SOUTH AFRICAN NATIONAL DEPARTMENT OF HEALTH BRIEF REPORT OF RAPID REVIEW COMPONENT: COVID-19

TITLE: **WHAT IS THE EFFICACY AND SAFETY OF VITAMIN D FOR THE TREATMENT OF CONFIRMED SARS-COV-2 INFECTION?**

DATE: **8 SEPTEMBER 2022**

KEY FINDINGS

Results of the review of health evidence

>	A rapid review was conducted to evaluate the efficacy, safety and effectiveness of vitamin D compared to any other medicine for the treatment of COVID-19 in patients with confirmed SARS-CoV-2 infection.
>	We searched the eCOVID-19 RecMap, the National Institutes of Health (NIH) and the National Institute for Health and Care Excellence (NICE) for guidelines and recommendations on 3 August 2022. Additionally, we searched the Cochrane Library COVID-19 study register and Epistemonikos (LOVE Platforms) for trials on the 3 August 2022. We identified two eligible systematic reviews and two additional randomised controlled trials.
>	Systematic reviews: Two systematic reviews were identified from the search. One was a Cochrane review published in 2021, and the other was published in 2022. The Cochrane review (Stroehlein *et al.*, 2021) included three eligible trials, while the other review (Hosseini *et al.*, 2022) included five trials. Based on our assessment of the quality off the reviews, we opted to use the Cochrane review as a baseline and added two additional trials to the analysis. Trials: Of the five eligible trials (three from the Cochrane review and the two additional trials), four were conducted in Spain, Brazil, Egypt, and Israel, and investigated the efficacy and safety of Vitamin D for treatment of confirmed SARS-CoV-2 infection in hospitalised patients aged between 52 and 71 years with co-morbidities. One was excluded as it did not report on the outcomes of interest.
>	Vitamin D compared to no vitamin D/placebo had little or no difference in mortality (risk ratio (RR) 1.08; 95% confidence interval (CI) 0.58 to 2.01; n = 234). This was considered very low certainty evidence. The estimated effect ranged from 6 more deaths per 1000 patients treated, ranging from 32 fewer deaths to 77 more. Vitamin D had little or no effect on duration of hospitalisation. The evidence for an impact on duration of hospitalisation was assessed as very low certainty, due to serious risk of bias and very serious imprecision. Murai *et al.*, 2021 reported a median (95% CI) duration of hospitalisation of 7.0 (4.0-10.0) days in patients receiving vitamin D vs 7.0 (5.0-13.0) days in patients receiving placebo (p = 0.94). Elamir *et al.*, 2022 reported a mean (sd) duration of hospitalisation of 5.5 +/- 3.9 days in those receiving vitamin D vs. 9.24+/-9.4 for those receiving no vitamin D (p=0.14). Vitamin D had little to no effect on progression to mechanical ventilation (RR 0.71; 95% CI 0.40 to 1.27; n = 184). This was also considered very low certainty evidence. The estimated effect ranged from 91 fewer to 41 more patients progressing to mechanical ventilation per 1000 treated. One trial (Elamir *et al.*, 2020) reported on adverse events. A reduction in glomerular filtration rate by >10% was seen in none of 25 patients receiving vitamin D (0/25) compared to 4/25 patients receiving no vitamin D (p=0.1) These results were assessed to be of very low certainty evidence due to serious risk of bias and very serious imprecision.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

TYPE OF RECOMMENDATION

We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
(strong)		(conditional)	(conditional)	(strong)
☐	☒	☐	☐	☐

health

Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

RECOMMENDATION

The Committee suggests that vitamin D not be used for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval *(conditional recommendation; very low certainty evidence)*

RATIONALE	LEVEL OF EVIDENCE
There remains significant uncertainty whether vitamin D is effective in treating patients with COVID-19.	**Very low certainty**

Therapeutic Guidelines Sub-Committee of the COVID-19 Management Clinical Guidelines Committee: Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish (Chair), Helen Rees, Gary Reubenson (Vice-chair). Secretariat: Ruth Lancaster (NDoH), Milli Reddy (BHPSA).

PROSPERO registration: CRD42021286710

Version	Date	Reviewer(s)	Recommendation and Rationale
1.0	8 September 2022	NT, DM, TL, TK, AG, KC	Vitamin D is not recommended for the treatment of COVID-19, as the evidence of effectiveness and safety is currently uncertain.

BACKGROUND

There are limited data suggesting that vitamin D supplementation is safe and may reduce the risk of acute respiratory infections when compared to placebo (1). However, there is uncertainty as to whether vitamin D is effective in the treatment of confirmed COVID-19. Recent studies also suggest an association between vitamin D deficiency and COVID-19 infection (2), and thus a rapid review was conducted to investigate vitamin D as a therapeutic agent for COVID-19.

Neither the Australian National COVID-19 Clinical Evidence Taskforce (3), the Pan American Health Organisation (PAHO) (4) nor NICE (5) (last updated 14 July 2022) recommend the use of vitamin D for the treatment of COVID-19 outside of randomised controlled trials with appropriate ethical approval. The US National Institutes of Health (NIH) (last updated 21 April 2021) suggests that there is insufficient evidence to recommend either for or against the use of vitamin D for the prevention or treatment of COVID-19 (6). An appraisal of the quality of these guidelines, their recommendations, and sources, is presented in Table 1.

Table 1: Summary of Vitamin D recommendations

Guideline	Source	Recommendation	AGREE scores
Australian National COVID-19 Clinical Evidence Taskforce Prevention and treatment of COVID-19. 2022 (pre-publication) [Černý, V., *et al*. Prevence a léčba COVID-19] Czech Health Research Council. Available from: https://kdp.uzis.cz/index.php?pg=kdp&id=52	COVID19 Recommendations https://covid19.recmap.org/recommendation/b03450e7-9809-499a-bf76-53f35998721d Accessed: 2022-08-13	According to the Australian National COVID-19 Clinical Evidence Taskforce, do NOT use vitamin D analogues (calcifediol/cholecalciferol) for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.	Scope and purpose: 83.3% Rigor of development: 78.1% Editorial Independence: 79.2% Certainty of evidence: Very Low Recommendation strength: Strong
PAHO Pan American Health Organization. (2021). Guidelines for Prophylaxis and Management of Patients with Mild and Moderate COVID-19 in Latin America and the Caribbean. Available at: https://iris.paho.org/handle/10665.2/55068	COVID19 Recommendations https://covid19.recmap.org/recommendation/d3434ad7-b983-4e64-8755-c2a25dd81f37 Accessed: 2022-08-13	It is not recommended to administer vitamin D for the treatment of patients with mild or moderate COVID-19, outside the context of clinical trials.	Scope and purpose: 97.2% Rigor of development: 69.8% Editorial Independence: 83.3% Certainty of evidence: Very Low Recommendation strength: Strong
NICE National Institute for Health and Care Excellence. (2022). COVID-19 rapid guideline: managing COVID-19 version 27.0 [NICE guideline	COVID19 Recommendations https://covid19.recmap.org/recommendation/d3434ad7-b983-4e64-8755-c2a25dd81f37 Accessed: 2022-08-13	Do not use vitamin D to treat COVID-19 except as part of a clinical trial.	Scope and purpose: 88.9% Rigor of development: 87.5% Editorial Independence: 87.5% Certainty of evidence: Very Low Recommendation strength: Conditional

[NG191]]. https://www.nice.org.uk/guidance/ng19			
NIH COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed [2022-08-13].	https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf Accessed: 2022-08-13	There is insufficient evidence to recommend either for or against the use of vitamin D for the prevention or treatment of COVID-19.	

The currently available evidence for vitamin D supplementation in the treatment of COVID-19 needs to be reviewed to provide guidance for the local South African context. This rapid review aimed to assess the efficacy, safety, and effectiveness of vitamin D in patients with confirmed SARS-CoV-2. The endpoints assessed were mortality, progression to hospitalisation, duration of hospitalisation, progression to ICU admission, duration of ICU stay, progression to mechanical ventilation, duration of mechanical ventilation, and adverse reactions.

RESEARCH QUESTION:

What is the efficacy, safety, and effectiveness of vitamin D for the treatment of confirmed SARS-CoV-2 infection?

