# PHILIPPINE COVID-19 LIVING CLINICAL PRACTICE GUIDELINES

*As of January 2022*

# ADJUNCT INTERVENTIONS for COVID-19

## EVIDENCE and RECOMMENDATIONS

## Implementing Agency:

Institute of Clinical Epidemiology, National Institutes of Health
University of the Philippines, Manila

## Cooperating Agency:

Philippine Society of Microbiology and Infectious Diseases

## Funding Agency:

Department of Health
Disease Prevention and Control Bureau

## Disclaimer

As a living guideline, the recommendations will be updated, and new recommendations will be added as the evidence evolves. The living recommendations are based on the best evidence available in scientific literature at the time of its formulation. However, this living CPG is not a comprehensive guide to all practice questions and management options on COVID-19. This is not meant to restrict the practitioner in using sound clinical judgement and sharing the decision with the patient, and from considering other management options according to the patient's particular needs and preferences. This CPG can serve to inform policy, but it is not meant to serve as a basis for approving or denying financial coverage or insurance claims merely because of nonconformance with recommendations. Neither are the recommendations supposed to be considered as legal rules for dictating certain modes of action to the exclusion of others.

## Contact Us

Send us an email at covidcpg.ph@gmail.com for any questions or clarifications on the outputs and process of this Living CPG. You may also suggest a clinical question for the consideration of the Living Clinical Practice Guidelines COVID-19 Taskforce.

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# Quick Guide on How to Interpret the Evidence

## Evidence on Therapy

Table 1. Ways of expressing effectiveness

| Outcome | Summary of result within each group | Comparison of results between two groups |
|---|---|---|
| Dichotomous (e.g. lived or died, BP controlled or not) | Proportion (e.g. deaths per 100 patients) | Relative risk reduction, absolute risk reduction, relative risk (see Table 2) |
| | Rate = e.g. deaths per 100 patients | Hazard ratio = rate in treatment/rate in control group |
| Continuous (e.g. blood pressure in mmHg, quality of life on a scale of 0 to 1) | Mean (e.g. mean blood pressure) | Mean difference = mean in control – mean in treatment group |

When researchers express the effect of treatment using the relative risk reduction, absolute risk reduction, or relative risk, they often give us a range of possibilities rather than a single estimate. This range of possibilities is called a '95% Confidence Interval (95% CI)' to mean 'we are 95% sure that the true effect of a drug lies in this range'. Go through Table 2, to discover how helpful 95% CIs are.

Table 2. Interpreting 95% Confidence Intervals (CIs)

| Measure of effectiveness and interpretation of estimates | Interpretation of 95% Confidence Intervals (CIs) | | | |
|---|---|---|---|---|
| | Superior (treatment surely better than control) | Inferior (treatment surely worse than control) | Inconclusive (we need more studies) | Equivalent (the treatments are equal)[a] |
| Relative Risk (RR) = $R_t$/ $R_c$ | Both ends of 95% CI <1.0 | Both ends of 95% CI > 1.0 | 95% CI wide; straddles 1.0 | 95% CI narrow; straddles 1.0 |
| <1.0 Treatment beneficial<br>=1.0 Treatment no effect<br>>1.0 Treatment harmful | Example: RR = 0.7 [95% CI: 0.6, 0.8] | Example: RR = 2.4 [95% CI: 1.8, 3.2] | Example: RR = 1 [95% CI: 0.2, 5.3] | Example: RR = 1 [95% CI: 0.9, 1.1] |
| Absolute Risk Reduction (ARR) = $R_c$ - $R_t$ (usually in percent) | Both ends of 95% CI >0% | Both ends of 95% CI <0% | 95% CI straddles 0%; either end is far from 0% | 95% CI straddles 0%; either end is close to 0% |
| >0% Treatment beneficial<br>=0% Treatment no effect<br><0% Treatment harmful | Example: ARR = 2% [95% CI: 1%, 3%] | Example: ARR = -3% [95% CI: -7%, -1%] | Example: ARR = 1% [95% CI: -20%, 32%] | Example: ARR =0.2% [95% CI: -0.1%, 0.5%] |

[a] In both inconclusive and equivalent results, the 95% CI interval straddles the point of no effect (ARR = 0% or RR = 1.0). One end reflects the worst possible harm, while the other end reflects the best possible benefit. The only difference is that, in equivalence, either end is close to "no effect" (i.e. any benefit is ignorable and any harm is ignorable too). Consider the ends of the 95% CI to make sure you agree that the benefits and harms are ignorable.

$R_c$ is the rate of the outcomes in the Control group
$R_t$ is the rate of the outcome in the Treatment group

*Note: The interpretations in this table only hold if the dichotomous events are expressed as adverse rather than desirable events, e.g. death rather than survival, treatment failure rather that cure, or disease rather than disease-free. When dichotomous outcomes are expressed as desirable events, the interpretation of benefit and harm is reversed.*

The balloons below (Figure 1) label the most important parts of the forest plot. Go through these labels and familiarize yourself with the anatomy of the graph. Once you feel sufficiently familiar with the anatomy, go through the notes below on what the forest plot can signify.

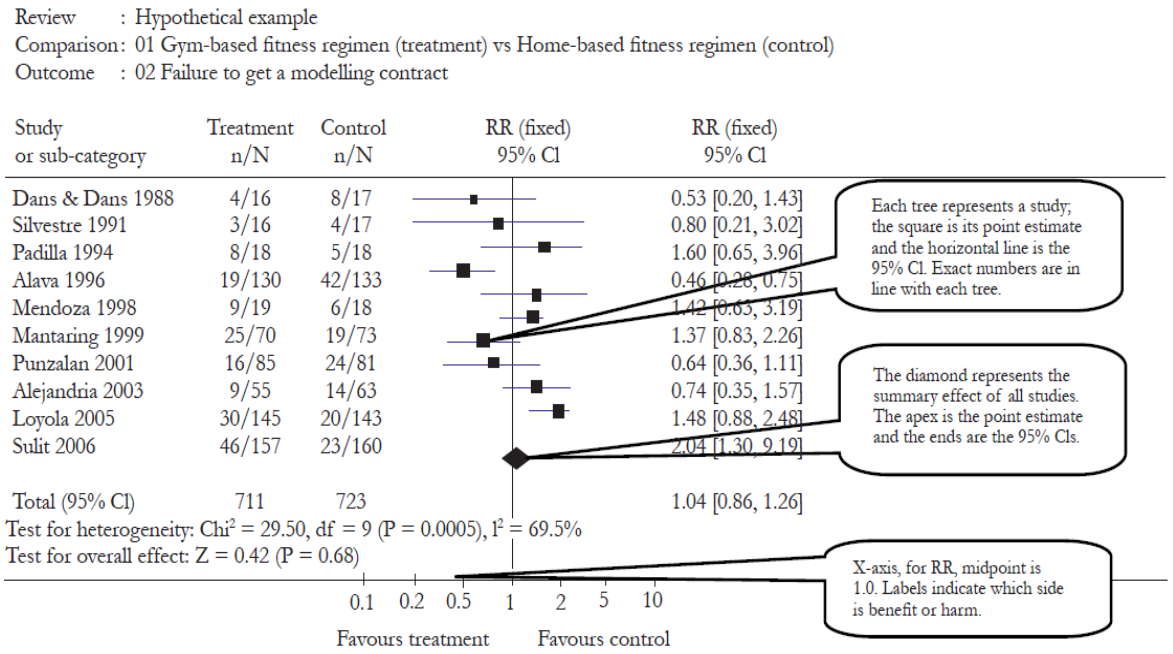



Figure 1. How to interpret forest plots

## REFERENCE

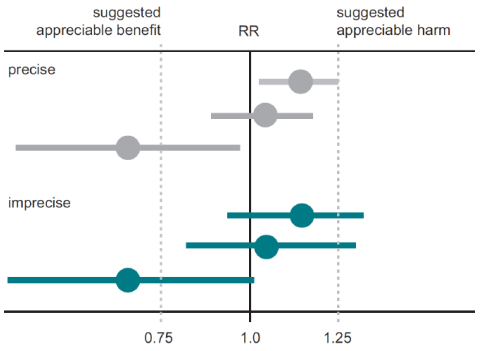
Dans, AL, et al. (2017). Painless Evidence-Based Medicine, 2nd Ed. UK: John Wiley & Sons Ltd.

# GRADE Approach in Assessing the Quality of Evidence

(GRADE: Grading of Recommendations Assessment, Development and Evaluation)

These quality ratings apply to the body of evidence assessed for the research question, not to individual studies. Evidence based on randomized controlled trials is initially given a high-quality rating and evidence from observational studies is given a low-quality rating. The level is then adjusted according to the following criteria.

Table 3. Standard criteria for grading of evidence

| Domain | Grade | Characteristic |
|---|---|---|
| Study Design | 0 | All randomized controlled trials |
| | -1 | All observational studies |
| Study Design Limitations | 0 | Most of the pooled effect provided by studies, with low risk of bias ("A") |
| | -1 | Most of the pooled effect provided by studies with moderate ("B") or high ("C") risk of bias. Studies with high risk of bias weighs <40% |
| | -2 | Most of the pooled effect provided by studies with moderate ("B") or high ("C") risk of bias. Studies with high risk of bias weighs ≥40% |
| | *Note:*<br>*Low risk of bias (no limitations or minor limitations) – "A"*<br><br>*Moderate risk of bias (serious limitations or potentially very serious limitations including unclear concealment of allocation or serious limitations, excluding limitations on randomization or concealment of allocation) – "B"*<br><br>*High risk of bias (limitations for randomization, concealment of allocation, including small blocked randomization (<10) or other very serious, crucial methodological limitations) – "C"* | |
| Imprecision | 0 | The confidence interval is precise according to the figure below.<br>The total cumulative study population is not very small (i.e. sample size is more than 300 participants) and the total number of events is more than 30.<br>  <br> |
| | -1 | One of the above-mentioned conditions is not fulfilled. |
| | -2 | The two above-mentioned are not fulfilled. |
| | *Note:*<br>*If the total number of events is less than 30 and the total cumulative sample size is appropriately large (e.g. above 3000 patients, consider not downgrading the evidence).*<br>*If there are no events in both intervention and control groups, the quality of evidence in the specific outcome should be regarded as very low.* | |
| Inconsistency | 0 | No severe heterogeneity ($I^2$< 60% or $X^2$<0.05) |
| | -1 | Severe, non-explained, heterogeneity ($I^2$ ≥60% or $X^2$<0.05) |

| Domain | Grade | Characteristic |
|---|---|---|
| | | If heterogeneity could be caused by publication bias or imprecision due to small studies, downgrade only for publication bias or imprecision (i.e. the same weakness should not be downgraded twice) |
| Indirectness | 0 | No indirectness |
| | -1 | Presence of indirect comparison, population, intervention, comparator, or outcome |
| Publication Bias | 0 | No evident asymmetry in the funnel plot or less than five studies to be plotted. |
| | -1 | Evident asymmetry in funnel plot with at least five studies |

Table 4. Quality of evidence in GRADE

| Quality Level | Definition |
|---|---|
| High | We are very confident that the true effect lies close to that of the estimate of the effect. |
| Moderate | We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. |
| Low | Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect. |
| Very Low | We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. |

## REFERENCE

Schünemann H, Brozek J, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group. Available at: https://gdt.gradepro.org/app/handbook/handbook.html.

# Evidence Base

## List of Questions

This section presents the evidence base for the recommendations on the adjunct interventions for COVID-19. The following key questions were addressed:

Q1. Should zinc be used as adjunctive treatment for COVID-19 infection?
Q2. Should B Vitamins be used as an adjunct in the treatment of COVID-19?
Q3. Should Vitamin C be used as adjunct treatment for COVID-19?
Q4. Among patients with COVID-19, should Vitamin D be used as adjunctive treatment?
Q5. Should melatonin be used in the adjunctive treatment of COVID-19?
Q6. Should virgin coconut oil be used in the adjunctive treatment of COVID-19?
Q7. Should Lagundi (Vitex negundo) be used as adjunctive treatment for COVID-19 infection?
Q8. Should Tawa-tawa (Euphorbia hirta) be used as adjunctive treatment for COVID-19 infection?
Q9. Should oral fatty acid supplements be used as adjunct treatment for patients with COVID-19?
Q10. Should N-acetylcysteine be used as an adjunct treatment for patients diagnosed with COVID-19?
Q11. Should RAAS blockers be continued in patients with COVID-19?
Q12. Should statins be used as adjunctive treatment in patients with COVID-19?
Q13. Does the concurrent use of Ibuprofen worsen COVID-19 outcomes?
Q14. Should aspirin, taken as maintenance therapy for underlying medical conditions, be discontinued in patients with COVID-19?
Q15. Should antiseptic mouthwashes/gargles be used be as adjunctive treatment for COVID-19 infection?
Q16. Should nasal sprays be used in the prevention and treatment of COVID-19 infection?

# Q1. Should zinc be used as adjunctive treatment for COVID-19 infection?

*As of 21 December 2021*

## RECOMMENDATION

**There is insufficient evidence to recommend zinc as adjunctive treatment for COVID-19 infection.** *(Low certainty of evidence)*

*Consensus Issues*
Despite the risk of adverse events (i.e., infusion site irritation and gastrointestinal side effects), the panelists agreed that the evidence of benefit and harm of zinc as an adjunct therapy for COVID-19 still poses uncertainty. From their experience with the use of oral zinc for prevention of other illnesses, there had been no significant events reported to identify oral zinc as a cause for concern. Its potential for benefit was still given high consideration, particularly pending the results of ongoing studies. One voted against its use due to the signal for harm (i.e., hospitalization) among ambulatory patients and the risk of adverse events in the zinc group.

## PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of zinc as adjunct treatment for patients with COVID-19 infection both in the outpatient and in-patient setting. *(Very low quality of evidence)*

*Consensus Issues*
There were no issues raised during the consensus panel meeting.

## WHAT'S NEW IN THIS VERSION?

This updated review now includes six RCTs, with the addition of four new RCTs that were made available or published after the initial review.

## KEY FINDINGS

This updated review showed inconclusive results on the efficacy of zinc as adjunctive treatment for COVID-19 for the outcomes of in-hospital mortality and hospitalization of outpatients. There was a significantly higher number of adverse events in the group that received zinc compared to control.

## INTRODUCTION

Zinc has been shown to inhibit viral reproduction of SARSCOV-2 in-vitro. It also plays a role in the immunological response, associated with the negative feedback that decreases the activity of nuclear factor kappa B, thereby diminishing excessive inflammation and risk for cytokine storm. It was also found to play a role in protecting the respiratory epithelium against oxyradicals and to enhance intestinal wound healing.[1-3]

Zinc supplementation has been used widely in the treatment of diarrhea and taste disorders, which are common among patients with COVID-19.[1] In addition, COVID-19 patients with zinc deficiency were found to have higher complication rates, prolonged hospital stay, and increased rates of mortality.[4]

## REVIEW METHODS

We comprehensively searched different electronic databases that included MEDLINE via PubMed, Cochrane Library, ClinicalTrials.gov, PubMed Clinical Queries, medRxIV, bioRxIV, and *epistemonikos.com* until November 19, 2021. Free search on Google was also performed. The following keywords were used: “zinc”, “zinc gluconate”, and “zinc sulfate” in free text as well as MeSH terms for “Zinc” and COVID-19 (see Appendix 2). We searched for randomized controlled trials. When systematic reviews were found, their individual component RCTs were tracked and assessed for eligibility. We excluded observational studies, case reports, case series and letters to the editor. We included studies according to the following eligibility criteria: P – patients diagnosed with COVID-19; I – zinc plus standard of care; C – placebo or no treatment plus standard of care; O – mortality, length of hospital stay, length of ICU stay, adverse effects; M – randomized control trials.

## RESULTS

We found a total of six RCTs [5-10] for this updated review on zinc as adjunctive treatment for COVID-19 (see Appendix 3). Two clearly stated that they enrolled ambulatory patients/outpatients [6,7], and the remaining four RCTs stated that either 1) hospitalized patients were enrolled, or 2) their population consisted of patients with COVID-19 across all severities. Among the six RCTs, there were four that used zinc as the sole adjunct, and two that used zinc along with other adjunctive agents.[7,9]

This review includes the mid-2020 RCT of Abd Elsalam et al. [5], which enrolled RT PCR-confirmed patients with COVID-19 (N=191) from three tertiary care centers in Egypt to investigate the effect of zinc added to hydroxychloroquine (HCQ) versus HCQ alone (currently is no longer recommended for treatment of COVID because of safety issues). Thomas et al. [6] enrolled outpatients and investigated the effect of zinc gluconate and ascorbic acid given independently and together, compared to receiving standard of care. The RCT by Kaplan et al. [7] was a Phase I/II study to confirm the safety and efficacy of maximally-tolerated doses of the combination of zinc and resveratrol, compared to placebo, for the treatment of outpatients with mild to moderate COVID-19. The RCT by Patel et al. [8] on high-dose intravenous zinc among hospitalized COVID patients initially planned to enroll 60 hospitalized non-ventilated patients, and 100 ventilated patients (N=160). The study did not reach its target enrolment and has been terminated, but an available publication allowed its inclusion in this review. The RCT by Darban et al. [9] investigated the efficacy of high-dose vitamin C, melatonin, and zinc in patients with severe COVID infection. Finally, the RCT by Abdelmaksoud et al. [10] assessed serum zinc levels among 134 patients with COVID-19, 105 of whom reported anosmia or hyposmia.

The pooled estimates for the outcomes of in-hospital mortality (two studies: RR 0.92, 95% CI 0.35-2.44, $i^2$=0%) and hospitalization of ambulatory outpatients (two studies: RR 1.35, 95%CI 0.40-4.67, $i^2$=0%) ) were inconclusive. Adverse events were significantly higher in the zinc group than in the control (two studies: RR 13.62; 95%CI 1.78-104.43, $i^2$=0%).

In the RCT by Kaplan et al. [9] (adverse events data not included in the pooling), the adverse events reported in the treatment group (diarrhea, nausea and abdominal pain) were deemed to be caused by the resveratrol component.

Overall certainty of the evidence was low, because of issues of imprecision and indirectness.

## EVIDENCE TO DECISION

No research evidence was found that analyzed the cost-effectiveness, equity, acceptability and feasibility of the use of zinc among patients with COVID-19. The estimated cost of zinc gluconate is Php 5.00 per tablet (70mg) while zinc sulfate (60mL) is Php 96.00.[11,12] Other nutritional supplements contain both vitamin C and zinc, with prices ranging from Php 8.00 to Php 12.75 per capsule or tablet in local drugstores.[13,14]

## RECOMMENDATIONS FROM OTHER GROUPS

The US-NIH COVID-19 Treatment Guidelines Panel found insufficient evidence for or against the use of zinc for the treatment of COVID-19. They recommend against using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial (BIII) (Last updated in April 2021).[15] Currently, there are no recommendations from CDC, WHO, and the Infectious Diseases Society of America on the use of zinc as an adjunct treatment in COVID-19.

## RESEARCH GAPS

As of November 2021, there are eight ongoing trials investigating the effectiveness of zinc as adjunctive treatment for COVID-19 (see Appendix 8).

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# Appendix 1. Evidence to Decision

Table 1. Summary of initial judgments prior to the actual panel meeting (n = 8)

| FACTORS | JUDGMENT | | | | | | RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS |
|---|---|---|---|---|---|---|---|
| **Problem** | No (1) | Yes (7) | | | | | • Zinc has been shown to inhibit viral reproduction of SARS-CoV-2 in-vitro.<br>• It also plays a role in immunological response, associated with the negative feedback decreasing the activity of nuclear factor kappa B, decreasing excessive inflammation and risk for cytokine storm. |
| **Benefits** | Large | Moderate | Small (2) | Uncertain (6) | | | • This updated review showed inconclusive results on the efficacy of zinc as adjunctive treatment for COVID-19, for the outcomes of in-hospital mortality and hospitalization of outpatients. |
| **Harm** | Large | Small (2) | Uncertain (6) | Varies | | | • There were significantly higher adverse events in the group of patients with COVID-19 that received zinc than in control. |
| **Certainty of Evidence** | High | Moderate | Low (4) | Very low (4) | | | • The overall certainty of evidence is low due to issues of indirectness and imprecision. |
| **Balance of effects** | Favors zinc (1) | Does not favor zinc (4) | Uncertain (3) | Varies | | | • Consider natural sources of zinc (panel who does not favor zinc) |
| **Values** | Important uncertainty or variability (1) | Possibly important uncertainty or variability (5) | Possibly NO important uncertainty or variability (1) | No important uncertainty or variability (1) | | | |
| **Resources Required** | Uncertain (2) | Large cost | Moderate Costs (2) | Negligible costs or savings (3) | Moderate savings (1) | Large savings | Estimated costs:<br>• Zinc gluconate is Php 5 per tablet (70 mg)<br>• Zinc sulfate (60 mL) is Php 96.<br>• Other nutritional supplement contains both vitamin C and zinc and price varies from Php 8 to Php 12.75 per capsule or tablet in local drugstores |
| **Certainty of evidence of required resources** | No included studies (7) | Very low (1) | Low | Moderate | High | | • Currently, no cost-effectiveness study on zinc as adjunctive treatment for COVID-19 infection is available for review. |
| **Cost effectiveness** | No included studies (6) | Favors the comparison | Does not favor either the intervention or the comparison (2) | Favors the intervention | | | • Currently, no cost-effectiveness study on zinc as adjunctive treatment for COVID-19 infection is available for review |
| **Equity** | Uncertain (6) | Reduced | Probably no impact (2) | Increased | | | • No research evidence found. |
| **Acceptability** | Uncertain (7) | No | Yes (1) | Varies | | | • No research evidence found. |
| **Feasibility** | Uncertain (1) | No | Yes (7) | Varies | | | • No research evidence found. |

## Appendix 2. Search Yield and Results

| Database | Date of Last Search | Search strategy | Yield | Matching articles |
|---|---|---|---|---|
| PubMed | October 31, 2021 | ((("COVID-19" [Supplementary Concept] OR "COVID-19 diagnostic testing" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [Supplementary Concept] OR "COVID-19 vaccine" [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 ((((((((((zinc [tiab]) OR (zinc gluconate [tiab])) OR (zinc sulfate [tiab])) OR (zinc supplement [tiab])) OR (antioxidant [tiab])) OR (supplement [tiab])) OR (zinc* [tiab])) OR (zinc[MeSH Terms])) OR (zinc gluconate [MeSH Terms])) OR (zinc sulfate [MeSH Terms])) OR (Zinc supplement [MeSH Terms])) OR (antioxidant[MeSH Terms])) OR (supplement[MeSH Terms]) | 1729 | 4 |
| Cochrane | Nov 15, 2021 | ((zinc):ti,ab,kw OR Zinc* OR MeSH descriptor: [Zinc] explode all trees) AND (COVID-19 OR SARS-CoV-2 OR MeSH descriptor: [COVID-19] explode all trees) | 111 | 4 |
| ClinicalTrials.gov | Nov 15, 2021 | “zinc” and “COVID” | 55 | |
| MedRxiV | Nov 15, 2021 | title "zinc" (match all words) and abstract or title "zinc" (match all words) and full text or abstract or title "zinc" (match whole all) and posted between "31 Dec, 2020 and 15 Nov, 2021" | 239 | 0 |
| CovidNMA | October 26, 2021 | zinc | 3 | 3 |
| WHO International Clinical Trials Registry Platform | November 19, 2021 | “zinc” and “COVID-19” | 0 | 0 |

# Appendix 3. Characteristics of Included Studies: Randomized Controlled Trials

| Study ID | Setting | Population | Intervention | Control | Outcomes |
|---|---|---|---|---|---|
| **Abd-Elsalam** | **Three tertiary care centers in Assiut, Tanta, and Cairo.**<br><br>*Egypt* | N = 191<br>Confirmed RT-PCR positive in three egyptian tertiary care centers from June 23 to August 23,2020<br><br>Divided into mild, moderate, severe and critical based on WHO classification | Zinc sulfate 220mg (elemental zinc 50mg) BID<br><br>HCQ (400mg BID D1, then 200mg BID x 4 days) | **Standard of care (15 days)**<br><br>HCQ (400mg BID D1, then 200mg BID x 5 days) | Recovery within 28 days<br><br>Death<br><br>**Need for mechanical ventilation**<br><br>Duration of hospital stay (days) |
| **Thomas** | **Multiple outpatient settings in Ohio and Florida**<br><br>*USA* | N=214<br><br>Patients > 18 years old who were newly diagnosed by RT-PCR in an outpatient setting<br>**From April 27 to October 14, 2020** | Zinc gluconate (50mg OD at bedtime) x 10 days<br>n=58<br>(20 did not complete follow-up: 11 lost, 9 discontinued intervention)<br><br>*58 zinc + ascorbic acid x 10 days (11 did not complete: 3 lost, 8 discontinued) | **Standard of care only (n=50)**<br><br>***Ascorbic acid (8000mg over 2-3x/day)**<br>**N=48 (14 did not complete, 7 lost, 7 discontinued)** | **Days required to reach 50% reduction in symptoms**<br><br>Death<br><br>Hospitalization<br><br>Serious adverse events |
| **Kaplan et al**<br><br>(Lancet Pre-print; not yet peer reviewed) | Out-patient<br><br>Phase 1/2 clinical trial<br><br>*USA* | N= 30<br><br>mild-moderate COVID | Zinc methionine/ cysteine (Life Extension) 150 mg daily total (50 mg capsules orally three times daily and resveratrol (Mega Resveratrol) 2000 mg orally twice daily for five days. | Placebo capsules | Primary outcome: Reduction in viral shedding<br><br>Secondary outcomes:<br>• Reduction of symptoms<br>• Adverse events<br>• Incidence of hospitalization<br>• Length of hospitalization<br>• Days on ventilator support<br>• Time until the 4-symptom score is zero<br>• Composite score at Day 5<br>• Hospitalization<br>• Deaths |
| Patel et al (2021) | In-hospital setting<br><br>*Australia* | N= 33<br><br>Hospitalized pts including severeand critical | Zinc chloride IV at a dose of 0.5 mg/kg/d<br><br>(Elemental zinc at 0.24 mkd) | Placebo | Analyzable outcomes from the published report: deaths, continuing hospitalization |
| Darban, et al, 2021 | In-hospital setting | N = 20 with severe COVID | Oral zinc sulfate (220 mg containing 50 mg elemental zinc, q6hr) for 10 days (5-7)<br><br>IV vitamin C (2g, q6hr), oral melatonin (6 mg, q6hr) plus standard of care | Standard cares were azithromycin (250 mg/day), lopinavir/ritonavir (100mg/25mg/day), glucocorticoids and necessary oxygen | Primary outcome: changes in severity pf hypoxemia (PaO2/ FiO2 ratio)<br><br>Other outcomes included inflammatory markers (LDH, ESR, ferritin, CRP at baseline, days 5 and 10 after treatment initiation) |
| Abdelmaksoud, et al 2021 | Quarantine department of hospitals in Egypt | N = 134 patients | Zinc therapy<br>(220 mg zinc sulfate equivocal to 50 mg elemental zinc twice daily [33]) plus the Egyptian protocol of treatment of COVID-19 | Egyptian protocol of COVID-19 treatment without zinc therapy | Mean serum zinc levels, median duration of recovery of gustatory/ olfactory function, median duration of complete recovery among those who had anosmia/hyposmia |

# Appendix 4. Detailed Study Appraisal

| Appraising Directness | Abd-Elsalam, 2020 | Thomas, 2021 | Kaplan, 2021 | Patel, 2021 | Darban, 2021 | Abdelmaksoud, 2021 |
|---|---|---|---|---|---|---|
| Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)? | Yes, it had similar population and outcomes, but different interventions (Zinc as add on to HCQ vs HCQ, which is not standard of care currently)<br><br>P= Patients with COVID (mild, moderate, severity)<br>I=Zinc+HCQ vs HCQ<br>O=Duration of hospital stay, recovery | Yes, similar population and intervention but different outcomes<br><br>P= Patients diagnosed with COVID<br>I= Zinc, ascorbic acid, ascorbic acid with zinc, standard of care<br>O= Reduction in severity or duration of symptoms | The population is similar (COVID patients), but the intervention (Zinc + resveratrol) and primary outcomes are different (reduction in viral shedding) | The population is similar, but the intervention(high-dose IV Zinc) and primary outcome are different (lowest oxygen saturation for non-ventilated and worst PaO2/ FiO2 for ventilated) | Similar population (COVID severe), different intervention (standard of care vs standard of care with oral melatonin, oral zinc, IV vit C), and different outcome (changes in hypoxemia and inflammatory markers) | Similar population (Patients with COVID of various severities), similar intervention (zinc therapy, but different outcome (Mean serum zinc levels, median duration of recovery of gustatory/ olfactory function, median duration of complete recovery) |
| **Appraising Validity** | | | | | | |
| 1. Were patients randomly assigned to treatment groups? | Yes, it was a randomized controlled study | Yes, it was a randomized clinical factorial open-label trial | Yes | Yes | Yes | Yes |
| 2. Was allocation concealed? | It was not mentioned | No, it was an open-label trial | Yes | Yes | No | Not mentioned |
| 3. Were baseline characteristics similar at the start of the trial? | Yes, the treatment groups had no significant difference at baseline | Yes, they were similar characteristics at baseline | Yes | Yes | Yes | Yes |
| 4. Were patients blinded to treatment assignment? | It was not mentioned | No | Yes | Yes | No | Not mentioned |
| 5. Were caregivers blinded to treatment assignment? | It was not mentioned | No | Yes | Yes | No | Not mentioned |
| 6. Were outcome assessors blinded to treatment assignment? | It was not mentioned | No | Yes | Yes | No | Not mentioned |
| 7. Were all patients analyzed in the groups to which they were originally randomized? | Yes | Yes | Yes | Yes | Yes | Yes |
| 8. Was follow-up rate adequate? | Yes | Yes | Yes | Yes | Yes | Yes |
| **Appraising Results** | | | | | | |
| 1. How large was the effect of treatment? | The Zinc group had a mean hospital stay of 13.51 ± 5.34 days, while | The primary endpoint was time to 50% reduction of symptoms, 5.9 (4.9) days in | In terms of primary outcome of reduction in viral shedding, there was | The study was unable to assess the primary | PaO2/FiO2 at day 10<br>Control: 222.2 ± 65 | Serum zinc level:<br>Mild: 0.67 ± 0.18<br>Common: 0.62 ± 0.14 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | the Zinc + HCQ group had 14.01 ± 6.26 days, with p=0.553<br><br>In terms of in hospital mortality, the risk difference in 0.05 (-0.06, 0.06) N | the Zinc group, 6.7 (4.4) days for SOC (p=0.38) | no statistically significant difference between the 2 groups (p=0.7)<br><br>In-hospital mortality:<br>Zinc: 0/14<br>Placebo: 0/16<br><br>2 were admitted- one each for the interventions.<br>- Zn: 46-day LOS with 30 days in the ICU<br>Placebo: 11-day LOS with 5 days in the ICU | outcomes due to its failure to meet target enrollment<br><br>In-hospital mortality (28-day outcome):<br>Zinc: 2/ 15 (14.3%)<br>Control: 3/18 (16.7%) | Treatment: 230.1 ± 59.1, p=0.2<br><br>Length of ICU stay:<br>Control: 15 ± 3.3 days<br>Treatment: 14.1 ± 4.2 days<br>p = 0.3 | Severe: 0.73 ± 0.18<br>Extremely severe: 0.72 ± 0.22<br>p= 0.084<br><br>Mean duration of recovery of olfaction:<br>Zinc arm: 7 days (range 5-9 days)<br>Control: 18 days (range 14-22 days)<br><br>Duration of complete recovery<br>Zinc arm: Median 12 (range 8–17 days)<br>Control: Median 12 (range 8–20 days) |
| 2. How precise was the estimate of the treatment effect? | Length of hospital stay:<br>Group 1: 13.51, 5.34 days<br>95% CI: 12.47 to 14.594<br>Group 2 : 14.01, 6.26 days<br>95% CI: 12.734 to 15.286 days<br>Mean difference: 0.500 (-1.16, 2.16), p=0.55<br><br>In-hospital mortality<br>Zinc: 5/96 (5.21%)<br>HCQ: 5/95 (5.26%)<br>Risk difference: 0.05 (-0.06, 0.06) NS | Zinc group: 95% CI: 0.40 (−1.77 to 2.58)<br>Ascorbic acid only: 95% CI 0.40 (−1.99 to 2.80)<br>Ascorbic acid with zinc: 95% CI: 0.07 (−1.94 to 2.09) | N/A | N/A | | |
| **Assessing Applicability** | | | | | | |
| 1. Are there biologic issues that may affect applicability of treatment? (Consider the influence of sex, co-morbidity, race, age and pathology) | None | None | None | None | No | No |
| 2. Are there socio-economic issues affecting applicability of treatment? | None | None | None | None | No | No |
| **Individualizing the Results** | | | | | | |
| 1. What is the likely effect of the treatment on your individual patient? | No significant difference in length of hospital stay, recovery, need for | No reduction in severity nor duration of COVID | No significant difference in reduction in viral shedding or in-hospital mortality | No evidence of benefit in using high-dose IV Zinc | No evidence of benefit in using IV vit C, oral zinc, oral melatonin in | No evidence of benefit in using zinc to decrease duration to recovery of |

| | | | | | | |
|---|---|---|---|---|---|---|
| | ventilation, survival between Zinc+HCQ and HCQ. | | | among hospitalized COVID patients | PaO2/FiO2, change in inflammatory markers, length of ICU stay among COVID patients | olfaction or full recovery from COVID |
| 2. Would you offer the treatment to your patients? | No | No | No | No | No | No |

## Appendix 5: Risk of bias

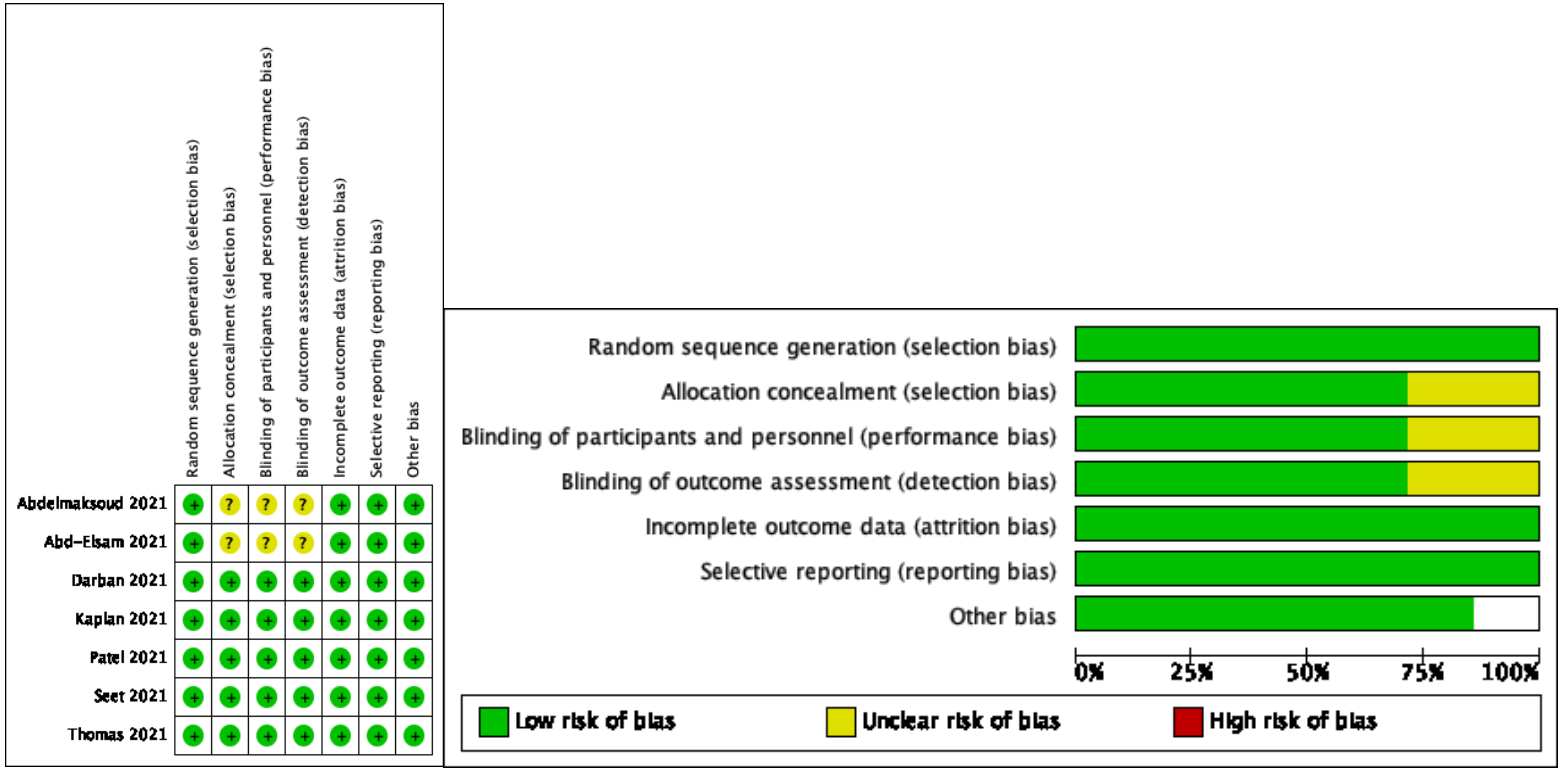



Figure 1. (Left) Risk of Bias Summary with judgements about each risk of bias item for each included study. (Right) Risk of Bias Graph with authors' judgements about each risk of bias item presented as percentages across all included studies.

