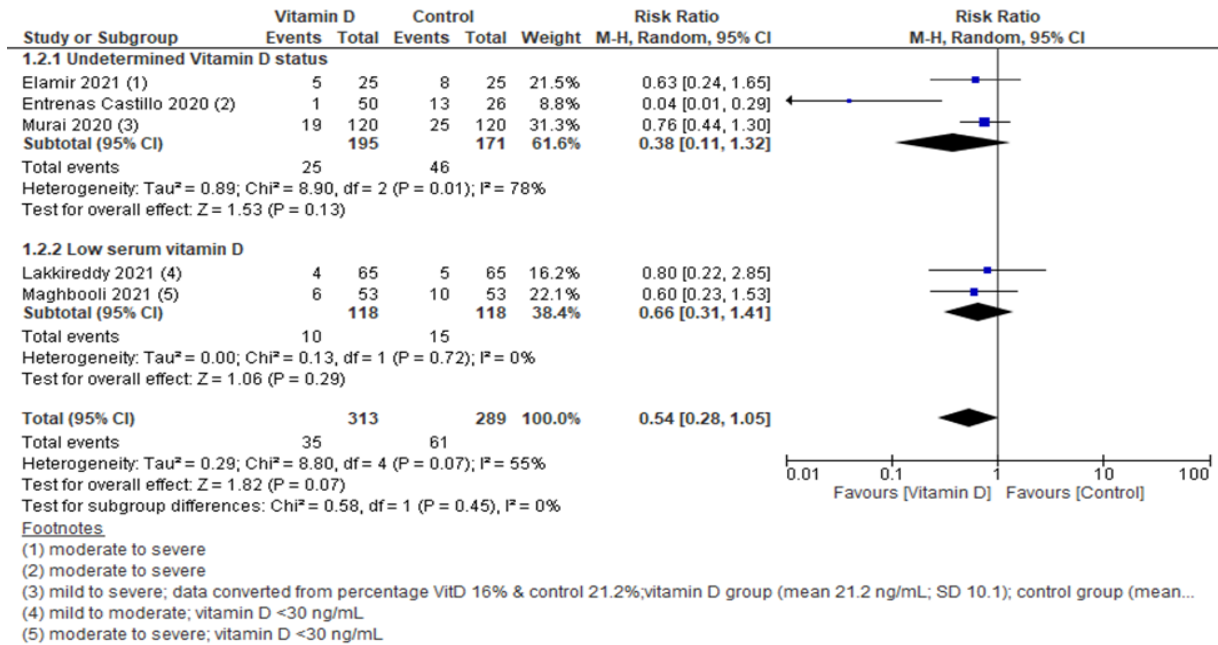


Figure 1.3. ICU admission (ITT).