METHODS

We searched the eCOVID-19 RecMap, the National Institutes of Health (NIH) and the National Institute for Health and Care Excellence (NICE) for guidelines and recommendations on 3 August 2022. Additionally, we searched the Cochrane Library COVID-19 study register, and Epistemonikos (LOVE Platforms) for trials. These databases systematically search PubMed, Embase, MedRxiv, WHO's ICTRP and clinicaltrials.gov. The search terms used are found in Appendix 1. Screening of records, and selection of articles was done independently by two reviewers (DM and NB) then cross-checked by a third (TK). Data extraction was done by two reviewers (DM) and (NB). The main characteristics of the included systematic review and trials and study outcomes are shown in Table 2. Table 3 presents the results of the search for planned/ongoing trials on the COVID-nma website.

We used Review Manager (Revman) 5 software to perform the analyses. AGREE II scores for guidelines were obtained from the eCOVID-19 RecMap team (https://covid19.recmap.org/about) (7) (Table 1). We assessed the quality of two reviews. The most recent reviews and an outdated Cochrane review (8,9) using the AMSTAR (10) tool (Appendix 2A, 2B). Assessments were performed independently by two reviewers (TL and DM). The risk of bias (ROB) for four included trials (11–14) was obtained from the COVID-nma website. The fifth trial (15) was appraised by two reviewers (DM and NB) used the Cochrane risk of bias 2.0 tool (16) as appropriate. We reported risk ratios for dichotomous data with 95% confidence intervals (CI). Means (standard deviation) or medians (interquartile ranges) were reported for continuous data where appropriate. GRADE was used to assess the overall confidence of the evidence considering various factors that might decrease the confidence in the trial finding, including risk of bias, inconsistency, imprecision, publication bias and indirectness (17). Tables 4 is a GRADE evidence profile for the comparison of vitamin D and no vitamin D/placebo in the treatment of COVID-19.

ELIGIBILITY CRITERIA FOR REVIEW

Population:	All patients with confirmed SARS-CoV-2 infection, no restriction to age, disease severity or setting
Intervention:	Vitamin D. No restriction on dose, formulation, frequency, or timing
Comparators:	Any comparator (e.g., standard of care; placebo; another intervention).
Outcomes:	1. Mortality 2. Progression to hospitalisation 3. Duration of hospitalisation 4. Progression to ICU admission 5. Duration of ICU stay 6. Progression to mechanical ventilation 7. Duration of mechanical ventilation 8. Adverse reactions
Study designs:	• Systematic reviews of randomised controlled trials • Randomised controlled trials

RESULTS

- SEARCH RESULTS

The literature search resulted in the retrieval of 109 records. After removing 1 duplicate record, 108 records remained and were screened based on their titles and abstracts. Forty-six records did not meet the prespecified inclusion criteria and were excluded. We screened the full texts, or, if these were not available, the trial register entries, of the remaining 62 references. Twelve records were excluded for being outdated and for having an incorrect comparator, and study design after full-text assessment. Additionally, we identified 48 ongoing records on Covid-nma that will be monitored for publication (Table 3). Finally, we included four records in our narrative synthesis. The search process is depicted in Figure 1.

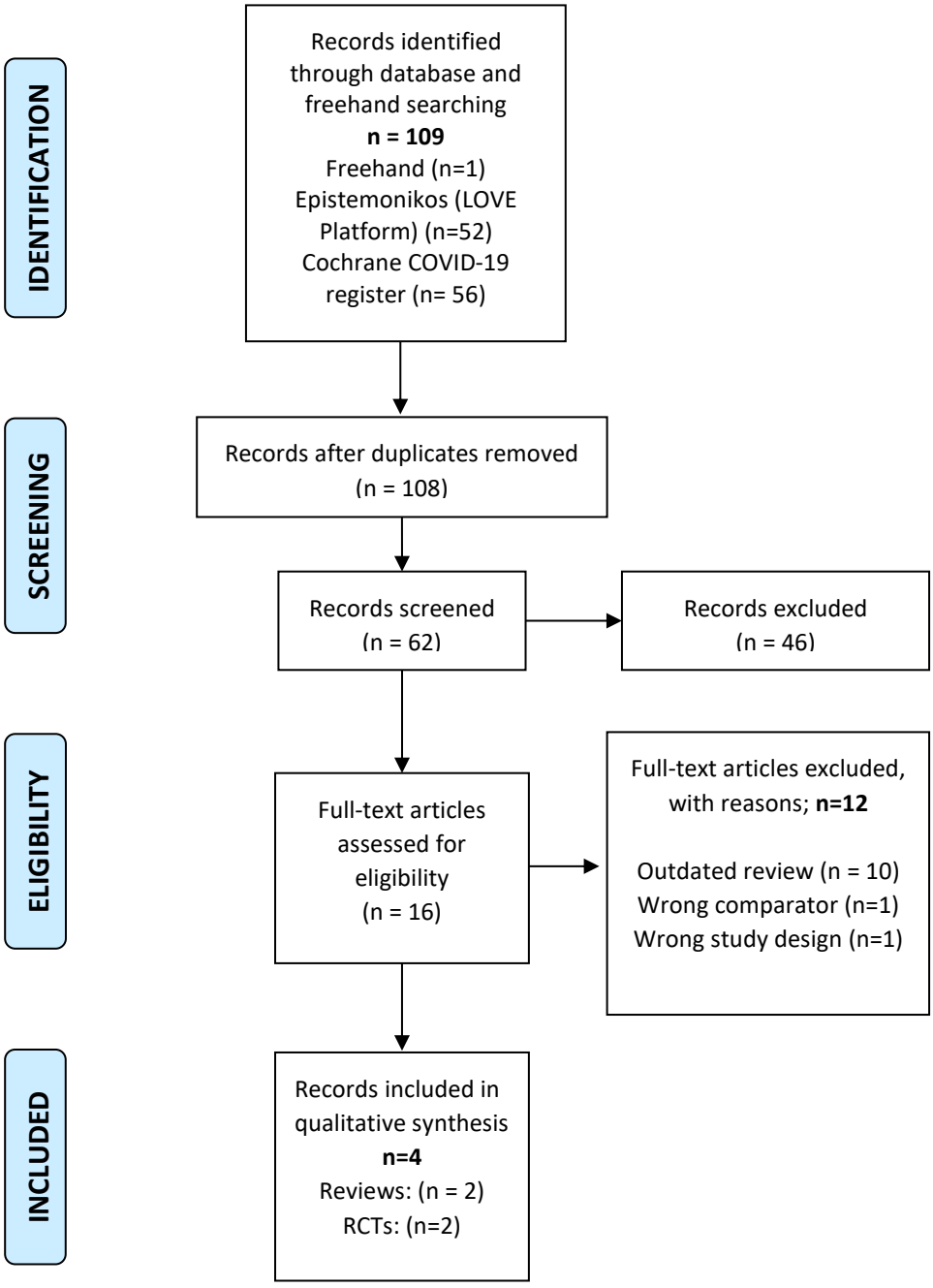


FIGURE 1: PRISMA FLOW DIAGRAM OF REVIEW

- **DESCRIPTION AND APPRAISALS OF SYTEMATIC REVIEWS AND TRIALS**

  - **Systematic review (n=2)**

    Two systematic reviews were identified from the search. One was a Cochrane review published in 2021 (11), the other was published in 2022 (10). The Cochrane review (Stroehlein *et al.*, 2021) included three eligible trials, while the review (Hosseini *et al.*, 2022) included five trials. Although the Hosseini *et al.*, 2022 review appeared more relevant for this rapid review, based on the low AMSTAR II appraisal assessment (Appendix 2A and 2B), we opted to use the better-quality Stroehlein *et al.*, 2021 review as baseline and added two additional trials to the analysis**.** Overall, the Stroehlein

et al., 2021 was assessed to be of high quality, presenting no critical or non-critical weakness (Appendix 2A). The Hosseini *et al.*, 2022 review was assessed to be of critically low quality due to having two critical flaws (Appendix 2B). The two critical weaknesses were identified in items 7 and 9 due to the authors not including a list of excluded studies with justifications, and the non-satisfactory technique for assessing risk of bias of individual studies included in the review. Of note, item 9 was particularly concerning since one of the included studies had major risk of bias concerns regarding incomplete outcome data and relied on industry funding. One of the included trials, one (NCT04483635) was terminated due to a significantly lower recruitment than planned. Additionally, a trial authored by the review authors was included in the analysis, giving rise to concerns around undeclared conflicts of interest. Lastly, one of the included trials (18), was retracted on 20 April 2021, before the date of acceptance and publication of the review (May 2022).