# Appendix 6. GRADE Evidence Profile

**Author(s):** Patricia Marie M. Lusica, MD; Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS Myzelle Anne J. Infantado, PTRP, MSc (cand.)
**Question:** Zinc with standard of care compared to standard of care alone for adunctive treatment of COVID-19
**Setting:** In and out-patients

| CERTAINTY ASSESSMENT | | | | | | | NO. OF PATIENTS | | EFFECT | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Zinc with standard of care | Standard of care alone | Relative (95% CI) | Absolute (95% CI) | CERTAINTY | IMPORTANCE |
| **In-hospital mortality** | | | | | | | | | | | | |
| 2 | Randomised trials | Not serious | Not serious | Serious[a] | Serious[b] | None | 7/111 (6.3%) | 8/113 (7.1%) | **RR 0.92** (0.35 to 2.44) | **6 fewer per 1,000** (from 46 fewer to 102 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Length of Hospital Stay (assessed with: days of confinement)** | | | | | | | | | | | | |
| 1 | Randomised trials | Not serious | Not serious | Not serious | Serious[b] | None | 96 | 95 | - | MD **0.5 days lower** (1.16 lower to 2.16 higher) | ⨁⨁⨁◯ Moderate | CRITICAL |
| **Hospitalization of Ambulatory Patient** | | | | | | | | | | | | |
| 2 | Randomised trials | Not serious | Not serious | Serious[a] | Serious[b] | None | 6/72 (8.3%) | 4/66 (6.1%) | **RR 1.37** (0.40 to 4.67) | **22 more per 1,000** (from 36 fewer to 222 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Adverse events** | | | | | | | | | | | | |
| 2 | Randomised trials | Not serious | Not serious | Not serious | Not serious | None | 13/73 (17.8%) | 0/68 (0.0%) | **RR 13.62** (1.78 to 104.43) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | ⨁⨁⨁⨁ High | CRITICAL |

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

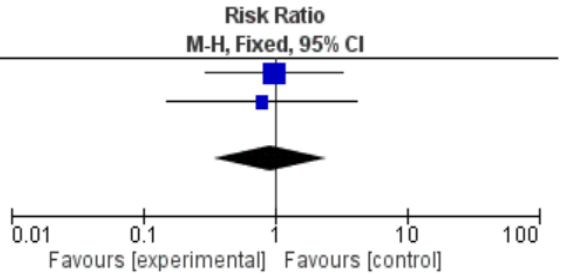
**Explanations**
[a] Experimental arm was zinc, used with other adjuncts
[b] Confidence interval crosses the null value

# Appendix 7. Forest plots

## A. In-hospital mortality

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Abd-Elsalam | 5 | 96 | 5 | 95 | 64.8% | 0.99 [0.30, 3.31] |
| Patel | 2 | 15 | 3 | 18 | 35.2% | 0.80 [0.15, 4.18] |
| **Total (95% CI)** | | **111** | | **113** | **100.0%** | **0.92 [0.35, 2.44]** |
| Total events | 7 | | 8 | | | |

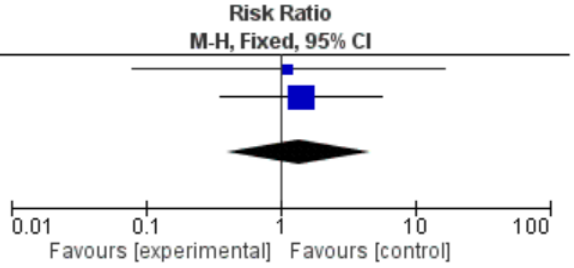
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)




## B. Hospitalization among ambulatory patients

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Kaplan | 1 | 14 | 1 | 16 | 22.5% | 1.14 [0.08, 16.63] |
| Thomas | 5 | 58 | 3 | 50 | 77.5% | 1.44 [0.36, 5.71] |
| **Total (95% CI)** | | **72** | | **66** | **100.0%** | **1.37 [0.40, 4.67]** |
| Total events | 6 | | 4 | | | |

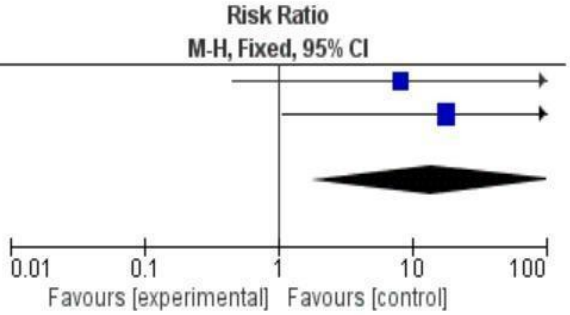
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.61)




## C. Adverse events

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Patel | 3 | 15 | 0 | 18 | 46.0% | 8.31 [0.46, 149.21] |
| Thomas | 10 | 58 | 0 | 50 | 54.0% | 18.15 [1.09, 302.17] |
| **Total (95% CI)** | | **73** | | **68** | **100.0%** | **13.62 [1.78, 104.43]** |
| Total events | 13 | | 0 | | | |

Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 2.51 (P = 0.01)



## Appendix 8. Ongoing Trials

| Study ID | Setting | Title | Intervention | Control | Outcomes | Status |
|---|---|---|---|---|---|---|
| NCT04 641195 | India | A Randomized Trial to Determine the Effect of Vitamin D and Zinc Supplementation for Improving Treatment Outcomes Among COVID-19 Patients in India | Dietary Supplement: Zinc (zinc gluconate) 40mg of zinc gluconate taken once per day from enrollment to 8 weeks<br>Dietary Supplement: Vitamin D3 (cholecalciferol) 180,000 international units (IU) of vitamin D3 at enrollment, followed by 2000 IU once per day from enrollment to 8 weeks<br>Dietary Supplement: Zinc (zinc gluconate) & Vitamin D (cholecalciferol) 180,000 IU of vitamin D3 at enrollment, followed by 2000 IU of vitamin D3 and 40mg of zinc gluconate once per day from enrollment to 8 weeks | Placebo | Time to recovery, all-cause mortality, necessity for assisted ventilation, individual symptoms duration, Vitamin D, Zinc, Interleukin 6 (IL-6) | Ongoing |
| NCT04 370782 | US | A Randomized Study Evaluating the Safety and Efficacy of Hydroxychloroquine and Zinc in Combination With Either Azithromycin or Doxycycline for the Treatment of COVID-19 in the Outpatient Setting | Hydroxychloroquine<br>Azithromycin<br>Zinc sulfate | Hydroxychloroquine<br>Doxycycline<br>Zinc sulfate | Time to Resolution of Symptoms relative to baseline (Days 5, 14, 21), Number of participants hospitalized and/or requiring repeat ER visits, ICU length of stay, number of days on ventilator | Completed, but no results posted yet |
| NCT04 542993 | Sweden | Can SARS-CoV-2 Viral Load and COVID-19 Disease Severity be Reduced by Resveratrol-assisted Zinc Therapy | Resveratrol and Zinc | Placebo | Reduction in SARS-CoV-2 Viral load, Reduction in Severity of COVID-19 Disease | Active, not recruiting |
| NCT04 351490 | France | Impact of Zinc and Vitamin D3 Supplementation on the Survival of Aged Patients Infected With COVID-19 | Zinc gluconate and 25-OH cholecalciferol | Group usual treatment | Survival rate in asymptomatic subjects at inclusion | Withdrawn |
| NCT04 828538 | Mexico | Vitamin D, Omega-3, and Combination Vitamins B, C and Zinc Supplementation for the Treatment and Prevention of COVID-19 | Vitamin D, Omega DHA / EPA, Vitamin C, Vitamin B complex and Zinc Acetate | Placebo | Covid infection rate, incidence of severe outcome | Active, not recruiting |
| NCT04 621461 | US | Placebo Controlled Trial to Evaluate **Zinc** for the Treatment of **COVID-19** in the Outpatient Setting | **Zinc** Sulfate | Placebo | Number of participants hospitalized and/or requiring repeat emergency room visits, number of participants admitted to ICU, Number of participants on a ventilator, all-cause mortality | Completed, but with only 3 actual enrollment |
| NCT04 342728 | US | Coronavirus 2019 (**COVID-19**)- Using Ascorbic Acid and **Zinc** Supplementation | Ascorbic acid, Zinc, Ascorbic acid+Zinc | Standard of care | Symptom reduction | Completed recruitment |
| NCT04 335084 | US | A Study of Hydroxychloroquine, Vitamin C, Vitamin D, and **Zinc** for the Prevention of **COVID-19** Infection | HCQ + Vit C + Vit D + Zinc | Placebo | Prevention of COVID-19 symptoms, safety | Ongoing recruitment |

## Q2. Should B Vitamins be used as an adjunct in the treatment of COVID-19?

*As of 30 June 2021*

RECOMMENDATION

**We suggest against the use of B vitamins as adjunct in the treatment of patients with COVID-19.** *(Very low certainty of evidence; Weak recommendation)*

*Consensus Issues*
Vitamin B plays an important role in cell functioning and boosting the immune system. Therefore, there is a need to assess the potential of Vitamin B as an adjunct treatment for COVID-19.

There were no studies that assessed the use of Vitamin B alone as an adjunct treatment for COVID-19 but there are still ongoing studies that can provide a clear picture on the use of Vitamin B as adjunct treatment. There were also no studies found that assessed the correlation of Vitamin B deficiency and cytokine storm. However, a prospective study that investigated the levels of Vitamin B12 and folate plasma level among patients admitted for COVID-19 pneumonia until they were transferred to ICU or death ensued suggested that there was a potential association between high plasma levels of Vitamin B12 and increased risk of mortality.

## KEY FINDINGS

There was one cohort study on the use of vitamin D/magnesium/vitamin B12 (DMB) supplementation on patients with COVID-19 infection. Likelihood of subsequent oxygen therapy including ICU support was significantly less for those taking DMB. However, there was no significant difference when looking at oxygen therapy alone or ICU support alone. There were no adverse events directly attributed to DMB use in the cohort study. There is very low certainty of evidence that suggests an association between excessive levels of Vitamin B12 and poorer outcomes in COVID-19 patients. Overall, there is very low certainty of evidence due to risk of bias based on the observational design, as well as issues with directness (DMB was given in combination with vitamin D and magnesium) and imprecision (due to limited sample size).

## INTRODUCTION

The B vitamins are as follows: B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folic acid) and B12 (cobalamin). When all these are combined, they are referred to as vitamin B complex [1].

These water-soluble vitamins contribute to cell functioning and energy metabolism to create and maintain healthy cells thus playing a major role in the body's immune system [2]. For instance, while vitamin B1 has some anti-inflammatory effects, vitamin B6 plays a role in T cell production, and vitamins B3 and B12 affect the immune system [3,4]. This combined boost to the immune system is hoped to translate to beneficial effects when B vitamins are taken as an adjunct for COVID-19 treatment [4].

## REVIEW METHODS

We conducted a search using Medline, Cochrane Central and Google Scholar using a combined MeSH and free text search on B vitamins – B1, B2, B3, B5, B6, B7, B9,

B12 - including riboflavin, thiamine, niacin, niacinamide, pantothenic acid, pyridoxine, pyridoxal, pyridoxamine, biotin, folic acid, hydroxocobalamin, mecobalamin, transcobalamins, cyanocobalamin, cobamides, vitamin B complex and coronavirus, COVID-19, SARS-CoV-2, or NCOV. We looked for randomized controlled trials (RCT) and, in cases when there were no RCTs, proceeded to search for observational studies.

## RESULTS

### Efficacy

As of this date, we found no randomized controlled trials on the use of B vitamins as adjunctive treatment on patients with COVID-19. There was, however, the cohort study of Tan et al. in Singapore, that compared patients given a short course of vitamin D/magnesium/vitamin B12 supplements (DMB) upon diagnosis of COVID-19 to those who were not given DMB [5]. This study included 43 consecutive patients who were SARS-CoV-2 positive by polymerase chain reaction (PCR) from nasopharyngeal or throat swab. The DMB was started on all consecutive patients who were above 50 years of age not requiring oxygen therapy, ICU support, or a combination of the two. The regimen consisted of a single daily oral 1000-IU dose of vitamin D3 (cholecalciferol), 150 mg of magnesium oxide, and 500 µg vitamin B12 (methylcobalamine) for ≤14 days. All those who were not given DMB at that time served as control group. The authors defined primary outcome as the requirement of oxygen therapy when oxygen saturation by pulse oximetry fell < 95%, intensive care unit (ICU) support, or both.

Results showed that fewer patients receiving DMB actually required subsequent oxygen therapy plus ICU support compared to controls, with an odds ratio (OR) of 0.13 (95% CI 0.03-0.59). No significant difference was seen for the outcomes of 1) requiring oxygen therapy with no ICU support (OR 0.3, 95% CI 0.06-1.63) and 2) requiring ICU support alone (OR 0.14, 95% CI 0.02- 1.25). Multivariate analysis also showed that DMB remained a significant protective factor after adjusting for age (OR=0.195, 95% CI 0.041-0.926) and hypertension (OR=0.182, 95% CI 0.038- 0.859). They also did a subgroup analysis, removing patients < 60 years of age with diabetes, but the analysis of the primary outcome did not show any significant difference because of the limited sample size.

This study had issues on risk of bias because of its observational design. There was also downgrading on directness because the study did not look at the effect of B vitamin alone since it was given in combination with vitamin D and magnesium. The limited sample size, leading to imprecision, also contributed to the downgrading of the quality. At best, the certainty of evidence for the use of vitamin B as adjunct for the treatment of COVID-19 patients is very low.

### Safety

Tan et al. reported that there were no side effects or adverse events with the use of DBM in their cohort study. There was also no death reported in the follow-up period [5].

The study of Dalbeni et al. investigated the levels of vitamin B12 and folate plasma level in patients admitted for COVID Pneumonia, who they followed prospectively until the outcome of transfer to ICU or death ensued [6]. Out of 49 patients, nine had the

outcome: these patients were significantly older (p = 0.01), had lower P/F ratio (p = 0.01) and higher plasma level of B12 (p = 0.02) compared with those who recovered. On multivariate analysis, however, only age was independently associated with a worse outcome (β±SEM 0.016 ± 0.005, p = 0.001). However, the study suggested a potential association between high plasma levels of vitamin B12 and increased risk of mortality, citing also previous literature where excessive vitamin B12 levels were associated with the same, in both the general population [7] and ICU patients [8].

Hypervitaminosis B6 due to excessive self-medication has been known to cause peripheral neuropathy with both motor and sensory deficits [9,10].

## RECOMMENDATIONS FROM OTHER GROUPS

The NIH Covid-19 Guidelines does not mention the use of B vitamins as supplement to COVID-19 treatment [11]. The Australian Guidelines for the clinical care of COVID-19, the Surviving Sepsis Campaign Guidelines on COVID-19, and the Infectious Disease Society of America (IDSA) on the Treatment and Management of Patients with COVID-19 were also silent with regard to B vitamin use [12-14].

## RESEARCH GAPS

There is no evidence yet on the efficacy of B complex vitamins in the following settings: 1) when used as the sole adjunct to standard therapy, 2) patients with COVID-19 who have normal versus deficient vitamin B levels, and 3) patients across various ages and comorbid conditions.

There are currently four ongoing randomized controlled trials listed in *ClinicalTrials.gov* on the use of B vitamins in COVID-19 patients [15]. There is one registered and published protocol of a randomized controlled trial on the impact of various vitamins including vitamin B on improvement and mortality rate in ICU patients with COVID-19 listed in Cochrane Central Register of Controlled Trials, whose corresponding author we reached out to, for the results of the study which should have completed recruitment in July 2020 [16]. This evidence summary will be updated as soon as those studies come out and are confirmed eligible for inclusion.

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## Appendix 1. Characteristics of Included Studies

| Study ID | Patients (n) | Interventions | Outcomes | Method |
|---|---|---|---|---|
| Tan 2020 | All consecutive COVID-19 patients ≥50 years of age admitted to a tertiary hospital.<br>Must be positive for severe acute respiratory syndrome coronavirus (SARS-CoV)-2 polymerase chain reaction (PCR) from nasopharyngeal or throat swab.<br>n = 43 | 1000-IU dose of vitamin D3 (colecalciferol), 150 mg of magnesium oxide, and 500 mg vitamin B12 (methylcobalamine) for 14 days given per orem once a day compared to usual care/standard care at that time (Jan 15 to April 15, 2020) | Primary outcome was requirement of oxygen therapy when oxygen saturation fell <95% detected by pulse oximetry, intensive care unit (ICU) support, or both | Cohort (non-randomized, observational) |

# Appendix 2. GRADE Evidence Profile

**Author(s)**: Sulit, Maria Vanessa; Villarta-de Dios, Namnama
**Question**: Vitamin B Supplements compared to Standard Care or Placebo for COVID-19
**Setting**: In-hospital
**Bibliography**: Tan CW, Pock L, Kalimuddin S, Cherng BPZ, Teh YE, Thien SW et al. Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B12 in combination on progression to severe outcomes in older patients with coronavirus (COVID-19). Nutrition. 2020; 79-80. https://doi.org/10.1016/j.nut.2020.111017

| CERTAINTY ASSESSMENT | | | | | | | NO. OF PATIENTS | | EFFECT | | CERTAINTY | IMPORTANCE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Vitamin B Supplements | Standard of care or placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **Requiring O2 therapy including ICU support (follow up: range 1 to 14 days)** | | | | | | | | | | | | |
| 1 | Observational studies | Very serious [a] | Not serious | Serious [b] | Serious [c] | All plausible residual confounding would reduce the demonstrated effect | 3/17 (17.6%) | 16/26 (61.5%) | **OR 0.13** (0.03 to 0.59) | **443 fewer per 1,000** (from 570 fewer to 130 fewer) | ⨁◯◯◯ VERY LOW | |
| **Requiring O2 therapy without ICU support (follow up: range 1 to 14 days)** | | | | | | | | | | | | |
| 1 | Observational studies | Very serious [a] | Not serious | Serious [b] | Serious [c] | All plausible residual confounding would reduce the demonstrated effect | 2/17 (11.8%) | 8/26 (30.8%) | **OR 0.30** (0.06 to 1.63) | **190 fewer per 1,000** (from 282 fewer to 112 more) | ⨁◯◯◯ VERY LOW | |
| **Requiring ICU support (follow up: range 1 to 14 days)** | | | | | | | | | | | | |
| 1 | Observational studies | Very serious [a] | Not serious | Serious [b] | Serious [c] | All plausible residual confounding would reduce the demonstrated effect | 1/17 (5.9%) | 8/18 (44.4%) | **OR 0.14** (0.02 to 1.25) | **344 fewer per 1,000** (from 429 fewer to 56 more) | ⨁◯◯◯ VERY LOW | |

**CI:** Confidence interval; **OR:** Odds ratio

**Explanations**
[a] This was a non-randomized, cohort study.
[b] Vitamin B12 was taken in combination with vitamin D and magnesium
[c] Sample size was limited to 17 patients in the DMB group and 26 patients in the control group.

## Appendix 3. Characteristics of Ongoing Studies

| Study Title | Patients (n) | Interventions | Outcomes | Method |
|---|---|---|---|---|
| Impact of vitamins A, B, C, D, and e supplementation on improvement and mortality rate in ICU patients with coronavirus-19 | 20-60 years old with clinical or definitive diagnosis of COVID-19 by PCR test | Vitamin A, Vitamin D, Vitamin E, Vitamin C is taken four times per day<br>B vitamins are taken as a daily Soluvit [which included thiamine nitrate, sodium riboflavin phosphate, nicotinamide, pyridoxine hydrochloride, sodium pantothenate, sodium ascorbate, biotin, folic acid, and cyanocobalamin.<br>The control group will not receive any supplements or placebo. | Weight, height, and BMI 2; Severity of pulmonary involvement according to CT scan; Respiratory support (invasive or non-invasive); Percentage of oxygen saturation (SpO2 level); Serum levels of WBC, CRP, ESR, IL6, IFN-G, and TNF-α 6; patient's body temperature; presence or absence of involvement of organs other than the lungs (e.g., heart, liver, kidneys); duration of hospitalization; Mortality rate | Randomized; parallel assignment with concealed allocation |
| Improvement of the Nutritional Status Regarding Nicotinamide (Vitamin B3) and the Disease Course of COVID-19 | 18 years and older with SARS-CoV-2 infection confirmed by laboratory findings<br>n = 840 | 1,000 mg nicotinamide [1x 500-mg conventional nicotinamide tablet and 1x 500-mg tablet with controlled-ileocolonic-release nicotinamide (CICR-NAM)] for 4 weeks versus matching placebo capsules taken daily | Frequency of:<br>- complete symptom resolution after 2 weeks<br>- complete symptom resolution after 4 weeks<br>- freedom from fatigue after 2 weeks<br>- severe COVID-19 (examination in an emergency department / hospitalisation with requirement for oxygen (at least 24 h), intensive care or ventilation / death by COVID-19)<br>Time from diagnosis to complete symptom resolution [days] | Randomized; parallel assignment with masking |
| Effects of Nicotinamide Riboside on the Clinical Outcome of Covid-19 in the Elderly. A Randomized Double-blind, Placebo-controlled Trial of Nicotinamide Riboside NR-COVID19 | 70 years and older diagnosed with COVID-19<br><br>n = 100 | 1 g of nicotinamide riboside versus placebo orally every morning for 14 days | - Hypoxic respiratory failure<br>- Mortality<br>- Sepsis<br>- Circulatory failure<br>- Days in hospital<br>- NAD levels | Randomized; parallel assignment with masking |
| Clinical Trial of Niagen to Examine Recovery in People With Persistent Cognitive and Physical Symptoms After COVID-19 Illness (Long-COVID) | 18-65 years old with COVID-19 sequelae and cognitive symptoms<br>n = 100 | Niagen (nicotinamide riboside or Truniagen or vitamin B3) versus placebo capsules taken daily | Examine the effect of Niagen on/in:<br>- Cognitive functioning as measured by executive functioning and memory composite scores<br>- Depression symptoms<br>- In anxiety symptoms<br>- In COVID- related physical symptoms | Randomized; parallel assignment with masking |
| Efficacy of Micronutrient Dietary Supplementation in Reducing Hospital Admissions for COVID-19: A Double-blind, Placebo-controlled, Randomized Clinical Trial | 45 – 80 years old with symptoms compatible with COVID-19: cough and fever who not fulfil criteria of hospitalization and will be in outpatient care; Positive polymerase chain reaction (PCR) or transcription-mediated amplification (TMA) test or rapid antigen test for severe acute respiratory syndrome Corona Virus-2 (SARS-CoV-2) or diagnostic test available | Tablet containing:<br>● Retinol (Vitamin A) 700 mcg<br>● Cholecalciferol (Vitamin D3) 10 mcg<br>● Alpha-Tocopherol (Vitamin E) 45 mg<br>● Ascorbic acid (vitamin C) 1000 mg<br>● Pyridoxine (Vitamin B6) 6.5 mg<br>● Cyanocobalamin (Vitamin B12) 9.6 mg<br>● Folic acid 400 mg<br>● Iron 5 mg<br>● Zinc 10 mg<br>● Selenium 110 mg<br>● Copper 0.9 mg<br>● Excipients<br>versus effervescent placebo tablet taken daily | - Need for hospital admission<br>- Micronutrient basal status<br>- Micronutrient status at hospital admission<br>- Micronutrient status at end of study<br>- Inflammatory parameters<br>- Thromboembolic disease<br>- Oxygen supplementation<br>- High-Flow oxygen supplementation<br>- Invasive mechanical ventilation<br>- Tracheostomy<br>and more… | Randomized; parallel assignment with masking |

## Q3. Should Vitamin C be used as adjunct treatment for COVID-19?

*As of 21 December 2021*

### RECOMMENDATION

**There is insufficient evidence to recommend the use of vitamin C as adjunctive treatment for patients with COVID-19.** *(Low certainty of evidence)*

*Consensus Issues*
The evidence still posed low certainty in terms of efficacy (i.e., reduction in length of hospital and ICU stay, need for mechanical ventilation for hospitalized patients, and mortality among both hospitalized and non-hospitalized patients) and safety. The panel could not suggest against the use of vitamin C since only one study for non-hospitalized patients showed inconclusive effects on mortality and adverse events.

### PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of intravenous vitamin C as adjunct treatment for patients with COVID-19 infection. (Low quality of evidence)

*Consensus Issues*
Since there is insufficient evidence to recommend the use of vitamin C as adjunct treatment for COVID-19 and the quality of evidence is rated low, this means that more randomized controlled trials on vitamin C as adjunct treatment for COVID-19 need to be done.

Intravenous administration was the route used by the included studies in this review. According to the search for pricing, intravenous vitamin C costs Php 430 for 40 ampules of 500mg/2ml but this pricing was from an online selling source; there were no data on pricing of intravenous vitamin C on pharmaceutical websites searched.

## WHAT'S NEW IN THIS VERSION?

This review contains four new additional randomized control trials, bringing to eight the studies included in this review. Data from four RCTs were pooled and analyzed in a meta-analysis, while the other four RCTs were individually reviewed and reported narratively for the relevant outcomes.

## KEY FINDINGS

There are eight RCTs included in this review but only four, that used intravenous vitamin C for hospitalized patients with moderate to severe COVID-19, were pooled. For the outcome of mortality, there was a trend towards benefit with small negligible harm. There was no significant benefit and inconclusive results for length of hospital stay, length of ICU stay and need for mechanical ventilation. One RCT using oral vitamin C in the outpatient setting and three RCTs using Vitamin C in addition to other adjunctive treatments showed inconclusive results. Adverse events reported were flushing, headache, nausea, vomiting, stomach pain, and diarrhea.

## INTRODUCTION

Vitamin C (VC), also known as ascorbic acid, is an essential water-soluble vitamin that is required as a cofactor in many enzymatic reactions.[1] It promotes phagocytosis and chemotaxis of leukocytes and development and maturation of T-lymphocytes.[2,3] It also exhibits antioxidant properties through its effect on the NFKB activation that

leads to the attenuation of inflammation and reduction in reactive oxygen species.[4] Early clinical trials show that VC can alleviate and prevent the common cold.[5,6] However, two observational studies on the effect of VC on COVID-19 showed no mortality benefit and increased hospitalization stay with VC treatment.[7,8]

## REVIEW METHODS

We performed a comprehensive, systematic search for relevant literature in PubMed, Cochrane Library, *ClinicalTrials.gov*, *epistemonikos.com* and *medRxiv.com*, *covid-nma.com* as well as freehand search using Google Scholar. We used the search terms "COVID-19", "SARS-CoV-2", "nCOV-19", "vitamin C", "ascorbic acid" and "sodium ascorbate". There was no limit as to the date, language and country of publication. We searched for randomized controlled trials. When systematic reviews were found, their individual component RCTs were tracked and assessed for eligibility. We excluded observational studies, case reports, case series and letters to the editor. Articles were included if they satisfied the following eligibility criteria:

| | |
|---|---|
| Population | COVID-19 patients any age, co-morbidities and severity |
| Intervention/Exposure | Vitamin C or Sodium Ascorbate or Ascorbic Acid as adjunctive treatment |
| Comparison | Usual care, standard of care, placebo, any active control |
| Outcomes | Mortality, clinical improvement, adverse effects |
| Methodological filter | Randomized controlled trials (RCTs) |

Data from randomized control trials that included all hospitalized patients with moderate to severe COVID-19 and given intravenous vitamin C were pooled together in a meta-analysis. Outcomes that were analyzed included mortality, length of hospital stay, length of ICU stay, need for mechanical ventilation, and adverse events. When appropriate, pooling of the estimates was done using Review Manager 5.4; risk ratio was used for dichotomous outcomes while standard mean difference was used for continuous outcomes. GRADE PRO was used to evaluate the quality of evidence.

Other randomized control trials that had dissimilar population and intervention arms were excluded from the meta-analysis and reviewed individually for the same outcomes as in the pooled RCTs.

## RESULTS

We performed a meta-analysis of four RCTs, all of which included hospitalized patients with moderate to severe COVID.[9,10,12,13] Vitamin C was given via the intravenous route at doses ranging from 50mg/kg/day to 24g/day and compared with the study-defined control treatment or standard of care.

Data on mortality rate were pooled from all four RCTs with a total of 150 subjects in the treatment group and 160 subjects in the control group. The overall estimate showed a trend to benefit with negligible harm of vitamin C for the outcome of mortality (RR 0.59, 95% CI 0.34-1.03).

The estimate for length of hospital stay was also pooled from all four RCTs that studied the outcome, and the results were inconclusive (MD -0.96, 95% CI -3.84-1.92).

Length of ICU stay was measured in only two studies [9,12] and the overall estimate from the pooled analysis showed inconclusive results (MD 1.35; 95% CI -0.12-2.83).

For the outcome of need for mechanical ventilation, the pooled estimate from three studies [9,10,12] showed inconclusive results (RR 0.93, 95% CI 0.60-1.44).

Data on adverse events was reported in only two out of the four RCTs reviewed. One using high dose intravenous vitamin C [9] reported no adverse events, while the other using oral vitamin C [11] reported having adverse events in 17 out of 78 (21.7%) participants given vitamin C. Adverse events included flushing, headache, nausea, vomiting, stomach pain, and diarrhea.

Three randomized control trials gave vitamin C in conjunction with other adjunctive treatments. Results from these RCTs [14-16] were reviewed individually.

The study of Darban et al. [14] included ICU-admitted patients with severe COVID-19 given intravenous vitamin C (2g q6hr), oral melatonin (6mg q6hr), and oral zinc sulfate (50mg elemental zinc q6hr) for 10 days. The study results showed no significant improvement in hypoxemia and inflammatory markers in the case group versus the control group.

Beigmohammadi et. al. [16] also included ICU-admitted patients with severe COVID-19, and gave vitamin C 500mg four times daily together with vitamin A 25,000IU daily, vitamin D 600,000IU for 1 dose, vitamin E 300IU twice daily and B complex once daily. The study showed significantly shorter length of hospital stay and significantly lower inflammatory markers including ESR, CRP, IL-6 and TNF-a and SOFA score in the intervention group. The outcome for reduction in mortality was not significant.

The study by Hakamifard et al. [15] included hospitalized patients with non-severe COVID-19, and gave as an intervention oral vitamin C 1gram daily with oral Vitamin E 400IU daily in addition to standard treatment, showing inconclusive results for improvement in clinical response, duration of hospitalization and mortality.

One study, that of Thomas et al. [11], included COVID patients managed as out-patient, divided into treatment arms: patients received either oral vitamin C, oral zinc gluconate, both agents or standard of care. The study was discontinued for futility, and results were inconclusive for symptom reduction, hospitalization, mortality and adverse events.

## EVIDENCE TO DECISION

There are no cost-effectiveness studies available on use of vitamin C among COVID-19 patients. There are also no local studies tackling perspectives of relevant stakeholders on use of vitamin C among these patients. In a local drugstore, a tablet of ascorbic acid (500 mg) is approximately Php2.75. [17]

## RECOMMENDATIONS FROM OTHER GROUPS

The World Health Organization (WHO) and IDSA did not mention the use of vitamin C for COVID-19 in their CPG. The US-NIH made no recommendation for or against use of vitamin C for COVID-19 due to insufficient evidence.

## RESEARCH GAPS

Currently, there are 13 ongoing studies on the efficacy of vitamin C as an adjunctive treatment for COVID-19 (see Appendix 6). More studies are needed to examine the use of either intravenous or oral vitamin C in suppressing cytokine storms in COVID-19. Furthermore, studies on the most appropriate and effective dose and route of administration are also needed in order to make clearer recommendations on the use of vitamin C for patients with COVID-19.