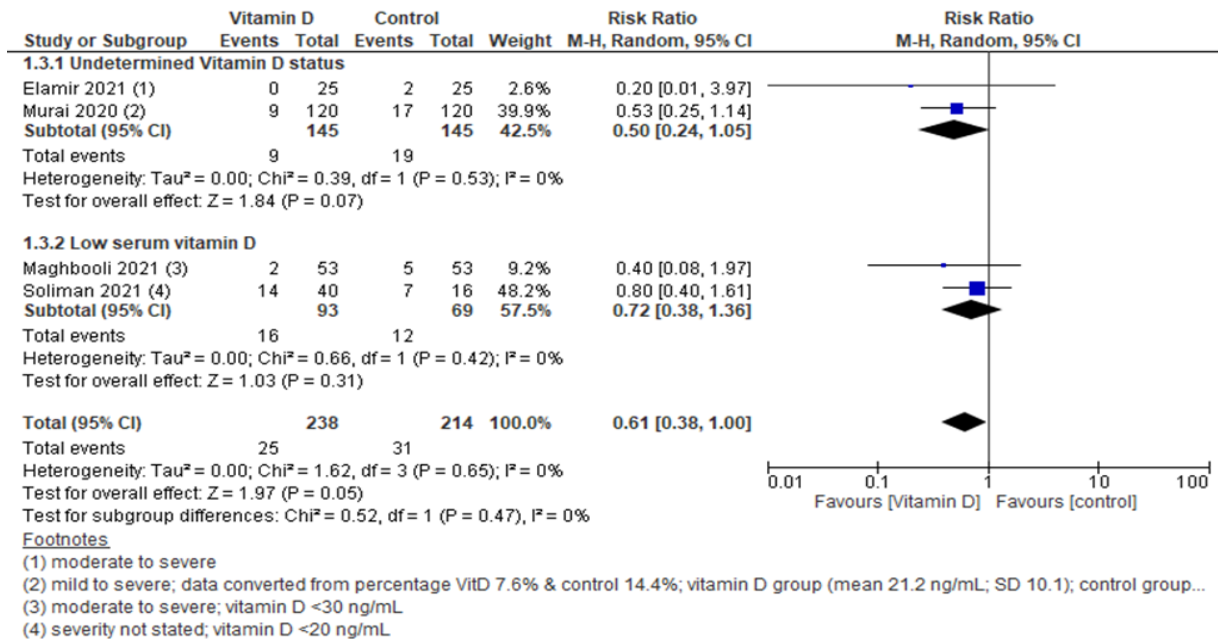


Figure 1.4. Need for Mechanical Ventilation (ITT).

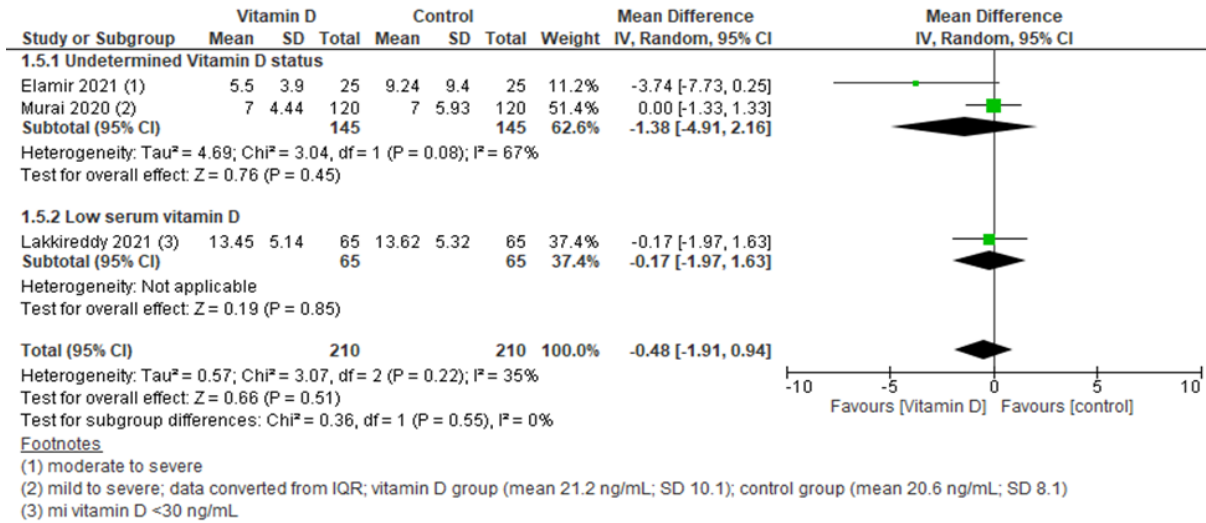


Figure 1.5. Length of Hospital Stay (ITT).

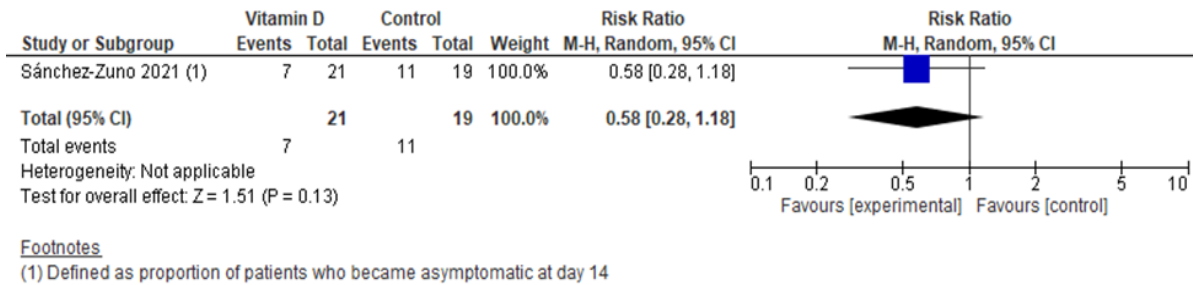


Figure 1.6. Clinical Improvement (ITT).