- **Randomised controlled trials (n=5**)

  We identified five eligible trials. One (Rastogi *et al.*, 2020) trial did not report on our outcomes of interest (13) and was therefore excluded from the analysis. The remaining four trials, conducted in Spain, Brazil, Egypt, and Israel, investigated the efficacy and safety of vitamin D for the treatment of confirmed SARS-CoV-2 infection in hospitalised patients aged between 52 and 71 years with co-morbidities (11,12,14,15). Specifically, one trial (Elamir *et al.,* 2020) compared calcitriol (0.5 µg daily) vs no treatment for 14 days (14), two trials (Soliman and Murai *et al.,* 2021) reported on vitamin D vs placebo (11,15), and another (Castillo *et al.,*) compared calcifediol (21,280 I/D/day calcifediol on day 1, 3 and 7, and then weekly) with no calcifediol for 4 weeks (12). Two trials (Soliman and Murai *et al.,* 2021) compared vitamin D vs placebo administered either intramuscularly (200 000 IU) for 6 weeks or orally (single bolus of 200 000 IU for 20 days) (11,15). All trials reported on mortality, three trials reported on progression to mechanical ventilation, two on duration of hospitalisation, three on the progression to ICU admission, and one reported on adverse reactions.

  Three trials were assessed as having an overall risk of bias of 'some concerns' (11,12,14) and one trial with had 'high' risk of bias (15). Castillo *et al.*, 2020 was an unblinded pilot study (outcome assessor, participants, and personnel/carers), that in addition did not mention allocation concealment. As a result, the primary outcome, mortality, was assessed to have a risk of bias of some concerns. Murai *et al.*, 2021 presented with low risk for all domains except for the selection of the reported results for adverse events since this outcome was not pre-specified in the trial registry. Elamir *et al.*, 2021 was assessed to have an overall risk of bias of 'some concerns' due to lack of randomisation, deviation from intervention, measurement of outcome (excluding mortality) and the selection of reported results. The protocol, statistical analysis plan (SAP) and registry were not available. No information on whether the result was selected from multiple outcome measurements or analyses of the data. No information on whether the trial was analysed as pre-specified. Soliman *et al*., 2022 presented with an overall 'high risk' of bias owed to the measurement of outcome domain for the progression to mechanical ventilation outcome. Additionally, the trial presented with a risk of 'some concerns' for the lack of allocation concealment, and a detailed SAP to ascertain pre-specification of the outcomes of interest.

EFFECTS OF THE INTERVENTION

Tables 4 shows the GRADE Evidence Profile, summarising the effects of the intervention for each of the following outcomes:

- **Mortality**

Overall, vitamin D compared to no vitamin D/placebo may result in little or no difference in mortality (RR 0.93; 95% CI 0.30 to 2.87; n = 234). This was assessed as very low certainty evidence (serious risk of bias and very serious imprecision). Figure 2 shows the forest plot for this comparison. Four trials reported on the effect of vitamin D on mortality: Castillo *et al* 2020 and Elamir *et al.*, 2022 on all-cause mortality, Murai *et al.*, 2021 on in-hospital mortality, and Soliman *et al* 2022 on mortality at week 6. Castillo *et al* 2020 reported 0/50 (0%) vs 2/26 (7.69%) deaths in the vitamin D vs no vitamin D arms, respectively. Of note, 7.7% of deaths reported in the no vitamin D arm were amongst those admitted to ICU (13/26). Murai *et al.*, 2021 reported 9/119 (7.6%) vs 6/118 (5.1%) deaths among the vitamin D vs placebo arms. Soliman *et al* 2022 reported 17/40 (17.5%) vs 3/14 (18.8%) deaths among the vitamin D vs placebo arms. Elamir *et al.*, 2022 reported 2/25 (0%) vs 3/25 (12%) deaths in the vitamin D vs no vitamin D arms.

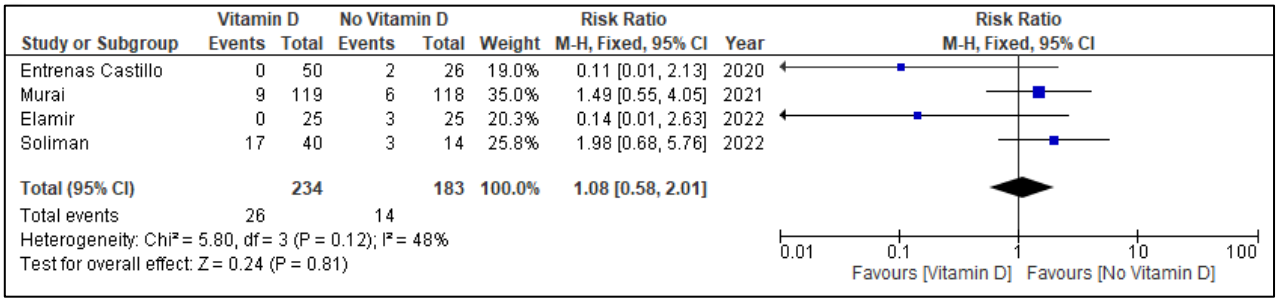


FIGURE 2: FOREST PLOT OF VITAMIN D *VS.* NO VITAMIN D/PLACEBO, MORTALITY

- **Progression to hospitalisation** – This outcome was not reported.

- **Duration of hospitalisation**

  Overall, data from two trials (Murai *et al.*, 2021 and Elamir *et al.,* 2022) reported on the duration of hospitalisation. Both were assessed as very low certainty evidence due to serious risk of bias and very serious imprecision. Murai *et al.*, 2021 reported a median duration of hospitalisation of 7.0 (4.0-10.0) days in those receiving vitamin D vs 7.0 (5.0-13.0) days in those receiving placebo (log-rank *P* = .59; unadjusted HR for hospital discharge, 1.07 [95% CI, 0.82-1.39]; *P* = .62; adjusted HR, 0.99 [95% CI, 0.71-1.37]; *P* = .94). Elamir *et al.*, 2022 reported a mean duration of hospitalisation of 5.5 +/- 3.9 days in those receiving vitamin D vs. 9.24+/-9.4 in those receiving no vitamin D (p=0.14).

- **Progression to ICU admission**
  Overall, data from three trials reported some protective effects in relation to ICU admission (RR 0.38; 95% CI 0.11 to 1.31; n = 194). This was assessed as very low certainty evidence (serious risk of bias and very serious imprecision). Castillo *et al.*, 2020 reported 1/50 (2%) vs 13/26 (50%) patients who progressed to ICU admissions in the vitamin D vs the no vitamin D arms, respectively. Murai *et al.*, 2021 reported 19/119 (16%) vs 25/118 (21.2%) patients who progressed to ICU in the vitamin D vs placebo groups. Elamir *et al.*, 2022 reported 5/25 (20%) vs 8/25 (32%) patients to have progressed to ICU admission in the vitamin D vs no vitamin D groups.

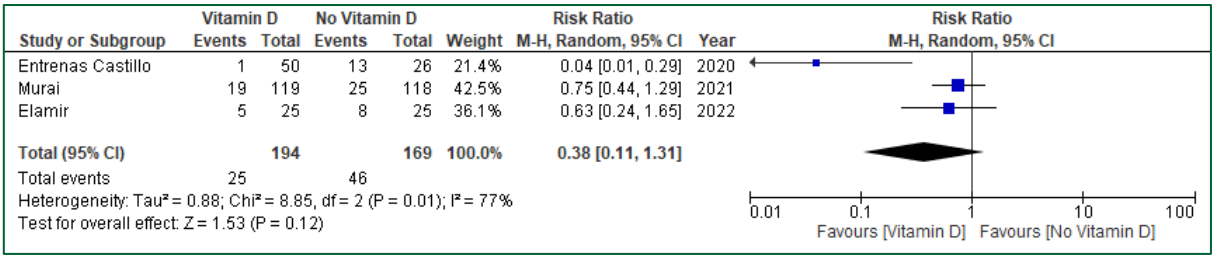


FIGURE 3: FOREST PLOT OF VITAMIN D *VS.* NO VITAMIN D/PLACEBO, PROGRESSION TO ICU ADMISSIONS

- **Duration of ICU stay** – This outcome was not reported.