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# Appendix 1. Evidence to Decision

Table 1. Summary of initial judgments prior to the actual panel meeting (n = 8)

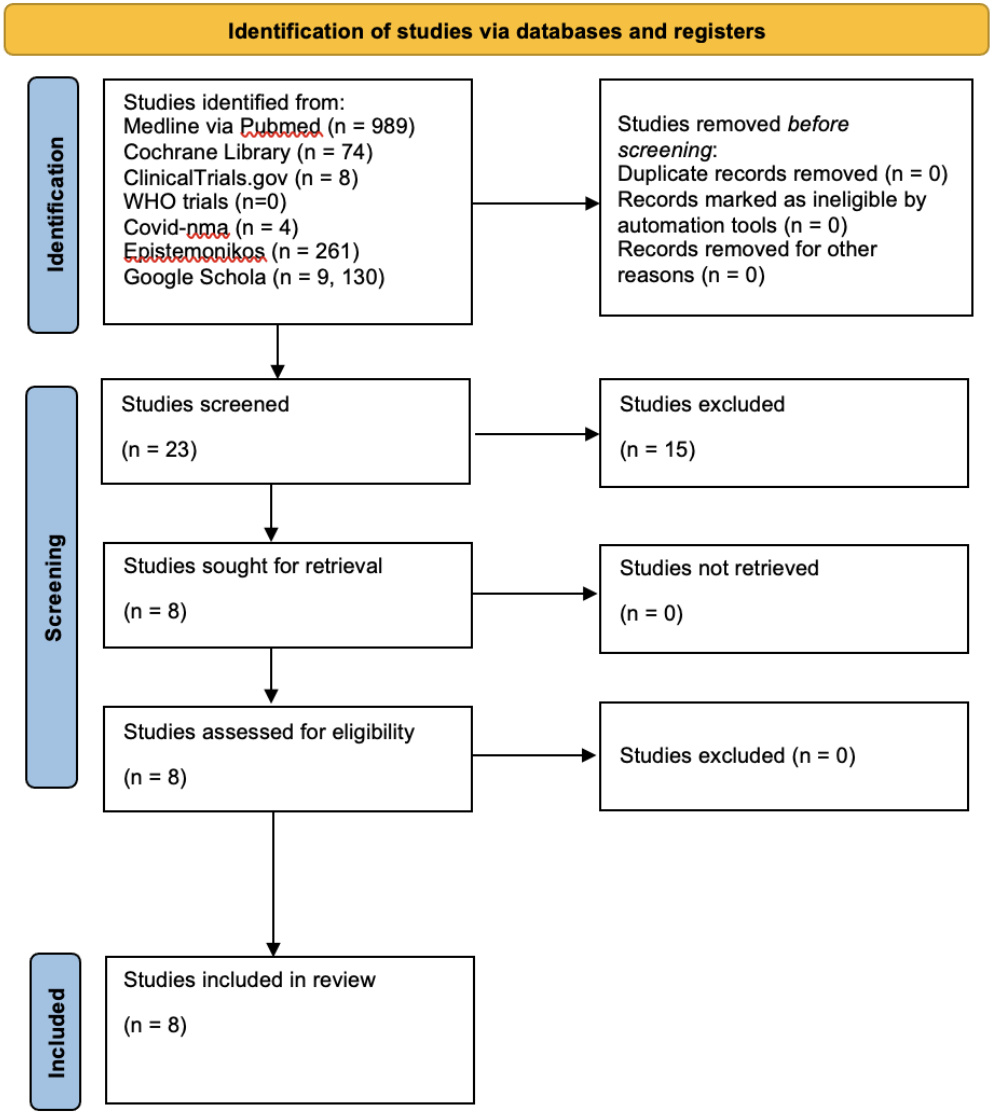
| FACTORS | JUDGMENT | | | | | | RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS |
|---|---|---|---|---|---|---|---|
| **Problem** | No | Yes (8) | | | | | • Early clinical trials show that VC can alleviate and prevent the common cold. However, two observational studies on the effect of VC on COVID-19 showed no mortality benefit and increased hospitalization stay with VC treatment. |
| **Benefits** | Large (1) | Moderate (2) | Small (3) | Uncertain (2) | | | • For the outcome of mortality there was trend towards benefit with small negligible harm (RR 0.59, 95 % CI 0.34 to 1.03).<br>• For the outcomes of length of hospital stay, length of ICU stay and need for mechanical ventilation, the results were inconclusive..<br>• *Panelist: Patients are using double dose of the recommended daily intake. Will this also be considered as part of our recommendation?* |
| **Harm** | Large | Small (8) | Uncertain | Varies | | | • Adverse events reported from taking oral vitamin C were flushing, headache, nausea, vomiting, stomach pain, and diarrhea among COVID-19 outpatients.<br>• There were no adverse events reported among hospitalized patients with COVID-19. |
| **Certainty of Evidence** | High | Moderate (1) | Low (7) | Very low | | | • The overall certainty of evidence is low primarily due to issues of inconsistency and imprecision. |
| **Balance of effects** | Favors vitamin C (7) | Does not favor vitamin C (1) | Uncertain | Varies | | | • For the outcome of mortality there was a trend towards benefit with small negligible harm (RR 0.59, 95 % CI 0.34 to 1.03).<br>• For the outcomes of length of hospital stay, length of ICU stay and need for mechanical ventilation, the results were inconclusive<br>• Adverse events reported from taking oral vitamin C were flushing, headache, nausea, vomiting, stomach pain, and diarrhea among COVID-19 outpatients.<br>• There were no adverse events reported among hospitalized patients with COVID-19. |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability (5) | Possibly NO important uncertainty or variability (3) | No important uncertainty or variability | | | |
| **Resources Required** | Uncertain | Large cost | Moderate Costs (3) | Negligible costs or savings (3) | Moderate savings (2) | Large savings | • There are no cost-effectiveness studies available on use of Vitamin C among COVID-19 patients. In a local drugstore, a tablet of ascorbic acid (500 mg) is approximately Php2.75. |
| **Certainty of evidence of required resources** | No included studies (5) | Very low (2) | Low (1) | Moderate | High | | • There are no cost-effectiveness studies available on use of Vitamin C among COVID-19 patients |
| **Cost effectiveness** | No included studies (4) | Favors the comparison (1) | Does not favor either the intervention or the comparison | Favors vitamin C (3) | | | • There are no cost-effectiveness studies available on use of Vitamin C among COVID-19 patients. |
| **Equity** | Uncertain (4) | Reduced | Probably no impact (2) | Increased (2) | | | • No research evidence found. |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Acceptability** | Uncertain (2) | No | Yes (6) | Varies | | • *Panelist who favors vitamin C: Encourage natural sources.* |
| **Feasibility** | Uncertain | No | Yes (8) | Varies | | • No research evidence found. |

## Appendix 2. Search Yield and Results

| Database | Date of Last Search | Search Strategy | Yield | Hit |
|---|---|---|---|---|
| MEDLINE via PubMed | 11/30/21 | ((("COVID-19" [Supplementary Concept] OR "COVID-19 diagnostic testing" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [Supplementary Concept] OR "COVID-19 vaccine" [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 (((((((((vitamin C[MeSH Terms]) OR (ascorbic acid[MeSH Terms])) OR (sodium ascorbate[MeSH Terms])) OR (Vitamin C [tiab])) OR (sodium ascorbate [tiab])) OR (ascorbic acid [tiab])) OR (antioxidant[MeSH Terms])) OR (antioxidant [tiab])) OR (supplement [tiab])) OR (supplement[MeSH Terms]) 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] | 989 | 6 |
| Cochrane Library | 11/30/21 | COVID-19 OR MeSH descriptor: [COVID-19] explode all trees OR coronavirus OR MeSH descriptor: [Coronavirus] explode all trees OR SARS-CoV-2 OR MeSH descriptor: [SARS-CoV-2] explode all trees AND "vitamin C"):ti,ab,kw OR MeSH descriptor: [Ascorbic Acid] explode all trees | 74 | 4 |
| covid-nma | 11/30/21 | Vitamin C | 6 | 4 |
| Epistemonikos | 11/30/21 | COVID-19 and Vitamin C | 261 | 12 |
| medRxiv | 11/30/21 | COVID-19 and (vitamin C or ascorbic acid) | 360 | 0 |
| Google Scholar | 11/1/21 | COVID-19 and Vitamin C and trial | 9,130 | 10 |

## Appendix 3. PRISMA Flow Diagram



# Appendix 4. Characteristics of Included Studies

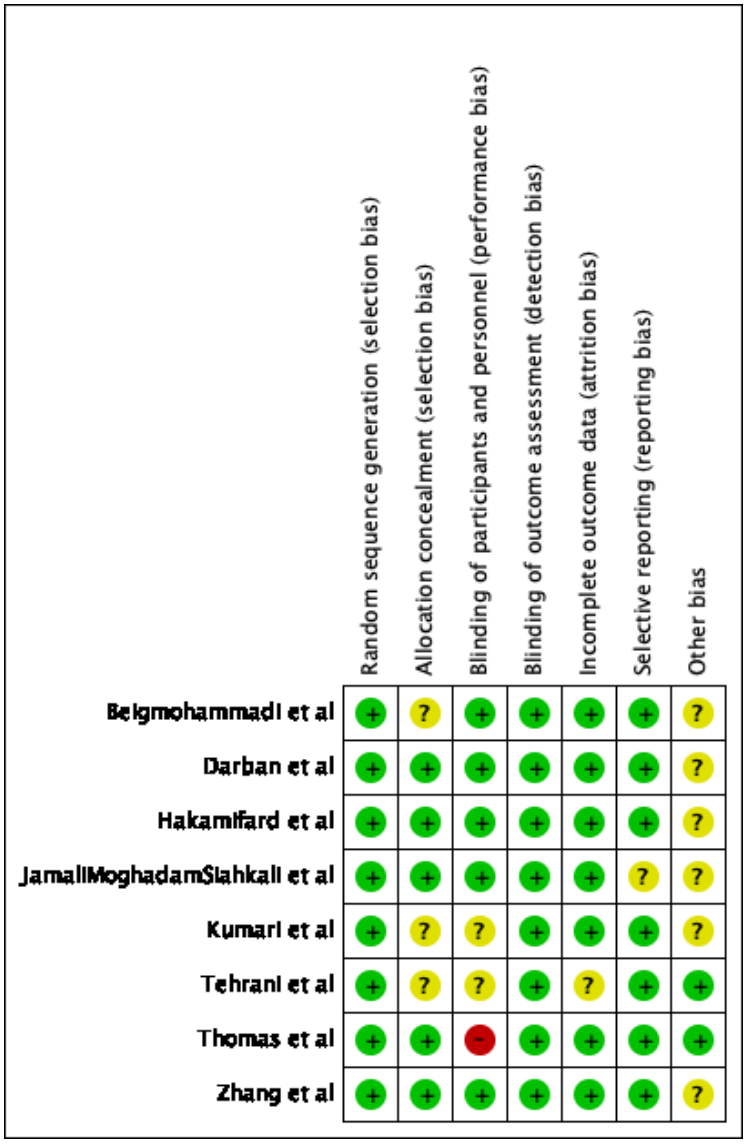
**Table 2**. Randomized clinical trials on Vitamin C versus standard treatment or placebo among hospitalized patients with moderate to severe COVID-19

| Author, Year | Patients (n) | Intervention | Comparator | Outcomes | Study Design |
|---|---|---|---|---|---|
| Jamalimoghadamsiahkali 2021 | COVID-19 confirmed patients by RT-PCR or by clinical symptoms, chest CT/HRCT, low oxygen saturation (n=60) | Vitamin C 1.5g Q6 x 5 days (6g/day) with lopinavir/ritonavir and HCQ | Lopinavir/ritonavir and HCQ with no Vitamin C | No significant difference in terms of mortality (p>0.05), patients on vitamin C had longer length of hospital stay (median 8.5 vs 6.5 days, p=0.028). Patients on vitamin C had higher SpO2 on 3rd day of admission (90.5% vs 88%; p=0.014) | Randomized controlled trial, open label |
| Kumari et al | Severe COVID-19 patients (n=150) | 50mg/kg/day intravenous vitamin C with standard therapy (antipyretics, dexamethasone, and prophylactic antibiotics) | Standard therapy, no vitamin C | There were no statistically significant differences between the two groups in terms of mortality and need for mechanical ventilation. Patients on HDIVC group had earlier symptom free status (7.1 ± 1.8 vs 9.6 ± 2.1 days, p<0.001) and spent fewer days in the hospital (8.1±1.8 vs 10.7±2.2 days, p<0.0001) compared to patients without vitamin C | Randomized controlled open label |
| Tehrani, et al., 2021 Single center clinical trial | Patients diagnosed with COVID-19 with moderate to severe symptoms (n=54) | Vitamin C 2g every 6 hours for 5 days in addition to standard treatment | Standard treatment (Hydroxicholoroquine (400 mg stat) and Kaletra (400/100 mg q 12 h) and Interferon beta-1a (44 micrograms three times)] | Oxygen saturation, respiratory rates, serum C-Reactive Protein (CRP) levels, lymphopenia and lung parenchymal involvement on CT, length of hospital stay, mortality<br><br>Due to the effectiveness of high doses of intravenous vitamin C on reducing lung involvement and improving clinical symptoms, further studies with a larger sample size are recommended to demonstrate the effects of this drug supplement. | Single center clinical trial |
| Zhang et al 2021 | Severe COVID-19 confirmed patients (n=56) | Vitamin C 24g/day IV x 7 days (HDIVC)<br>In addition, other general treatments followed the latest COVID-19 guidelines depending on the patient's situation: oseltamivir, azithromycin in the general ward; low-molecular weight heparin for those in ICU; piperacillin/tazobactam for patients on tracheal intubation | No vitamin C | No statistically significant difference between the two groups in terms of invasive mechanical ventilation-free days, 28-day mortality, 28-day mortality for severe (SOFA ≥3 ). Patients on HDIVC had higher P/F ratio compared to the placebo group. The SOFA score increased in the placebo group and decreased in the HDIVC group. The delta P/F from day 1 to 7 was (20±96.7 in HDIVC and -51.9±150.7 in the control group<br>No study related adverse events in the trial. | Randomized, placebo controlled |

**Table 3.** Clinical trials investigating effects of Vitamin C in combination with other dietary supplements among COVID-19 patients

| Author, Year | Patients (n) | Intervention | Comparator | Outcomes | Study Design |
|---|---|---|---|---|---|
| Darban, et al, 2021 | Patients with severe COVID admitted to the ICU (n=20) | IV Vitamin C (2g q6hr), oral melatonin (6mg q6hr), oral zinc sulfate (220mg containing 50mg elemental zinc q6hr) for 10 days + standard of care | Standard of care | High-dose vitamin C, melatonin and zinc added to standard of care is not associated with improvement in hypoxemia (PaO2/FiO2 ratio), and inflammatory markers including LDH, ESR, ferritin, CRP | Randomized single-center, active-controleed, opne-label, parallel group, compassionate-use study |
| Hakamifard, et al, 2021 | Hospitalized non-severe COVID-19 patients (n=72) | Oral Vitamin C 1g daily and oral vitamin E 400IU daily + standard treatment | Standard treatment | Co-administration of Vitamin C and E did not have a improvement in clinical response of patients at the end of treatment (either cure, improvement, or failure), the duration of hospitalization, and the mortality rate | Randomized controlled clinical trial |
| Beigmohammadi et al, 2021 | ICU-admitted patients with COVID-19 (n=60) | 25,000 IU daily of vitamins A, 600,000 IU once during the study of D, 300 IU twice daily of E, 500 mg four times daily of C, and one amp daily of B complex for 7 days. | No vitamins (placebo) | Significant changes were detected in serum levels of vitamins ($p < 0.001$ for all vitamins), ESR ($p < 0.001$), CRP ($p = 0.001$), IL6 ($p = 0.003$), TNF-a ($p = 0.001$), and SOFA score ($p < 0.001$) after intervention compared with the control group. The effect of vitamins on the mortality rate was not statistically significant (p=0.112). The prolonged hospitalization rate to more than 7 days was significantly lower in the intervention group than the control group (p=0.001). Supplementation with vitamins A, B, C, D, and E could improve the inflammatory response and decrease the severity of disease in ICU-admitted patients with COVID-19. | Randomized, single-blinded clinical trial |
| Thomas et al, 2021 | COVID-19 confirmed patients treated as outpatient (n=214) | Vitamin C 8,000mg/day<br><br>Zinc gluconate 50mg<br><br>Both zinc and vitamin c | Standard of care | The study was discontinued for futility.<br>there was no significant difference among the 4 study groups in terms of days required to reach a 50% reduction in symptoms. Moreover, there was no significant difference in any of the secondary outcomes. | RCT, open label trial (with four treatment arms) |

## Appendix 4. Detailed Study Appraisal



# Appendix 5. GRADE Evidence Profile

**Author(s):** Ina Chiu, MD and Mark Milan MD, Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS Myzelle Anne J. Infantado, PTRP, MSc (cand.)
**Question:** Vitamin C with standard treatment compared to standard treatment alone for adjunctive treatment of COVID-19
**Setting:** Inpatient

| CERTAINTY ASSESSMENT | | | | | | | NO. OF PATIENTS | | EFFECT | | CERTAINTY | IMPORTANCE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Vitamin C with standard treatment | Standard treatment alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality** | | | | | | | | | | | | |
| 4 | Randomised trials | Not serious | Not serious | Not serious | Serious[a] | None | 16/150 (10.7%) | 29/160 (18.1%) | **RR 0.59** (0.34 to 1.03) | **65 fewer per 1,000** (from 111 fewer to 4 more) | ⊕⊕⊕◯ Moderate | CRITICAL |
| **Length of Hospital Stay** | | | | | | | | | | | | |
| 4 | Randomised trials | Not serious | Serious[b] | Not serious | Serious[a] | None | 150 | 160 | - | MD **0.96 lower** (3.84 lower to 1.92 higher) | ⊕⊕◯◯ Low | CRITICAL |
| **Length of ICU stay** | | | | | | | | | | | | |
| 2 | Randomised trials | not serious | Not serious | Not serious | Serious[a] | None | 57 | 59 | - | MD **1.35 higher** (0.12 lower to 2.83 higher) | ⊕⊕⊕◯ Moderate | CRITICAL |
| Need for mechanical ventilation | | | | | | | | | | | | |
| 3 | Randomised trials | Not serious | Not serious | Not serious | Serious[a] | None | 28/132 (21.2%) | 31/134 (23.1%) | **RR 0.93** (0.60 to 1.44) | **12 fewer per 1,000** (from 79 fewer to 72 more) | ⊕⊕⊕◯ Moderate | CRITICAL |
| **Adverse events from vitamin C (oral vitamin C: flushing, headache, nausea, vomiting, stomach pain, and diarrhea)** | | | | | | | | | | | | |
| 2 | Randomised trials | not serious | Serious | Not serious | Serious | None | 17/78 (21.8%) | 0/50 (0%) | **RR 36.43** (2.25 to 589.34) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | ⊕⊕◯◯ Low | CRITICAL |

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

**Explanations**

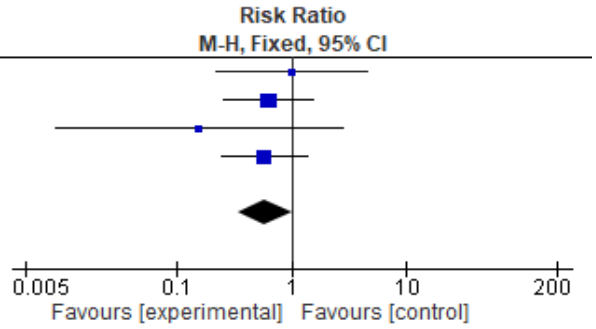
[a] Confidence interval crosses the null value
[b] I2 = 71%
[c] Low number of included studies
[d] Variability in patient population: outpatient and severe
[e] Wide confidence interval

# Appendix 6. Forest Plots

## A. Mortality Outcome

| Study or Subgroup | Vitamin C Events | Vitamin C Total | Control Events | Control Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| JamaliMoghadamSiahkali et al | 3 | 30 | 3 | 30 | 10.6% | 1.00 [0.22, 4.56] |
| Kumari et al | 7 | 75 | 11 | 75 | 38.8% | 0.64 [0.26, 1.55] |
| Tehrani et al | 0 | 18 | 4 | 26 | 13.1% | 0.16 [0.01, 2.76] |
| Zhang et al | 6 | 27 | 11 | 29 | 37.4% | 0.59 [0.25, 1.36] |
| **Total (95% CI)** | | **150** | | **160** | **100.0%** | **0.59 [0.34, 1.03]** |
| Total events | 16 | | 29 | | | |

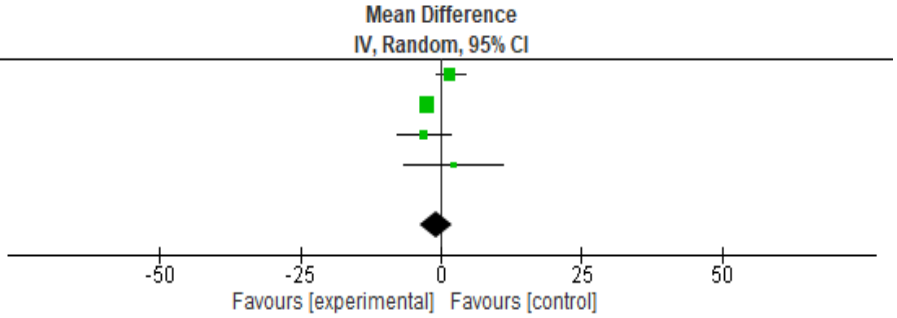
Heterogeneity: Chi² = 1.30, df = 3 (P = 0.73); I² = 0%
Test for overall effect: Z = 1.84 (P = 0.07)




## B. Length of Hospital Stay

| Study or Subgroup | Vitamin C Mean | Vitamin C SD | Vitamin C Total | Control Mean | Control SD | Control Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| JamaliMoghadamSiahkali et al | 9.2 | 3.89 | 30 | 7.57 | 6.23 | 30 | 31.1% | 1.63 [-1.00, 4.26] |
| Kumari et al | 8.1 | 1.8 | 75 | 10.7 | 2.2 | 75 | 41.1% | -2.60 [-3.24, -1.96] |
| Tehrani et al | 14 | 8 | 18 | 17 | 8 | 26 | 19.4% | -3.00 [-7.81, 1.81] |
| Zhang et al | 35 | 17 | 27 | 32.8 | 17 | 29 | 8.4% | 2.20 [-6.71, 11.11] |
| **Total (95% CI)** | | | **150** | | | **160** | **100.0%** | **-0.96 [-3.84, 1.92]** |

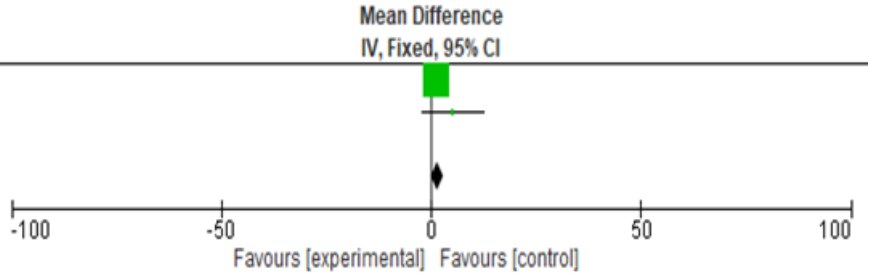
Heterogeneity: Tau² = 5.15; Chi² = 10.46, df = 3 (P = 0.02); I² = 71%
Test for overall effect: Z = 0.65 (P = 0.51)



## C. Length of ICU Stay

| Study or Subgroup | Vitamin C Mean | Vitamin C SD | Vitamin C Total | Control Mean | Control SD | Control Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| JamaliMoghadamSiahkali et al | 6.9 | 3.89 | 30 | 5.7 | 1.57 | 30 | 96.0% | 1.20 [-0.30, 2.70] |
| Zhang et al | 22.9 | 14.8 | 27 | 17.8 | 13.3 | 29 | 4.0% | 5.10 [-2.29, 12.49] |
| Total (95% CI) | | | 57 | | | 59 | 100.0% | 1.35 [-0.12, 2.83] |

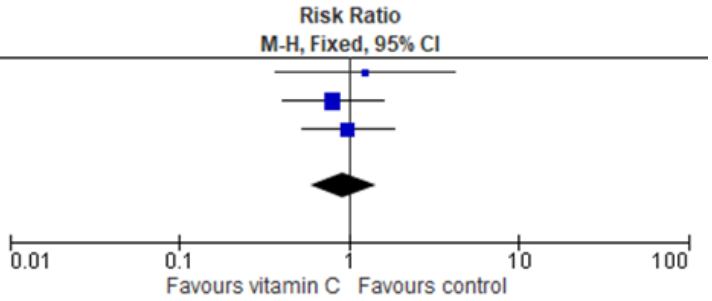
Heterogeneity: Chi² = 1.03, df = 1 (P = 0.31); I² = 3%
Test for overall effect: Z = 1.80 (P = 0.07)




## D. Need for mechanical ventilation

| Study or Subgroup | Vitamin C Events | Vitamin C Total | Control Events | Control Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| JamaliMoghadamSiahkali et al | 5 | 30 | 4 | 30 | 13.1% | 1.25 [0.37, 4.21] |
| Kumari et al | 12 | 75 | 15 | 75 | 49.1% | 0.80 [0.40, 1.59] |
| Zhang et al | 11 | 27 | 12 | 29 | 37.9% | 0.98 [0.53, 1.85] |
| Total (95% CI) | | 132 | | 134 | 100.0% | 0.93 [0.60, 1.44] |
| Total events | 28 | | 31 | | | |

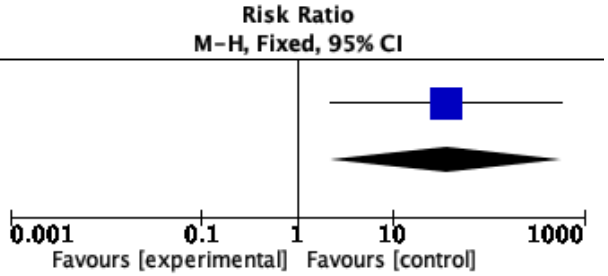
Heterogeneity: Chi² = 0.44, df = 2 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)




## E. Adverse events

| Study or Subgroup | Vitamin C Events | Vitamin C Total | Control Events | Control Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| JamaliMoghadamSiahkali et al | 0 | 30 | 0 | 30 | | Not estimable |
| Thomas et al | 17 | 48 | 0 | 50 | 100.0% | 36.43 [2.25, 589.34] |
| Total (95% CI) | | 48 | | 50 | 100.0% | 36.43 [2.25, 589.34] |
| Total events | 17 | | 0 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.53 (P = 0.01)



## Appendix 7. Table of Ongoing Studies

| Clinical Trial Identifier/Title | Study Design | Country | Population | Intervention | Outcome | Estimated Date of Completion |
|---|---|---|---|---|---|---|
| (1) NCT04664010<br>Efficacy and Safety of High-dose Vitamin C Combined With Traditional Chinese Medicine in the Treatment of Moderate and Severe Coronavirus Pneumonia (COVID-19) | Randomized Controlled Trial, parallel assignment | China | COVID-19 | High dose Vitamin C in combination with traditional Chinese Medicine | Primary Outcome: Recovery time<br><br>Secondary outcome: Relief of Symptoms; Conversion time from positive to negative COVID-19 | January 31, 2021<br><br>(No results posted yet) |
| (2) NCT04363216<br>Pharmacologic Ascorbic Acid as an Activator of Lymphocyte Signaling for COVID-19 Treatment | Randomized sequential Assignment | USA | COVID-19 | Ascorbic Acid vs routine care | Primary Outcome: Clinical Improvement<br><br>Secondary Outcome: Patient status upgraded to ICU level, Oxygen supplementation, days with fever, days to discharge, SAEs | May 2021<br><br>(Not yet recruiting) |
| (3) NCT04710329<br>High-Dose Vitamin C Treatment in Critically Ill COVID-19 Patients, A Retrospective Cohort Study | Retrospectiv e Cohort Study | Turkey | ARDS Covid-19 | Ascorbic Acid | Primary Outcome: Short term mortality, Length of ICU stay | Feb 10, 2021<br>(No results posted yet) |
| (4) NCT04584437<br>The Treatment and Prevention of Covid-19 Pandemic Using Infrared and /or Vitamin C. | Single group assignment | Canada | All patients seeking prevention and treatment of COVID-19 | Infrared Energy | Treatment and prevention of COVID-19 | May 10, 2021<br><br>(Withdrawn; no financial support) |
| (5) NCT04530539<br>The Effect of Melatonin and Vitamin C on COVID-19 | Randomized parallel assignment | USA | COVID-19 patients | Ascorbic Acid<br>Melatonin<br>Vs Placebo | Primary Outcome: Symptom severity<br><br>Secondary Outcome: Symptom progression | Dec. 1, 2021<br>(Still recruiting) |
| (6)<br>NCT04323514<br>Use of Ascorbic Acid in Patients With COVID 19 | Single group assignment, open label | Italy | COVID-19 patients | Vitamin C | Primary Outcome: In-hospital Mortality<br><br>Secondary Outcomes: PCR levels, lactate clearance, hospital stay, symptoms, positive swab, tomography imaging | Mar 13, 2021<br><br>(No results posted yet) |
| (7) NCT04558424<br>Randomized, Double -Blind, Placebo Controlled, Trial to Evaluate the Effect of Zinc and Ascorbic Acid Supplementation in COVID-19 Positive Hospitalized Patients in BSMMU | Randomized, Double - Blind, Placebo Controlled, Trial | Bangladesh | COVID-19 | Vitamin C and Zinc | Primary outcome: Symptoms reduction time frame<br><br>Secondary Outcome: Symptom resolution | Sept 1, 2021<br><br>(No results posted yet) |
| (8) NCT04468139<br>The Study of Quadruple Therapy Zinc, Quercetin, Bromelain and Vitamin C on the Clinical Outcomes of Patients Infected With COVID-19 | Single group assignment | Saudi Arabia | COVID-19 | Quercetin<br>Bromelain<br>Zinc<br>Vitamin C | Primary Outcome: Hospital Stay after treatment | July 2020<br><br>(No results posted yet) |
| (9) NCT04395768<br>Therapies to Prevent Progression of COVID-19, Including Hydroxychloroquine, Azithromycin, Zinc, Vitamin D, Vitamin B12 With or | Randomized parallel assignment | Australia | COVID 19 | Vitamin C in combination with, Hydorxychloroquine, Azithromycin, Zinc, Vitamin B12 and Vitamin D3 vs control | Symptoms, length of hospital stay, invasive mechanical ventilation | Sept 30, 2021<br><br>(No results posted yet) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Without Vitamin C, a Multi-centre, International, Randomized Trial: The International ALLIANCE Study | | | | | | |
| (10) NCT04357782<br>Administration of Intravenous with hypoxemia Vitamin C in Novel Coronavirus Infection and Decreased Oxygenation (AVoCaDO): A Phase I/II Safety, Tolerability, and Efficacy Clinical Trial | Non-Randomized, single group assignment, open label | USA | COVID-19 with hypoxemia | L-Ascorbic acid | Primary Outcome: Incidence of Adverse events, serious adverse reactions<br><br>Secondary Outcome: Ventilator-free days, ICU-free days, hospital-free days, all-cause mortality, change in S/F ratio, CRP, LDH, D-dimer, lymphocyte count, NLR, serum ferritin | Oct 13, 2020<br><br>(No results posted yet) |
| (11) NCT04682574<br>Efficacy of Mega Dose Vitamin C in Critically Ill COVID-19 Patients | Randomized parallel assignment | Pakistan | Critically Ill COVID-19 patients | Vitamin C vs placebo | Primary Outcome: Partial pressure of Oxygen in arterial blood to fraction of inspired Oxygen (P/F ratio) [ Time Frame: 2 to 7 day<br><br>Secondary Outcome: Duration of hospital stay | Jan 10, 2021<br><br>(No results posted yet) |
| (12) NCT04401150<br>Lessening Organ Dysfunction With VITamin C - COVID-19 | multicentre concealed-allocation parallel-group blinded randomized controlled trial | Canada | Confirmed COVID-19 | Vitamin C vs placebo | Primary Outcome: Death or persistent organ dysfunction | November 2021<br><br>(On-going) |
| (13) NCT04357782<br>Administration of Intravenous Vitamin C in Novel Coronavirus Infection and Decreased Oxygenation (AVoCaDO): A Phase I/II Safety, Tolerability, and Efficacy Clinical Trial | Non Randomized Single Group Assignment | USA | COVID-19 patients with decreased oxygenation | Intravenous Vitamin C for mild hypoxemia, vs Intravenous Vitamin C for severe hypoxemia | Primary Outcome: Incidence of adverse events, serious adverse events, adverse reactions<br><br>Secondary outcome:<br>Ventilator free days, ICU free days, hospital free days, all cause mortality, change in SF ratio, CRP, LDH, D-dimer, lymphocyte count, NLR, serum ferritin | Oct 13, 2020<br><br>(No results posted yet) |

## Q4. Among patients with COVID-19, should Vitamin D be used as adjunctive treatment?

*As of 03 December 2021*

### RECOMMENDATION

**There is insufficient evidence to recommend the use of Vitamin D supplementation as an adjunct treatment for patients with COVID-19 infection.** *(Very low certainty of evidence)*

***Consensus Issues***

The panel members perceived that the quality of evidence, showing negligible benefit, is still very low. A panel member voted against using Vitamin D as an adjunct due to (1) the possibility of it being prescribed despite the inconclusive evidence of benefit, (2) additional expenses that would be incurred if prescribed, and (3) probable drug interactions with other medications.

### PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of Vitamin D supplementation as adjunct treatment for patients with COVID-19 infection. *(Very low quality of evidence)*

*Consensus Issues*

There were no issues raised during the panel meeting

## WHAT'S NEW IN THIS VERSION?

This version includes eight randomized controlled trials, because of the addition of five new RCTs published in peer-reviewed journals that were not yet available at the time of initial review.

## KEY FINDINGS

We found eight randomized controlled trials of COVID-19 patients who were given vitamin D as adjunctive treatment. We found no significant benefit for the following outcomes: mortality, ICU admission, need for mechanical ventilation, hospital length of stay, clinical improvement, and virologic clearance. Subgroup analysis revealed that vitamin D status did not significantly change our estimates. These results must be interpreted in the context of very low certainty of evidence due to serious risk of bias, serious inconsistency, and serious imprecision among the included studies.

## INTRODUCTION

At the start of the pandemic, nutritional supplements (e.g., vitamins A, C and D) were identified as potential treatments for COVID-19 based on indirect evidence of their effectiveness against respiratory viruses and other coronaviruses. Small cohort studies initially found a lower risk of progression of oxygen support requirement and lower risk of mortality among patients with COVID-19 who received oral vitamin D supplementation.[1,2] One early systematic review identified vitamin D deficiency as a significant risk factor for increase in COVID-19 severity.[3] However, a recent systematic

review and meta-analysis with a search date until February 2021 showed that low levels of vitamin D was not significantly associated with increased risk for mortality.[4]

The SARS-CoV-2 virus upregulates renin and angiotensin- converting enzyme (ACE2) expression. This leads to a buildup of angiotensin II causing inflammation, enhanced lung permeability, and acute respiratory distress syndrome via the angiotensin 1 receptor pathway. Recent studies suggest that vitamin D lowers the risk of COVID-19 complications by attenuating cytokine release through lowering renin and angiotensin-converting enzyme expression. Vitamin D may also lower inflammation, fibrosis, and apoptosis.[5–7]

Currently, the evidence for benefit is based on observational studies. This review updates and summarizes the available evidence from randomized controlled trials to answer whether the use of vitamin D as adjunctive treatment has benefits in patients with COVID-19.

## REVIEW METHODS

An updated systematic search was done from July 2021 until November 14, 2021. We included electronic databases (MEDLINE, Cochrane COVID-19 Study Register), trial registries (Chinese Clinical Trial Registry, Clinicaltrials.gov, EU Clinical Trials Register), and the COVID-NMA initiative. We also checked the included studies from other living guidelines or systematic reviews on COVID-19. Only randomized controlled trials that compared vitamin D against placebo or standard of care (SOC) were included in this review. Outcomes of interest included mortality, clinical deterioration or improvement, development of acute respiratory syndrome, need for mechanical ventilation, need for hospitalization, duration of hospitalization, time to clinical recovery, improvement of radiographic findings, virologic clearance, and adverse events. No limits were placed on age of patients, COVID-19 severity, hospitalization status, and dosing strategy of vitamin D. We performed sensitivity analysis to assess the robustness of the results when studies with serious risk of bias concerns were excluded. We also planned to do a subgroup analysis among patients with sufficient and low serum vitamin D levels, according to the sufficiency category given or defined by each study (see Appendix 3).

## RESULTS

The search yielded 302 records, of which eight were RCTs (N=740) and included in this review.[8–15] All eight RCTs used vitamin D as adjunct treatment among hospitalized patients with COVID-19 in Brazil, Egypt, India, Iran, Mexico, Spain, and USA. Sample size in the individual studies ranged from 40 to 240. At least four studies included COVID-19 severe cases.[8,9,12,13] Four studies [10,11,13,14] only included participants who had low serum level of vitamin D (below 20–30 ng/mL).

Seven studies administered oral vitamin D, while one study administered vitamin D through the intramuscular route.[14] Multiple oral forms and dosages of vitamin D were also used: two studies used calcifediol [9,13], one used calcitriol [12], three used cholecalciferol [10,11,15], and one was unspecified [8] (see Appendix 3).

Risk of bias was rated very serious in one out of eight studies and serious in three studies. All studies had adequate randomization. At least six of the eight studies had high risk for detection bias from unblinded assessors, and performance bias from unblinded investigators. Three studies had high risk for attrition bias due to incomplete data (see Appendix 4).

The overall certainty of evidence was rated very low for the outcomes of mortality, ICU admission, and clinical improvement due to serious risk of bias, serious inconsistency as reflected in the different dosages and forms of vitamin D, and serious imprecision from wide confidence intervals. For the outcomes of need for mechanical ventilation and hospital length of stay, the certainty of evidence was rated as low because there was serious imprecision from the small number of event rates and the wide confidence interval (see Appendix 5).

**Mortality and ICU admission**

For overall mortality (pooled RR 0.73, 95% CI 0.38-1.40; $I^2$=11%, 6 RCTs) [8,9,11–14] and ICU admission (pooled RR 0.54, 95% CI 0.28-1.05; $I^2$=55%, 5 RCTs) [8,9,11–13], the pooled estimates for vitamin D were inconclusive. The pooled estimates in subgroup analysis according to serum vitamin D levels likewise yielded inconclusive results for the outcomes of overall mortality (pooled RR 0.65, 95% CI 0.30-1.45; $I^2$=0%, 3 RCTs) [11,13,14] and ICU admission (pooled RR 0.66, 95% CI 0.31-1.41; $I^2$=0%, 2 RCTs) [11,13] (see Appendix 6).

**Need for Mechanical Ventilation and Length of Hospital Stay**

For the outcome of need for mechanical ventilation, the pooled estimate for Vitamin D as adjunctive treatment showed that it may provide benefit or only be equivalent to standard of care (pooled RR 0.61, 95% CI 0.38-1.00; $I^2$=0%, 4 RCTs).[8,12–14] The effect of adjunctive treatment with vitamin D on the length of hospital stay was also inconclusive when compared to placebo or standard of care (MD -0.48, 95% CI -1.91-0.94; $I^2$=35%, 3 RCTs).[8,11,12] While it was noted that Maghbooli et al. reported no significant difference in hospital length of stay between participants who received vitamin D (median 5 days) compared to placebo (median 6 days), the results were not pooled due to inadequate data. Subgroup analysis according to serum vitamin D levels revealed inconclusive results for both mechanical ventilation (pooled RR 0.72, 95% CI 0.38-1.36; $I^2$=0%, 2 RCTs)[13,14] and hospital length of stay (MD -0.17, 95% CI -1.97-1.63, 1 RCT).[11]

**Clinical Improvement and Virologic Clearance**

The estimates for the effect of Vitamin D on clinical improvement (RR 0.58, 95% CI 0.28-1.18, 1 RCT)[15] and virologic clearance (RR 0.58, 95% CI 0.19-1.79; $I^2$=16, 2 RCTs)[10,15] were inconclusive.

**Safety outcomes / Adverse events**

Among the eight RCTs that used vitamin D as adjunctive treatment, only one patient who received vitamin D was documented to have vomiting. No episodes of hypercalcemia or hyperphosphatemia were observed. Based on these studies, we report no adverse events directly attributable to vitamin D supplementation among COVID-19 patients.

**Pediatric Population**

We found no RCTs that used vitamin D as adjunctive treatment for COVID-19 in the pediatric population. We found only one systematic review that investigated the association between vitamin D levels and COVID-19 severity in children with search date until June 2021.[16] We found no additional observational studies from our literature search until November 4, 2021. Based on the systematic review, they found two small (n=40-103) retrospective cohort studies conducted in Turkey among children <18 years of age.[17,18] We analyzed both cohort studies and found that low serum vitamin D level (<30 ng/mL) was not significantly associated with a higher risk for COVID-19 severity (OR 2.66, 95% CI 0.94-7.55; $I^2$=0%, 2 studies). No mortalities were reported for both studies. We found insufficient evidence to determine whether vitamin D is associated with benefits or harms for COVID-19 in children; large well conducted randomized controlled trials are needed (see Appendix 7).