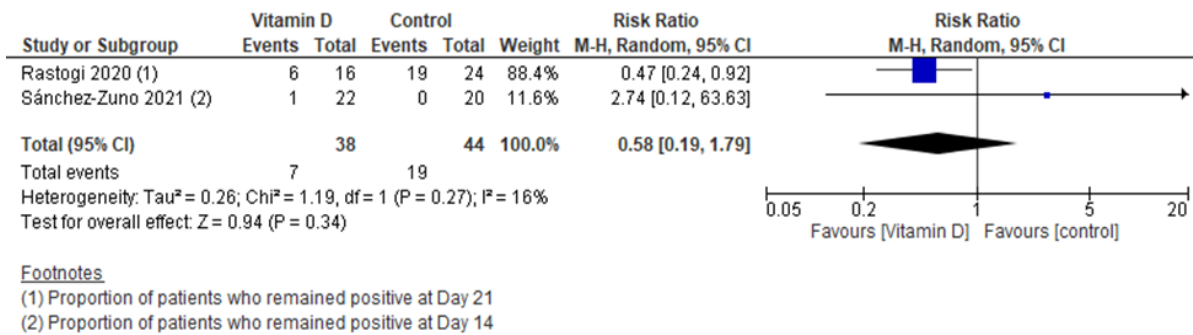


Figure 1.7. Virologic Clearance (ITT).



Appendix 5: Table of Ongoing Studies

Clinical Trial Identifier (Location)	Official Title	Methodology	Outcome Measures	Population	Estimated Date of Completion
NCT04502667 Mexico	Efficacy of Vitamin D Treatment in Pediatric Patients Hospitalized by COVID-19: Open Controlled Clinical Trial	Randomized open controlled trial	Primary outcomes: Serum interleukins, ferritin, D-dimer levels at 7 days post-admission Secondary outcome: Serum vitamin D level at study completion (average of 21 days)	40 children hospitalized with COVID-19	April 2022
NCT05043116 Denmark	High-dose Vitamin D Supplement for the Prevention of Acute Asthma-like Symptoms in Preschool Children - a Double-blind, Randomized, Controlled Trial	Double-blind randomized controlled trial	Primary outcome: Number of acute asthma exacerbations within 1 year Secondary outcome: Time to first asthma exacerbation, duration of symptoms, need for medical treatment Blood/urine calcium levels Adverse events COVID-19 infection risk, symptom burden, infection length	320 preschool children	October 2031



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Appendix 6. Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 9)

FACTORS	JUDGEMENT (N = 9)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS	
Problem	No (1)	Yes (6)		Varies (1)		Uncertain (1)		
Benefits	Large	Moderate	Small (1)	Trivial (1)	Varies		Uncertain (7)	<ul style="list-style-type: none"> Inconclusive results for prevention and treatment
Harm	Large	Moderate	Small (2)	Trivial (1)	Varies		Uncertain (6)	
Certainty of evidence	High	Moderate		Low (1)		Very low (8)		<ul style="list-style-type: none"> Rated very low due to indirectness, imprecision and serious risks of bias
Balance of effects	Favors drug	Probably favors drug (2)	Does not favor drug or no drug	Probably favors no drug	Favors no drug		Varies	Uncertain (7)
Values	Important uncertainty or variability	Possibly important uncertainty or variability (1)		Probably no important uncertainty or variability (5)		No important uncertainty or variability (3)		
Resources required	Uncertain (1)	Varies	Large costs (1)	Moderate costs (5)	Negligible costs or savings (2)	Moderate savings	Large savings	<ul style="list-style-type: none"> Vitamin D3 100 IU/mL oral drops: Php 200.00/30mL bottle Vitamin D3 200 IU/5mL oral syrup: Php 250.00/250mL bottle Vitamin D3 800 IU/capsule: Php 6.75/cap
Certainty of evidence of resources required	No included studies (9)		Very low	Low	Moderate	High		
Cost-effectiveness	No included studies (9)	Varies	Favors the comparison	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention	Favors the intervention	
Equity	Uncertain (8)	Varies	Reduced	Probably reduced (1)	Probably no impact	Probably increased	Increased	
Acceptability	Uncertain (6)	Varies	No	Probably no	Probably yes (3)	Yes		
Feasibility	Uncertain (3)	Varies	No (1)	Probably no	Probably yes (4)	Yes (1)		

Additional Comments

- Vitamin D may be too expensive for the mid- to low-income families. Supplementation may be beneficial for the Filipino children with already low vitamin D levels.