- **Progression to mechanical ventilation**
  Data from three trials contributed to the meta-analysis of this outcome. Overall, vitamin D vs no vitamin D/placebo had some effect on the progression to mechanical ventilation (RR 0.71; 95% CI 0.40 to 1.27; n = 184). This was assessed as very low certainty evidence (serious risk of bias and very serious imprecision). Elamir *et al.*, 2022 reported 2/25 (8%) vs 0/25 (0%) patients to have progressed to mechanical ventilation (referred to as endotracheal intubation) in the vitamin D vs no vitamin D groups. Murai *et al.*, 2021 reported 9/119 (7.56%) vs 17/118 (14.40%) patients to have progressed to mechanical ventilation in the vitamin D vs placebo groups. Soliman *et al.*, 2022 reported 14/40 (35%) vs 7/16 (43.8%) patients to have progressed to mechanical ventilation (referred to as intubation) in the vitamin D vs placebo arms.

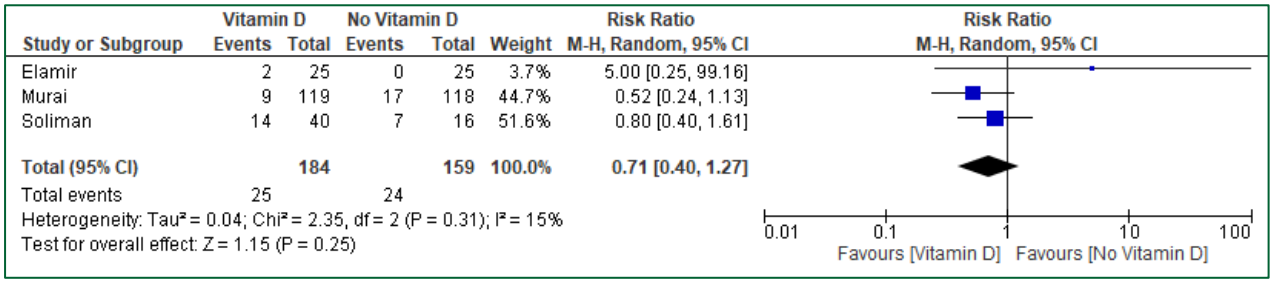


FIGURE 4: FOREST PLOT OF VITAMIN D *VS.* NO VITAMIN D/PLACEBO, PROGRESSION TO MECHANICAL VENTILATION

- **Duration of mechanical ventilation** – This outcome was not reported.

- **Adverse reactions**
  One trial (Elamir *et al.*, 2020) reported on adverse reactions. The trial reported 0/25 patients receiving vitamin D vs 4/25 receiving no vitamin D (p=0.1) reduction in glomerular filtration rate by >10%. These results were assessed to be of very low certainty evidence (serious risk of bias and very serious imprecision). No participants in either treatment arms developed hypercalcemia, hyperphosphatemia or renal calculi.

CONCLUSION

Reviewers: Andy Gray, Karen Cohen, Tamara Kredo, Trudy Leong, Ntombifuthi Blose, Denny Mabetha.

Declaration of interests: TK (Cochrane South Africa, South African Medical Research Council (SAMRC) and Division of Clinical Pharmacology, Department of Medicine and Division of Epidemiology and Biostats, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University; TK is co-director of the South African GRADE Network. TK, NB, DM and TL are partly supported by the Research, Evidence and Development Initiative (READ-It) project and the Collaboration for Evidence Based Health Care and Public Health in Africa COVID-19 project funding (CEBHA+). READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies).

Table 2: Characteristics of RCTs; n=5 trials

Citation	Study design	Population	Treatment	Main findings	Risk of Bias (Cochrane Handbook risk of bias tool 2.0 and covid-nma)
Castillo, M.E.; Costa, L.M.E.; Barrios, J.M.V.; Díaz, J.F.A.; Miranda, J.L.; Bouillon, R.; Gomez, J.M.Q. 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, 203, 105751.	Pilot RCT, Spain	Patients hospitalised with COVID-19 infection Mean (SD) age: calcifediol 53.14 +/-1 0.77 *vs* no calcifediol 52.77 +/-9.35 years old Male: calcifediol 27/50 (54%) *vs* no calcifediol 18/26 (69%)	**Intervention:** 21,280 IU/day vitamin D on day 1, 3 and 7, and then weekly until discharge or ICU admission (n = 50) **Control:** no vitamin D supplementation (n = 26) **Duration:** 4 weeks	• **Mortality**: calcifediol: 0/50 *vs*. no calcifediol 2/26 (7.69%) * **Among ICU admissions, n=13* • **Progression to ICU admission**- 13/26 (50%) *vs* 1/50 (2%) between no treatment/treatment groups. Univariate: 0.02 (95 %CI 0.002− 0.17) adjusting by Hypertension and T2DM: 0.03 (95 %CI: 0.003−0.25).	**Overall**: Some concerns (https://covid-nma.com/living_data/rob_pharmaco.php?i=115) Low risk for missing outcome data only. **Deviations from intervention and measurement of outcome (mortality):** Unblinded study (outcome assessor, participants, and personnel/carers) **Randomisation**: No information about allocation concealment
Murai, I.H.; Fernandes, A.L.; Sales, L.P.; Pinto, A.J.; Goessler, K.F.; Duran, C.S.; Silva, C.B.; Franco, A.S.; Macedo, M.B.; Dalmolin, H.H.; 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.	RCT, Brazil	Patients hospitalised with COVID-19 infection Mean (SD age: vitamin D_3 56.5 – (13.8) *vs* Placebo 56.0 (15.0) years old Male: vitamin D_3 70/119 (58.8%) *vs* no vitamin D_3 63/118 (53.4%)	**Intervention:** single bolus of 200,000 IU vitamin D_3 (n = 119) **Control:** placebo (n = 118) **Duration:** 20 days	• **Mortality** - No significant differences between the vitamin D_3 and placebo groups for in-hospital mortality (9/119 (7.6%) *vs* 6/118 (5.1) %; difference, 2.5% [95% CI, –4.1% to 9.2%]; *P* = .43) • **Duration of hospitalisation** – (Median) vitamin D group and placebo group (7.0 [4.0-10.0] days) and the (7.0 [5.0-13.0] days) (log-rank *P* = .59; unadjusted HR for hospital discharge, 1.07 [95% CI, 0.82-1.39]; *P* = .62; adjusted HR, 0.99 [95% CI, 0.71-1.37]; *P* = .94) • **Progression to ICU admission**: (referred to as admission to ICU) – 19/119 (16.0%) *vs* 25/118 (21.2%); difference, –5.2% [95% CI, –15.1% to 4.7%]; *P* = .30) • **Progression to mechanical ventilation** – vitamin D 9/119 (7.6%) *vs* placebo 17/118 (14.4%); difference, –6.8% [95% CI, –15.1% to 1.2%]; *P* = .09) • **Duration of mechanical ventilation** -vitamin Dand the placebo group (vitamin D 15.0 *vs* placebo 12.8 days; difference, 2.2 [95% CI, –8.4 to 12.8]; *P* = .69) • Adverse reactions – NR 1/119 vitamin D *vs* 0/118 placebo (any grade – lab results)	**Overall**: Some concerns (https://covid-nma.com/living_data/rob_pharmaco.php?i=202) Low risk for all domains, except for the selection of reported (adverse events) results domain which had some concerns ***Adverse events:*** *were not an outcome specified in the registry*. • Neither the protocol nor the statistical analysis plan was available. • No information on whether the result was selected from multiple outcome measurements or analyses of the data. • No information on whether the trial was analysed as pre-specified. • Time to clinical improvement was pre-specified as "lengths of hospitalisation, combined with death. The published report split those outcomes and presented those separately • Trial probably not analysed as pre-specified
Rastogi, A.; Bhansali, A.; Khare, N.; Suri, V.; Yaddanapudi, N.; Sachdeva, N.; Puri, G.D.; Malhotra, P. Short term, high dose vitamin D supplementation for COVID-19 disease: A randomised, placebo-controlled, study (SHADE study). Postgrad. Med. J. 2020, 98, 87–90.	RCT, India	Asymptomatic or mildly symptomatic cases of COVID-19 Median (IQR) age: vitamin D 50.0 (36 +/- 51) *vs* placebo 47.5 (39.3 +/- 49.2) years old Male: vitamin D 6/16 (37.5%) *vs* no vitamin D 14/24 (58.3%)	**Intervention:** vitamin D: 60,000 IU/day; (n = 16) (with therapeutic target 25 OHD > 125 nmol/day) **Control**: identical placebo (n = 24) **Duration:** 7 days or more if needed	Primary outcome: Proportion of SAR-CoC-2 negatives before 3 weeks. Other outcomes: Inflammatory marker with treatment	**Overall:** n/a
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. *Proceedings of Singapore Healthcare*. June 2022. doi:10.1177/20101058211041405	Pilot RCT, Egypt	Hospitalised vitamin D deficient diabetic elderly patients with SARS-CoV-2) Mean age (SD) – vitamin D: 71.30 (4.16) *vs* placebo: 70.19 (4.57) Males and females aged > 60 years.	**Intervention:** vitamin D single intramuscular injection (200,000 IU) (n = 40) **Control**: placebo (n = 16) **Duration:** 6 weeks	• **Mortality** – vitamin D: 17/40 (17.5) *vs* placebo: 3/14 (18.8%) (p=0.838) **Progression to mechanical ventilation** (*referred to as intubation)* – vitamin D:14/40 (35.0%) *vs* placebo: 7/16 (43.8%) (p=0.541)	**Overall:** High • **Mortality:** Some concerns for lack of allocation concealment and detailed SAP **Progression to mechanical ventilation:** High for Measurement of outcome: Ascertainment of outcome (lack of SAP) and lack of allocation concealment
Yasmine M. Elamir, Hajira Amir, Steven Lim, Yesha Patel Rana, Carolina Gonzalez Lopez, Natalia Viera Feliciano, Ali Omar, William Paul Grist, Michael A. Via,	Pilot RCT, Israel	Hospitalised patients with COVID-19.	**Intervention:** calcitriol 0.5 µg daily (n=25) **Control**: no treatment (n=25)	• **Mortality** – no treatment 3/25 *vs* calcitriol 0/25 (p=0.23) • **Duration of hospitalisation** (*referred to as average length of hospital stay in days*) - no treatment 9.24+/-9.4 *vs* calcitriol 5.5 +/- 3.9 (p=0.14)	**Overall**: Some concerns (covid-nma: https://covid-nma.com/living_data/index.php?treatment1=vitamin+D&submit=Validate#comparisons_div)