## EVIDENCE TO DECISION

Vitamin D is available locally in two forms (Calcitriol and Cholecalciferol). Based on the 2021 Drug reference price index, only the fixed dose combination of Calcium Carbonate 500/600mg + Cholecalciferol (vitamin D3) 400 IU at 4.00Php per tablet is registered in the Philippine National Formulary. Calcitriol and cholecalciferol are not included in the formulary list.

| Vitamin D forms | |
|---|---|
| Calcitriol 0.25mcg/cap | ₱32.00 |
| Cholecalciferol 800 IU/cap | ₱8.00 |

## 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.

| Group/Society/Network | Recommendations |
|---|---|
| US NIH (4 November 2021) [19] | Does not recommend for or against the use of vitamin D for the prevention or treatment of COVID-19 |
| Australian COVID-19 Living CPG (3 November 2021) [20] | Does not recommend the use of vitamin D outside of trials |
| NICE Guidelines (3 November 2021) | Does not recommend the use of vitamin D in the prevention or treatment of COVID-19 |
| Cochrane Systematic Review (March 2021) [21] | There is insufficient evidence to determine the benefits or harms of vitamin D supplementation as treatment for COVID-19. |

## RESEARCH GAPS

As of September 2021, there are 24 ongoing clinical trials investigating the efficacy of vitamin D as adjunctive treatment for COVID-19 that are listed in COVID-19 NMA database [22] (see Appendix 8).

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# Appendix 1. Evidence to Decision

Table 1. Summary of initial judgments prior to the actual panel meeting (n = 5)

| FACTORS | JUDGMENT | | | | | | RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS |
|---|---|---|---|---|---|---|---|
| **Problem** | No | Yes (5) | | | | | • COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity. |
| **Benefits** | Large | Moderate | Small (2) | Uncertain (3) | | | • Benefit: Inconclusive results for the following outcomes: mortality, ICU admission, need for mechanical ventilation, hospital length of stay, clinical improvement, and virologic clearance; even Vitamin D status did not significantly change our estimates. |
| **Harm** | Large | Small (4) | Uncertain (1) | Varies | | | • One patient who received vitamin D had vomiting.<br>• No episodes of hypercalcemia or hyperphosphatemia were reported.<br>• We generally found no adverse events directly attributable to vitamin D supplementation among COVID-19 patient |
| **Certainty of Evidence** | High | Moderate | Low (2) | Very low (3) | | | • These results must be interpreted in the context of very low certainty of evidence due to serious risk of bias, serious inconsistency, and serious imprecision among the included studies. |
| **Balance of effects** | Favors Vitamin D (3) | Does not favor Vitamin D (1) | Uncertain (1) | Varies | | | |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability (1) | Possibly NO important uncertainty or variability (3) | No important uncertainty or variability (1) | | | |
| **Resources Required** | Uncertain | Large cost | Moderate Costs (2) | Negligible costs or savings | Moderate savings (3) | Large savings | • Vitamin D is available locally in two forms (Calcitriol and Cholecalciferol). Only the fix dose combination of calcium carbonate 500/600mg + cholecalciferol (vitamin D3) 400 IU at 4.00 php per tablet is registered in the Philippine National Formulary.<br>• Calcitriol and cholecalciferol are not included in the formulary list. Calcitriol 0.25mcg/cap = ₱32.00. Cholecalciferol 800 IU/cap = ₱8.00 |
| **Certainty of evidence of required resources** | No included studies (5) | Very low | Low | Moderate | High | | • No research evidence found on cost-effectiveness of vitamin D as an adjunctive treatment for COVID-19. |
| **Cost effectiveness** | No included studies (5) | Favors the comparison | Does not favor either the intervention or the comparison | Favors the intervention | | | • No research evidence found on cost-effectiveness of vitamin D as an adjunctive treatment for COVID-19. |
| **Equity** | Uncertain (4) | Reduced | Probably no impact (1) | Increased | | | • No research evidence found. |
| **Acceptability** | Uncertain (4) | No | Yes (1) | Varies | | | • No research evidence found. |
| **Feasibility** | Uncertain (2) | No | Yes (3) | Varies | | | • Vitamin D is available locally in two forms (calcitriol and cholecalciferol). |

# Appendix 2. Search Strategy (as of 4 November 2021)

| Information Source | Search Strategy | Yield | Eligible |
|---|---|---|---|
| MEDLINE (PubMed) | ((Vitamin D OR "Vitamin D"[Mesh] OR (Ergocalciferol OR Cholecalciferol)) AND ((((("COVID-19" [Supplementary Concept] OR "COVID-19 diagnostic testing" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [Supplementary Concept] OR "COVID-19 vaccine" [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])))) | Nov 4: 239 | 3 |
| Cochrane COVID-19 Study Register | “Vitamin D”; Limits: randomized controlled trials & reporting results | Nov 4: 20 | 0 |
| COVID-NMA initiative<br>https://covid-nma.com/ | | Nov 4: 5 | 0 |
| ClinicalTrials.gov<br>https://clinicaltrials.gov/ | Condition or disease: COVID<br>Other terms: Vitamin D OR Ergocalciferol OR Cholecalciferol<br>Filter: Completed | Nov 4: 36 | 1 |
| Chinese Clinical Trial Registryhttp://www.chictr.org.cn/searchprojen.aspx | Intervention: Vitamin D, Cholecalciferol<br>Target Disease: COVID | Nov 4: 0 | 0 |
| EU Clinical Trials Register<br>https://www.clinicaltrialsregister.eu/ | “Covid-19 AND Vitamin D”<br>Filter: Trial with results | Nov 4: 2 | 0 |

# Appendix 3. Characteristics of Included Studies

Table 2. Adjunctive treatment with Vitamin D versus placebo or standard care (8 RCTs)

| | Clinical Trial ID/ Title | Population | Sample Size | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|---|
| 1 | Murai 2020<br><br>Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19<br><br>Brazil | Hospitalized patients with mild to severe COVID-19<br><br>Adults aged 18>yrs<br><br>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<br>• Mortality<br>• ICU admission<br>• Need for mechanical ventilator<br>• Duration of mechanical ventilator<br>• Serum vitamin D levels |
| 2 | Entrenas Castillo 2020<br><br>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<br><br>Spain | Hospitalized patients with moderate to severe COVID-19 infection<br><br>Clinical picture of acute respiratory infection<br>confirmed by a radiographic pattern of viral pneumonia<br><br>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).<br><br>1 capsule on days 3, 7, 14, 21, 28 until discharge or ICU admission.<br><br>Plus standard of care<br>(N=50) | Standard of care (N=26)<br><br>Defined as:<br>1) Hydroxychloroquine 400mg every 12 hours on first day and 200 mg every 12 hours for the following 5 days<br>2) Azithromycin 500 mg orally for 5 days,<br>3) For patients with pneumonia and NEWS score >5, Ceftriaxone 2 g intravenously every 24 hours was given for 5 days. | • ICU admission<br>• Mortality |
| 3 | Rastogi 2020<br><br>Short term, high-dose vitamin D supplementation forCOVID-19 disease: a randomized, placebo-controlled,<br>study (SHADE study)<br><br>India | Hospitalized patients with asymptomatic to mild COVID-19<br><br>With or without co-morbidities (hypertension, diabetes mellitus, chronic obstructive<br>airway disease, chronic liver disease, chronic kidney disease)<br><br>With vitamin D deficiency defined as levels<br>below 20 ng/ml | N=40 | 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<br>(N=16)<br><br>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<br><br>Plus standard of care | Placebo (5 ml distilled water)<br>(N=24)<br><br>Plus standard of care | 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) |

| | | | | | | |
|---|---|---|---|---|---|---|
| 4 | Lakkireddy 2021<br><br>Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease<br><br>India | Hospitalized patients with mild to moderate COVID-19<br><br>with vitamin D defined as levels below 30 ng/mL | N=130 | 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)<br><br>Plus standard of care | Standard of care (N=65) | • Inflammatory markers and vitamin D levels before and after intervention (vitamin D levels, CRP, LDH, IL6, Ferritin, N/L ratio)<br>• Mortality<br>• ICU admission<br>• Mean hospital stay<br>• Adverse events |
| 5 | Elamir 2021<br><br>A randomized pilot study using calcitriol in hospitalized COVID-19 patients<br><br>USA | Hospitalized patients with COVID-19 with moderate to severe COVID-19 | N=50 | Calcitriol 0.5 ug daily for 14 days or discharge whichever came first.<br><br>Plus 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 | Standard of care<br><br>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 | • Oxygen requirements<br>• Length of hospital stay<br>• Need for ICU admission<br>• Mortality<br>• Readmission. |
| 6 | Maghbooli 2021<br><br>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<br><br>Iran | Hospitalized patients with moderate to severe COVID-19 | N=106 | Calcifediol 25 mg per orem once daily for 30 days<br><br>Plus standard of care: a combination of hydroxychloroquine, azithromycin, and ceftriaxone for patients with pneumonia | Placebo<br><br>Plus standard of care: a combination of hydroxychloroquine, azithromycin, and ceftriaxone for patients with pneumonia | • Length of Stay<br>• Need for Mechanical Ventilation<br>• Mortality<br>• ADE<br>• Admission to ICU |
| 7 | Soliman 2021<br><br>Impact of Vitamin D Therapy on the Progress COVID-19: Six Weeks Follow-Up Study of Vitamin D Deficient Elderly Diabetes Patients<br><br>Egypt | 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 | • Mortality<br>• Need for Mechanical Ventilation |
| 8 | Sánchez-Zuno 2021<br><br>Vitamin D Levels in COVID-19 Outpatients from Western Mexico: Clinical Correlation and Effect of Its Supplementation | 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 | • Clinical Improvement (D7)<br>• Virologic Clearance (D14) |

## Appendix 4. Methodological Quality Assessment of Included Studies

| Studies | Risk of bias | Random assignment | Allocation concealment | Similar baseline characteristics | Patients blinded | Caregivers blinded | Assessors blinded[1] | Intention-to-treat analysis | Adequate follow-up rate | Peer-reviewed |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. Murai | Serious | Yes | Yes | Yes | Yes | Yes | Yes | No | No[1] | Yes |
| 2. Entrenas Castillo | Not serious | Yes | Unclear | Yes[2] | No | No | No | Yes | Yes | Yes |
| 3. Rastogi | Not serious | Yes | Unclear | Yes[3] | No | Unclear | Unclear | Yes | Yes | Yes |
| 4.Lakkireddy | Very serious | Yes | Unclear | No[4] | No | No | No | No | No[5] | Yes |
| 5. Elamir | Not serious | Yes | No | Yes | No | No | No | Yes | Yes | Yes |
| 6. Maghbooli | Serious | Yes | Yes | Yes | Yes | Unclear | Unclear | Yes | No[6] | Yes |
| 7. Soliman | Not serious | Yes | Unclear | Yes | Unclear | Unclear | Unclear | Yes | Yes | Yes |
| 8. Sánchez-Zuno | Serious | Yes | Unclear | Yes | Unclear | Unclear | Unclear | Unclear | Yes | Yes |

Legend
Green: not serious; Yellow: serious; Red: very serious

[1] Vitamin D group 119/120 analyzed, Placebo group 118/120 analyzed, 3 drop out
[2] Except for high blood pressure and diabetes mellitus
[3] Except for serum calcium level
[4] Vitamin D group had higher inflammatory markers (CRP, LDH, IL-6, Ferritin, N/L ratio) at the start of the study despite randomization.
[5] High drop-out rate for the vitamin D group 19/65 (29%) and the control group 18/65 (28%) with only 87 participants in the final analysis. Reasons as follows: discharged prior to repeat analysis of inflammatory markers (n= 35) and non-adherence (n=2)
[6] High drop-out rate for the vitamin D group 16/53 (30%) and the control group 21/53 (40%) at 1 month follow up. No reasons were provided.

# Appendix 5. GRADE Evidence Profile

**Author(s)**: Marquis Von Angelo Syquio Go Joson, MD, Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS, Myzelle Anne Infantado, PTRP, MSc (cand.)
**Question**: Should Vitamin D supplements compared to placebo in 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 | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (ITT) (follow-up: range 30 days to 60 days)** | | | | | | | | | | | | |
| 6[a] | Randomised trials | Serious[b] | Serious[c] | Not serious | 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] | Not serious | 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] | Not serious | 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) | ⨁⨁◯◯ Low | CRITICAL |
| **Hospital length of stay** | | | | | | | | | | | | |
| 3 | Randomised trials | Not serious | Serious[c] | Not serious | Serious[d] | None | 210 | 210 | - | MD 0.48 days lower (1.91 lower to 0.94 higher) | ⨁⨁◯◯ Low | CRITICAL |
| **Clinical Improvement (follow-up: mean 7 days)** | | | | | | | | | | | | |
| 1 | Randomised trials | Very serious[h] | Not serious | Not serious | Serious[g] | 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 |
| **Virologic Clearance (follow-up: range 14 days to 21 days)** | | | | | | | | | | | | |
| 2 | Randomised trials | Serious[i] | Not serious | Not serious | Serious[g] | 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) | ⨁⨁◯◯ Low | IMPORTANT |

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

**Explanations**

[a] 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.

[b] 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

[c] Serious inconsistency due to differences in dosage and formulation of vitamin D.

[d] Serious imprecision due to wide confidence interval

[e] 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

[f] Serious risk for inconsistency; high heterogeneity I2=55%

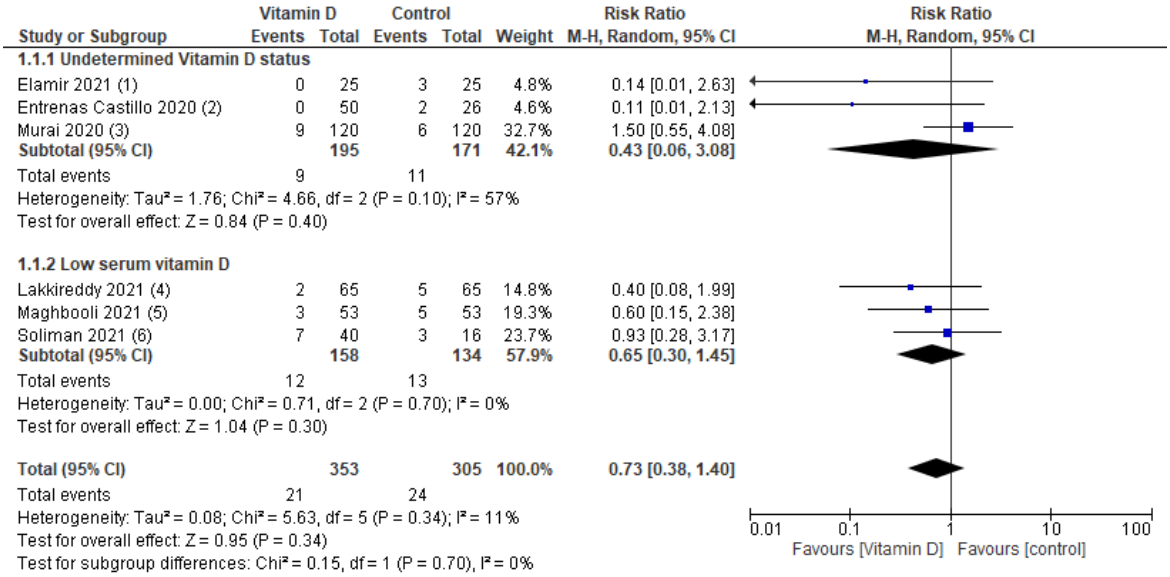
[g] Imprecision downgraded by 1 level: due to low number of event rate and wide confidence interval.

[h] Serious risk of bias due to unblinded patients and outcome assessors which may have affected how symptoms were reported

[i] Risk of bias downgraded by 1 level: some concerns due to unclear randomization and allocation concealment, and lack of blinding in participants and personnel.

# Appendix 6. Forest Plots from Studies that Enrolled Adult Participants (November 4 2021)

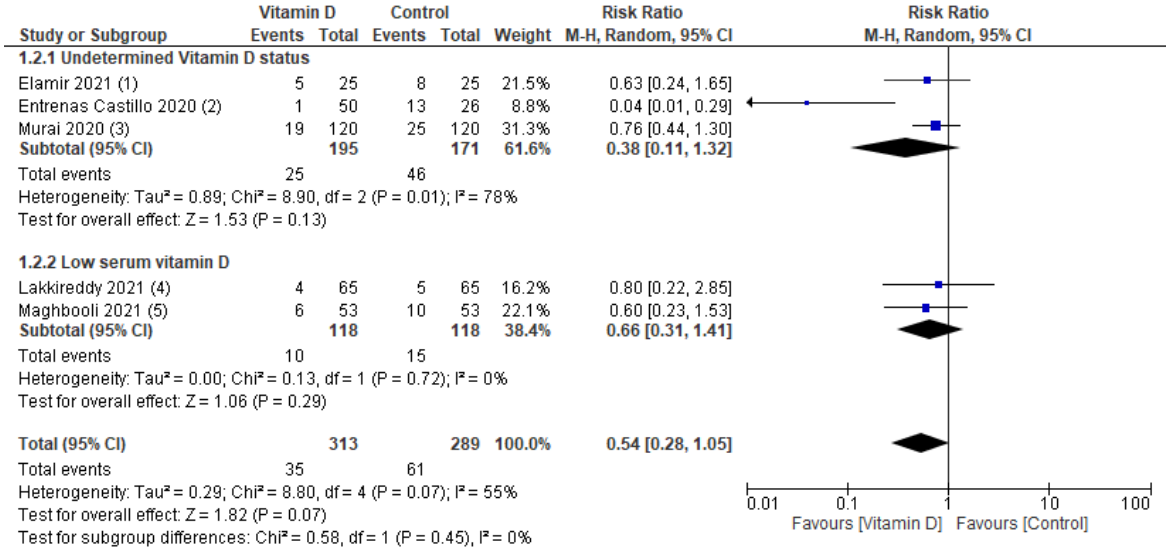
## A. Mortality, overall (ITT)




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

## B. ICU admission (ITT)

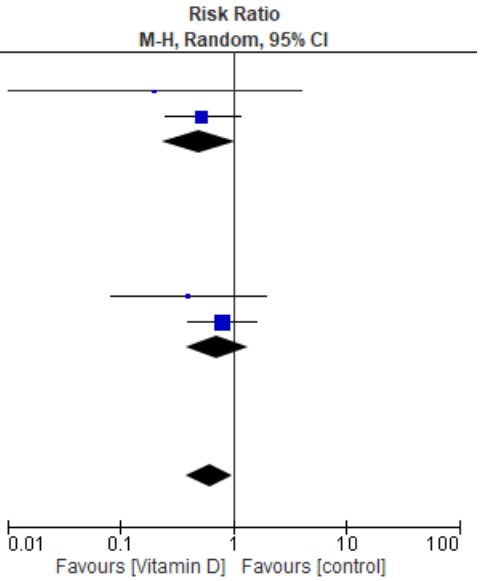



Footnotes

(1) moderate to severe
(2) moderate to severe
(3) mild to severe; data converted from percentage VitD 16% & control 21.2%;vitamin D group (mean 21.2 ng/mL; SD 10.1); control group (mean...
(4) mild to moderate; vitamin D <30 ng/mL
(5) moderate to severe; vitamin D <30 ng/mL

## C. Need for Mechanical Ventilation (ITT)

| Study or Subgroup | Vitamin D Events | Vitamin D Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.3.1 Undetermined Vitamin D status** | | | | | | |
| Elamir 2021 (1) | 0 | 25 | 2 | 25 | 2.6% | 0.20 [0.01, 3.97] |
| Murai 2020 (2) | 9 | 120 | 17 | 120 | 39.9% | 0.53 [0.25, 1.14] |
| **Subtotal (95% CI)** | | **145** | | **145** | **42.5%** | **0.50 [0.24, 1.05]** |
| Total events | 9 | | 19 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.39, df = 1 (P = 0.53); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.84 (P = 0.07) | | | | | | |
| **1.3.2 Low serum vitamin D** | | | | | | |
| Maghbooli 2021 (3) | 2 | 53 | 5 | 53 | 9.2% | 0.40 [0.08, 1.97] |
| Soliman 2021 (4) | 14 | 40 | 7 | 16 | 48.2% | 0.80 [0.40, 1.61] |
| **Subtotal (95% CI)** | | **93** | | **69** | **57.5%** | **0.72 [0.38, 1.36]** |
| Total events | 16 | | 12 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.03 (P = 0.31) | | | | | | |
| **Total (95% CI)** | | **238** | | **214** | **100.0%** | **0.61 [0.38, 1.00]** |
| Total events | 25 | | 31 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.62, df = 3 (P = 0.65); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.97 (P = 0.05) | | | | | | |
| Test for subgroup differences: Chi² = 0.52, df = 1 (P = 0.47), I² = 0% | | | | | | |




Footnotes

(1) moderate to severe

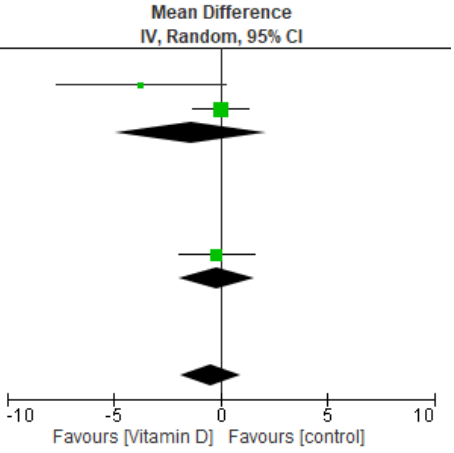
(2) mild to severe; data converted from percentage VitD 7.6% & control 14.4%; vitamin D group (mean 21.2 ng/mL; SD 10.1); control group...

(3) moderate to severe; vitamin D <30 ng/mL

(4) severity not stated; vitamin D <20 ng/mL

## D. Length of Hospital Stay

| Study or Subgroup | Vitamin D Mean | Vitamin D SD | Vitamin D Total | Control Mean | Control SD | Control Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.5.1 Undetermined Vitamin D status** | | | | | | | | |
| Elamir 2021 (1) | 5.5 | 3.9 | 25 | 9.24 | 9.4 | 25 | 11.2% | -3.74 [-7.73, 0.25] |
| Murai 2020 (2) | 7 | 4.44 | 120 | 7 | 5.93 | 120 | 51.4% | 0.00 [-1.33, 1.33] |
| **Subtotal (95% CI)** | | | **145** | | | **145** | **62.6%** | **-1.38 [-4.91, 2.16]** |
| Heterogeneity: Tau² = 4.69; Chi² = 3.04, df = 1 (P = 0.08); I² = 67% | | | | | | | | |
| Test for overall effect: Z = 0.76 (P = 0.45) | | | | | | | | |
| **1.5.2 Low serum vitamin D** | | | | | | | | |
| Lakkireddy 2021 (3) | 13.45 | 5.14 | 65 | 13.62 | 5.32 | 65 | 37.4% | -0.17 [-1.97, 1.63] |
| **Subtotal (95% CI)** | | | **65** | | | **65** | **37.4%** | **-0.17 [-1.97, 1.63]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.19 (P = 0.85) | | | | | | | | |
| **Total (95% CI)** | | | **210** | | | **210** | **100.0%** | **-0.48 [-1.91, 0.94]** |
| Heterogeneity: Tau² = 0.57; Chi² = 3.07, df = 2 (P = 0.22); I² = 35% | | | | | | | | |
| Test for overall effect: Z = 0.66 (P = 0.51) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.36, df = 1 (P = 0.55), I² = 0% | | | | | | | | |




Footnotes

(1) moderate to severe

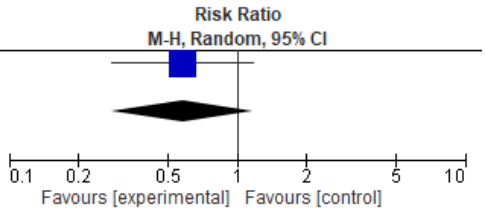
(2) mild to severe; data converted from IQR; vitamin D group (mean 21.2 ng/mL; SD 10.1); control group (mean 20.6 ng/mL; SD 8.1)

(3) mi vitamin D <30 ng/mL

### E. Clinical Improvement

| Study or Subgroup | Vitamin D Events | Vitamin D Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Sánchez-Zuno 2021 (1) | 7 | 21 | 11 | 19 | 100.0% | 0.58 [0.28, 1.18] |
| **Total (95% CI)** | | **21** | | **19** | **100.0%** | **0.58 [0.28, 1.18]** |
| Total events | 7 | | 11 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.51 (P = 0.13)

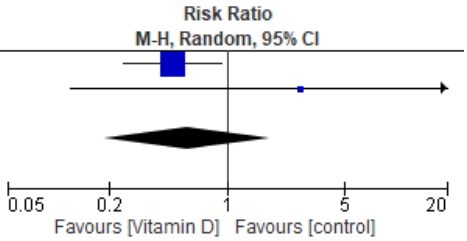



Footnotes
(1) Defined as proportion of patients who became asymptomatic at day 14

### F. Virologic Clearance

| Study or Subgroup | Vitamin D Events | Vitamin D Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Rastogi 2020 (1) | 6 | 16 | 19 | 24 | 88.4% | 0.47 [0.24, 0.92] |
| Sánchez-Zuno 2021 (2) | 1 | 22 | 0 | 20 | 11.6% | 2.74 [0.12, 63.63] |
| **Total (95% CI)** | | **38** | | **44** | **100.0%** | **0.58 [0.19, 1.79]** |
| Total events | 7 | | 19 | | | |

Heterogeneity: Tau² = 0.26; Chi² = 1.19, df = 1 (P = 0.27); I² = 16%
Test for overall effect: Z = 0.94 (P = 0.34)



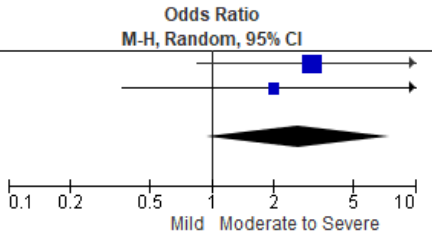

Footnotes
(1) Proportion of patients who remained positive at Day 21
(2) Proportion of patients who remained positive at Day 14

## Appendix 7. Forest Plot from Studies that Enrolled Pediatric Participants (November 4 2021)

### COVID-19 Severity

| Study or Subgroup | Low vitamin D Events | Low vitamin D Total | Sufficient vitamin D Events | Sufficient vitamin D Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Bayramoglu2021 | 31 | 84 | 3 | 19 | 63.3% | 3.12 [0.84, 11.57] |
| Yilmaz2021 | 9 | 29 | 2 | 11 | 36.7% | 2.02 [0.36, 11.34] |
| **Total (95% CI)** | | **113** | | **30** | **100.0%** | **2.66 [0.94, 7.55]** |
| Total events | 40 | | 5 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.84 (P = 0.07)



## Appendix 8. Table of Ongoing Studies (September 2021)

| | Treatment (per arm) | Sample size | Severity at enrollment | Reg. number |
|---|---|---|---|---|
| 1 | To Study the Role of Vitamin D in the Treatment of Confirmed COVID-19 Infection<br><br>(1) Vitamin D vs (2) Standard of care | 100 | Moderate/severe | CTRI/2020/12/030083 |
| 2 | Prevention and treatment with Calcifediol of respiratory problems caused by COVID-19<br><br>(1) Vitamin D vs (2) Standard of care | 1008 | No restriction on type of patients | EUCTR2020-001717-20-ES |
| 3 | High dose Vitamin D in Preventing Aggravation of COVID-19<br><br>(1) Vitamin D vs (2) Placebo | 480 | Mild | EUCTR2020-001793-30-DK |
| 4 | Efficacy of vitamin D treatment in patients diagnosed with pneumonia who require hospital admission and have vitamin D deficiency and a positive diagnosis for SARS-Cov-2 (COVID-19)<br><br>(1) Vitamin D vs (2) Placebo | 108 | Moderate/severe | EUCTR2020-001960-28-ES |
| 5 | Evaluation of the likely beneficial effects of vitamin D on infection with coronavirus<br><br>(1) Vitamin D3 vs (2) Standard of care | 60 | No restriction on type of patients | EUCTR2020-002274-28-ES |
| 6 | Clinical trial, randomized, open-label, to evaluate the efficacy of high-dose vitamin D in patients with COVID-19 pneumonia<br><br>(1) Vitamin D vs (2) Vitamin D | 82 | Moderate/severe | EUCTR2020-002312-43-ES |
| 7 | Effect of vitamin D supplementation in novel corona virus 2019<br><br>(1) Vitamin D vs (2) Vitamin D vs (3) Vitamin D | 210 | Mild/moderate | IRCT20110726007117N11 |
| 8 | Evaluation of the efficacy of oral 25-hydroxyvitamin D3 on COVID-19<br><br>(1) Vitamin D vs (2) Placebo | 260 | Mild | IRCT20200401046909N1 |
| 9 | Effect of Vitamin D Administration on Prevention and Treatment of Mild Forms of Suspected Covid-19<br><br>(1) Vitamin D vs (2) Standard of care | 200 | Mild | NCT04334005 |
| 10 | COvid-19 and Vitamin D Supplementation: a Multicenter Randomized Controlled Trial of High Dose Versus Standard Dose Vitamin D3 in High-risk COVID-19 Patients (CoVitTrial)<br><br>(1) Vitamin D vs (2) Vitamin D | 260 | Moderate/severe | NCT04344041 |
| 11 | High-dose vitamin D versus placebo to prevent complications in COVID-19 patients: A structured summary of a study protocol for a randomized controlled trial (CARED-TRIAL)<br><br>(1) Vitamin D vs (2) Placebo | 1264 | Moderate | NCT04411446 |
| 12 | The Effect of Weekly 50,000 IU Vitamin D3 Supplements on the Serum Levels of Selected Cytokines Involved in Cytokine Storm of Covid-19; A Randomized Clinical Trial in the Covid-19 Uninfected Jordanian People With Vitamin D Deficiency<br><br>(1) Vitamin D3 vs (2) Standard of care | 100 | Healthy volunteers | NCT04476745 |
| 13 | The Role of Vitamin D in Mitigating COVID-19 Infection Severity: Focusing on Reducing Health Disparities in South Carolina<br><br>(1) Vitamin D3 vs (2) Vitamin D3 vs (3) Placebo | 140 | Mild | NCT04482673 |
| 14 | Efficacy of Vitamin D Treatment in Pediatric Patients Hospitalized by COVID-19: Open Controlled Clinical Trial<br><br>(1) Vitamin D vs (2) Standard of care | 40 | No restriction on type of patients | NCT04502667 |

| | | | | |
|---|---|---|---|---|
| 15 | High Dose Vitamin-D Substitution in Patients With COVID-19: a Randomized Controlled, Multi Center Study<br><br>(1) Vitamin D vs (2) Placebo | 80 | Moderate/severe/ critical | NCT04525820 |
| 16 | Effect of Vitamin D on Morbidity and Mortality of the COVID-19<br><br>(1) Vitamin D3 vs (2) Standard of care | 80 | No restriction on type of patients | NCT04552951 |
| 17 | Efficacy of Treatment With Vitamin D in Patients Diagnosed With Pneumonia Requiring Hospital Admission and Presenting Vitamin D Deficit and Positive Diagnosis for SARS-Cov-2<br><br>(1) Vitamin D vs (2) Placebo | 108 | Moderate/severe | NCT04621058 |
| 18 | Vitamin D Supplementation and Covid-19: a Randomized, Double- Blind, Controlled Study<br><br>(1) Vitamin D vs (2) Placebo | 100 | No restriction on type of patients | NCT04636086 |
| 19 | The Effect of Vitamin D Therapy on Morbidity and Mortality in Patients With SARS-CoV 2 Infection<br><br>(1) Vitamin D3 vs (2) Placebo | 56 | No restriction on type of patients | NCT04733625 |
| 20 | Vitamin D3 Levels in COVID-19 Outpatients From Western Mexico: Clinical Correlation and Effect of Its Supplementation<br><br>(1) Vitamin D3 vs (2) Standard of care | 42 | No restriction on type of patients | NCT04793243 |
| 21 | Short Term, High Dose Vitamin D Supplementation in Moderate to Severe COVID-19 Disease<br><br>(1) Vitamin D vs (2) Placebo | 90 | Severe | NCT04952857 |
| 22 | The effect of vitamin D and magnesium supplementation on clinical symptoms, inflammatory markers and oxidative stress in patients with COVID-19: double-blind randomized control clinical trial<br><br>(1) Vitamin D vs (2) Vitamin D3 + magnesium sulfate vs (3) Magnesium sulfate vs (4) Placebo | 104 | Mild/moderate | IRCT20210702051763N1 |
| 23 | A study of vitamin D supplementation on clinical outcome of COVID-19 infected patients with pneumonia<br><br>(1) Vitamin D vs (2) Standard of care | 400 | Moderate/severe | TCTR20210906005 |
| 24 | A prospective, double-blind, parallel assignment, randomized controlled study to evaluate the effectiveness and safety of high dose Vitamin D supplementation and effects and associations of low vitamin D levels in patients with symptomatic SARS CoV-2 infection<br><br>(1) Vitamin D vs (2) Placebo | 258 | Mild/moderate | SLCTR/2021/019 |

## Q5. Should melatonin be used in the adjunctive treatment of COVID-19?

*As of 30 June 2021*

RECOMMENDATION

**There is insufficient evidence to recommend the use of melatonin as adjunct treatment for patients with COVID-19 infection.** *(Very low certainty of evidence)*

***Consensus Issues***
There were no consensus issues raised during the panel meeting.

### KEY FINDINGS

There was only one very low quality RCT that compared melatonin with standard treatment, and it showed significant reduction in cough, dyspnea, and fatigue, and significantly shorter hospital stay and return to baseline health in those given melatonin. There was no significant difference in the proportion of patients discharged on day 14. No adverse events were observed in the use of melatonin among COVID-19 patients.

### INTRODUCTION

Melatonin, a well-known anti-inflammatory and anti-oxidative molecule, is protective against acute lung injury or acute respiratory distress syndrome caused by viral and other pathogens [1]. It is being proposed as an adjunctive therapy for patients with COVID 19 due to its antioxidant, anti-inflammatory, and immunomodulatory effects, as well as its possible antiviral action [2]. In addition, melatonin may restore the optimal circadian rhythm from sleep-wake cycle disruption brought about by social isolation and to control delirium in severely affected patients in the intensive care unit [3].

In a case series of ten COVID-19 patients admitted in a hospital in Manila, the use of high-dose melatonin therapy resulted in clinical stabilization and/or improvement within 4-5 days. No significant adverse events were noted at high doses except for sleepiness which was deemed favorable for patients who had anxiety and symptom-related sleeping problems [4].

### REVIEW METHODS

We performed a systematic literature search in online databases such as MEDLINE, CENTRAL, and Google Scholar. Additional searches in MedRxiv, WHO ICTRP, and clinicaltrials.gov were also done to look for articles awaiting publication and ongoing clinical trials, respectively. We used search terms such as “melatonin,” “N-acetyl-5-methoxytryptamine,” and “COVID-19.” References from review articles were also manually searched for additional articles.

### RESULTS

The initial search from all the databases retrieved 180 references. We screened the title and abstracts of 14 references. After removing duplicates, letters, commentaries, narrative reviews, and studies not meeting the inclusion criteria, we retrieved one full text article (Appendix 1).

There is one unpublished (preprint) randomized controlled trial [5] that included 74 patients admitted for mild to moderate COVID-19. Patients were randomized to receive melatonin 3mg three times daily for 2 weeks in addition to standard of care versus standard of care alone. Both patients and outcome assessors were blinded to treatment assignment. There was no mention of allocation concealment and there was a significant drop out rate (40%), with only 44 patients included in the final per-protocol analysis.

Patients receiving melatonin showed a significant improvement in cough (4.2% vs. 25%; P = 0.045), dyspnea (0% vs. 15%; P = 0.049), and fatigue (8.3% vs. 30%; P = 0.020). No patient died in either of the two groups. Patients in the melatonin group also had a significantly shorter hospital stay (4.65 ± 3.37 vs. 8.15 ± 5.97; P = 0.021 days). At day 14, more patients showed radiologic improvement of pulmonary involvement (4% vs 25%; RR 0.17, 95% CI 0.21-1.3), and a higher proportion of patients were discharged on day 14 in the melatonin group (92% vs 85%; RR 0.56, 95% CI 0.1-3), but both of these were not significant. After four weeks of follow-up, patients given melatonin showed a significantly faster return to baseline health than controls (15.09 ± 8.69 vs. 29.6 ± 21.12; P = 0.004)). No adverse event from melatonin was observed in the trial.