Citation	Study design	Population	Treatment	Main findings	Risk of Bias (Cochrane Handbook risk of bias tool 2.0 and covid-nma)
A randomized pilot study using calcitriol in hospitalized COVID-19 patients, Bone,Volume 154, 2022, 116175, ISSN 8756-3282, https://doi.org/10.1016/j.bone.2021.11675		Median (IQR) age: no treatment: 64+/-16 *vs* calcitriol: 69+/-18 (p=0.16) Males: no treatment: 13 *vs* calcitriol: 12 (p=0.77)	**Duration:** 14 days	• **Progression to ICU admission (ICU admission)** – no treatment 8/25 vs calcitriol 5/25 (p=0.33) • **Progression to mechanical ventilation** (*referred to as endotracheal intubation*) - no treatment 2/25 *vs* calcitriol 0/25 (p=0.48) • **Adverse reactions**: ○ Reduction in glomerular filtration rate by >10% - no treatment 4/25 vs calcitriol 0/25 (p=0.1) ○ Hypercalcemia - no treatment 0/25 vs calcitriol 0/25 ○ Hyperphosphatemia - no treatment 0/25 vs calcitriol 0/25 ○ Renal calculus - no treatment 0/25 vs calcitriol 0/25	Low risk for missing outcome data all other domains were assessed to have a risk of bias of some concerns (randomisation, deviation from intervention, measurement of outcome and the selection of reported results.) The protocol, statistical analysis plan and registry were not available. No information on whether the result was selected from multiple outcome measurements or analyses of the data. No information on whether the trial was analysed as pre-specified. Risk assessed to be some concerns for the outcomes: Mortality

Table 3: Planned and ongoing trials (10 August 2022)

Citation	Sample size	Sponsor/Funder	Intervention/Comparator	Registration number	Severity at enrolment
https://clinicaltrials.gov/show/NCT04621058	108	Bioaraba Health Research Institute	(1) Vitamin d vs (2) Placebo	NCT04621058	Moderate/severe
https://clinicaltrials.gov/show/NCT04536298	2024	Brigham and Women's Hospital	(1) Vitamin d vs (2) Vitamin d vs (3) Placebo vs (4) Placebo	NCT04536298	Mild
http://en.irct.ir/trial/63195	80	Shahid Beheshti University of Medical Sciences	(1) Coenzyme q10 + melatonin + probiotics + vitamin b + vitamin d vs (2) Placebo	IRCT20140804018677N21	Patients recovered from covid
https://clinicaltrials.gov/show/NCT05415254	86	RenJi Hospital	(1) Vitamin d vs (2) Standard of care	NCT05415254	Moderate/severe/critical
https://clinicaltrials.gov/show/NCT05356936	150	University Hospitals Cleveland Medical Center	(1) Vitamin d3 + vitamin k2 vs (2) Standard of care	NCT05356936	Patients recovered from covid
https://anzctr.org.au/ACTRN12622000386730.aspx	300	AProf Dr Karin Ried	(1) Doxycycline + famotidine + ivermectin + vitamin c + vitamin d + zinc vs (2) Doxycycline + ivermectin + vitamin c + vitamin d + zinc	ACTRN12622000386730	Mild
https://clinicaltrials.gov/show/NCT04937556	41	ProbiSearch SL	(1) Lactobacillus salivarius + vitamin d + zinc vs (2) Placebo	NCT04937556	Mild
https://clinicaltrials.gov/show/NCT05384574	200	University Hospital of Split	(1) Vitamin d vs (2) Standard of care	NCT05384574	Critical
https://clinicaltrials.gov/show/NCT04636086	50	University of Liege	(1) Vitamin d vs (2) Placebo	NCT04636086	No restriction on type of patients
https://clinicaltrials.gov/show/NCT05269017	60	Menoufia University	(1) Vitamin d3 vs (2) Budesonide	NCT05269017	Patients recovered from covid
https://clinicaltrials.gov/show/NCT04386850	1500	Tehran University of Medical Sciences	(1) Vitamin d vs (2) Vitamin d vs (3) Placebo vs (4) Placebo	NCT04386850	No restriction on type of patients
http://en.irct.ir/trial/57413	104	Bandare-abbas University of Medical Sciences	(1) Vitamin d vs (2) Magnesium sulfate + vitamin d3 vs (3) Magnesium sulfate vs (4) Placebo	IRCT20210702051763N1	Mild/moderate
https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002274-28/ES	60	FundaciÃ³n para la InvestigaciÃ³n y la InnovaciÃ³n Biosanitaria del Principado de Asturias (FINBA)	(1) Vitamin d3 vs (2) Standard of care	EUCTR2020-002274-28-ES	No restriction on type of patients
https://clinicaltrials.gov/show/NCT04502667	45	CoordinaciÃ³n de InvestigaciÃ³n en Salud, Mexico	(1) Vitamin d vs (2) Standard of care	NCT04502667	No restriction on type of patients
https://clinicaltrials.gov/show/NCT04579640	6200	Queen Mary University of London	(1) Vitamin d vs (2) Vitamin d vs (3) Standard of care	NCT04579640	Healthy volunteers
https://clinicaltrials.gov/show/NCT05008003	50	Ayub Teaching Hospital	(1) Vitamin d vs (2) Standard of care	NCT05008003	Mild
https://clinicaltrials.gov/show/NCT04334005	200	Universidad de Granada	(1) Vitamin d vs (2) Standard of care	NCT04334005	Mild