## RECOMMENDATIONS FROM OTHER GROUPS

Clinical practice guidelines from WHO, IDSA, US NIH, UK NHS, or PSMID made no recommendation on the use of melatonin as adjunctive treatment of COVID-19.

## ONGOING STUDIES

There are currently 15 ongoing randomized clinical trials investigating the effect of melatonin as adjunct in the treatment of COVID-19 patients (Appendix 3).

## REFERENCES


1. Zhang R, Wang X, Ni L, et al. COVID-19: Melatonin as a potential adjuvant treatment. Life Sci [Internet]. 2020 Jun;250(January):117583. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0024320520303313
2. Cardinali DP, Brown GM, Pandi-Perumal SR. Can Melatonin Be a Potential “Silver Bullet” in Treating COVID-19 Patients? Diseases. 2020;8(4):44.
3. Brusco LI, Cruz P, Cangas AV, Rojas CG, Vigo DE, Cardinali DP. Efficacy of melatonin in non-intensive care unit patients with COVID-19 pneumonia and sleep dysregulation. Melatonin Res. 2021;4(1):173–88.
4. Castillo RR, Quizon GRA, Juco MJM, et al. Melatonin as adjuvant treatment for coronavirus disease 2019 pneumonia patients requiring hospitalization (MAC-19 PRO): a case series. Melatonin Res. 2020;3(3):297–310.
5. Farnoosh G, Akbariqomi M, Badri T, et al. Efficacy of a Low Dose of Melatonin as an Adjunctive Therapy in Hospitalized Patients with COVID-19: A Randomized, Double-blind Clinical Trial. Authorea Prepr [Internet]. 2020; Available from: https://www.authorea.com/doi/full/10.22541/au.160734344.45295921/v1?commit=5be3e7266256468d59e81ff82a1b125710ba7459

# Appendix 1: Characteristics of Included Study

| Title/Author | Study design | Sample Size | Population | Intervention Group(s) | Control | Outcomes |
|---|---|---|---|---|---|---|
| Farnoosh, 2020 | Randomized double blind, controlled trial | N=44 | Mild to moderate COVID-19 | Melatonin 3mg 3 times a day for 14 days | Standard of care | mortality, radiographic improvement, adverse events, symptomatic improvement |

# Appendix 2: GRADE Evidence Profile

**Author(s)**: Anna Angelica Macalalad Josue, MD, FPCP, DPSEDM, MSc (cand)
**Question**: Melatonin compared to standard therapy for COVID-19
**Setting**: Hospitalized patients with confirmed mild to moderate COVID-19 at
**Bibliography**: Farnoosh

| CERTAINTY ASSESSMENT | | | | | | | NO. OF PATIENTS | | EFFECT | | CERTAINTY | IMPORTANCE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Melatonin | Standard therapy | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (follow up: 4 weeks; assessed with: at day 28)** | | | | | | | | | | | | |
| 1 | Randomised trials | Very serious | Not serious | Not serious | Serious | None | 0/24 (0.0%) | 0/20 (0.0%) | not estimable | | ⨁◯◯◯ VERY LOW [a,b] | CRITICAL |
| **Time to clinical recovery (follow up: 4 weeks; assessed with: number of days)** | | | | | | | | | | | | |
| 1 | Randomised trials | Very serious | Not serious | Not serious | Serious | None | 24 | 20 | - | MD **14.51 days lower** (18.86 lower to 10.16 lower) | ⨁◯◯◯ VERY LOW | IMPORTANT |
| **Hospital length of stay (follow up: 4 weeks; assessed with: number of days)** | | | | | | | | | | | | |
| 1 | Randomised trials | Very serious | Not serious | Not serious | Serious | None | 24 | 20 | - | MD **3.5 days lower** (6.24 lower to 0.76 lower) | ⨁◯◯◯ VERY LOW | IMPORTANT |
| **Pulmonary involvement (radiographic) (follow up: 4 weeks; assessed with: radiographic evaluation at 14 days)** | | | | | | | | | | | | |
| 1 | Randomised trials | Very serious | Not serious | Not serious | Serious | None | 1/24 (4.2%) | 5/20 (25.0%) | **RR 0.17** (0.02 to 1.31) | **208 fewer per 1,000** (from 245 fewer to 78 more) | ⨁◯◯◯ VERY LOW | NOT IMPORTANT |
| **Adverse outcome (follow up: 4 weeks)** | | | | | | | | | | | | |
| 1 | Randomised trials | Very serious | Not serious | Not serious | Serious | None | 0/24 (0.0%) | 0/20 (0.0%) | not estimable | | ⨁◯◯◯ VERY LOW | CRITICAL |

**CI:** Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

**Explanations**

[a] Imprecision downgraded due to low event rate, wide confidence interval due to small sample size
[b] Risk of bias downgraded due to significant drop out rate (40%), not intention-to-treat analysis

## Appendix 3. Characteristics of Ongoing Studies

| Trial ID | Scientific title | Population | Intervention | Outcome |
|---|---|---|---|---|
| | Melatonin as Adjuvant treatment for COVID-19 in Patients Requiring hospitalization (MAC19 PRO): A Randomized, Double-Blind, Placebo-Controlled Trial (RCT) | Hospitalized COVID-19 | High dose melatonin | Observable clinical outcomes and tolerability |
| **IRCT 20200411047030N1** | Evaluation of adding melatonin to routine treatment on outcomes and quality of sleep in COVID-19 patients | COVID-19 | Melatonin 3mg/night (in addition to hydroxychloroquine and azithromycin) | Time to stop the fever |
| **IRCT 20200408046988N1** | Evaluation of the efficacy of melatonin tablets as auxiliary medication in accelerating the improvement of the COVID-19 symptoms and clinical findings: A double-blind randomized and placebo controlled trial | COVID-19 | Melatonin 3mg/night (in addition to HCQ) | No mention |
| **IRCT 20151228025732N52** | A study on melatonin and Vitamin C and zinc efficacy in patients with COVID19 hospitalized in intensive care unit of Semnan Kowsar Hopsital | COVID-19 | Melatonin 40mg/day | Respiratory rate |
| **EUCTR 2020-001808-42-ES** | Phase ii clinical trial, single-blind, randomized, placebo controlled to explore the effectiveness and safety of melatonin i.v. in patients with covid-19 entered into the icu (melcovid study) - melcovid | Severe COVID-19 (ICU) | Melatonin 6mg/IV | mortality |
| **IRCT 20200506047323N5** | Evaluation of the efficacy and safety of Melatonin in patients with COVID-19: a randomized clinical trial | Moderate COVID-19 | Melatonin 50mg once a day | Body temperature |
| **IRCT 20200922048804N1** | Inflammation control in patients with COVID-19 using melatonin supplement compare to controls referred to Imam Khomani Hospital | Mild to moderate COVID-19 | Melatonin 6mg x 2 weeks | headache |
| **IRCT 20200426047206N4** | Evaluating the effect of Melatonin in prognosis and clinical improvement in patients with COVID-19: A Randomized Clinical Trial | Mild to moderate COVID-19 | Melatonin 18mg 2x a day x 7 days | Need for oxygen theraoy |
| **NCT04409522** | Evaluation of Therapeutic Effects of Melatonin by Inhibition of NLRP3 Inflammasome in COVID19 Patients | Moderate to severe COVID-19 | Melatonin 9mg/day for 7-10 nights | No mention |
| **NCT04474483** | Safety and Efficacy of Melatonin in Outpatients Infected With COVID-19 (COVID-19) | COVID-19 (outpatient) | Melatonin 10mg 3x a day for 14 days | Cumulative Incidence of Treatment-Emergent Adverse Events |
| **NCT04530539** | The Effect of Melatonin and Vitamin C on COVID-19 | Symptomatic COVID-19 (outpatient) | Melatonin 10mg at bedtime, Vitamin C 1000 mg/day, vs placebo | Symptom severity |
| **NCT04531748** | Selective Estrogen Modulation and Melatonin in Early COVID-19 | COVID-19 | Toremifene 60mg + Melatonin 100mg vs Melatonin 100mg; vs placebo | Peak increase in COVID-19 Sign and Symptom score |
| **NCT04568863** | A Phase II, Single-center, Double-blind, Randomized Placebo-controlled Trial to Explore the Efficacy and Safety of Intravenous Melatonin in Patients With COVID-19 Admitted to the Intensive Care Unit (MelCOVID Study) | Severe COVID-19 (ICU) | Melatonin<br>7 days of 5 mg per Kg of actual body weight per day of intravenous melatonin every 6 hours | mortality |
| **NCT04570254** | Open Clinical Trial of the Use of Antioxidants and Pentoxifylline as Adjuvant Therapy to Standard Therapy in Patients With and Without Septic Shock Secondary to COVID-19 Severe Pneumonia | Severe COVID-19 | Vitamin C vs Vitamin E vs Melatonin 50mg/day vs N-acetyl cysteine, in addition to Pentoxifylline | Death from any cause; Percentage of patients who required orotracheal intubation |

## Q6. Should virgin coconut oil be used in the adjunctive treatment of COVID-19?

*As of 30 June 2021*

RECOMMENDATION

**There is no evidence to recommend the use of virgin coconut oil as adjunct treatment for patients with COVID-19 infection.**

*Consensus Issues*
There were no issues raised during the consensus panel meeting.

## KEY FINDINGS

Virgin coconut oil (VCO) is rich in lauric acid and pharmacologically active metabolite monolaurin. In vitro studies have found that VCO has anti-inflammatory, antioxidant, antibacterial, antifungal, and antiviral properties. In a clinical trial involving HIV and AIDS patients, VCO treatment led to an increase in CD4+ and lymphocyte counts as well as reduction in viral load. Currently, there are no published studies assessing the efficacy and safety of virgin coconut oil as an adjunctive treatment for COVID-19.

## INTRODUCTION

There has been a growing interest in the use of virgin coconut oil (VCO) as an adjunctive treatment of COVID-19 due to its anti-inflammatory and antiviral properties [1]. This would be very advantageous for the Philippines, who is considered to be one of the leading producers of coconut oil in the world [2]. VCO is naturally extracted from coconut kernel without the application of high temperature and chemical treatment [3]. It contains high amounts of medium chain saturated fatty acid (MCFA), predominantly lauric acid [4], which are easily hydrolyzed in the GI tract [5] and can generate sufficient quantities of the pharmacologically active compounds such as monolaurin [6]. Monolaurin compounds are the major metabolite responsible for its efficacy [7]. In vitro studies show that fermented VCO possesses antibacterial activities against a variety of strains including Candida [8] and Staphylococcus aureus [9]. It also exhibits anti-inflammatory properties that lead to reduction in TNF □,IFN□ IL-6, IL-8, and IL-5 [10]. In addition, VCO also contains a high percentage of phenolic acids which are known antioxidants; these contribute to its oxidative stability as well as nutritional and organoleptic properties [11]. In vitro studies found that VCO has antiviral activity against enveloped viruses such as influenza and coronavirus [12]. Furthermore, Bartolotta et al. showed that lauric acid was able to reduce virus yields of several attenuated and pathogenic strains of Junin virus in a dose-dependent manner without affecting the cell viability [13]. A clinical trial done by Dayrit et al. found that VCO was able to increase CD4+ and lymphocyte counts as well as reduce viral load among HIV and AIDS patients [14].

## REVIEW METHODS

We performed a comprehensive systematic search of related literature from Medline and CENTRAL. We also searched for ongoing clinical trials using ClinicalTrial.gov and Clinicaltrialsregister.eu. Freehand search using Google was also done to check for other sources of information including the Love Platform App. There were no limits placed, even with regard to the date, language and country of publication. We also searched for indirect evidence (i.e., use of VCO for treatment of SARS-CoV-1, MERS-

COV and HIV/AIDS). Search was conducted using the following search terms: COVID-19, SARS-CoV-2, virgin coconut oil and coconut oil.

Eligible articles were evaluated using the following criteria:

| | |
|---|---|
| Population | COVID-19 patients any age, co-morbidities and severity |
| Intervention/ Exposure | Virgin coconut oil |
| Comparison | Usual standard of care, placebo, any active control |
| Outcomes | Clinical improvement, mortality, adverse effects |
| Methodological filter | randomized controlled trials (RCT), observational clinical studies, systematic review and meta-analysis available |

## RESULTS

We did not find any articles that matched our criteria.

## RECOMMENDATIONS FROM OTHER GROUPS

Currently there are no clinical practice guidelines that make any recommendations on the use of VCO as adjunctive treatment of COVID-19.

## ONGOING STUDIES

There are two ongoing studies on the efficacy of virgin coconut oil as adjunctive treatment for COVID-19 (Appendix 1).

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## Appendix 1. Characteristics of Ongoing Studies

| Clinical Trial Identifier/Title | Population | Intervention | Comparator | Outcome |
|---|---|---|---|---|
| **NCT04594330**<br><br>**Pilot Trial for the Benefit of Virgin Coconut Oil (VCO) as a Potential Adjuvant Therapy in COVID-19 Patients** | Patients diagnosed with COVID-19 in Central Public Hospital Dr. Sardjito, Teaching Hospital of Universitas Gadjah Mada (UGM), and Yogyakarta COVID-19 referral hospitals (RSUD Wonosari and Sleman) | Virgin coconut oil and placebo | Placebo | Primary outcome: Clinical improvement<br><br>Secondary Outcome: Leukocyte count, lymphocyte count, neutrophil count, NLR, D-dimer, TNF-alpha, IL-6, ferritin, procalcitonin, chest radiology outcome |
| **Virgin coconut oil as adjunctive treatment for COVID-19 patients** | Patients admitted at the Philippine General Hospital with moderate to severe COVID-19 | Virgin coconut oil and standard care | Standard Care | Primary outcome: recovery/resolution of symptoms stratified according to severity of disease<br><br>Secondary Outcome: duration of hospital stay, time to first receiving ventilation or admitted to intensive care, white blood cell count, IL-6, ferritin, CRP, immunoglobulin, CD4+ counts (baseline, at one week and at two weeks, negative test result for COVID |

## Q7. Should Lagundi (*Vitex negundo*) be used as adjunctive treatment for COVID-19 infection?

*As of 29 October 2021*

RECOMMENDATION

**There is no evidence to recommend Lagundi (*Vitex negundo*) as adjunctive treatment for patients with COVID-19 infection.**

*Consensus Issues*
Considerations of the panel were the lack of completed studies to date and the possibility of misinterpretation, stemming from anecdotal accounts of relief of symptoms, which could lead to its use even without definite benefits.

### KEY FINDINGS

Lagundi (*Vitex negundo*), a medicinal herbal cough remedy widely used in the Philippines, was considered a potential adjunctive treatment for COVID-19. We found no published studies on *Vitex negundo* on patients with COVID-19 but there is one completed local clinical trial whose full results are not yet available.

### INTRODUCTION

There has been a resurgence of interest in *Vitex negundo*, already being used for other medical indications, for its potential as adjunctive treatment for COVID-19.

Lagundi is a woody shrub with bluish purple flowers recognized by the Department of Health as a treatment for respiratory complaints like cough and asthma.[1] The in vivo study by Haq et al. showed that the n-butanol fraction of *Vitex negundo* demonstrated inhibition of cough reflex in a dose-dependent manner.[2] The study of Patel et al. also showed that it can inhibit histamine formation through mast cell stabilization.[3] The iridoid and flavonoid fractions of the plant extract exhibited anti-inflammatory effects through inhibition of chemotaxis, phagocytosis and complement activation.[4] *Vitex negundo* also contains papaverine-like phosphopodiesterase inhibitors partly explaining its bronchodilatory effect.[5] Molecular docking studies show its inhibitory activity against papain like protease of SARS-CoV-2 indicating its potential use as an antiviral agent for COVID-19.[6] There was also a double-blind placebo-controlled trial which showed that Lagundi significantly improved the frequency of cough and color of sputum among older children.[7]

### REVIEW METHODS

We performed a comprehensive systematic search of related literature from MEDLINE, MedRxiv.org, WHO Clinical Trials Registry, WHO Therapeutics and COVID 19 Living Guidance, WHO Institutional Repository for Information Sharing, HERDIN Plus, and clinicaltrials.gov. Freehand search using Google was also done. There was no limit as to date, language, and country of publication. The search was conducted using the following terms: “herbal medicine”, “Vitex negundo”, “Lagundi”, “COVID-19”, “severe acute respiratory syndrome coronavirus 2”, “2019-nCoV”, “viral illness”, “cough”. We also contacted local specialists for possible information on studies being conducted on these two plants.

Our PICO for this review was as follows: Population – patients with COVID-19; Intervention – lagundi; Control – standard treatment, supportive treatment or no treatment; Outcome – mortality, ICU stay, need for ventilation, length of hospital stay, days to recovery, worsening of symptoms and viral load/cycle threshold. We searched for randomized controlled trials, observational studies, systematic reviews and meta-analyses.

## RESULTS

We found no published articles that matched our criteria.

Communication with a local expert led us to a completed yet unpublished, local study on *Vitex negundo.* We are awaiting the full paper of Lazarte and co-investigators who conducted a two-stage, adaptive, multicenter parallel randomized clinical trial to determine 1) the appropriate dose and 2) the efficacy of Lagundi plus standard of care in patients with COVID-19.[8]

## EVIDENCE TO DECISION

*Vitex negundo* is available in drugstores and health outlets, as well as online shopping sites, which show one price at Php8.00 per 600mg tablet.[9] The 2020 Philippine Drug Price Reference Index (DPRI) shows the mean price of the same preparation at Php2.90.[10]

## RECOMMENDATIONS FROM OTHER GROUPS

Currently there are no clinical practice guidelines listed by the National Institute of Health, American College of Physicians, Center for Disease Control, National Guidelines Clearinghouse and Australian Clinical Practice Guideline, that make a recommendation on the use of Lagundi as adjunctive treatment for COVID 19.

## RESEARCH GAPS

Randomized controlled trials investigating the efficacy and safety of Lagundi with specific dosing regimen for adult or pediatric patients with COVID-19 are needed.

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# Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the actual panel meeting: Lagundi (N = 8)

| FACTORS | JUDGEMENT | | | | | | RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS |
|---|---|---|---|---|---|---|---|
| **Problem** | No (3) | Yes (5) | | | | | |
| **Benefits** | Large | Moderate (1) | Small (2) | Uncertain (5) | | | • No research evidence found.<br>• Experience from a mild case: can relieve symptoms of COVID such as cough, fever, headache and there could be more promising outcomes if studies are continued. (n=1) |
| **Harm** | Large | Small (2) | Uncertain (5) | Varies | | | • No research evidence found. |
| **Certainty of Evidence** | High | Moderate (2) | Low (3) | Very low (3) | | | • None |
| **Balance of effects** | Favors drug (1) | Does not favor drug | Uncertain (7) | Varies | | | • No research evidence found. |
| **Values** | Important uncertainty or variability (2) | Possibly important uncertainty or variability (2) | Possibly NO important uncertainty or variability (3) | No important uncertainty or variability | | | |
| **Resources Required** | Uncertain | Large cost | Moderate Cost (2) | Negligible cost (1) | Moderate savings (3) | Large savings (2) | • 1 cap of 600 mg of Lagundi – Php 3.75 to 8 per cap |
| **Certainty of evidence of required resources** | No included studies (2) | Very low (2) | Low (1) | Moderate (4) | High | | • No cost-effectiveness studies available. |
| **Cost effectiveness** | No included studies (5) | Favors the comparison (1) | Does not favor either the intervention or the comparison (1) | Favors the intervention (1) | | | • No cost-effectiveness studies available. |
| **Equity** | Uncertain (3) | Reduced (2) | Probably no impact (1) | Increased (2) | | | • No cost-effectiveness studies available. |
| **Acceptability** | Uncertain (6) | No | Yes (2) | Varies | | | • *Panel: Lagundi is used for other respiratory diseases.* |
| **Feasibility** | Uncertain (1) | No (1) | Yes (6) | Varies | | | • No local studies available. |

# Appendix 2. Search Yield and Results

| Database | Search terms | Yield | Hits |
|---|---|---|---|
| PubMed | ((((((((((((((((((herbal* [tiab]) OR (herbal medicine)) OR (herbal medicine[MeSH Terms])) OR (integrative medicine[MeSH Terms])) OR (chinese medicine, traditional[MeSH Terms])) OR (complementary medicine[MeSH Terms])) OR (complementary therapies[MeSH Terms])) OR (alternative medicine[MeSH Terms])) OR (Vitex negundo)) OR (Vitex negundo [tiab])) OR (lagundi [tiab])) OR (integrative medicine [tiab])) OR (chinese medicine [tiab])) OR (complementary medicine)) OR (alternative medicine)) AND ("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 ((((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]) | 2986 | 0 Lagundi<br>3 Other Chinese medicine |
| Pubmed | ((((clinical trial [tiab]) OR (randomized controlled trial [tiab])) OR (randomized controlled trial[Publication Type])) AND (Vitex negundo)) OR (Vitex negundo [tiab])) OR (lagundi [tiab])) OR (herbal* [tiab])) OR (herbal medicine)) OR (herbal medicine[MeSH Terms]))) AND ("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") | 52 | 0 Lagundi |
| HERDIN | Lagundi | 2 | 1 |
| | | Completed but not published Dr Cecilia Lazarte | |
| Google Scholar | Viral infection AND Lagundi vitex negundo | 51 | 0 |
| Google Scholar | Viral infection AND Lagundi | 70 | 0 |

## Appendix 3. Characteristics of Ongoing Studies

| Clinical Trial Identifier/ Title | Population | Intervention | Comparator | Outcome |
|---|---|---|---|---|
| PHRR210126-002992<br><br>2-stage, Randomized, double-blind, placebo-controlled clinical trial on the efficacy and safety of Lagundi (Vitex negundo) tablets/syrup (NIRPROMP formulation) with standard treatment compared to placebo with standard treatment in patients with mild COVID disease without comorbidities | Patients diagnosed with Mild COVID 19 aged 19-55 years old (278) | Lagundi (NIRPROMP Formulation tablet or syrup) | Placebo | Primary:<br>Mean clinical recovery time (normalization of fever <37.3C, respiratory rate <25, oxygen saturation >94% on room air and alleviation of cough for 72hours)<br><br>Secondary:<br>Time to RTPCR negative, Time to defervescence, Time to absent symptoms in days, Number of patients progressing to moderate disease and Type, frequency and severity of adverse effects |

## Q8. Should Tawa-tawa (*Euphorbia hirta*) be used as adjunctive treatment for COVID-19 infection?

*As of 29 October 2021*

RECOMMENDATION

**There is no evidence to recommend Tawa-tawa (*Euphorbia hirta*) as adjunctive treatment for patients with COVID-19 infection.**

***Consensus Issues***

Due to the lack of evidence, the panel decided not to make a recommendation for the use of Tawa-tawa as adjunctive treatment for COVID-19. One panelist opted to abstain from the vote because her inclination was to suggest against the use of Tawa-tawa. While it has been used in the treatment of dengue, it has no proven benefits for COVID-19 infection and may cause harm.

### KEY FINDINGS

Tawa-tawa (*Euphorbia hirt*a) is a medicinal herb widely used for febrile illness in the Philippines; it is considered as a potential adjunctive treatment for COVID-19. We found no published studies on *Euphorbia hirta* in patients with COVID-19. There is one ongoing local clinical trial.

### INTRODUCTION

*Euphorbia hirta* is a common herb in the Philippines characterized by its hairy stem, forked reddish leaves and purple flowers.[1] An ethnographic study done in 2018 showed that *Euphorbia hirta* has been used since the early 1940s for fever.[2] Aqueous extracts of the herb are shown to strongly reduce the release of prostaglandins I2, E2 and D2, explaining its antipyretic property.[3] In spite of only a few formal studies, *Euphorbia hirta* is being used by the residents of the Cordillera Region as adjunctive treatment for Dengue Fever.[4,5,6] The study of Tayone et al. on animals showed significant platelet-increasing activity as well as reduction in plaque formation of dengue virus serotype 1.[7] One in vitro study by Saptawati et al. also demonstrated inhibition of dengue virus serotype 2.[8] Molecular docking studies also showed promising results, wherein the phytochemical components of *Euphorbia hirta* showed binding with dengue targets, indicating its antiviral efficacy.[9]

### REVIEW METHODS

We performed an exhaustive comprehensive systematic search of related literature from MEDLINE, MedRxiv.org, WHO Clinical Trials Registry, WHO Therapeutics and COVID 19 Living Guidance, WHO Institutional Repository for Information Sharing, HERDIN Plus, and clinicaltrials.gov. Freehand search using Google was also done. There was no limit as to date, language, and country of publication. The search was conducted using the following terms: “herbal medicine”, “*Euphorbia hirta”, “*Tawa-tawa”, “COVID-19”, “severe acute respiratory syndrome coronavirus 2”, “2019-nCoV”, “viral illness”, “cough”. We also contacted local specialists for possible information on studies being conducted on this plant.

Our PICO for this review was as follows: Population – patients with COVID-19; Intervention – tawa-tawa; Control – standard treatment, supportive treatment or no treatment; Outcome – mortality, ICU stay, need for ventilation, length of hospital stay,

days to recovery, worsening of symptoms and viral load/cycle threshold. We searched for randomized controlled trials, observational studies, systematic reviews and meta-analyses.

## RESULTS

We found no published articles that matched our criteria.

## ONGOING TRIAL

We found one ongoing local trial for *Euphorbia hirta* registered at HERDINPLUS by Padilla and co-investigators from the University of the Philippines–Visayas. It is an interventional, randomized controlled phase II dose-finding study design to evaluate the effects of standardized aqueous spray-dried extract of E. hirta (U4bext®) on the progression of and symptom resolution from COVID-19 versus current guidelines for standard of care.[10]

According to the protocol registration information, the primary outcome of interest for the said study is clinical improvement, which the investigators defined as “at least 2 categories of improvement from baseline in the 7-category Ordinal Scale of patient status.” Secondary outcomes include time to improvement of at least 2 categories relative to baseline, time to clinical failure (defined as the period measured from first dose to time of death, mechanical ventilation, ICU admission, or study withdrawal), time to resolution of symptoms, time to normalization of biochemical/hematological parameters, time to hospital discharge, duration of time on supplemental oxygen, percentage of participants with adverse events, time to RT-PCR virus negativity, and proportion of participants with post-treatment infection.

## EVIDENCE TO DECISION

*Euphorbia hirta* is available in drugstores and health outlets, as well as online shopping sites at P 185.00 the price of a bottle that contains 60 pieces of the 500-mg capsule.[11] The Philippine Drug Price Reference Index (DPRI) does not list tawa-tawa or Euphorbia.

## RECOMMENDATIONS FROM OTHER GROUPS

Currently there are no clinical practice guidelines listed by the National Institute of Health, American College of Physicians, Center for Disease Control, National Guidelines Clearinghouse and Australian Clinical Practice Guidelines that make a recommendation on the use of *Euphorbia hirta* as adjunctive treatment for COVID 19.

We were able to reach ten pediatric and adult infectious disease specialists whose expert opinion we requested as to the use of *Euphorbia hirta* as an adjunct for COVID-19. Currently none of them use *Euphorbia hirta*. While they recognize the inherent and potential use of the herb for COVID-19, they are currently awaiting further recommendations prior to using it in their practice.

## RESEARCH GAPS

There is no available literature on the dosing regimen for these herbal preparations in patients with COVID-19. There is also no information on the use in adult versus pediatric patients with COVID-19, or on the adverse effects of such dosing.

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# Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the actual panel meeting (N = 8)

| FACTORS | JUDGEMENT | | | | | | RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS |
|---|---|---|---|---|---|---|---|
| **Problem** | No (4) | Yes (4) | | | | | |
| **Benefits** | Large | Moderate (1) | Small (2) | Uncertain (5) | | | • **No research evidence found.**<br>• *There is a need to conduct more studies for tawa-tawa. (n = 1)* |
| **Harm** | Large | Small (1) | Uncertain (7) | Varies | | | • **No research evidence found.**<br>• *There is a need to conduct more studies for tawa-tawa. (n = 1)* |
| **Certainty of Evidence** | High (1) | Moderate | Low (1) | Very low (6) | | | • **No research evidence found.**<br>• *There is a need to conduct more studies for tawa-tawa. (n = 1)* |
| **Balance of effects** | Favors drug | Does not favor drug | Uncertain (8) | Varies | | | • **No research evidence found.**<br>• *There is a need to conduct more studies for tawa-tawa. (n = 1)* |
| **Values** | Important uncertainty or variability (1) | Possibly important uncertainty or variability | Possibly NO important uncertainty or variability (3) | No important uncertainty or variability (4) | | | |
| **Resources Required** | Uncertain (5) | Large cost (1) | Moderate Cost (1) | Negligible cost (1) | Moderate savings | Large savings | • No synthetic preparation of tawa-tawa |
| **Certainty of evidence of required resources** | No included studies (4) | Very low | Low (2) | Moderate (1) | High (1) | | • No synthetic preparation of tawa-tawa |
| **Cost effectiveness** | No included studies (8) | Favors the comparison | Does not favor either the intervention or the comparison | Favors the intervention | | | • No available evidence to date |
| **Equity** | Uncertain (6) | Reduced | Probably no impact (2) | Increased | | | |
| **Acceptability** | Uncertain (6) | No | Yes (2) | Varies | | | • *Panel: Tawa-tawa is locally available and abundant* |
| **Feasibility** | Uncertain (1) | No (1) | Yes (6) | Varies | | | • *Panel: Tawa-tawa is locally available and abundant (n=1)* |

# Appendix 2. Search Yield and Results

| Database | Search terms | Yield | Hits |
|---|---|---|---|
| **PubMed** | ((((((((((((((((((herbal* [tiab]) OR (herbal medicine)) OR (herbal medicine[MeSH Terms])) OR (integrative medicine[MeSH Terms])) OR (chinese medicine, traditional[MeSH Terms])) OR (complementary medicine[MeSH Terms])) OR (complementary therapies[MeSH Terms])) OR (alternative medicine[MeSH Terms])) OR (euphorbia hirta[MeSH Terms])) OR (tawa-tawa [tiab])) OR (integrative medicine [tiab])) OR (chinese medicine [tiab])) OR (complementary medicine)) OR (alternative medicine)) AND ("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 ((((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]) | **2986** | **0 Tawa-tawa**<br>**3- Other Chinese medicine** |
| **Pubmed** | ((((clinical trial [tiab]) OR (randomized controlled trial [tiab])) OR (randomized controlled trial[Publication Type])) AND (((((((euphorbia hirta[MeSH Terms]) OR (tawa-tawa [tiab])) OR (herbal* [tiab])) OR (herbal medicine)) OR (herbal medicine[MeSH Terms])))) AND ("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") | **52** | **0 Tawa-tawa** |
| **Google** | COVID and Tawa tawa | **Ongoing trial**<br>**Dr. Phillip Padilla**<br>Target completion: Sep 2021 | |
| **HERDIN** | Tawa tawa | **22** | **0** |
| **Google Scholar** | Viral infection AND Tawa tawa | **90** | **1** |
| | | **Background purpose only** | |

## Appendix 3. Characteristics of Ongoing Studies

| Clinical Trial Identifier/ Title | Population | Intervention | Comparator | Outcome |
|---|---|---|---|---|
| PHRR210412-003475<br><br>**A randomized controlled clinical trial on the efficacy and safety of Tawa-tawa (*Euphorbia hirta* L.) extract as an adjunctive treatment for mild to moderate COVID-19 patients** | Patients with Mild or Moderate COVID-19 patients aged 18 to 59 years | Standardized aqueous spray-dried extract of *E. hirta* (U4bext®) | Current Guidelines for standard of care | Primary:<br>Clinical improvement, defined as at least 2 categories of improvement from baseline<br><br>Secondary:<br>Time to Improvement of at least 2 Categories Relative to Baseline, Time to Clinical Failure [From first dose to time of death, mechanical ventilation, ICU admission, or study withdrawal], Time to resolution of symptoms, Time to normalization of biochemical/haematological parameters, Time to Hospital Discharge, Duration of Time on Supplemental Oxygen, Percentage of Participants with Adverse Events, Time to Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) Virus Negativity, Proportion of Participants with Post-Treatment Infection |

## Q9. Should oral fatty acid supplements be used as adjunct treatment for patients with COVID-19?

*As of 30 June 2021*

RECOMMENDATION

**There is insufficient evidence to recommend the use of fatty acid supplements as adjunct treatment for patients with COVID-19.** *(Low certainty of evidence)*

*Consensus Issues*

There were no reported adverse events in the study that assessed the effect of addition of 1000mg omega-3-fatty acid supplementation to enteral feeding of hospitalized patients with COVID-19. There was no significant difference in reported adverse events between groups given fatty acid supplementation or placebo in critically-ill ICU patients (non-COVID).

In terms of cost, a capsule of 1000mg omega-3-fatty acid may cost less than Php 20.00 in the market. It was also remarked that patient preference may be a factor because of the fishy taste.

## KEY FINDINGS

There is low certainty of evidence based on one RCT (N=128) that compared omega-3-fatty acid supplementation of high-protein enteral feeding versus high-protein enteral feeding alone in hospitalized patients with COVID-19, which showed significant reduction in mortality (available case analysis, RR 0.85, [0.73, 0.99]). The RCT did not report adverse events. Indirect evidence on adverse events from two meta-analyses of RCTs on critically-ill ICU patients (non-COVID), mostly with ARDS, given fatty acid supplementation versus control, which showed that gastrointestinal adverse events were common but did not differ significantly between groups (RR 1.04, 95% CI 0.96-1.13; moderate certainty of evidence).

## INTRODUCTION

Essential fatty acids (EFA) are polyunsaturated fatty acids (PUFA) that are necessary for health but must be provided by foods because they cannot be synthesized by the body. There are two families of EFA, omega-3 (ω-3) and omega-6 (ω-6). The main omega-3-fatty acids are alpha-linolenic acid (ALA), an essential fatty acid obtained from plant food (flaxseed, soybean, canola) and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), from shellfish and fish [1]. They can also be found in dietary supplements and prescription medications [2]. Linoleic acid is a polyunsaturated omega-6 fatty acid.

Omega-3-fatty acids and its bioactive lipid mediators may reduce inflammatory markers, reduce oxidative stress, mitigate hypercoagulation, and thus, potentially lower the cardiovascular complications due to COVID-19 [3].

Omega-3-supplementation is recommended by the American Heart Association to prevent clinical CVD events in patients with prevalent CHD, such as a recent MI [4], and as monotherapy or as an adjunct to other lipid-lowering agents in patients with hypertriglyceridemia [5].

In an app-based survey of 327,720 UK participants, the use of omega-3 fatty acids, was associated with a lower risk of SARS-CoV-2 infection by 13% (95% CI 8%-16%), after adjusting for potential confounders [6]. A cross-sectional study of 100 hospitalized patients with COVID-19 at a US medical center showed that there was no significant association between adequate levels (≥5.7%) versus inadequate levels ( <5.7%) of omega-3 index (O3I, RBC EPA+DHA levels) and death (adjusted OR for age and sex 0.28 (0.03, 1.26 , P=0.11)] [7].

Three meta-analyses of RCTs (25 unique RCTs; N=1015 to 3574) that compared fatty acid supplements given to critically-ill adult patients with ARDS (non-COVID) in the ICU showed no significant difference in mortality between groups given and not given, although ventilation duration was significantly reduced (very low to low certainty of evidence) [8–10]. Adverse events in the 2 meta-analyses [8,9] did not differ significantly between groups.

## REVIEW METHODS

We included studies with the following inclusion criteria:

- P – Patients diagnosed with COVID-19
- I – Oral fatty acid supplements plus Standard of care
- C – Placebo or No treatment plus Standard of care
- O – mortality, clinical deterioration/ development of ARDS, need for mechanical ventilation, hospital length of stay, time to clinical improvement/ recovery, improvement in Chest CT Scan/ X-ray, virologic clearance by PCR test, adverse effects
- S – RCTs, CCTs, observational studies (cohorts, case-control studies, case reports)
- Subgroup analysis - Severity of disease (mild, moderate, severe); Oxygen requirement (non-O2 requiring, O2 requiring, mechanically ventilated), age, comorbidity, dosage (if this is variable among studies)

We excluded virgin coconut oil since there is a separate Philippine Living COVID CPG review on this topic. We also excluded studies on prevention of COVID-19.

We searched the following until 3 April 2021:

a. COVID living evidence databases such as COVID-19 Open Living Evidence Synthesis: https://covid-nma.com/; Australian Guidelines for the Clinical Care of People with COVID-19 (https://covid19evidence.net.au/, WHO Therapeutics and COVID-19: living guideline: https://www.who.int/publications/i/item/therapeutics-and-covid-19-living-guideline and UpToDate.com
b. MEDLINE (through PubMed), CENTRAL, MedrXIV/BiorxIV, ChinaXIV, Clinicaltrials.gov, and WHO-ICTRP, using search strategies with the concepts of COVID and fatty acids

## RESULTS

**Efficacy**

We found one RCT (N=128) that investigated the addition of omega-3 1000 mg capsule into a high-protein formula (30 kcal/kg/d) through enteral feeding, compared to high-protein formula alone. Doaei et al. enrolled patients with COVID-19 who were critically ill and admitted to Razi Hospital in Iran from May to July 2020 (mean age 64-

66 years, males 54-62%; BMI 27.4 to 27.7 kg/m$^2$). The authors reported significantly higher survival rate at one month in the fatty acid group compared with the control group (21% vs 3%, P = 0.003) [11]. When we did available- case analysis, where patients who died were included in the analysis, we found statistically significant reduction in mortality (29/35 vs 78/80; RR 0.85, 95% CI 0.73-0.99). Sensitivity analysis was also done to consider the impact of missing data of 7/42 (17%) for FA group vs 6/86 (7%) for control group. Worst-case scenario sensitivity analysis, assuming that all missing participants in the fatty acid group died, changed the conclusion to no significant difference (36/42 vs 78/86; RR 0.95, 95% CI 0.82-1.09), while conclusion for best case scenario remained unchanged but with a wider confidence interval (29/42 vs 84/86; RR 0.71, 95% CI 0.58-0.87) [11]. Evidence for this study was downgraded to low certainty of evidence due to high risk of attrition bias that changed conclusion with worst-case sensitivity analysis, and imprecision (wide CI crossing line of appreciable benefit, RR<0.75).

**Safety**

The study by Doaei did not contain adverse event reporting on the use of fatty acids. Indirect evidence from two systematic reviews and meta-analyses on patients with non-COVID 19 ARDS showed that adverse effects were mostly gastrointestinal, such as diarrhea, nausea/vomiting and abdominal distension. They were common in both groups given and not given fatty acids (range of 14 to 52%), the occurrence of which was not significantly different between the groups in both reviews (16%, 33/209 versus 14%, 30/218; RR 0.91, 95% CI 0.67-1.23 [8]; 52%, 321/620 versus 50%, 310/616; RR 1.04, 95% CI 0.96-1.13; very low quality of evidence because of indirectness) [9].

## RECOMMENDATIONS FROM OTHER GROUPS

The CDC, WHO and IDSA have no recommendations on the use of dietary supplements in the treatment nor prevention of COVID-19.

## RESEARCH GAPS

There are 16 registered trials on fatty acid supplementation in patients with COVID-19 (Appendix 3).

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## Appendix 1. Characteristics of Included Studies

| Study ID | Sample Size | Participants (age, sex, clin severity, etc) (inclusion/exclusion) | Intervention (generic/brand name; dosage, duration) | Comparator (generic/brand name; dosage, duration) | Outcomes |
|---|---|---|---|---|---|
| **Direct Evidence** | | | | | |
| **Doaei 2021** | N=128 | patients with COVID-19 who were hospitalized and critically ill (mean age 64-66 years, males 54-62%; BMI 27.4 to 27.7 kg/m2). | Omega-3 1000 mg capsule into a high-protein formula (30 kcal/kg/d) through enteral feeding, | High-protein formula through enteral feeding | Mortality<br>Laboratory markers |
| **Safety-Indirect Evidence** | | | | | |
| **Koekkoek 2019 meta-analysis**<br><br>**Searched Jan 2018** | 24 RCTs (N=3574) | Critically ill adult patients (>95% of patients >18 y of age).<br><br>8 on ARDS<br>3 on sepsis<br>3 trauma<br>7 general ICU | Enteral supplementation of FO (v-3 fatty acids) or FO-containing<br>EN<br>Excluded:<br>Parenteral FO | control or placebo intervention. | Mortality, ICU or hospital LOS, duration of mechanical ventilation, and infectious complications |
| **Langlois 2018 meta-analysis**<br><br>**Search date not stated** | 12 RCTs (N=1280) | Intensive care unit (ICU) patients with ARDS | Omega-3-FA | Placebo | PaO2/FiO2 ratio evaluated early (3-4 days) and later (7-8 days), mortality,<br>ICU/hospital length of stay (LOS), length of mechanical ventilation (MV) and infectious complications. |

## Appendix 2: GRADE Evidence Profile

| CERTAINTY ASSESSMENT | | | | | | | SUMMARY OF FINDINGS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates | | Relative effect (95% CI) | Anticipated absolute effects | |
| | | | | | | | With control | With FA | | Risk with control | Risk with FA |
| **Mortality (Available-case analysis) (follow up: 1 month** | | | | | | | | | | | |
| 115 (1 RCT) | Serious [a] | Not serious | Not serious | Serious [c] | None | ⨁⨁◯◯ LOW | 78/80 (97.5%) | 29/35 (82.9%) | **RR 0.85 (**0.73 to 0.99) | 975 per 1,000 | **146 fewer per 1,000** (from 263 fewer to 10 fewer) |
| **Mortality (Sensitivity analysis - Worst-case scenario) (follow up: 1 month)** | | | | | | | | | | | |
| 128 (1 RCT) | Serious [b] | Not serious | Not serious | Not serious | None | ⨁⨁⨁◯ MODERATE | 78/86 (90.7%) | 36/42 (85.7%) | **RR 0.95** (0.82 to 1.09) | 907 per 1,000 | **45 fewer per 1,000** (from 163 fewer to 82 more) |
| **Mortality (Sensitivity analysis - Best-case scenario) (follow up: 1 month)** | | | | | | | | | | | |
| 128 (1 RCT) | Serious [b] | Not serious | Not serious | Serious [c] | None | ⨁⨁◯◯ LOW | 84/86 (97.7%) | 29/42 (69.0%) | **RR 0.71** (0.58 to 0.87) | 977 per 1,000 | **283 fewer per 1,000** (from 410 fewer to 127 fewer) |

**CI:** Confidence interval; **RR:** Risk ratio

**Explanations**

[a] Available-case analysis used due to lost to ffup due to discontinued enteral feeding

[b] Attrition bias for the lost to ff-up due to discontinued enteral feeding

[c] Wide CIs with lower limit crossing appreciable benefit of RR<0.75

*Note: AE were not reported*

# Appendix 3: Characteristics of Ongoing Studies

| No. | Title/Study ID | Participants (age, sex, clin severity, etc) (inclusion/exclusion) | Intervention (generic/brand name; dosage, duration) | Comparator (generic/brand name; dosage, duration) | Outcomes |
|---|---|---|---|---|---|
| 1 | Control of inflammatory parameters with omega-3 fatty acid supplementation in adult patients with parenteral nutrition and respiratory infection by SARS-CoV-2: randomized clinical trial COVID-19.<br><br>EudrACT 2020-000705-86<br><br>Estimated primary completion date: 26-08-2020<br><br>Phase 4 RCT (N = 117)<br><br>Spain; univ hospital | 18-65 y.o. inclusion criteria:<br>• Age ≥ 18 years.<br>• Patients with at least 5 days of PN.<br>• Baseline liver parameters before PN: GGT, alkaline phosphatase < 100 U/dL and direct bilirubin <1.2 mg/dL al inicio de NP.<br>• Liver parameter alterations: GGT ≥ 300 U/dL, alkaline phosphatase ≥ 200 U/dL or direct bilirubin ≥1.8 mg/dL<br>• Forseeing to receive at least 5 days of PN.<br>• Admitted in the ICU of the Valle Hebron University Hospital<br>Principal exclusion criteria: - Lipids administration contraindicated<br>- Have a history of hypersensitivity of idiosincratic reactions to any component of intravenous lipid emulsions.<br>- Home parenteral nutrition patients<br>- Liver transplantation<br>- Liver parameters alterations before PN: 20% above upper normal values | TPN emulsion with 30% omega FA<br><br>OMEGAVEN (Omega-3-Fatty Acids 90 10%) | NUTRIFLEX LIPID SPECIAL (Essential amino acids 56%; GLUCOSE ANHYDROUS PH EUR 158%; LONG-CHAIN TRIGLYCERIDES 5%)<br><br>OMEGAFLEX SPECIAL (Essential amino acids 4%; GLUCOSE ANHYDROUS PH EUR 158%; Long chain TG 4%)<br><br>OLIMEL N9 (Essential AA 57%; GLUCOSE ANHYDROUS PH EUR 11%; Long chain TG 4%)<br><br>SMOFKABIVEN (Essential AA 5%; GLUCOSE ANHYDROUS PH EUR 125%; Long chain TG 36%)<br><br>SMOFLIPID (Long chain TG 20%) | Primary end point(s): Primary end point is the change of liver function parameters: GGT ; from the value the day of inclusion to the end of PN.<br><br>Secondary end point(s): Infection rate, hyperglycemia rate, hypertrygliceridemia rate, ICU and hospital length of stay. |
| 2 | A Randomised, Double-blind, Placebo Controlled Study of Eicosapentaenoic Acid (EPA-FFA) Gastro-resistant Capsules to Treat Hospitalised Subjects With Confirmed SARS-CoV-2<br>NCT04335032<br><br>Not yet recruiting<br>November 9, 2020 - July 31, 2021<br>RCT (N=284) | Inclusion: 18 y.o. and up; moderate-severe COVID<br><br>Exclusion: requiring oxygen support | EPA-FFA | Placebo | Primary: time to treatment failure;<br><br>Secondary: time to and amount of clinical improvement, change in recovery and survival rate |
| 3 | Use of a Medical Device, Viruxal Oral and Nasal Spray, for Treating the Symptoms of COVID-19 Via Application to the Naso- and Oropharyngeal Mucosa<br><br>NCT04357990<br>Recruiting<br>September 4, 2020 to March 2021 | Inclusion: 18 and up; symptomatic; mild-moderate disease.<br><br>Exclusion: severe disease | Viruxal Oral and Nasal Spray | Placebo spray | Primary: number of days until complete resolution of symptoms per group; number of hospital admissions per group.<br>Secondary: number of days until reduction of symptoms; number of adverse events per group |

| No. | Title/Study ID | Participants (age, sex, clin severity, etc) (inclusion/exclusion) | Intervention (generic/brand name; dosage, duration) | Comparator (generic/brand name; dosage, duration) | Outcomes |
|---|---|---|---|---|---|
| | RCT (N=128)<br><br>Iceland, National Hospital of Iceland | | | | |
| 4 | Nebulised surfactant for the treatment of severe COVID-19 in adults (COV-Surf): A structured summary of a study protocal for a randomized controlled trial<br><br>NCT04362059<br>EudraCT number: 2020-001886-35<br>Recruiting<br>October 2020 - November 2021<br>RCT (N=12)<br><br>England, 2 university hospitals | Inclusion: 18 and up; requiring endotracheal intubation.<br><br>Exclusion: imminent expected death within 24 hours; stage 4 chronic kidney disease | Lung surfactant | Placebo | Primary: improvement in oxygenation; pulmonary ventilation.<br><br>Secondary: adverse events, adverse device effects, change in pulmonary compliance, change in PEEP requirement of ventilatory support, clinical improvement, mechanical ventilation |
| 5 | An Investigation on the Effects of Icosapent Ethyl (VascepaTM) on Inflammatory Biomarkers in Individuals With COVID-19 (VASCEPA-COVID-19)<br><br>NCT04412018<br>Recruiting<br>June - December 2020<br>RCT (N=100)<br><br>Canada, Diagnostic and Cardiology clinic | Inclusion: 18 and up, symptomatic.<br><br>Exclusion: hospitalized, life expectancy < 3 months, acute end-organ injury, active severe liver disease, pancreatitis, pregnant, hemodynamic instability | Icosapent ethyl | Usual care | Primary: hs-CRP levels |
| 6 | PREPARE-IT. Prevention of COVID19 With EPA in Healthcare Providers at Risk - Intervention Trial<br><br>NCT04460651<br>Recruiting<br>August 2020 - January 2021<br>RCT N=2000<br>Argentina, Clinic | Inclusion: 18 and up, medical workers, with exposure to aerosol-generating procedure with COVID patients, relatives of COVID-19 index cases, lab staff running COVID-19 tests | Icosapent ethyl | Placebo | Primary: COVID positive, highest mean WHO descriptive score of COVID-19.<br><br>Secondary: hospital length of stay, mechanical ventilation, hospital admissions, rate of total events |
| 7 | Randomized, Open-label, Parallel Study to Investigate Safety and Efficacy of CARDIO Softgels Plus Best Standard-of-care vs. Best Standard-of-care Alone on a Former Smoker and/or Steroid-resistant Asthma Population With COVID-19 Infection | Inclusion: 18-75 yo, former smoker, admitted, mild-moderate disease, not of child-bearing potential or using birth control for duration of study.<br><br>Exclusion: antiretroviral agents, oxygen support, uncontrolled hypotension, renal impairment, GI symptoms | CARDIO softgel + standard of care | Standard of care | Primary: oxygenation requirements.<br><br>Secondary: clinical improvement, clinical status, CT or X-ray findings, time to clinical recovery, hospitalization period, amount of time on ventilator, ICU stay, QoL, all-cause mortality, temperature |

| No. | Title/Study ID | Participants (age, sex, clin severity, etc) (inclusion/exclusion) | Intervention (generic/brand name; dosage, duration) | Comparator (generic/brand name; dosage, duration) | Outcomes |
|---|---|---|---|---|---|
| | NCT04465513<br>Not yet recruiting<br>August 2020 - August 2021<br>RCT (N=100)<br><br>Canada | | | | measurements, oxygen saturation measurements, COVID-19 QoL measurements |
| 8 | The Effect of Omega-3 Supplements on the Serum Levels of Selected Cytokines Involved in Cytokine Storm of Covid-19; A Randomized Clinical Trial in the Covid-19 Uninfected Jordanian People<br><br>NCT04483271<br>Enrolling by invitation<br>October - December 2020<br>RCT N=100<br><br>Jordan | Inclusion: 20-66 y.o. with no medical diagnosis of COVID-19 infection.<br><br>Exclusion: chronic immune problems, pregnant, breastfeeding, using hormonal contraceptives | 1000mg wild salmon and fish oil complex, which contains 300mg of omega3-FA | No intervention | Primary: IL-1 beta, IL-6, TNF alpha.<br><br>Secondary: lipid profile, fasting blood glucose |
| 9 | Omega-3 Supplementation for the Treatment of COVID-19 Infection-Related Olfactory Dysfunction<br><br>NCT04495816<br>Recruiting<br>August - November 2020<br>RCT N=176 | Inclusion: 18 and up with olfactory dysfunction associated with COVID-19.<br><br>Exclusion: pre-existing olfactory dysfunction, chronic rhinosinusitis, hsitory of sinus surgery, current use of nasal steroid sprays or omega-3 supplementation | Omega-3 supplementation | Placebo | Brief Smell Identification Test |
| 10 | A Pragmatic Randomized Trial of Icosapent Ethyl for High-Cardiovascular Risk Adults (MITIGATE)<br><br>NCT04505098<br>Recruiting<br>August 2020 - August 2021<br>RCT N=16500<br><br>United States, California | Inclusion: 50 and up, no history of confirmed COVID-19, established ASCVD.<br><br>Exclusion: receipt of IPE within 12 months before enrollment, omega-3 fatty acid usage, pregnant or planning to become pregnant, hospitalization for MI and/or elective PCI within past month, receiving triple anti-thrombotic therapy, stage D heart failure, severe liver disease, end-stage renal disease, metastatic cancer, institutionalized and/or palliative care | Icosapent ethyl | Usual care | Primary: moderate-severe confirmed viral URIs, worst clinical status due to URI.<br><br>Secondary: all-case mortality, CV event, hospitalization, ED visits |
| 11 | A Randomized, Parallel-group Treatment, Quadruple Masked, Two-arm Study, to Assess the Effectiveness of Cod Liver Oil Compared to Placebo in the Prevention of | Inclusion: 18 years and older.<br><br>Exclusion: renal failure, hypercalcemia, liver cirrhosis, sarcoidosis, granulomatous disease, | Cod liver oil | Corn oil | Primary: COVID positive; respiratory tract infection. |

| No. | Title/Study ID | Participants (age, sex, clin severity, etc) (inclusion/exclusion) | Intervention (generic/brand name; dosage, duration) | Comparator (generic/brand name; dosage, duration) | Outcomes |
|---|---|---|---|---|---|
| | Covid-19 and Airway Infections in Healthy Adults<br><br>NCT04609423<br>Recruiting<br>November 2020 - May 2021<br>RCT N=80000<br><br>Norway, university hospital | pregnancy or planned pregnancy, vegan diet, age >75, previous COVID-19 disease | | | Secondary: hospitalization due to COVID-19, ICU due to COVID-19, all-cause hospitalization, number of visits at GP for infections, number of GP visits |
| 12 | Resolving Inflammatory Storm in COVID-19 Patients by Omega-3 Polyunsaturated Fatty Acids - A Single-blind, Randomized, Placebo-controlled Feasibility Study<br><br>NCT04647604<br>Recruiting<br>June 2020 - April 2021<br>RCT N=40<br><br>Sweden | Inclusion: 18 and up, COVID-19 positive, requiring hospitalization.<br><br>Exclusion: according to intervention contraindications, pregnancy and breastfeeding | Docosahexaenoic acid(DHA) + eicosapentaenoic acid (EPA) | Placebo | Primary: inflammatory biomarkers<br><br>Secondary: length of hospital stay, ICU need, mortality |
| 14 | Efficacy and Safety of Ozonised Oil (HOO) as Adjuvant Nutrition Supplement in COVID-19 Patients With Mild-to-Moderate Disease - HOO-COVID Project<br><br>NCT04651387<br>Not yet recruiting<br>January- June 2021<br>RCT N=74 | Inclusion: 18-80 yo, COVID-19 severity score < 6, hospitalized < 48 hours.<br><br>Exclusion: pregnancy and breastfeeding, severe COVID, ventilator, requiring oxygen support, liver failure, alcohol and drug abuse | Ozonised oil capsule | Standard of care | Primary: viral load.<br><br>Secondary: virologic clearance, SaO2, hospitalization stay, ICU, COVID severity score, in-hospital mortality |
| 15 | Anti-inflammatory/Antioxidant Oral Nutrition Supplementation in COVID-19 (ONSCOVID19)<br><br>NCT04323228<br>Not yet recruiting<br>May 1 - October 1, 2020<br>RCT (N=40)<br><br>Saudi Arabia | 18-65 yrs old, SARS-COV-2 patients, stable, not requiring ICU admission | Enriched Oral Nutritional Supplement (ONS) (enriched in eicosapentaenoic acid, gamma-linolenic acid and antioxidants)<br>14.8 g protein, 22.2 g fat, 25 g carbohydrate, 355 kcal, 1.1 g EPA, 450 mg DHA, 950 mg GLA, 2840 IU vitamin A as 1.2 mg β-carotene, 205 mg Vitamin C, 75 IU vitamin E, 18 ug Selenium, and 5.7 mg Zinc | Control-ONS<br><br>(iso-caloric -isonitrogenous product)<br><br>Will have the same macronutrient composition, calorie density, and normal concentrations of vitamin A, C, E, Selenium and zinc | Change from baseline score of Nutrition risk screening-2002;<br><br>Serum ferritin; IL-6;CRP; serum TNF-alpha;MCP-1 (Time frame: 3 months) |

| No. | Title/Study ID | Participants (age, sex, clin severity, etc) (inclusion/exclusion) | Intervention (generic/brand name; dosage, duration) | Comparator (generic/brand name; dosage, duration) | Outcomes |
|---|---|---|---|---|---|
| 16 | Treatment with Omega-3 polyunsaturated fatty acids in COVID-19 patients. A single-blind, randomized, placebo-controlled feasibility study<br><br>EUCTR2020-002293-28-SE<br>RCT | 18 years of age; COVID-19 positive or typical CT image of COVID-19 infection; Clinical status requiring hospitalization. | INTERVENTION: Trade Name: Omegaven IV Emulsion for infusion Other descriptive name: HIGHLY REFINED FISH OIL | Placebo | PRIMARY OUTCOME: Changes in a panel of inflammatory biomarkers measured in blood samples, urine samples and released from ex vivo stimulated leukocytes after 5 days of treatment.<br><br>SECONDARY OUTCOME:<br><br>1. Changes in proresolving mediators after 5 days of treatment<br><br>2. Changes in omega-3 index in the erythrocyte fraction after 5 days of treatment<br><br>3. Changes in cardiac biomarkers (Troponin, NTproBNP) after 5 days of treatment<br><br>4. Changes in biomarkers of organ damage (LD, creatinine) after 5 days of treatment<br><br>5. Changes in thrombosis and coagulation parameters (platelet count, coagulation) after 5 days of treatment<br><br>6. Changes in infectious load (PCT, SARS-CoV2-RNAemia, antibodies) after 5 days of treatment<br><br>7. Effects on clinical parameters (NEWS2, oxygen need, length of hospital stay, ICU need, complications, mortality) |

## Q10. Should N-acetylcysteine be used as an adjunct treatment for patients diagnosed with COVID-19?

*As of 30 June 2021*

RECOMMENDATION

**We recommend against the use of intravenous N-acetylcysteine as adjunct treatment for patients with COVID-19 infection.** *(Moderate certainty of evidence; Strong recommendation)*

***Consensus Issues***

The panel distinguished between the oral and intravenous (IV) preparations of N-acetylcysteine (NAC), noting in part the cost of the IV agent.

A study included in this review which compared NAC and placebo among suspected or confirmed COVID-19 patients found no significant difference on its primary and secondary outcomes (i.e., mortality, invasive mechanical ventilation and ICU admission). However, NAC may essentially still be used for its other clinical indications (i.e., as mucolytic) on patients with COVID-19, but not necessarily for the treatment of COVID-19.

There were also a few studies included in the review that compared IV-NAC and placebo among ARDS patients, and although it was also noted that NAC has no ancillary role on the treatment of ARDS, it is used for intubated patients for its mucolytic and immunomodulating properties.

## KEY FINDINGS

One randomized controlled trial comparing NAC to placebo with 135 participants was found to have no significant difference compared to control for mortality, invasive mechanical ventilation, ICU admission, length of hospital and ICU stay. A case series of ten respirator-dependent patients who responded to IV NAC showed reduction in inflammatory markers wherein six patients rebounded once NAC was discontinued and eight were discharged while two remained hospitalized. Indirect evidence in a low-quality systematic review of NAC vs placebo in patients with Acute Respiratory Distress Syndrome failed to show any difference in the mortality, but significantly reduced ICU stay.

## INTRODUCTION

N-acetylcysteine, a well-known mucolytic and antidote against paracetamol intoxication, is a thiol precursor of reduced glutathione with antioxidant properties. Its potential role in COVID-19 treatment has been postulated by several studies to be due to its antioxidant and anti-inflammatory properties with its conversion to reduced glutathione (GSH). It is found to inhibit reactive oxygen species (ROS) formation and pro-inflammatory cytokines and increase the number of CD4+ T cells and nitric oxide (NO) production [1,2]. NAC has also been shown to inhibit the NLRP3 inflammasome pathway and gene expression of TNF-$\alpha$, both linked to inflammatory cell death in SARS-1 patients [3]. Its antibacterial properties, including inhibition of biofilm formation and biofilm disruption, may reduce the risk of secondary bacterial infection as a complication of COVID-19 [4]. The protective effect of NAC in reestablishing

glutathione levels, scavenging reactive oxygen and supporting mitochondrial bioenergetics may also be of benefit for COVID-19-related liver injury [5].

## REVIEW METHODS

Existing randomized controlled trials and living systematic reviews, including COVID-19 databases and CPGs (NICE CENTRAL), publications (PubMed, Google Scholars, Ovid, Herdin), including pre-print (Medrxiv, Biorxiv, Chinaxiv) and trial registries (WHO, ICTRN, ChiCTR, EU) were searched using the following keywords: “N-acetylcysteine”, “acetylcysteine”, “N-acetyl-L-cysteine”, ”NALC”, “NAC” and “adjunct”, RCT, systematic reviews and COVID-19 related terms in the search strategy.

The following PICO criteria were used:

| | |
|---|---|
| Population | COVID-19 patients, adults 18 years and above, positive for COVID-19, mild-to severe cases, inpatient and outpatient |
| Intervention | N-acetylcysteine, oral or intravenous form, as single agent used adjunctively with usual care or as per institution/center/hospital standard protocols |
| Comparator | Placebo with usual care or standard protocols |
| Outcome/s | Mortality, Clinical deterioration/ development of ARDS, Need for mechanical ventilation, Hospital length of stay, Time to clinical improvement/ recovery, Improvement in Chest CT Scan/ X-ray, Virologic clearance by PCR test, Adverse effects, O2 requirement, Severity of disease, Dosage, |
| Study Designs | Randomized controlled trials, Systematic Reviews, Cohort studies |

## RESULTS

There was one randomized controlled trial that compared NAC to placebo in 135 adults with suspected (5%) or confirmed (95%) COVID-19. Patients had a mean age of 58 years, 2/3 of whom had more than 50% findings on computed tomography and required oxygen supplementation. All except one were classified as category 4 or 5 in the WHO 7-point scale. A dose of 21 grams/L of NAC was administered intravenously in two doses over 20 hours for the intervention group (IG) and placebo for control. All patients received standard of care, which included $O_2$ supplementation, invasive ventilation and empiric ceftriaxone 2g/day and azithromycin 500 mg/day. They found no significant differences between treated patients and controls in all the primary (need for intubation and invasive mechanical ventilation) and secondary outcomes (time of mechanical ventilation, length of ICU stay (median = 9, range = 5-14; p = 0.557), length of hospital stay (median = 11, range = 5.5-19; p = 0.872), and mortality. While NAC is commonly associated with nausea, vomiting and other gastrointestinal symptoms, there was no observable side effect in this study [8].

There was one case series of ten respirator-dependent COVID-19 patients where IV NAC was administered after one severely affected patient with G6PD-deficiency fully recovered. 30 grams NAC was given in three divided doses over 24 hours. There was overall reduction in inflammatory markers (C-reactive protein and ferritin) which rebounded in six patients following discontinuation of NAC. Eight of the 10 were eventually discharged [9].

We found a low-quality systematic review (SR) on NAC among adults with Acute Respiratory Distress Syndrome published in 2019 [7]. It included eight RCTs (n=289) and showed no significant difference in mortality (RR 0.83, 95% CI 0.62-1.11; p =0.21; $I^2$= 0%). However, NAC significantly shortened ICU stay in the random effects model (MD = -4.47 days, 95 %CI: -8.79 to -0.14; p=0.04; $I^2$=46%). There was substantial heterogeneity, small population sizes, and unclear to high risk of bias making the grade of evidence low for this SR [7].

## RECOMMENDATIONS FROM OTHER GROUPS

The Australian National COVID-19 Clinical Evidence Task Force does not recommend the use of N-acetylcysteine for the treatment of COVID-19 outside of randomized controlled trials with appropriate ethical approval. NAC, however, should still be used for its other established indications in people who have COVID-19.

Clinical practice guidelines from WHO, NICE, Canadian Task Force, UK NHS, EU CDC or PSMID made no recommendations for the use of N-acetylcysteine as an adjunctive treatment of COVID-19.

## ONGOING STUDIES

There are currently 13 registered clinical trials on NAC as an adjunct to treatment, five of which use NAC in combination with other therapeutic drugs and antioxidants. Eight clinical trials with N-acetylcysteine alone, in comparison to other drugs, are listed in Appendix 4.

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## Appendix 1: Characteristics of Included Studies

| Author, Year | Type of Study | POPULATION | INTERVENTION | COMPARATOR | OUTCOMES |
|---|---|---|---|---|---|
| De Alencar, 2020 Sept | RCT | 135 severe COVID-19 patients (confirmed or suspected) with O2 sat <94% or RR>24/min | 21 gm IV NAC for 20 hours (14 gm in first 4 hours then 7 gm in next 16 hours) | Dextrose 5% | Primary endpoint: need for mechanical ventilation<br><br>Secondary endpoint: time of mechanical ventilation, admission to ICU, time in ICU, mortality |
| Ibrahim, 2020 | Case series | One severe case of COVID-19 with G6PD deficiency and 9 respirator-dependent COVID-19 patients | 2 received bolus doses of 30gm and 20gm each; 8 received 600 mg q12h for 1 week; 8 requiring VV ECMO | None | Outcome noted: hospital discharge; reduction in serum CRP and ferritin levels; |
| Lu, 2019 | Meta-analysis | 8 studies included with N = 289 ICU patients; 6 reported mortality; 5 reported $PaO_2/FiO_2$; ; 3 reported length of ICU stay; population of ARDS patients | IV NAC (n =148) dose range 40-190 mg/kg | Placebo (5% dextrose or isotonic saline solution) (n= 141) | Primary outcome: overall mortality;<br><br>Secondary outcomes: length of ICU stay, duration of mechanical ventilation, glutathione levels, $PaO_2/FiO_2$ |

# Appendix 2: GRADE Evidence Profile

**Question**: NAC compared to placebo for COVID-19
**Setting**: Adults with mild to severe COVID-19

| CERTAINTY ASSESSMENT | | | | | | | NO. OF PATIENTS | | EFFECT | | CERTAINTY | IMPORTANCE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | NAC | Placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (follow up: range 5 days to 19 days)** | | | | | | | | | | | | |
| 1 | Randomised trials | Not serious | Not serious | Not serious | Serious [a] | None | 9/68 (13.2%) | 9/67 (13.4%) | **RR 1.01** (0.43 to 2.40) | **1 more per 1,000** (from 77 fewer to 188 more) | ⊕⊕⊕◯ MODERATE | |
| **Invasive mechanical ventilation (follow up: range 4 days to 15 days)** | | | | | | | | | | | | |
| 1 | Randomised trials | Not serious | Not serious | Not serious | Serious [a] | None | 14/68 (20.6%) | 16/67 (23.9%) | **RR 1.16** (0.62 to 2.18) | **38 more per 1,000** (from 91 fewer to 282 more) | ⊕⊕⊕◯ MODERATE | |
| **ICU admission (follow up: range 4 days to 15 days)** | | | | | | | | | | | | |
| 1 | Randomised trials | Not serious | Not serious | Not serious | Serious [a] | None | 32/68 (47.1%) | 29/67 (43.3%) | **RR 0.92** (0.63 to 1.33) | **35 fewer per 1,000** (from 160 fewer to 143 more) | ⊕⊕⊕◯ MODERATE | |

**CI:** Confidence interval; **RR:** Risk ratio

**Explanations**
[a] Confidence intervals are wide and traverses 1 in all outcomes, and therefore does not differ significantly from placebo.

**Question**: NAC compared to placebo for Acute Respiratory Distress Syndrome
**Setting**: Adults years and above with moderate to severe ARDS

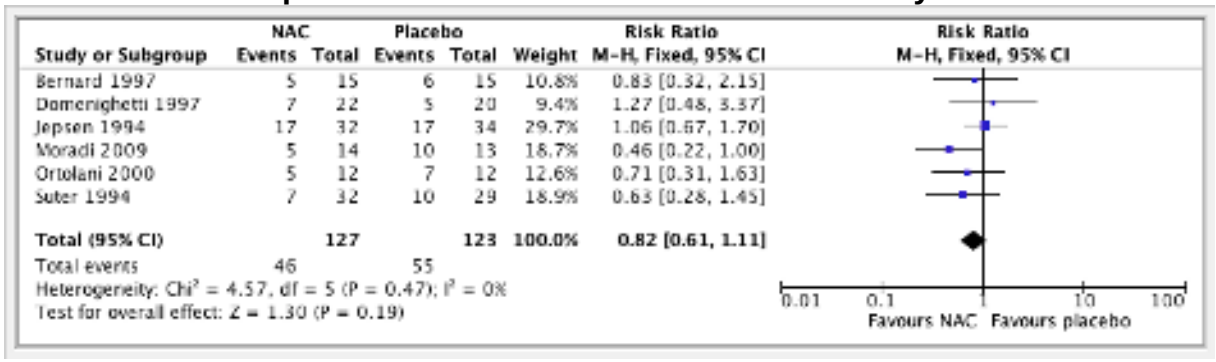
| CERTAINTY ASSESSMENT | | | | | | | NO. OF PATIENTS | | EFFECT | | CERTAINTY | IMPORTANCE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | NAC | Placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (follow up: range 5 days to 19 days)** | | | | | | | | | | | | |
| 6 | Randomised trials | Serious [a] | Serious [b] | Not serious | Not serious | None | 55/123 (44.7%) | 46/127 (36.2%) | **RR 0.82** (0.57 to 1.11) | **65 fewer per 1,000** (from 156 fewer to 40 more) | ⊕⊕◯◯ LOW | |

**CI:** Confidence interval; **RR:** Risk ratio

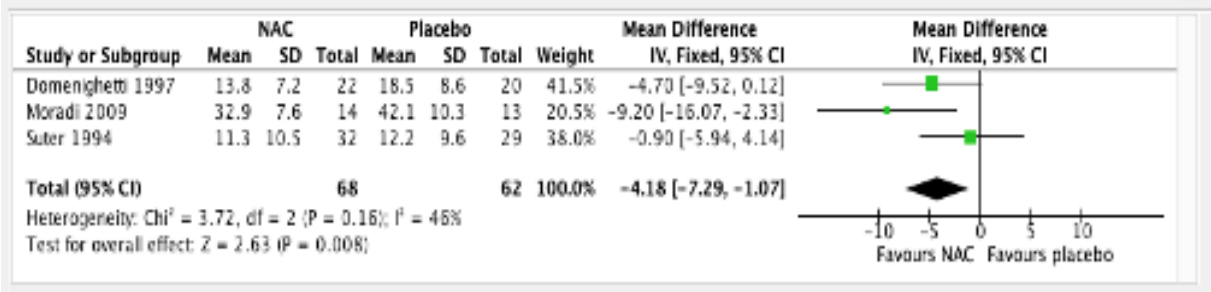
**Explanations**
[a] Only one study had low risk of bias. the rest were either unclear or had high risk with respect to randomization, allocation concealment)
[b] The studies had differences in their diagnostic criteria for ARDS, the formulation of NAD administration and mortality endpoints

## Appendix 3: Forest Plots

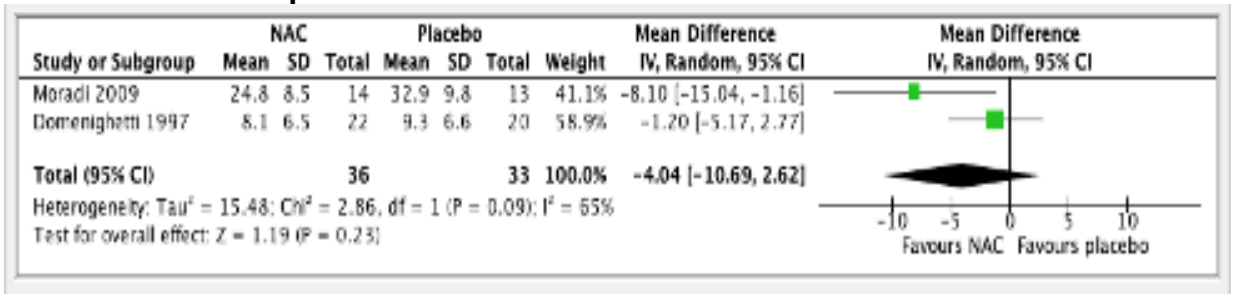
**A. NAC vs Placebo in ARDS. Forest plot of 6 studies which measured mortality.**




**B. NAC vs placebo in ARDS. Forest plot on the duration of stay in the ICU in mean number of days (3 RCTs)**




**C. NAC vs placebo in ARDS. Forest plot on the duration of mechanical ventilation in mean number of days. (2 RCTs)**



## Appendix 4: Characteristics of Ongoing Studies

| | TITLE | POPULATION | INTERVENTIONS | COMPARATOR | OUTCOME MEASURES |
|---|---|---|---|---|---|
| 1 | Treatment of 2019-nCoV pneumonia with NAC; UTN U1111-1250-3564 | Adults >18 years admitted with ARDS secondary to COVID; 140 patients to be recruited | IV NAC 300mg/kg total dose; 1st dose 200mg/kg then 100 mg/kg in 16 hours | Placebo IV | ABGs, reduction in in-hospital MR; reduction in need for endotracheal intubation |
| 2 | Evaluation of the efficacy and safety of oral N-acetylcysteine in treatment and recovery of patients with COVID-19 who are under treatment with routine protocols; IRCT 20200623047897N1 | Adults admitted with COVID-19 moderate to severe but stable | Regimen 1 OR Regimen 2 + 600 mg oral NAC TID | Regimen 1: Kaletra + HCQ and Regimen 2: Atazanavir + Ritonavir + HCQ | Fever/cough/dyspnea/o2 level/duration of; time to improv; secondary = O2 sat, rehospitalization, duration of hospitalization symptoms, i.e. cough shortness of lethargy; administration/laboratory parameters/ radiologic changes/ICU admission/death |
| 3 | A Study of N-acetylcysteine in Patients With COVID-19 Infection; NCT04374461 | Adults 18 years and older moderate-severe; 84 patients to be recruited | NAC | Peripheral blood | Outcome Measures: Arm A: no. of patient successfully extubated and/or transferred out of critical care due to clinical improvement; Arm B: no. of patients who are discharged from the hospital due to clinical improvement |
| 4 | Trial of Famotidine & N-Acetyl Cysteine for Outpatients With COVID-19; NCT04545008 | Adult 18 years and older diagnosed with COVID-19 (severity not mentioned); 42 participants | Arm 1: Oral NAC 600 mg TID; Arm 2 Oral NAC 1200 mg TID; Arm 3 Oral NAC 1800 mg TID | Combinations of NAC 600 mg, 1200mg, 1800 mg TID with Famotidine 20mg, 40 mg, 80 mg TID | Resolution of Covid; No. of participants with treatment-related adverse events as assessed by CTCAE v5.0; rate of hospitalization; |
| 5 | Inflammatory Regulation Effect of NAC on COVID-19 Treatment; NCT04455243 | Adult 18 years and older admitted to hospital, on oxygen supplement; 1180 participants | NAC 150 mg/kg q12hrs x 14 days (oral/IV) | Placebo | Time to recovery |
| 6 | Efficacy of N-Acetylcysteine (NAC) in Preventing COVID-19 From Progressing to Severe Disease; NCT04419025 | Adult 18 years and older, healthy, known or suspect with mild to moderate COVID-19 disease; 200 participants | Inpatients: NAC 25mg/kg PO q4hrs until discharge; NAC 1200 PO BID x 1 week post-discharge; OPD NAC 2400 mg PO then 1200 mg PO BID x 2 weeks | No NAC | Decrease in respiratory rate; hospital length of stay (LOS); need for mechanical ventilation; length of time intubated; need for hospitalization; recovery disposition |
| 7 | A Study to Evaluate OP-101 (Dendrimer N-acetyl-cysteine) in Severe Coronavirus Disease 2019 (COVID-19) Patients; NCT04458298 | Adult 18 years and older with severe COVID-19; 24 participants | OP-101 (dendrimer NAC) on single IV infusion of 1) OP-101 2 mg/kg; 2) 4 mg/kg; and 3) 8mg/kg | Placebo | No. of participants with Adverse events (assessed by CTCAE v4.0); time to improvement in clinical status assessment (WHO 7-pt ordinal scale); time to resolution of fever (>48 hours) without antipyretics for patients with fever; time to improved O2'n; Change in WHO 7-pt ordinal scale; time to discharge from hospital; %age of alive patients; No. of days with Resting RR > 24/min, hypoxemia, |
| 8 | Antioxidants as Adjuvant Therapy to Standard Therapy in Patients With COVID-19; NCT04570254 | Child, adult, older adult; 11 participants | 1) Vitamin C 1 gm q12hr; 2) Vitamin E 800 mg q24 hours; 3) Melatonin 50 mg q24h; 4) NAC 600 mg q12h (all for 5 days) | Pentoxifylline 400 mg q12hrs administered to all patients | Death from any cause; percentage required orotracheal intubation, assisted mechanical ventilation, stay in ICU, measure lipoperoxidation in base and post-therapy samples, total antioxidant capacity, oxidative and antioxidant stress; effect of antioxidant therapy at level of organ failure |

## Q11. Should RAAS blockers be continued in patients with COVID-19?

*As of 30 June 2021*

RECOMMENDATION

**We recommend continuing maintenance RAAS blockers for hypertension among patients with COVID-19 infection.** *(Moderate certainty of evidence; Strong recommendation)*

*Consensus Issues*
There were no issues raised during the consensus panel meeting.