Citation	Sample size	Sponsor/Funder	Intervention/Comparator	Registration number	Severity at enrolment
https://clinicaltrials.gov/show/NCT04979065	80	Indonesia University	(1) Probiotics + vitamin d vs (2) Placebo	NCT04979065	Health workers
https://clinicaltrials.gov/show/NCT04603690	50	Liaquat University of Medical & Health Sciences	(1) Curcumin + quercetin + vitamin d3 vs (2) Standard of care	NCT04603690	Moderate/severe
https://clinicaltrials.gov/show/NCT04476745	100	Applied Science Private University	(1) Vitamin d3 vs (2) Standard of care	NCT04476745	Healthy volunteers
https://clinicaltrials.gov/show/NCT05092698	110	Federal Research Clinical Center of Federal Medical & Biological Agency, Russia	(1) Vitamin d vs (2) Placebo	NCT05092698	Critical
https://clinicaltrials.gov/show/NCT04641195	700	Harvard School of Public Health (HSPH)	(1) Vitamin d3 vs (2) Zinc vs (3) Vitamin d3 + zinc vs (4) Placebo	NCT04641195	Moderate/severe
https://clinicaltrials.gov/show/NCT05130671	50	King Edward Medical University	(1) Curcumin + quercetin + vitamin d vs (2) Standard of care	NCT05130671	Mild
https://clinicaltrials.gov/show/NCT04363840	0	Louisiana State University Health Sciences Center in New Orleans	(1) Aspirin vs (2) Aspirin + vitamin d vs (3) Standard of care	NCT04363840	Mild
https://clinicaltrials.gov/show/NCT04535791	321	CoordinaciÃ³n de InvestigaciÃ³n en Salud, Mexico	(1) Vitamin d vs (2) Placebo	NCT04535791	Health workers
https://clinicaltrials.gov/show/NCT04952857	90	Postgraduate Institute of Medical Education and Research	(1) Vitamin d vs (2) Placebo	NCT04952857	Severe
https://clinicaltrials.gov/show/NCT04844658	51	Tilman S.A.	(1) Curcumin + quercetin + vitamin d3 vs (2) Vitamin d3	NCT04844658	Moderate/severe
http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=54420	160	AIIMS Patna	(1) Cilnidipine + telmisartan vs (2) Magnesium sulfate + vitamin d3 vs (3) Cilnidipine + magnesium sulfate + telmisartan + vitamin d vs (4) Standard of care	CTRI/2021/03/032385	No restriction on type of patients
http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=46899	100	Pulse Pharmaceuticals Pvt Ltd	(1) Vitamin d vs (2) Standard of care	CTRI/2020/12/030083	Moderate/severe
http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=45075	500	Suraksha Pharma Private Limited	(1) Magnesium sulfate + vitamin d3 + vitamin k2 vs (2) Standard of care	CTRI/2020/06/026191	Health workers
https://clinicaltrials.gov/show/NCT04828538	1800	Hospital de la Soledad	(1) Omega dha/epa + vitamin b + vitamin c + vitamin d + zinc vs (2) Omega dha/epa + vitamin d vs (3) Vitamin b + vitamin c + vitamin d + zinc vs (4) Vitamin d vs (5) Omega dha/epa + vitamin b + vitamin c + zinc vs (6) Omega dha/epa vs (7) Placebo vs (8) Standard of care	NCT04828538	Mild
https://clinicaltrials.gov/show/NCT05002530	10000	Kafrelsheikh University	(1) 13 cis retinoic acid + vitamin d vs (2) All trans retinoic acid + vitamin d vs (3) Placebo	NCT05002530	Patients recovered from covid
https://clinicaltrials.gov/show/NCT04883203	130	University of Monastir	(1) Vitamin d vs (2) Placebo	NCT04883203	Patients recovered from covid
https://clinicaltrials.gov/show/NCT04793243	42	University of Guadalajara	(1) Vitamin d3 vs (2) Standard of care	NCT04793243	No restriction on type of patients
https://clinicaltrials.gov/show/NCT04780061	200	The Canadian College of Naturopathic Medicine	(1) Vitamin c + vitamin d + vitamin d3 + vitamin k2 + zinc vs (2) Placebo	NCT04780061	Mild
https://clinicaltrials.gov/show/NCT04733625	56	Kasr El Aini Hospital	(1) Vitamin d3 vs (2) Placebo	NCT04733625	No restriction on type of patients
https://clinicaltrials.gov/show/NCT04734886	161	Ã–rebro University, Sweden	(1) Probiotics + vitamin d vs (2) Placebo	NCT04734886	Healthy volunteers
https://clinicaltrials.gov/show/NCT04351490	0	University Hospital, Lille	(1) Vitamin d + zinc vs (2) Standard of care	NCT04351490	No restriction on type of patients
https://clinicaltrials.gov/show/NCT04449718	240	University of Sao Paulo	(1) Vitamin d vs (2) Placebo	NCT04449718	Moderate/severe
https://clinicaltrials.gov/show/NCT04459247	40	Postgraduate Institute of Medical Education and Research	(1) Vitamin d vs (2) Standard of care	NCT04459247	Mild
https://clinicaltrials.gov/show/NCT04525820	80	Prof. Dr. JÃ¶rg Leuppi	(1) Vitamin d vs (2) Placebo	NCT04525820	Moderate/severe/critical
https://www.thaiclinicaltrials.org/show/TCTR20210906005	400	Faculty of Medicine Ramathibodi Hospital; Mahidol University	(1) Vitamin d vs (2) Standard of care	TCTR20210906005	Moderate/severe
https://clinicaltrials.gov/show/NCT05037253	128	Federal State Budgetary Institution, V. A. Almazov Federal North-West Medical Research Centre, of the Ministry of Health	(1) Vitamin d vs (2) Magnesium sulfate + vitamin d3	NCT05037253	Health workers
https://slctr.lk/trials/slctr-2021-019	258129	Base Hospital; Homagama	(1) Vitamin d vs (2) Placebo	SLCTR/2021/019	Mild/moderate
https://clinicaltrials.gov/show/NCT04400890	100	Marvin McCreary, MD	(1) Resveratrol + vitamin d3 vs (2) Vitamin d3	NCT04400890	Mild/moderate

Citation	Sample size	Sponsor/Funder	Intervention/Comparator	Registration number	Severity at enrolment
https://clinicaltrials.gov/show/NCT04411446	218	Vitamin D Study Group	(1) Vitamin d vs (2) Placebo	NCT04411446	Moderate
http://en.irct.ir/trial/56509	40	Shahid Beheshti University of Medical Sciences	(1) Astaxanthin + omega 3 fatty acid + vitamin d + vitamin e vs (2) Placebo	IRCT20140804018677N9	Mild/moderate
http://en.irct.ir/trial/48287	140	Mashhad University of Medical Sciences	(1) Vitamin d vs (2) Vitamin d vs (3) Vitamin d	IRCT20110726007117N11	Mild/moderate
https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001793-30/DK	480	Copenhagen University Hospital of Bispebjerg	(1) Vitamin d vs (2) Placebo	EUCTR2020-001793-30-DK	Mild
https://clinicaltrials.gov/show/NCT04483635	34	St. Justine's Hospital	(1) Vitamin d vs (2) Placebo	NCT04483635	Health workers
http://en.irct.ir/trial/55074	135	Sabzevar University of Medical Sciences	(1) Vitamin a + vitamin b + vitamin c + vitamin d + vitamin e vs (2) Standard of care	IRCT20151226025699N5	Critical
https://clinicaltrials.gov/show/NCT04482673	140	Medical University of South Carolina	(1) Vitamin d3 vs (2) Vitamin d3 vs (3) Placebo	NCT04482673	Mild
https://clinicaltrials.gov/show/NCT04552951	80	FundaciÃ³n para la InvestigaciÃ³n Biosanitaria del Principado de Asturias	(1) Vitamin d3 vs (2) Standard of care	NCT04552951	No restriction on type of patients
https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002119-23/IT	80	ISTITUTO EUROPEO DI ONCOLOGIA	(1) Vitamin d vs (2) Placebo	EUCTR2020-002119-23-IT	Mild
http://en.irct.ir/trial/46875	260	Tehran University of Medical Sciences	(1) Vitamin d vs (2) Placebo	IRCT20200401046909N1	Mild
http://en.irct.ir/trial/47010	540	Tehran University of Medical Sciences	(1) Vitamin d vs (2) Placebo	IRCT20200401046909N2	Close contacts to covid patients
http://en.irct.ir/trial/47508	30	Sabzevar University of Medical Sciences	(1) Vitamin c vs (2) Vitamin d vs (3) Standard of care	IRCT20140305016852N4	No restriction on type of patients
http://en.irct.ir/trial/46732	100	Abadan University of Medical Sciences	(1) Acetylcysteine vs (2) Acetylcysteine + vitamin d vs (3) Vitamin d vs (4) Standard of care	IRCT20200324046850N1	Moderate
http://en.irct.ir/trial/47093	100	Shahroud University of Medical Sciences	(1) Vitamin d vs (2) Standard of care	IRCT20200411047024N1	No restriction on type of patients
https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001717-20/ES	1008	FundaciÃ³n para la InvestigaciÃ³n BiomÃ©dica de CÃ³rdoba	(1) Vitamin d vs (2) Standard of care	EUCTR2020-001717-20-ES	No restriction on type of patients
https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001903-17/ES	120	HOSPITAL UNIVERISTARIO DE MOSTOLES	(1) Tocilizumab vs (2) Tocilizumab + vitamin d	EUCTR2020-001903-17-ES	Moderate/severe/critical
https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001960-28/ES	108	Investigation Institute Bioaraba	(1) Vitamin d vs (2) Placebo	EUCTR2020-001960-28-ES	Moderate/severe