## KEY FINDINGS

Based on two RCTs (N=811) with moderate certainty of evidence, there is probably little or no significant reduction in the risk of deaths and severe disease for patients with hypertension and COVID-19 who continued RAAS blockers compared to those who discontinued RAAS blockers.

## INTRODUCTION

Renin-angiotensin-aldosterone system (RAAS) blockers have been hypothesized to be a double-edged sword in patients with COVID-19. By upregulating the angiotensin-converting enzyme 2 (ACE2) receptors, RAAS blockers may worsen COVID-19 since it is through the ACE2 enzyme that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters human cells. On the other hand, these drugs may be beneficial since they counteract the increase in angiotensin II formation that leads to increased pulmonary vascular permeability, thus preventing the consequent pulmonary edema and the end effect of further reduction of pulmonary function. Two recent systematic reviews (34 observational studies) showed definite benefit for reduction of mortality in patients with COVID-19 on RAAS blockers, compared to those not on RAAS blockers, but this was based on very low quality of evidence.

## REVIEW METHODS

We searched the following websites (COVID-19 Open Living Evidence Synthesis, Living Evidence on COVID-19, National COVID-19 Clinical Evidence Taskforce, WHO Therapeutics and COVID-19: living guideline) for living evidence on the topic. We searched trial registries (Clinicaltrials.gov, Chinese CTR and WHO ITCRP) for ongoing or completed trials. We also searched PubMED and the Cochrane Database of Systematic Reviews up to December 26, 2020 based on the following inclusion criteria:

| | |
|---|---|
| P | Patients with HTN and COVID-19 |
| I | Continuation of RAAS blockers |
| C | Discontinuation of RAAS blockers |
| O | Mortality, severe COVID, ICU admission, mechanical ventilation, adverse events |
| S | RCTs, controlled clinical trials |

# RESULTS

## Efficacy

We found two RCTs (N=811) that compared continuation versus discontinuation of RAAS blockers (Cohen 2021; Lopes 2021) [1,2]. The first RCT (REPLACE-COVID trial) (N=152) was a randomized open-label trial conducted in 20 large referral hospitals in seven countries worldwide. Admitted patients with COVID-19 and hypertension, who were on RAAS blockers were recruited [1]. Around half of the patients had mild COVID-19 disease on admission, while one-third had moderate disease; severe disease was seen in only 12% to 13% of patients. The most common comorbidities were diabetes (56% vs 48%) and dyslipidemia (45 vs 52%) in the continuation and discontinuation groups, respectively. The second RCT (BRACE-CORONA trial) (N=659) was conducted in 29 centers in Brazil which recruited patients with hypertension and mild to moderate COVID-19 who were taking RAAS blockers prior to admission. Median use of RAAS blockers was five years in both groups. The most common comorbidity was diabetes, reported in around a third of patients in both groups (33 vs 31%). Off label and adjuvant COVID- 19 therapies administered during follow-up were similar between groups.

Pooled analysis showed no significant difference in mortality (pooled RR 1.08, 95% CI 0.60-1.97; N=811; $I^2$=0%), and in ICU admission or mechanical ventilation (pooled RR 0.93, 95% CI 0.62-1.38; N=811; $I^2$=0%), with moderate certainty of evidence. Downgrading was done due to imprecision. In the Cohen study, there was a trend towards reduced risk of COVID-19 progression in those who continued RAAS blockers (RR 0.84, 95% CI 0.68-1.04).

Cohen also reported a lower global rank score for the continuation group (73, 95% CI 40-110) compared to discontinuation group (81, 95% CI 38-117), but this was not significant (beta coefficient [8, - 13 to 29]; p=0.61). A lower rank score means greater COVID severity. Subgroup analysis showed no effect modification by age, sex, race, baseline ACEI versus ARB therapy, chronic kidney disease, diabetes, or body-mass index for the primary endpoint or for length of hospitalization.

Based on the second study (Lopes), there was no significant reduction in in-hospital mortality (RR 0.80, 95% CI 0.30-2.12) and cardiovascular events (RR 0.80, 95% CI 0.30-2.12), but there was a significant reduction in mean length of hospitalization (MD -1.10, -2.15, -0.05; P=0.04). Subgroup analysis done in the same study did not show significant differences based on age, obesity, type of RAAS blockers, day of symptom onset to randomization, and opacities on chest CT scan. However, there was a significant interaction found among the treatment effect, oxygen saturation, and COVID-19 clinical severity on admission, with results slightly favoring the continuation group among patients with lower oxygen saturation and greater disease severity at presentation.

## Adverse events

The risk of any SAE was reported in the RCT by Cohen [1] in 39% (29/75) of the Continuation group and 36% (28/77) of the Discontinuation group (RR 1.06, 95% CI 0.71-1.60). For both RCTs, some outcomes reported as SAEs were also efficacy outcomes (e.g. all-cause death, ICU transfer for Cohen, and respiratory failure requiring mechanical ventilation for Lopes). The other reported SAEs were mainly

cardiovascular, renal, and neurological (i.e. shock requiring vasopressors, acute arrhythmia, acute myocardial infarction, myocarditis, new or worsening congestive heart failure, acute kidney injury requiring dialysis, delirium and encephalopathy, pulmonary embolism or deep vein thrombosis). There were no significant differences in all reported serious events (Cohen). There was also no indication if these events were related to the RAAS blockers or not. The reasons for switching of the assigned intervention as reported by Cohen for the Continuation group were: hypotension (n=11), hyperkalemia (n=2), poor oral intake with concern for volume depletion, and other reasons for clinical decision (n=4). For the Discontinuation group, ACEIs or ARBs were re-initiated due to hypertension (n=6) and acutely worsening heart failure (n=1). Both groups of patients switched after a median of 5 days (IQR 3-7). Sensitivity analysis using switching “as-treated” data showed no change in conclusion for mortality (pooled RR 0.84, 95% CI 0.42- 1.69) and for ICU admission or mechanical ventilation (pooled RR 0.90, 95% CI 0.61-1.34). As-treated analysis by Lopes for all SAEs and for one SAE by Cohen – namely, hypotension requiring hemodynamic support – did not show any significant difference from main ITT analysis.

## RECOMMENDATIONS FROM OTHER GROUPS

Position statements from numerous organizations and groups support the continuation of ACEIs/ARBs in patients with COVID-19 (including ESC, ISH, AHA) (March 2020) [5–7]. The WHO issued a scientific brief stating that patients on long-term therapy with ACE inhibitors or ARBs are not at higher risk of poor outcomes from COVID-19, but this came from low-certainty evidence (7 May 2020) [8]. NICE Guidance (May 2020) did not find any evidence that showed either increased or decreased risk of COVID-19 and its complications. Findings were based on two low-quality observational studies [9,10] from its search until April 1, 2020; NICE noted the well-understood risks of stopping treatment with an ACEI or an ARB, such as worsening heart failure or hypertension [11]. The Australian Guidelines for the clinical care of people with COVID-19 stated that there is currently no evidence to deviate from usual care, and strongly recommended that the use of ACEIs/ARBs should be continued unless contraindicated (4 March 2021) [12]. This was based on the substantial net benefits of the recommended alternative despite the lack of RCTs at the time the recommendations were drafted. Thus, the recommendation was based only on very low quality evidence from three large systematic reviews of observational studies, which reported that there was high certainty of evidence of harm from abruptly stopping the medications which could result in acute heart failure or unstable blood pressure [13–15].

## ONGOING STUDIES

There are nine registered clinical trials: one completed trial (IRCT20151113025025N3) has not been published, one suspended trial (NCT04330300), and seven ongoing trials (Appendix 4).

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## Appendix 1. Characteristics of Included Studies

| Study ID/Country/Setting | Sample Size | Participants | Intervention | Comparison | Cointerventions | Outcomes |
|---|---|---|---|---|---|---|
| **Cohen**<br><br>7 countries worldwide/20 large referral hospitals | N=152 | Inclusion: aged 18 years and older who were admitted to hospital with COVID-19 and HTN and were receiving a renin–angiotensin system inhibitor before admission<br>All were RT-PCR for SARS-CoV-2 positive except for 1 in RAAS continuation group due to limited testing ability and who died in the interim<br>Exclusion: contraindications to continuation or discontinuation of renin–angiotensin system inhibitor therapy<br>Mean age of participants was 62 years (SD 12), 68 (45%) were female, mean BMI, 33 kg/m² (SD 8), and 79 (52%) had diabetes<br>Baseline char: similar, except for ACEI slightly more common in discontinue RAAS group (49%) than continue RAAS (33%)<br>Severity of disease: Mild in 51% (Continue RAAS) and 55% (discontinue RAAS); Severe in 12 vs 13 | Continuation of RAAS group n=75 | Discontinuation RAAS group n=77 | Co-interventions:<br>Remdesivir: 23 vs 18%<br>HCQ: 4 vs 8<br>Systemic anticoag: 15 vs 10<br>High dose steroids: 15 vs 10<br>Convalescent plasma: 3 vs 1<br>Lopinavir/ritonavir: 1 vs 3 | Primary outcome: Global rank score*<br><br>Secondary outcomes: Time to all cause death; Length of hosp. stay; Length of ICU stay or invasive mechanical ventilation; AUC of the SOFA<br><br>Exploratory endpoints: ICU admission or invasive mechanical ventilation; Hypotension requiring haemodynamic support; Any severe adverse event † |
| **Lopes**<br><br>Brazil/26 hospitals | N= 659 | Hospitalized patients with HTN and mild to moderate COVID-19 who were taking ACEIs or ARBs prior to hospitalization<br>Median age 55.1 years (IQR, 46.1-65.0 years), 14.7%were aged 70 years or older, 40.4% were women | Continuation (n = 325) of ACEIs or ARBs.<br>for duration of 30 days | Discontinuation (n = 334)<br>for duration of 30 days | Concomitant therapies:<br>Azithromycin 91.1 vs 90.1 %<br>Anticoag 67.1 vs 66.5<br>Antiviral 41.5 vs 42.5<br>CQ or HCQ 17.8 vs 21.6<br>Tocilizumab 2.2 vs 5.1<br>Corticosteroid 48.3 vs 50.6<br><br><u>Cointervention:</u><br>Did not recommend any specific treatment modification beyond discontinuing or continuing use of ACEIs or ARBs.<br>The study team provided oversight on drug replacement, and those decisions were made based on current treatment guidelines<br>Patients were treated for COVID-19 according to current local standards of supportive care without systematic use of experimental therapies. | Primary: Mean days alive and out of hospital<br><br>Secondary outcomes: Length of hospitalization; Death; In-hospital death; Cardiovascular death; COVID-19 progression; Respiratory failure requiring invasive mechanical ventilation; Shock requiring vasopressors<br><br>Cardiovascular outcomes: Acute MI; New or Worsening heart failure; Acute Kidney failure requiring hemodialysis;<br><br>Thromboembolic events: Stroke or TIA |

* incorporates: time to death, duration of mechanical ventilation, time on renal replacement or vasopressor therapy, and multiorgan dysfunction during the hospitalisation (lower rank score signifies more severe COVID)

† Worsening dyspnea or resp. failure; AKI requiring RRT; AKI >2x creatinine increase; Acute arrythmia; Pulmonary embolism or DVT; AMI; Myocarditis; New or worsening HF; Delirium or encephalopathy

# Appendix 2. GRADE Evidence Profile

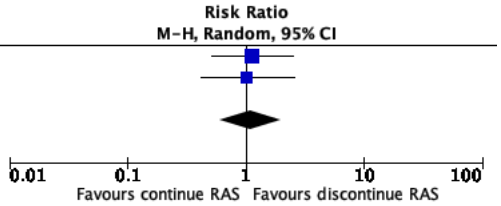
| CERTAINTY ASSESSMENT | | | | | | | NO. OF PATIENTS | | EFFECT | | CERTAINTY | IMPORTANCE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | RAAS blockers be continued | Discontinued | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality** | | | | | | | | | | | | |
| 2 (N=811) (Cohen; Lopes) | randomised trials | not serious | not serious | not serious | serious [a] | none | 20/400 (5.0%) | 19/411 (4.6%) | **RR 1.08** (0.60 to 1.97) | **4 more per 1,000** (from 18 fewer to 45 more) | ⊕⊕⊕◯ MODERATE | |
| **ICU or Mech ventilation** | | | | | | | | | | | | |
| 2 (N=811) (Cohen; Lopes) | randomised trials | not serious | not serious | not serious | serious [a] | none | 41/400 | 46/411 | **RR 0.93** (0.62 to 1.38) | **8 fewer per 1,000 (from 43 fewer to 43 more)** | ⊕⊕⊕◯ MODERATE | |
| **COVID progression** | | | | | | | | | | | | |
| 1 (N=659) (Lopes) | not serious | not serious | not serious | serious [a] | none | | 105/325 (32.3%) | 128/334 (38.3%) | **RR 0.84** (0.68 to 1.04) | **61 fewer per 1,000** (from 123 fewer to 15 more) | ⊕⊕⊕◯ MODERATE | |
| **Any SAE** | | | | | | | | | | | | |
| 1 (N=152) (Cohen) | not serious | not serious | not serious | serious [a] | none | | 29/75 (38.7%) | 28/77 (36.4%) | **RR 1.06** (0.71 to 1.60) | **22 more per 1,000** (from 105 fewer to 218 more) | ⊕⊕⊕◯ MODERATE | |

# Appendix 3. Forest plots from pooled RCTs

## A. Mortality: continuation vs discontinuation of RAAS

| Study or Subgroup | Continue RAS Events | Total | Discontinue RAS Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Cohen | 11 | 75 | 10 | 77 | 56.8% | 1.13 [0.51, 2.50] |
| Lopes | 9 | 325 | 9 | 334 | 43.2% | 1.03 [0.41, 2.56] |
| Total (95% CI) | | 400 | | 411 | 100.0% | 1.08 [0.60, 1.97] |
| Total events | 20 | | 19 | | | |

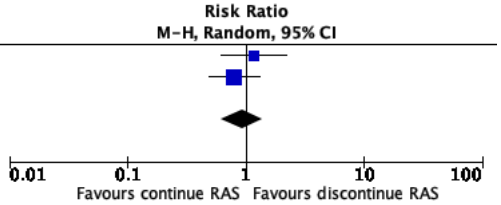
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 1 (P = 0.88); $I^2 = 0\%$
Test for overall effect: Z = 0.26 (P = 0.79)




## B. ICU or mechanical ventilation: Continue vs discontinue RAAS

| Study or Subgroup | Continue RAS Events | Total | Discontinue RAS Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Cohen (1) | 16 | 75 | 14 | 77 | 37.7% | 1.17 [0.62, 2.23] |
| Lopes (2) | 25 | 325 | 32 | 334 | 62.3% | 0.80 [0.49, 1.32] |
| Total (95% CI) | | 400 | | 411 | 100.0% | 0.93 [0.62, 1.38] |
| Total events | 41 | | 46 | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.84$, df = 1 (P = 0.36); $I^2 = 0\%$
Test for overall effect: Z = 0.38 (P = 0.70)

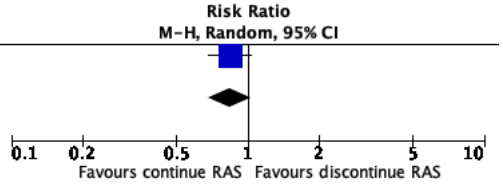



Footnotes
(1) ICU or mechanical ventilation
(2) Resp failure requiring invasive mechanical ventilation

## C. COVID progression: Continue vs discontinue RAAS

| Study or Subgroup | Continue RAS Events | Total | Discontinue RAS Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Lopes | 105 | 325 | 128 | 334 | 100.0% | 0.84 [0.68, 1.04] |
| Total (95% CI) | | 325 | | 334 | 100.0% | 0.84 [0.68, 1.04] |
| Total events | 105 | | 128 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.61 (P = 0.11)



## Appendix 4: Characteristics of Ongoing Studies

| | Clinical Trial ID / Title | Sample Size | Population | Intervention Group(s) | Comparison Group(s) | Clinical Outcomes |
|---|---|---|---|---|---|---|
| 1 | NCT04330300<br><br>CORONAvirus Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers InvestigatiON: A Randomized Clinical Trial (CORONACION) | N=2414 | Men and non-pregnant women aged 60 or over with known diagnosis of hypertension, currently using ACEi or ARB for the treatment of hypertension and COVID-19 naïve (i.e. not known to be infected) | Continue ACEi/ARB antihypertensive | Alternative anti-hypertensive medication Switch to an alternative BP medication (specifically a Calcium channel blocker [CCB] or Thiazide/Thiazide-like diuretic at an equipotent blood pressure lowering dose). The choice of either CCB or Thiazide/Thiazide-like anti-hypertensive provided as alternative therapy will be at the discretion of the physician | Primary: Death (All-cause mortality)<br><br>Secondary: Intubation in ICU; Hospitalization for non-invasive ventilation (NIV) |
| 2 | NCT04351581<br><br>Effects of Discontinuing Renin-angiotensin System Inhibitors in Patients With COVID-19 | N=215 | Verified COVID-19; Hospital admitted; Daily administration of RAAS-inhibiting therapy; Age 18 years and above | Continuation of ACEi/ARB | Discontinuation of ACEi/ARB | Primary: Days alive and out of hospital<br><br>Secondary: Worsening of COVID-19; Severe respiratory insufficiency; Referral to ICU, 30-d mortality, etc. |
| 3 | NCT04353596<br><br>Stopping ACE-inhibitors in COVID-19 | N=208 | Proven and symptomatic SARS-CoV2 infection ≤ 5 days; Age ≥ 18 years; Chronic (≥ 1 month) ACEI/ARB therapy for treatment of arterial hypertension, diabetes mellitus, heart failure or coronary artery disease; Stable hemodynamic conditions allowing to stop or continue treatment with ACEI/ARB (systolic blood pressure ≤180mmHg) | Continuation of ACEi/ARB | Discontinuation of ACEi/ARB | Primary: Combination of maximum Sequential Organ Failure Assessment (SOFA) Score and death<br><br>Secondary: Maximum SOFA, Non-invasive ventilation, Renal replacement therapy, etc. |
| 4 | IRCT20151113025025N3<br><br>Clinical Trial of renin-angiotensin-aldosterone system inhibitors with halting their administration and the effect on clinical outcomes of patients with corona virus disease-2019 (COVID-19) referring to Sina Hospital in 2020 | N=60 | Patients who have suggestive signs of COVID-19 in their chest computed tomography scan, reported by a radiologist. Patients consuming angiotensin-converting enzyme inhibitors or angiotensin receptor blockers | Continuation of RAAS inhibitors | Discontinuation of RAAS inhibitors and shift to calcium blocker or beta-blocker | Primary: Death, ICU |
| 5 | NCT04364893<br>Suspension of Angiotensin Receptor Blockers and Angiotensin-converting Enzyme Inhibitors and Adverse Outcomes in Hospitalized Patients With Coronavirus Infection (COVID-19). A Randomized Trial | N=700 | Diagnosis of coronavirus (SARS-CoV)-2 infection confirmed by polymeRAASe chain reaction (PCR) test < 4 days before Visit 1 with signs of an acute respiratory infection<br>Age > 18 and < 70 years<br>CRP > 50 and < 150 mg/l<br>Admitted to a hospital or controlled facility (home quarantine is not sufficient) | Maintenance of ARBs and ACEIs | Suspension of ARBs and ACEIs | Primary: Median days alive and out of the hospital<br><br>Secondary: Number of participants with adverse cardiovascular outcomes and new worsening heart failure; Cardiovascular biomarkers related to COVID-19 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 6 | NCT04508985<br>Management of Renin-Angiotensin-Aldosterone System Blockade in Patients Admitted in Hospital With Confirmed Coronavirus Disease (COVID-19) Infection: The McGill RAAS-COVID-19 Randomized Controlled Trial | N=40 | Age ≥ 18 years old.<br>Hospitalization with a Covid-19 infection<br>Chronically treated with RAAS blockers (ACE inhibitors or ARBs on the last prescription prior to admission with a treatment duration ≥ 1 month | Temporarily holding the RAAS inhibitor [intervention] | RAAS inhibitor [continued standard of care] | Primary: Global rank score |
| 7 | EU CTR 2020-001206-35<br><br>Stopping ACE-inhibitors in COVID-19 - a randomized, controlled clinical trial | N=798 | Age: >18 yrs<br>Patients with proven SARS-CoV2 infection | discontinuation of prescribed ACEI/ARB-medication | Continuation of prescribed ACEI/ARB-medication | Primary: combination of the maximum SOFA scores measured during the course of the disease (≤30 days) and death; combination of intensive care admission, intubation and death. |
| 8 | NCT04493359<br>Switch or Maintenance of Renin-Angiotensin System Inhibitors in Patients With Covid-19: A Randomized Proof of Concept Trial | N=240 | Age: 18 to 80 yrs<br>Hypertension in use of renin-angiotensin system inhibitors<br>Confirmed COVID-19 infection by rt-PCR, serology tests or typical clinical presentation and chest CT.<br>Symptoms onset < 96h | Switch therapy: Renin-angiotensin system inhibitors will be changed for other anti-hypertensive classes | Maintenance therapy: Renin-angiotensin system inhibitors will be kept during in-hospital stay | Primary: Need for ICU or mortality<br><br>Secondary: High sensitivity troponin levels and covid-19 severity; ACE-2 activity and disease severity; ACE-2 activity with different Renin-angiotensin system inhibitors; Blood control and acute renal failure |
| 9 | EudraCT Number: 2020-001544-26<br>Effects of discontinuing renin-angiotensin system inhibitors in patients with COVID-19 | N=215 | 1. Verified COVID-19<br>2. Hospital admitted<br>3. Daily administration of RAAS-inhibiting therapy<br>4. Age 18 years and above | Continued treatment with angiotensin-converting enzyme inhibitors or angiotensin-II receptor antagonists | Discontinued treatment with angiotensin-converting enzyme inhibitors or angiotensin-II receptor antagonists | Primary: days alive and out of hospital within 14 days after recruitment<br><br>Secondary: occurrence of worsening of COVID-19, occurrence and time to occurrence of each of the components of the primary composite endpoint, kidney function (as assessed by plasma creatinin and eGFR), duration of index hospitalisation, 30 days-mortality, number of days alive during the intervention period, discharge beyond 30 days and number of readmissions after 30 days |

## Appendix 5. Summary of Serious Adverse Events

| Type of SAE | No. of studies (No. of participants) | Continue RAS blocker No. (%) | Discontinue RAS blocker No. (%) | RR (95% CI) |
|---|---|---|---|---|
| Acute myocardial infarction (ITT) | 2 (811) | 16/400 (4) | 26/411 (6.3) | 0.63 [0.34, 1.16] |
| Shock requiring vasopressors (ITT) | 2 (811) | 32/400 (8) | 36/411 (8.8) | 0.92 [0.58, 1.44] |
| Shock requiring vasopressors (AT) | 2 (691) | 21/367 (5.7) | 31/324 (9.6) | 0.60 [0.35, 1.03] |
| Myocarditis (ITT) | 2 (811) | 1/400 (0.25) | 2/411 (4.9) | 0.51 [0.05, 5.54] |
| Pericarditis (ITT) | 1 (659) | 0/325 (0) | 1/344 (0.29) | 0.34 [0.01, 8.41] |
| Hypertensive crises (ITT) | 1 (659) | 3/325 (0.92) | 1/344 (0.29) | 3.08 [0.32, 29.49] |
| Hypertensive crises (AT) | 1 (539) | 2/302 (0.66) | 1/237 (0.42) | 1.57 [0.14, 17.21] |
| New or worsening heart failure (ITT) | 2 (811) | 17/400 (4.25) | 14/411 (3.4) | 1.23 [0.62, 2.43] |
| AKI requiring dialysis (ITT) | 2 (811) | 18/400 (4.5) | 15/411 (3.6) | 1.23 [0.63, 2.41] |
| Thromboembolic events (ITT) | 2 (811) | 8/400 (2) | 7/411 (1.7) | 1.34 (0.24, 7.41) |
| Stroke or TIA (ITT) | 1 (659) | 3/325 (0.92) | 3/344 (0.87) | 1.03 [0.21, 5.05] |

*ITT, Intent to treat; AT, As treated; AKI, acute kidney injury; TIA Transient ischemic attack*

## Q12. Should statins be used as adjunctive treatment in patients with COVID-19?

*As of 29 October 2021*

RECOMMENDATION

**There is insufficient evidence to recommend statins as adjunctive treatment in patients with COVID-19.** *(Very low certainty of evidence)*

*Consensus Issues*
Due to perceived risk of harm, two panelists were inclined to suggest against the use of statins as adjunctive treatment in patients with COVID-19.

## KEY FINDINGS

Statins are lipid-lowering drugs known to have pleiotropic effects against inflammation and thrombosis. Very low quality of evidence from two randomized clinical trials showed that among COVID-19 patients admitted to the ICU, the only significant finding was a decrease in hospital stay. There was no significant benefit for the following outcomes: composite risk for adjudicated venous or arterial thrombosis, the risk for ECMO treatment, the risk for all-cause mortality, or the individual components of adjudicated venous thromboembolism, all-cause mortality, or need for mechanical ventilation.

## INTRODUCTION

Coronavirus disease (COVID-19) is characterized by a hyperactive immune system and a prothrombotic state.[1] Severe inflammation and thrombotic events, such as arterial thrombosis and venous thromboembolism, have been implicated in mortality of some COVID-19 patients.[2,3] Patients with a higher risk of COVID-19 disease include those with cardiovascular disease, many of whom are on maintenance statin therapy. Statins are a class of drugs known to decrease risk of thrombosis and are also known to have anti-inflammatory effects.[4] However, statins also upregulate the ACE2, which is the receptor through which the SARS-CoV-2 virus enters human cells.[5] Hence, it is important to establish whether statins can be continued during treatment for COVID-19 and whether statins can be used as an adjunct to COVID-19 treatment. This review aimed to study the effects of statins on clinical outcomes of COVID-19 patients.

There are several meta-analyses of observational studies that showed reduced mortality and reduced risk for severe COVID-19 among patients treated or maintained on statins, [6-9] with the meta-analyses of Diaz-Arocutipa et al. [6], Kollias et al. [7] and Yetmar et al. [8] adjusting for other factors. All these reviews included studies that had high variability in the type, dose, and duration of the statin that was used, the chronicity of intake, as well as patient admission type (outpatients, inpatients and/or ICU patients only). Several patients had comorbidities such as hypertension, coronary heart disease, and diabetes. Effect estimates were adjusted by methods such as propensity matching to reduce the effect of confounding factors but there was still risk of residual confounding in the observational studies. This highlights the need for more robust evidence on statin use in COVID-19 patients, particularly from randomized controlled trials.

## REVIEW METHODS

We conducted a literature search for studies published in 2019 to September 16, 2021. Databases searched were Pubmed, Cochrane Central Register of Controlled Trials (CENTRAL), Epistemonikos, and Google Scholar. Registries for ongoing or completed clinical trials were also searched (Clinicaltrials.gov, ISRCTN registry, World Health Organization International Clinical Trials Registry Platform). The following search terms were used: “statin”, “atorvastatin”, “ lovastatin”, “pravastatin”, “simvastatin” or “meglutol” together with “COVID-19”, “coronavirus”, “SARS-Cov-2” or “nCoV”. References of all studies were reviewed to identify other studies. Searches were limited to human studies, but were not limited in terms of language or country. The study types included were randomized controlled trials, systematic review and meta-analysis of randomized controlled trials as well as observational studies.

The PICO was as follows: Population – patients diagnosed with COVID-19; Intervention – statin therapy, whether as continuing maintenance medication or initiated only during hospitalization for COVID-19; Comparator – standard of care, no control, placebo; Outcomes – mortality, ICU admission, need for mechanical ventilation, length of hospital stay, days to recovery, viral load or cycle threshold, and worsening of symptoms. Adverse events were also included.

## RESULTS

Of 272 records identified from the search, only two randomized controlled trials were available for review: one by Bikdelli et al. [1,10] and another by Davoodi et al. [11] The former, though unpublished at this current time, was presented at the American College of Cardiology Scientific Session on May 16, 2021 in sufficient detail to allow appraisal and inclusion in this review.

It studied the clinical outcomes of critically-ill COVID-19 patients treated with atorvastatin versus placebo. The overall design was a 2x2 factorial design randomized controlled trial, where researchers investigated the safety and efficacy of two pharmacological regimens on outcomes of critically-ill patients with COVID-19. The first randomization involved an open-label assignment to intermediate versus standard dose prophylactic anticoagulation, and the second was a double-blind assignment of the included patients to atorvastatin 20mg daily versus matching placebo. The hypothesis was that statin therapy, compared to placebo, would reduce the composite of VTE, need for ECMO, or all-cause mortality.

The primary efficacy outcome was the composite adjudicated venous thromboembolism, arterial thrombosis, treatment with ECMO or all-cause mortality. Secondary efficacy outcomes included the individual components of all-cause mortality and adjudicated venous thromboembolism, ventilator-free days, objectively clinically-diagnosed type I acute myocardial infarction and objectively clinically-diagnosed stroke. The safety outcomes assessed were fatal bleeding, major bleeding, or clinically-relevant non-major bleeding (BARC 2 to 5), clinically diagnosed myopathy and rise in liver enzymes.[10]

The certainty of the evidence was assessed to be low for both the primary efficacy outcome and all-cause mortality due to serious imprecision and suspected publication bias. For the adjudicated venous thromboembolism, there was a very wide confidence

interval. Hence, imprecision was classified as very serious and the evidence was assessed to be of very low certainty.

Though the manuscript of the trial by Bikdeli et al. is still unpublished, the study results were presented in the American College of Cardiology Scientific Session on May 16, 2021. Hence, we were able to include the results of the trial in this evidence summary. Results of the study are presented in the GRADE evidence profile (see Appendix 5). For the primary efficacy outcome, there was decreased risk in the statin group but this was not statistically significant (RR 0.90, 95% CI 0.72-1.13; p=0.36). For the all-cause mortality, the risk ratio of statin use was 0.89 (95% CI 0.71-1.13; p=0.35). For the adjudicated venous thromboembolism, the risk ratio was 0.68 (95% CI 0.25-1.89; p=0.46). The mean ventilator-free days for both intervention and control was 30 days (p=0.08). There was no incident of clinically diagnosed myocardial infarction. There was only one incident of clinically-diagnosed stroke in the placebo group and none in the statin group (RR 0.34, 95% CI 0.01-8.35; p=0.51). The outcome for the individual component of arterial thrombosis was not presented.[10]

In terms of safety outcomes, there was no significant difference between the intervention and control for fatal bleeding, clinically-relevant non-major bleeding, and rise in liver enzymes. There was signal for harm, but it was noted that the effects of the anticoagulation therapy could not be extricated from the statin analysis. It must be noted that there was increased risk for the statin group for major bleeding (RR 2.25, 95% CI 0.79-6.4; p=0.13) but this was not statistically significant, perhaps due to the small number of events that occurred.[10]

On the other hand, the double-blind, randomized controlled trial by Davoodi et al. studied the effect of atorvastatin plus lopinavir/ritonavir on newly hospitalized adult COVID-19 patients without cardiovascular diseases.[11] The control was lopinavir/ritonavir which is a standard of care in Iran, where the study was held. The primary outcome was the duration of hospitalization. The secondary outcomes included the need for interferon or immunoglobulin, need for invasive mechanical ventilation, oxygen saturation and C-reactive protein levels. Atorvastatin 40mg daily was given along with lopinavir/ritonavir for five days.

The certainty of evidence from the Davoodi et al. trial was assessed to be moderate for length of hospital stay and low for need for mechanical ventilation due to serious imprecision, and suspected publication bias. Results of the Davoodi et al. trial are shown in Appendix 5. The duration of hospitalization was decreased by a mean of 1.8 days (p value 0.012) in the atorvastatin group. For the need for mechanical ventilation, the relative risk of the atorvastatin group was 0.33 (95% CI 0.01 to 7.72, p=0.49).

## RECOMMENDATIONS FROM OTHER GROUPS

On August 4, 2021, the NIH COVID-19 Treatment Guidelines Panel recommended that COVID-19 patients who were already on statins prior to infection should not discontinue taking the statin during acute management of COVID-19 (Strong recommendation based on Expert Opinion).[12] It also recommended against the off-label use of statins to treat COVID-19, except in a clinical trial (Strong recommendation based on Expert Opinion).[12] Currently, there are no local guidelines providing recommendations on the use of statins in COVID-19 patients.

## EVIDENCE TO DECISION

There are no cost-effectiveness studies available to further evaluate the use of statins. It was only identified in some reviews that costs are one of the common causes of nonadherence to chronic statin use aside from its side effects, presence of comorbidities, and lack of health insurance.[13, 14] The estimated cost of statins ranges from PHP 138.60 to PHP 1,115.10 for 30 days of treatment [15] while the estimated cost of hospitalization or in-patient management for probable or confirmed case of COVID-19 varies from Php 143, 267 to Php 786,384 for moderate to critical cases [16]. Actual costs may still vary.