Tables 4: GRADE evidence profile for the comparison of Vitamin D, compared to no Vitamin D/placebo

Question: Vitamin D compared to no Vitamin D/placebo for management of COVID-19
Bibliography: Vitamin D for No Vitamin D

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	vitamin D	no Vitamin D/placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
4	randomised trials	serious[a]	not serious[b]	not serious	very serious[c]	none	26/234 (11.1%)	14/183 (7.7%)	**RR 1.08** (0.58 to 2.01)	**6 more per 1,000** (from 32 to 77 more)	⨁◯◯◯ Very low	
Progression to hospitalisation - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Duration of hospitalisation												
2	randomised trials	serious[d]	not serious	not serious	very serious[e]	none	Murai *et al.*, 2021 reported a median duration of hospitalisation (days) of 7.0 [4.0-10.0] days vitamin D vs 7.0 [5.0-13.0] days placebo (log-rank *P* = .59; unadjusted HR for hospital discharge, 1.07 [95% CI, 0.82-1.39]; *P* = .62; adjusted HR, 0.99 [95% CI, 0.71-1.37]; *P* = .94 Elamir *et al.*, 2022 reported a mean duration of hospitalisation (days) of 5.5 +/- 3.9 vitamin D vs. 9.24+/-9.4 no vitamin D (p=0.14).				⨁◯◯◯ Very low	
Progression to ICU admission												
3	randomised trials	serious[f]	not serious	not serious	very serious[c]	none	25/194 (12.9%)	46/169 (27.2%)	**RR 0.38** (0.11 to 1.31)	**169 fewer per 1,000** (from 242 fewer to 84 more)	⨁◯◯◯ Very low	
Duration of ICU stay - not reported												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	vitamin D	no Vitamin D/placebo	Relative (95% CI)	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	
Progression to mechanical ventilation												
3	randomised trials	serious[g]	not serious	not serious	very serious[c]	none	25/184 (13.6%)	24/159 (15.1%)	**RR 0.71** (0.40 to 1.27)	**44 fewer per 1,000** (from 91 fewer to 41 more)	⨁◯◯◯ Very low	
Duration of mechanical ventilation - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Adverse Reactions												
1	randomised trials	serious[h]	not serious	not serious	very serious[e]	none	5/144 (3.5%)	0/143 (0.0%)	**RR 5.48** (0.65 to 46.34)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	

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

Explanations

a. Downgraded by 1 for serious risk of bias. All included trials had some concerns for risk of bias, with Soliman specifically having raised concerns about selection bias, and other having poor reporting on allocation concealment or lack of blinding (Castillo),

b. Despite moderate degree of heterogeneity (I-squared = 48%), we did not downgrade for inconsistency. The differences may be explained by different settings, slightly different populations (e.g., Vitamin D deficient), different dosing.

c. Downgraded by 2 levels for very serious imprecision: small sample size, low event rates, absolute value confidence interval ranges from substantial benefit to substantial harm,

d. Downgraded by 1 level for serious risk of bias: Murai has overall low risk of bias assessment for the outcome mortality, but Elamir has some concerns with randomisation, deviation from intervention, measurement of outcome and the selection of reported results.

e. Downgraded by 2 levels for very serious imprecision: small sample sizes

f. Downgraded by 1 level for serious risk of bias: all trials (Elamir, Murai and Castillo) had some concerns with reporting on methodological limitations

g. Downgraded by 1 level for serious risk of bias: Murai has overall low risk of bias assessment for the outcome mortality, but Elamir and Soliman have some concerns with randomisation, deviation from intervention, measurement of outcome and the selection of reported results.

h. Downgraded by 1 level for serious risk of bias: Elamir had concerns with randomisation, deviation from intervention, measurement of outcome and the selection of reported results.

APPENDIX 1: SEARCH STRATEGY

DATE: 3 August 2022

e-COVID-rec-Map – 3 August 2022

Search terms: vitamin D and covid-19

Filters: COVID-19 confirmed and Treatment and Rehabilitation

World Health Organisation – 3 August 2022

https://www.covid19treatmentguidelines.nih.gov/therapies/supplements/vitamin-d/

Cochrane COVID Study Register (https://covid-19.cochrane.org/)

Database: Cochrane COVID-19 Study Register

Search strategy: "vitamin d" or calciferol or cholecalciferol or ergocalciferol or "25-hydroxyvitamin d"

Limits: Intervention assignment – Randomised

Study aim – Treatment and management

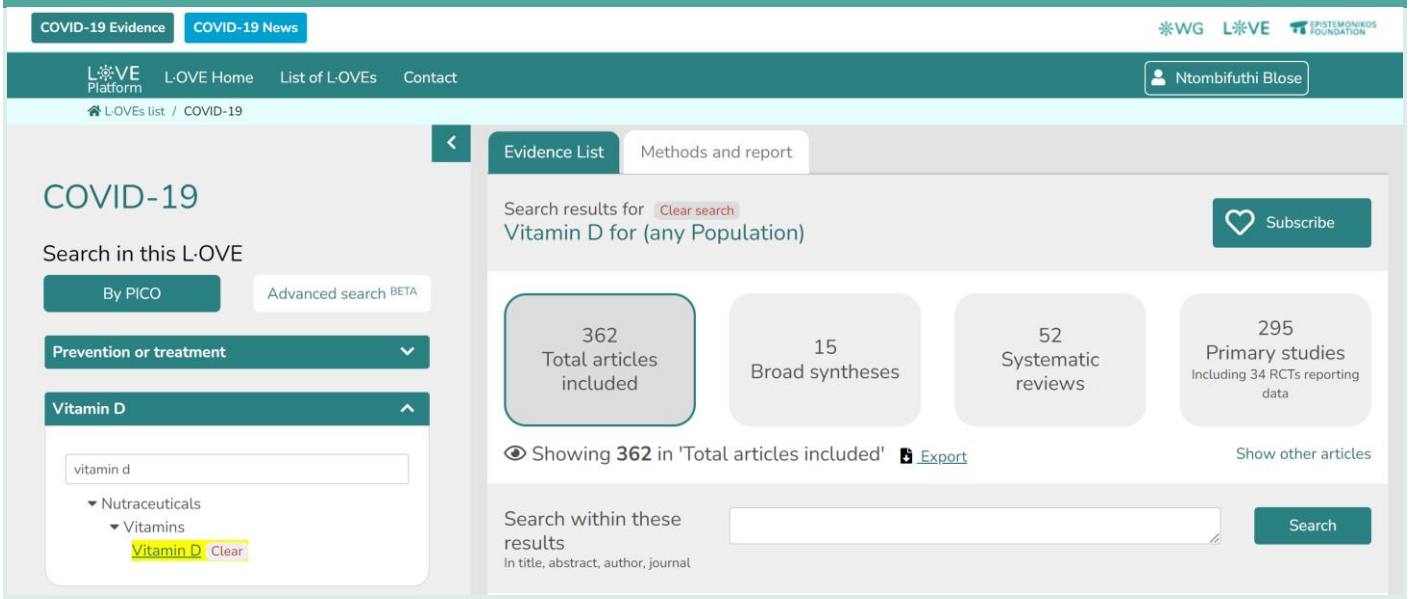
Date – 1 February 2021 to 31 July 2022

No. of records retrieved: 49 studies with 56 references

DATE: 3 August 2022

Epistemonikos L*OVE evidence platform:

Filters: PICO àPrevention or treatment Vitamin D



APPENDIX 2: AMSTAR ASSESMENT (Stroehlein *et al*., 2022 and Hosseini *et al*., 2022)

Appendix 2A: Evaluating the methodological quality of the Stroehlein *et al.,* (2022)[1] systematic review and meta-analysis – AMSTAR 2 tool (Shea 2017[2])

No.	Criteria	Yes/ Partial Yes/ No	Comment
1	Research questions and inclusion criteria for the review included the components of PICO	Yes	-
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	Yes	Protocol registered prior to the conduct of the review with PROSPERO on 21 January 2021, and deviations between protocol and report was described (pg. 91)
3	Review authors explained selection of the study designs for inclusion in the review	Yes	Randomised controlled trials (including cluster-randomised and cross-over trials)
4*	Review authors used a comprehensive literature search strategy	Yes	-
5	Review authors perform study selection in duplicate	Yes	-
6	Review authors perform data extraction in duplicate	Yes	-
7*	Review authors provided a list of excluded studies and justify the exclusions	Yes	-
8	Review authors described the included studies in adequate detail	Yes	-
9*	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	Yes	"To assess bias in included studies, we used the Cochrane risk of bias tool (ROB 2) for RCTs"
10	Review authors reported on the sources of funding for the studies included in the review.	Yes	-
11*	For meta-analyses, review authors used appropriate methods for statistical combination of results	Yes	-
12	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	Yes	-
13*	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	Yes	-
14	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Yes	Subgroup analysis and investigation of heterogeneity was conducted
15*	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	Yes	We had planned to explore potential publication bias by generating a funnel plot and statistically testing this by conducting a linear regression test for meta-analyses involving at least 10 trials (Sterne 2019). We would have considered P <0.1 as significant for this test. The review only retrieved 3 RCTs, thus a funnel plot was not possible. However, subgroup analyses were conducted to investigate heterogeneity

[1] Stroehlein J, J W, C I, A M, MI M, C B, *et al.* Vitamin D supplementation for the treatment of COVID-19: a living systematic review (Review). Cochrane Database Syst Rev. 2017;94(3):36–46

[2] Shea BJ, Reeves BC, Wells G, *et al.* AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008. https://pubmed.ncbi.nlm.nih.gov/28935701/

16	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Yes	The research was part of a project supported by the German Federal Ministry of Education and Research (NaFoUniMedCovid19, funding number: 01KX2021; part of the project "CEOSys"). The contents of this document reflect only the authors' views and the German Ministry is not responsible for any use that may be made of the information it contains.

** Critical domains = 2, 4, 7, 9, 11, 13, 15*

Rating overall confidence in the results of the review

• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

• *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review, and it may be appropriate to move the overall appraisal down from moderate to low confidence).

OVERALL ASSESMENT: The systematic review was assessed as high quality.

Rationale: No critical or one non-critical weaknesses was identified

Conclusion: The AMSTAR assessment suggests that high quality review have no or one non-critical weakness and provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.

Appendix 2B: Evaluating the methodological quality of the Hosseini *et al.,* (2022)[3] systematic review and meta-analysis – AMSTAR 2 tool (Shea 2017[4])

No.	Criteria	Yes/ Partial Yes/ No	Comment
1	Research questions and inclusion criteria for the review included the components of PICO	Partial yes	Not explicitly stated, but implied. Of note that the question, "What is the effect of vitamin D intake supplementation on the COVID-19 related outcomes?" is stated on the PROSPERO-registered protocol.
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	Yes	The study protocol was registered in PROSPERO (registration number: CRD42021254424) on 14 May 2021, with subsequent amendments on 27 July 2021 and 15 October 2021 (no detailed information of changes)
3	Review authors explained selection of the study designs for inclusion in the review	Yes	Studies were eligible if they were randomised RCTs or NRISs, that is, quasi experimental studies, cohorts, and case–control studies
4*	Review authors used a comprehensive literature search strategy	Yes	-
5	Review authors perform study selection in duplicate	Yes	-
6	Review authors perform data extraction in duplicate	Yes	-
7*	Review authors provided a list of excluded studies and justify the exclusions	No	-
8	Review authors described the included studies in adequate detail	Yes	-
9*	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	No	"For randomised clinical trials, methodological quality was assessed by the Cochrane Handbook risk of bias tool [20], based on the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias, including industry funding". Two assessors reviewed the RoB BH and HAE. Of note is that BH authored one of the primary RCTs, which was assessed as low risk of bias across all domains. Of note is that the cited study (NCT04483635) was "Terminated (A premature discontinuation was recommended by the Data Safety Monitoring Board and agreed upon by the principal investigator, because the significantly lower recruitment than planned, in the context of mass vaccination of the target population)". The authors (BH and HAE) also declared no conflicts of interest.
10	Review authors reported on the sources of funding for the studies included in the review.	No	-

[2] Shea BJ, Reeves BC, Wells G, *et al*. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008. https://pubmed.ncbi.nlm.nih.gov/28935701/

[3] Hosseini B, El Abd A, Ducharme FM. Effects of Vitamin D Supplementation on COVID-19 Related Outcomes: A Systematic Review and Meta-Analysis. Nutrients. 2022 May 20;14(10):2134. https://pubmed.ncbi.nlm.nih.gov/35631275/

11*	For meta-analyses, review authors used appropriate methods for statistical combination of results	Yes	-
12	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	Yes	"A sensitivity analysis was conducted on primary outcomes after excluding studies with an uncertain or high risk of bias".
13*	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	Partial yes	Not explicitly stated but implied throughout the narrative of the results section.
14	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Yes	"Therefore, we advise caution in the interpretation of subgroup analyses because incomplete reporting of characteristics, heterogeneity of characteristics within trials, and absence of individual patient data prevented us from conducting meta-regressions that could have better untangled the concurrent impact of study design, participant, or intervention on effect size".
15*	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	Yes	Funnel plot showed publication bias for RCTs.
16	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Partial yes	This work was funded by a donation from Jamieson Wellness Inc. and a Post-Doctoral Scholarship from the research grant #172650 funded by the Canadian Institutes of Health Research. Sponsors had no role in the study design, conduct or interpretation of results. The authors declared no conflict of interest, but see point 9, above.

** Critical domains = 2, 4, 7, 9, 11, 13, 15*

Rating overall confidence in the results of the review

• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

• *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

OVERALL ASSESMENT: This systematic review assessed as critically low quality

Rationale: More than one critical flaw with or without non-critical weaknesses

Conclusion: The AMSTAR assessment suggests that if the review has more than one critical flaw and it should not be relied on to provide an accurate and comprehensive summary of the available studies.

APPENDIX 3: EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☐ None ☒ Uncertain ☐	*Compared to placebo/no vitamin D:* Current evidence shows that vitamin D has no effect on mortality, the need for invasive mechanical ventilation, hospitalisation, intensive care unit (ICU) admission or time to discharge from hospital – all effect sizes were statistically not significant (see table 4, above).
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☐ Small ☐ None ☐ Uncertain ☒	*Compared to placebo/no vitamin D:* There remains significant uncertainty whether vitamin D is safer than placebo/ no vitamin D for the treatment of COVID-19.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☐ Intervention = Control or Uncertain ☒	There remains significant uncertainty whether vitamin D is more effective and safer than placebo/ no vitamin D for the treatment of COVID-19.
QUALITY OF EVIDENCE	**What is the certainty/quality of evidence?** High ☐ Moderate ☒ Low ☐ Very Low ☐	Moderate.
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes ☐ No ☐ Uncertain ☒	Irrational use of vitamin D for the treatment of COVID-19 may divert use from proven evidence-based indications and cause undue supply challenges.

Based on the information till now, it was concluded by the Committee that further evaluation of the table would not add any further benefit to the analysis.

RESOURCE USE	**How large are the resource requirements?** More intensive ☐ Less intensive ☐ Uncertain ☐	**Medicine prices:** **Medicine** | **Contract price*** Calcitriol 0.5 mcg daily for 14 days (Elimar) | R187.96** Vitamin D 60 000IU/day for 7 days (Rastogi) | R350.73*** *Contract circular HP09-2021SD, accessed 16 August 2022 **Calcitriol 0.25mcg, 30 capsules=R152 *** Vitamin D 5000 IU/ml, 15 ml = R62.63 *(Note: Vitamin D injection is currently not on tender)*

VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor ☐ Major ☐ Uncertain ☐ **Is the option acceptable to key stakeholders?** Yes ☐ No ☐ Uncertain ☐	Not applicable
EQUITY	**Would there be an impact on health equity?** Yes ☐ No ☐ Uncertain ☐	Not applicable

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