## RESEARCH GAPS

The outcomes for patients with asymptomatic or mild COVID-19 is unknown. We also do not know if the continuation of statins in patients already taking the drug is beneficial. As of the time of this review, there were eight records of other randomized clinical trials but their results have not been reported or published (see Appendix 6).

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# Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the actual panel meeting: statins (N = 8)

| FACTORS | JUDGEMENT | | | | | | RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS |
|---|---|---|---|---|---|---|---|
| **Problem** | No (1) | Yes (7) | | | | | |
| **Benefits** | Large (1) | Moderate (2) | Small (4) | Uncertain (1) | | | • INCONCLUSIVE BENEFITS and HARM (adjudicated venous thromboembolism, arterial thromboembolism, arterial thrombosis, treatment with ECMO, all-cause mortality); need for interferon or immunoglobulin, need for invasive mechanical ventilation, major bleeding, fatal bleeding<br>• BENEFIT: decrease of length of hospital stay (days)<br>• *Experience: Do not lower cholesterol level even with good compliance (n =1)*<br>• *Needs wider or larger study group (n = 1)* |
| **Harm** | Large (1) | Small (7) | Uncertain | Varies | | | • INCONCLUSIVE BENEFITS and HARM (adjudicated venous thromboembolism, arterial thromboembolism, arterial thrombosis, treatment with ECMO, all-cause mortality); need for interferon or immunoglobulin, need for invasive mechanical ventilation, major bleeding, fatal bleeding |
| **Certainty of Evidence** | High | Moderate | Low (4) | Very low (4) | | | • The overall certainty of evidence: VERY LOW |
| **Balance of effects** | Favors drug (4) | Does not favor drug | Uncertain (4) | Varies | | | • Most outcomes show inconclusive benefits and harm.<br>• Moderate quality of evidence shows benefit in terms of length of hospital stay (reduction of 2 days) among hospitalized non-ICU patients without cardiovascular diseases. |
| **Values** | Important uncertainty or variability (4) | Possibly important uncertainty or variability (2) | Possibly NO important uncertainty or variability | No important uncertainty or variability (2) | | | |
| **Resources Required** | Uncertain | Large cost | Moderate Cost (6) | Negligible cost | Moderate savings | Large savings (2) | • **No cost-effectiveness studies available.**<br>Price range: PHP 138.60 – PHP 1,115.10 (estimated cost of drug for 30 days of treatment); Estimated cost of hospitalization (ADB, 2020) for in-patient management for probable or confirmed case of COVID-19: Php 143, 267 to Php 786,384 – moderate to critical cases (Actual costs may vary)<br>• *Panel: It is an added cost. (n = 1)* |
| **Certainty of evidence of required resources** | No included studies (4) | Very low (2) | Low (2) | Moderate | High | | • No cost-effectiveness studies available. |
| **Cost effectiveness** | No included studies (6) | Favors the comparison | Does not favor either the intervention or the comparison (1) | Favors the intervention (1) | | | • No cost-effectiveness studies available. |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Equity** | Uncertain (5) | Reduced (1) | Probably no impact (2) | Increased | | • No local studies available. |
| **Acceptability** | Uncertain (4) | No | Yes (4) | Varies | | • Common causes of nonadherence to chronic statin use are costs, side effects, presence of comorbidities, and lack of health insurance.<br>• *Panel: Acceptability depends on ability to control dyslipidemia, decreased or no adverse reactions, and purchasing capacity. (n =1)* |
| **Feasibility** | Uncertain (3) | No | Yes (5) | Varies | | • No local studies available. |

## Appendix 2. Search Yield and Results

| Database | Date of Last Search | Search strategy | Yield | Matching articles |
|---|---|---|---|---|
| Pubmed | September 16, 2021 | ((((((((((statin[MeSH Terms]) OR (atorvastatin[MeSH Terms])) OR (lovastatin[MeSH Terms])) OR (pravastatin[MeSH Terms])) OR (simvastatin[MeSH Terms])) OR (meglutol[MeSH Terms])) OR (statin [tiab])) OR (atorvastatin [tiab])) OR (lovastatin [tiab])) OR (pravastatin [tiab])) OR (simvastatin [tiab])) OR (meglutol [tiab])) AND ((((((((COVID-19[MeSH Terms]) OR (coronavirus[MeSH Terms])) OR (sars-cov-2[MeSH Terms])) OR (nCoV [tiab])) OR (COVID-19)) OR (COVID-19 [tiab])) OR (coronavirus [tiab])) OR (SARS-CoV-2 [tiab])) | 222 | 41 |
| Cochrane Library CENTRAL | September 16, 2021 | (statin):ti,ab,kw AND (covid-19):ti,ab,kw | 27 | 10 |
| Clinicaltrials.gov | September 20, 2021 | COVID-19 AND statin | 23 | 11 |
| Epistemonikos | September 26, 2021 | (title: (statin) or abstract:(statin)) AND (title:(covid-19) OR abstract:(covid-19)) | 111 | 48 |

## Appendix 3. Characteristics of Included Studies

| Study ID | Setting | Population | Intervention | Control | Outcomes |
|---|---|---|---|---|---|
| Bikdeli 2021 | Iran | Adult patients (≥18 years old) with RT-PCR confirmed COVID-19 admitted at ICU within 7 days of hospitalization | Atorvastatin 20 mg/day initiated at admission<br><br>Exact duration of intervention not specified. | Matching placebo | Primary efficacy outcome: Composite of adjudicated venous thromboembolism, arterial thrombosis, treatment with ECMO, or all-cause mortality within 30 days<br>Secondary efficacy outcome:<br>Individual components of primary outcome, ventilator free days<br>Safety outcomes: rise in liver enzymes >3x times upper normal limit, myopathy, BARC 3 or 5 bleeding, CRNMB, severe thrombocytopenia |
| Davoodi 2021 | Iran | Adult patients (between 20 and 50 years old), hospitalized, with RT-PCR confirmed COVID-19, CT scan findings of COVID-19, and respiratory symptoms <10 days | Atorvastatin 40 mg 1 tablet per day plus lopinavir/ritonavir 400/100 mg 2 tablets per day<br><br>Duration of treatment was 5 days | Matching placebo 1 tablet per day plus lopinavir/ritonavir 400/100 mg 2 tablets per day | Primary: duration of hospitalization<br>Secondary: Need for interferon or immunoglobulin, need for invasive mechanical ventilation, O2 saturation on Days 1 and 6, CRP on Days 1 and 6 |

# Appendix 4. Detailed Study Appraisal

| | Bikdeli et al. Trial | Davoodi et al. Trial |
|---|---|---|
| **Appraising Directness** | | |
| Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)? | Yes | Yes |
| **Appraising Validity** | | |
| 1. Were patients randomly assigned to treatment groups? | Yes | Yes |
| 2. Was allocation concealed? | Yes | Yes |
| 3. Were baseline characteristics similar at the start of the trial? | Yes | Yes |
| 4. Were patients blinded to treatment assignment? | Yes | Yes |
| 5. Were caregivers blinded to treatment assignment? | No | No |
| 6. Were outcome assessors blinded to treatment assignment? | Yes | Yes |
| 7. Were all patients analyzed in the groups to which they were originally randomized? | Yes | Yes |
| 8. Was follow-up rate adequate? | Yes | No. Treatment was only up to 5 days. After discharge, patients were not able to be followed up. |
| **Appraising Results** | | |
| 1. How large was the effect of treatment? | See GRADE evidence profile | See GRADE evidence profile |
| 2. How precise was the estimate of the treatment effect? | See GRADE evidence profile | See GRADE evidence profile |
| **Assessing Applicability** | | |
| 1. Are there biologic issues that may affect applicability of treatment? (Consider the influence of sex, co-morbidity, race, age and pathology) | Yes. Study is mainly composed of adults 40-60 years old. | No |
| 2. Are there socio-economic issues affecting applicability of treatment? | No | No |
| **Individualizing the Results** | | |
| 1. What is the likely effect of the treatment on your individual patient? | | |
| 2. Would you offer the treatment to your patients? | No | |

# Appendix 5. GRADE Evidence Profile

## EFFICACY OUTCOMES

**Author(s)**: Furqaan Lim, Maria Teresa Sanchez-Tolosa, Myzelle Infantado

**Question: Should statins be used as adjunctive treatment in patients with COVID-19?**

Setting: Iran

**Bibliography**: Bikdeli Behnood, Talasaz A, Rashidi F, et al. Atorvastatin vs Placebo in Patients with COVID-19 Admitted to the ICU: The INSPIRATION-S Trial

| CERTAINTY ASSESSMENT | | | | | | | NO. OF PATIENTS | | EFFECT | | CERTAINTY | IMPORTANCE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Statin | Placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **Composite of adjudicated venous thromboembolism, arterial thrombosis, treatment with ECMO, or all-cause mortality (follow-up: 30 days; assessed with: Number of events)** | | | | | | | | | | | | |
| 1 | Randomised trials | Not serious | Not serious | Not serious | Serious [a] | Publication bias strongly suspected [b] | 95/290 (32.8%) | 108/297 (36.4%) | **RR 0.90** (0.72 to 1.13) | **36 fewer per 1,000** (from 102 fewer to 47 more) | ⨁⨁◯◯ Low | CRITICAL |
| **All-cause mortality (follow-up: 30 days)** | | | | | | | | | | | | |
| 1 | Randomised trials | Not serious | Not serious | Not serious | Serious [a] | Publication bias strongly suspected [b] | 90/290 (31.0%) | 103/297 (34.7%) | **RR 0.89** (0.71 to 1.13) | **38 fewer per 1,000** (from 101 fewer to 45 more) | ⨁⨁◯◯ Low | CRITICAL |
| **Adjudicated venous thromboembolism (follow-up: 30 days)** | | | | | | | | | | | | |
| 1 | Randomised trials | Not serious | Not serious | Not serious | Very serious [c] | Publication bias strongly suspected [d] | 6/290 (2.1%) | 9/297 (3.0%) | **RR 0.68** (0.25 to 1.89) | **10 fewer per 1,000** (from 23 fewer to 27 more) | ⨁◯◯◯ Very low | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio

**Explanations**

[a] The risk ratio has a wide confidence interval

[b] Only 1 randomized controlled trial is available for review and is currently unpublished. There are 9 ongoing or possibly finished trials that have not yet reported their results.

[c] The risk ratio has very wide confidence interval and touches the line of null effect

[d] Only 1 randomized controlled trial studying this effect is available for review and is currently unpublished.

**Author(s): Furqaan Lim, Maria Teresa Sanchez-Tolosa, Myzelle Infantado**
**Question:** Should statins be used as adjunct treatment in patients with COVID-19?
**Setting:** Iran
**Bibliography:** Davoodi L, Jafarpour H, Oladi Z et al. Atorvastatin therapy in COVID-19 adult inpatients: A double-blind, randomized controlled trial. IJC Heart & Vasculature 14 Sept 2021. Available from https://www.sciencedirect.com/science/article/pii/S2352906721001639?via%3Dihub

| CERTAINTY ASSESSMENT | | | | | | | NO. OF PATIENTS | | EFFECT | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Atorvastatin plus lopinavir/ ritonavir | Lopinavir/ ritonavir | Relative (95% CI) | Absolute (95% CI) | CERTAINTY | IMPORTANCE |
| **Length of hospital stay** | | | | | | | | | | | | |
| 1 | Randomised trials | Not serious | Not serious | Not serious | Not serious | Publication bias strongly suspected[a] | 20 | 20 | - | MD **1.8 lower** (3.14 lower to 0.46 lower) | ⨁⨁⨁◯ Moderate | IMPORTANT |
| **Need for mechanical ventilation** | | | | | | | | | | | | |
| 1 | Randomised trials | Not serious | Not serious | Not serious | Serious[b] | Publication bias strongly suspected[a] | 0/20 (0.0%) | 1/20 (5.0%) | **RR 0.33** (0.01 to 7.72) | **33 fewer per 1,000** (from 50 fewer to 336 more) | ⨁⨁◯◯ Low | CRITICAL |

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

**Explanations**
[a] Only two randomised controlled trials are available for review and one is currently unpublished. There are eight ongoing or possibly finished trials that have not yet reported their results.
[b] The risk ratio has wide confidence interval and touches the line of null effect

# SAFETY OUTCOMES

**Author(s)**: Furqaan Lim, Maria Teresa Sanchez-Tolosa, Myzelle Infantado
**Question**: [Should statins be used as adjunctive treatment in patients with COVID-19?
**Setting**: Iran
**Bibliography**: Bikdeli Behnood, Talasaz A, Rashidi F, et al. Atorvastatin vs Placebo in Patients with COVID-19 Admitted to the ICU: The INSPIRATION-S Trial

| CERTAINTY ASSESSMENT | | | | | | | NO. OF PATIENTS | | EFFECT | | CERTAINTY | IMPORTANCE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Statin | Placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **Fatal bleeding (follow-up: 30 days)** | | | | | | | | | | | | |
| 1 | Randomised trials | Not serious | Not serious | Not serious | Very serious [a] | Publication bias strongly suspected [b] | 2/290 (0.7%) | 2/297 (0.7%) | **RR 1.02** (0.15 to 7.22) | **0 fewer per 1,000** (from 6 fewer to 42 more) | ⨁◯◯◯ Very low | CRITICAL |
| **Major bleeding BARC 3 or 5 (follow-up: 30 days)** | | | | | | | | | | | | |
| 1 | Randomised trials | Not serious | Not serious | Not serious | Very serious [a] | Publication bias strongly suspected [b] | 11/290 (3.8%) | 5/297 (1.7%) | **RR 2.25** (0.79 to 6.40) | **21 more per 1,000** (from 4 fewer to 91 more) | ⨁◯◯◯ Very low | CRITICAL |

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

**Explanations**
[a] There is a wide confidence interval
[b] Only one randomized controlled trial is available for review and is currently unpublished. There are eight ongoing or possibly finished trials that have not yet reported their results.

## Appendix 6. Characteristics of Ongoing Studies

| Study ID | Setting | Title | Intervention | Control | Outcomes |
|---|---|---|---|---|---|
| NCT04380402 | USA | Prospective Randomized Open-label Trial of Atorvastatin as Adjunctive Therapy of COVID-19 (STATCO19) | Atorvastatin 40 mg | Standard care | Proportion of patients progressing to severe or critical requiring ICU admission and/or emergency salvage therapy or death within 30 days<br>Clinical status at Day 7 and 30<br>Proportion of patients who test negative for SARS-CoV-2 on Day 7 |
| IRCT20210426051090N1 | Iran | The effect of atorvastatin on on inflammatory factors and prognosis outcomes in patients with Covid 19, hospitalized in Hajar Hospital, Shahrekord University of Medical Sciences, 2021 | Atorvastatin 40 mg | Placebo | ALT, AST, Alkaline phosphatase, bilirubin, BUN, Na, K, Creatine, CBC, CRP, ESR, FBS, Ferritin, IL-6, LDH, O2 saturation, PT/PTT, INR, Lipid profile on Day 1, 7 and 14 |
| NCT04904536 | Australia | An International, Investigator Initiated and Conducted, Pragmatic Clinical Trial to Determine Whether 40mg Atorvastatin Daily Can Improve Neurocognitive Function in Adults With Long COVID Neurological Symptoms | Atorvastatin 40 mg for 18 months | Standard care | Neurologic Recovery<br>Brain imaging |
| IRCT20200408046990N3 | Iran | Evaluation of atorvastatin tablet efficacy as an adjuvant treatment for patients with mild to moderate COVID-19 in Qaem Hospital, Mashhad: A double-blind randomized placebo controlled clinical trial | Atorvastatin 40 mg | Placebo | Fever, clinical response, radiologic response, laboratory response (CBC and CRP), adverse reaction, duration of hospitalization, clinical outcome |
| EUCTR2020-001319-26-ES | Spain | Multicenter, randomized, controlled, open-label clinical trial to assess the prognostic implications of rosuvastatin treatment in patients discharged after hospitalization for COVID-19 Positive | Rosuvastatin | Not indicated | Death, MI, Stroke within 12 months<br>Admission due to heart failure, readmission from any cause |
| IRCT20201128049508N1 | Iran | Evaluation of statin effect on COVID 19 duration and complications | Statin | Standard care | Mortality, lung fibrosis, recovery |
| CTRI/2020/07/026791 | India | A Randomised Control Trial of Statin and Aspirin as Adjuvant Therapy in Patients with SARS-CoV-2 Infection (RESIST Trial) - RESIST Trial | Atorvastatin 40 mg<br>Aspirin | Standard care | Clinical deterioration (intubation, mechanical ventilation, pressor agents, dialysis, ECMO, mortality)<br>Inflammatory markers<br>ICU admission<br>Length of hospital stay<br>Length of ICU stay<br>Progression to ARDS, shock<br>Safety concerns |
| NCT04801940 | UK | HElping Alleviate the Longer-term Consequences of COVID-19 (HEAL-COVID): a National Platform Trial | Atorvastatin 40 mg for 12months<br>Apixaban | Standard care | Survival, mortality, readmission, adverse reactions, FACIT-fatigue, modified MRC dyspnoea scale, COVID-19 core outcome measure for recovery, PHQ-2, GAD-2, PTSD, quality of life, intervention tolerability |

# Q13. Does the concurrent use of Ibuprofen worsen COVID-19 outcomes?

*As of 30 June 2021*

RECOMMENDATION

**We suggest that Ibuprofen may still be used as symptomatic treatment of patients with COVID-19 infection if clinically warranted. Concurrent use of ibuprofen is not associated with worsening of COVID-19 outcomes.** *(Very low certainty of evidence; Weak recommendation)*

***Consensus Issues***

There were no issues raised during the consensus panel meeting.

## KEY FINDINGS

There has been concern on the use of ibuprofen in COVID-19. Fang et al. reported that the point of entry for SARS-COV-2 is through angiotensin- converting enzyme 2 receptor, which is believed to be upregulated by ibuprofen. Based on six observational studies assessed, there was no significant association between ibuprofen use and worse COVID-19 outcomes: composite outcome (death, acute respiratory distress syndrome, ICU admission, shock) OR 1.06 (95% CI 0.81-1.40), Death OR 1.07 (95% CI 0.35-3.24), and progression of symptoms after propensity score matching. Five clinical trials on Ibuprofen use in COVID-19 are still on-going.

## INTRODUCTION

One of the most common symptoms of COVID-19 is fever [1] and among the most frequently used antipyretic agents is ibuprofen. There has been concern with regards to the use of ibuprofen in COVID-19 [2,3]. On March 11, 2020, The Lancet published an article based on the observation by Fang et al. that the SARS-COV-2 point of entry for its pathogenesis is through angiotensin-converting enzyme 2 receptor, which is believed to be upregulated by ibuprofen [4]. However, the World Health Organization and the European Medicines Agency (EMA) released a statement that there is currently no direct scientific evidence to support this claim and advised against avoidance of ibuprofen as treatment of fever if it is clinically warranted [5,6]. A systematic review by Yousefifard et al. which included six studies failed to associate NSAID intake with worsened outcomes among patients with viral respiratory infections, although none of these trials have been performed on COVID-19, SARS or MERS-CoV [7]. Furthermore, among adult patients with acute respiratory infection, the effects of NSAIDs on the risk for ischemic and haemorrhagic stroke and myocardial infarction are unclear [8-9]. There is little or no evidence that ibuprofen increases death from all causes, hospitalization for any cause, acute renal failure, and acute gastrointestinal bleeding among children with fever compared with paracetamol [10-11].

## REVIEW METHODS

We performed a comprehensive systematic search of the literature from two electronic databases, Medline and CENTRAL. We also searched for ongoing clinical trials using ClinicalTrials.gov and Clinicaltrialsregister.eu. We did freehand search using Google to check for other sources of information, including the Love Platform App. The search

was conducted using the following search terms: COVID-19, SARS-CoV-2, ibuprofen and non-steroidal anti-inflammatory agents.

Eligible articles were appraised using accepted standard processes evaluating directness, validity, and applicability using the following:

| | |
|---|---|
| Population | COVID-19 patients |
| Intervention/Exposure | Ibuprofen |
| Comparison | Paracetamol; No ibuprofen use |
| Outcomes | Increased risk of infection, worsening of symptoms, increase in severity of symptoms or death |
| Methodological filter | Randomized controlled trials (RCT), observational clinical studies, systematic review and meta-analysis available, case series |

## RESULTS

A total of six observational studies met the inclusion criteria and were included in this review. There were five cohort studies and one cross-sectional study. All studies included COVID-19 confirmed patients by RT-PCR given ibuprofen for symptomatic relief of fever and pain.

A prospective cohort study [12] looked into several risk factors for disease progression including the impact of drugs such as angiotensin II receptor blockers [ARB], ibuprofen, and dipeptidyl peptidase-4 inhibitors [DPP4i], and the therapeutic effect of lopinavir/ritonavir. They included patients with confirmed COVID-19 infection by RT-PCR from March 5-18, 2020 with final follow up on April 4, 2020. The outcome was classified into either disease progression or improvement/stabilization group. They conducted a propensity-score matched case-control study to control for possible confounding variables using the result of the univariable analysis. After PS-matching, prior history of drug use, including ibuprofen, ARB, DPP-4i, was not statistically significant. The effect of these drugs on prognosis did not significantly differ in patients with hypertension and diabetes mellitus. However, the retrospective, single center and limited number of patients in the progression group (30 vs 263) may limit the wider applicability of the result. Moreover, other potential hidden biases and confounding factors not controlled by propensity score matching might have influenced the results.

Another prospective cohort study done by Esba et al. in 2020 [13] aimed to assess the association of acute and chronic ibuprofen use of NSAIDs with worse COVID-19 outcomes. A total of 503 patients with confirmed COVID-19 infection were included in the study from April 12 to June 1, 2020. Information of ibuprofen or NSAID use was collected using a telephone questionnaire. The primary outcome was 30-day mortality and the secondary outcomes were severe COVID-19 infection, hospital admission and for admitted patients, time to clinical improvement, oxygen support, and length of hospital stay. After adjusting for covariates, results showed that acute ibuprofen use was not associated with a greater risk of mortality HR 0.63 (95% CI 0.07-5.44; p=0.68). It was also not significantly associated with mortality (RR 2.70, 95% CI 0.33 – 22.00; p=0.35), risk of admission (RR 1.18, 95% CI 0.59–2.36; p=0.64), oxygen support (RR 1.45, 95% CI 0.44–4.81; p=0.55), and severe COVID-19 (RR 1.85, 95% CI 0.42–8.13; p=0.42). Being an observational study, causal relationship between ibuprofen use and severe outcomes could not be established. Concerns for possible bias were likewise noted. Specifically, there could be selection bias with regard to recruitment since the

study was done at the early stage of the pandemic. There could also be recall bias since the respondents were asked through a telephone questionnaire.

An observational retrospective cohort study by Kraghold et al. [14] assessed the association between prescribed ibuprofen and severe covid-19 infection. They included 4,002 COVID-19 confirmed patients, 264 of which filled out ibuprofen prescriptions. Data were obtained using the Danish National Prescription Registry for ibuprofen prescription claims and identified COVID-19 positive patients using the Danish National Patient Registry. The two groups, ibuprofen and non-ibuprofen COVID-19 patients were standardized by age, sex, and co-morbidity distribution using the multivariate Cox regression. The outcome of interest was the 30-day composite of acute respiratory syndrome, intensive care unit admission, or death. Results showed that there was no statistical difference between the ibuprofen and non-ibuprofen groups with regard to the 30-day composite outcome with absolute and average risk ratios of 16.3% (95% CI 12.1–20.6) vs. 17.0% (95% CI 16.0–18.1), P = 0.74; and 0.96 (95% CI 0.72–1.23) respectively. The standardized absolute risks of the composite outcome for patients with ibuprofen prescription claims >14 days before COVID-19 and <14 days of COVID-19 were 17.1% (95% CI 12.3–22.0) vs. 14.3% (95% CI 7.1–23.1). They found no significant association between ibuprofen prescription claims and severe COVID-19. However, given the retrospective and observational nature of the study causal relationship could not be established. It must be noted that the study did not look into individual outcomes and whether ibuprofen use had an effect on each of them. In addition, certain assumptions were made with regard to ibuprofen use that may prove inaccurate since the claiming of prescriptions does not translate to patients actually taking ibuprofen. Also, they were not able to ascertain the duration of ibuprofen use, as it may have been continued even during admission.

In one retrospective cohort study that evaluated the clinical outcomes among patients with COVID-19 taking NSAIDS [15], NSAID use was ascertained using patients' electronic medical records. The primary outcome was a composite of death, respiratory failure requiring intubation, and shock requiring vasopressors, occurring within 28 days of ED presentation. After controlling for other variables such as co-morbidities and use of other medications, they found that NSAID use was not an independent predictor of critical COVID-19 illness (OR 0.05, 95% CI -0.57 - 0.73). However, the type of NSAIDS the patients were taking was not specified in the paper.

The retrospective cohort study of Rinott et al. [16] was done among patients with confirmed COVID-19 infection in Israel from March 15 to April 15, 2020 and aimed to evaluate whether the administration of ibuprofen to COVID-19 patients was associated with worsened clinical outcome compared with paracetamol or no antipyretic. They collected data through telephone questionnaire (mean 13 days after diagnosis, range 2-30 days) including information about age, gender, chronic diseases and medications, date of diagnosis, symptoms and factors relating to the clinical course of disease (admission to the hospital and the intensive care unit, need for oxygen or ventilation) and intake of ibuprofen or paracetamol or dipyrone one week prior to diagnosis. Severe disease was defined as needing any respiratory support (supplemental oxygen administration or ventilation), admission to intensive care unit or death. A total of 403 confirmed cases were included in the study. Using Chi square test of independence, Wilcoxon Rank – Sum test and Fischer's Exact test, the authors found no statistically significant difference between the "without Ibuprofen intake"

group and the “with ibuprofen intake” group in terms of receiving supplemental oxygen (8.5% vs 5.7%; p=0.53), being mechanically ventilated (4.1% vs 4.6%; p>0.95), admission to ICU (4.1% vs 5.7%; p=0.72), administration of respiratory support (11.1% vs 10.3%; p>0.95), and death (9% vs 3%; p>0.95). Also, when the exclusive ibuprofen group was compared with the exclusive paracetamol group in terms of death, there was also no statistically significant difference (0% vs 3%; p=0.3). This study had a lot of biases. They did not attempt to control possible confounders, and recall bias in particular was a major concern since patients were asked through telephone questionnaire.

A cross-sectional study done by Samimagham et al. [17] included 158 patients with confirmed COVID-19 infection who consumed ibuprofen for at least 1 week in the past 3 months. The patients were grouped into mild, moderate and severe groups. In this study, they found out that there was a significant relationship between ibuprofen consumption and severity of the disease (p<0.001). After adjustment, there was a statistically significant relationship between ibuprofen consumption and mortality among patients with COVID-19 (OR 2; p=0.001). As this was a cross-sectional study design, neither temporal association nor causation could be established. There could also be channeling bias wherein ibuprofen was given to patients who had more severe symptoms since it has a more potent anti-inflammatory property than paracetamol. The outcome was biased especially with regard to the intensive care unit (ICU) admission because there was no standard criteria given for admission. Instead, it depended on the judgment of the attending physician. There is also a question on the generalizability of the study since it only included 158 patients.

All of the studies included confirmed COVID-19 patients by RT-PCR with no specific severity. In 3 studies, the exposure to ibuprofen was during the infection whereas in the other 3 studies, the exposure was prior to the infection. Only one study described the dose given to patients. Most of these studies used EMR and telephone questionnaire to gather data.

## RECOMMENDATIONS FROM OTHER GROUPS

The World Health Organization (WHO) and the European Medicines Agency (EMA) released a statement that there is currently no direct scientific evidence to support that ibuprofen could worsen COVID-19 and does not recommend against the use of ibuprofen as treatment of fever if it is clinically warranted [5,6].

## ONGOING STUDIES

There are five ongoing clinical trials (shown on Appendix 3).

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# Appendix 1. Characteristics of Included Studies

| Author , Year | Patients (n) | Intervention | Comparator | Outcomes | Study Design |
|---|---|---|---|---|---|
| Choi et al, 2020 | COVID-19 confirmed patients (n=293) | the impact of drugs (angiotensin II receptor blockers [ARB], ibuprofen, and dipeptidyl peptidase-4 inhibitors [DPP4i]) and the therapeutic effect of lopinavir/ritonavir. | Propensity score – matching control | No statistical difference between the progression and improvement/stabilization group when it comes to ibuprofen use 6 vs 2 p 0.261, after propensity score matching, ibuprofen 6 vs 6 p >0.99, For risk for progression free survival using Cox Regression Analysis OR, 2.72; (1.13 – 6.24) p 0.025 | Retrospective Cohort, propensity score matched case control |
| Esba et al. 2020 | COVID-19 confirmed patients (n=503) | Ibuprofen or other NSAID use | Non Ibuprofen/NSAID users | After adjustment for covariates, results showed that acute ibuprofen use was not associated with a greater risk of mortality HR 0.632 (95% CI, 0.073-5.44; P=0.6758). It was also not associated with mortality, risk of admission, oxygen support, and severe COVID-19 with fully adjusted RR 2.6951; (95% CI, 0.3302 – 21.9964) P=3547 (mortality), RR 1.1.1819 (95% CI, 0.5917–2.3606) P=0.6359 (admission), RR 1.4482 (95% CI, 0.4361–4.8089) P=0.5454 (oxygen support) and RR 1.8484 (0.4202–8.1314) P=4163 (severe COVID-19). | Observational, Prospective cohort study |
| Kraghol m et al., 2020 | COVID-19 confirmed patients (n=4,002) | Prescribed Ibuprofen | Non-Ibuprofen | no statistical difference between the ibuprofen and non-ibuprofen groups when it comes to the 30 day composite outcome with absolute and average risk ratios of 16.3% (95% confidence interval (CI) 12.1–20.6) vs. 17.0% (95% CI 16.0–18.1), OR 0.91;(95% CI; 0.64-1.27) P = 0.74 and 0.96 (95% CI 0.72–1.23) respectively. | Retrospective Cohort |
| Perkins et al, 2020 | COVID-19 confirmed patients (n=422) | NSAID users | Non NSAID users | NSAID use was not found to be an independent predictor of critical COVID-19 illness (odds ratio = 0.05 (95% CI; -0.57 - 0.73) | Retrospective cohort study |
| Rinott et al., 2020 | COVID-19 confirmed patients (n=403) | Ibuprofen intake | No antipyretic or paracetamol | no statistically significant difference observed between the without Ibuprofen intake and with ibuprofen intake in terms of receiving supplemental oxygen 8.5% vs 5.7% P=0.53, mechanically ventilated 4.1% vs 4.6% P>0.95, admission to ICU 4.1% vs 5.7% P=0.72, administration of respiratory support 11.1% vs 10.3% P>0.95 and death 9% vs 3% P>0.95. Also when exclusive ibuprofen group was compared with exclusive paracetamol group in terms of death, there was also no statistically significant difference between the two groups 0% vs 3% P=0.3 | Retrospective cohort study |
| Samima ghal et al. 2020 | COVID-19 confirmed patients(n =158) | Ibuprofen | Non-ibuprofen | significant relationship between ibuprofen consumption and severity of the disease with a P<0.001. After adjustment of the odds ratio 2, P=0.001 there was a significant relationship between ibuprofen consumption and mortality among patients with COVID-19 | Cross sectional |

# Appendix 2: GRADE Summary of Findings (SoF) table

**Summary of findings:**

## Ibuprofen compared to usual standard of care/paracetamol for COVID-19

**Patient or population**: COVID-19
**Setting**:
**Intervention**: Ibuprofen
**Comparison**: usual standard of care/paracetamol

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with usual standard of care/paracetamol | Risk with Ibuprofen | | | | |
| Composite Outcome (Death, ARDS, ICU, Shock) | 193 per 1,000 | **203 per 1,000** (163 to 251) | **OR 1.06** (0.81 to 1.40) | 4582 (3 observational studies) | ⨁◯◯◯ VERY LOW a,b,c | |
| Death | 30 per 1,000 | **32 per 1,000** (11 to 90) | **OR 1.07** (0.35 to 3.24) | 800 (2 observational studies) | ⨁◯◯◯ VERY LOW a,c | |
| Progression of Symptoms | After PS matching, Ibuprofen was not associated with progression of symptoms among COVID-19 patients | | | 293 (1 observational study) | ⨁◯◯◯ VERY LOW a,c | |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **OR:** Odds ratio

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Explanations**

a. interviewer bias, measurement bias, recall bias and channeling bias
b. The study of Samimagham had different results compared with the other two
c. The exposure in 1 study was prior to the diagnosis of COVID-19

## Appendix 3: Characteristics of Ongoing Studies

| Clinical Trial Identifier (Location) | Official Title | Methodology | Groups | Estimated Date of Completion |
|---|---|---|---|---|
| NCT04500639 | Do Common Medications Alter the Course of COVID-19? | Observational, Case Control Propective Study | Not provided | Dec 31, 2020 |
| NCT04382768 | Extended Compassionate Use Program (UCA) With Inhalational Ibuprofen in Patients With Acute Respiratory Pathology, Mediated by COVID-19. | Interventional<br>Open label<br>Single group Assignment | Experimental: Luarprofen<br>Inhaled Hypertonic Ibuprofen 50mg TID | January 2021 |
| NCT04334629 | Lipid Ibuprofen Versus Standard of Care for Acute Hypoxemic Respiratory Failure Due to COVID-19: a Multicentre, Randomised, Controlled Trial (LIBERATE) | Randomized, double blind, parallel assignment | Experimental: Lipid Ibuprofen<br><br>No intervention: Standard of Care | May 25, 2021 |
| NCT04383899 | Role of Ibuprofen and Other Medicines on Severity of Coronavirus Disease 2019 (COVID-19) Infections: a Case-control Study | Case Control | Case: severe COVID patients<br>Control: Non severe COVID patients | Oct. 31, 2020 |
| 2020-001203-16 | Lipid ibuprofen versus standard of care for acute hypoxaemic respiratory failure due to COVID-19: a multicentre, randomised, controlled trial | Randomized, double blind, parallel assignment | Experimental: Lipid Ibuprofen<br><br>No intervention: Standard of Care | May 25, 2021 |

## Q14. Should aspirin, taken as maintenance therapy for underlying medical conditions, be discontinued in patients with COVID-19?

*As of 30 June 2021*

RECOMMENDATION

**There is insufficient evidence to recommend discontinuation of aspirin as maintenance therapy for underlying medical conditions in patients with COVID-19.** *(Very low certainty of evidence)*

***Consensus Issues***

Further studies are needed for the panel to make a recommendation on the discontinuation of aspirin as maintenance therapy in patients with COVID-19. There is certainty of benefit for continuing aspirin for underlying medical conditions. However, the benefit of its use among patients with COVID-19 is still uncertain.

### KEY FINDINGS

Very low-quality evidence from three retrospective cohort studies was found on the continuation of aspirin as maintenance for underlying medical conditions among patients with COVID-19. There was no significant decrease in the odds of mortality in the use of aspirin. However, there was a significant increase in the odds of the composite outcome of mortality or discharge to hospice with continuation of aspirin. Thromboembolic and adverse events were not examined in these studies.

### INTRODUCTION

Aspirin, a cyclooxygenase (COX)-1 inhibitor, is currently recommended for primary and secondary prevention of atherosclerotic cardiovascular disease and ischemic stroke [1,2]. It also has antiviral and anti-inflammatory effects at much higher doses. The use of aspirin may prevent COVID-19- associated thromboembolic complications, which have been reported in 25–43% of severe to critical COVID-19 patients [3-6]. It has been shown in an observational study that use of antiplatelet therapies in severe COVID-19 patients with risk of thrombosis resulted in improved gas exchange efficiency and increased arterial oxygenation [7].

### METHODS

We searched MEDLINE thru PubMed and Cochrane CENTRAL for randomized controlled trials, cohort studies. systematic reviews and meta-analysis using the following free and MeSH terms: “COVID-19” AND “aspirin” on April 26, 2021 without language, country and disease severity restrictions. We also searched ChinaXiv, MedRxiv and BioRxiv for preprints and ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform and Chinese Clinical Trial Registry for ongoing studies. We further searched COVID-19 Open Living Evidence and Living Evidence on COVID-19 for published and ongoing studies. We included RCTs that assessed efficacy of the continuation of aspirin as maintenance for underlying medical conditions among patients with COVID-19. In the absence of RCTs, we included cohort studies instead. We excluded case series and case-control studies, studies that combined aspirin with drugs other than the standard of care or compared aspirin with other drugs.

## RESULTS

### Characteristics of included studies

We found 3 retrospective cohort studies, one preprint [10], involving 15,049 (aspirin n=7,485, no aspirin n=7,564) patients with COVID-19 [8,9,10]. The patients on aspirin had underlying medical conditions, which include coronary artery disease, hypertension and diabetes. In one study, patients had severe to critical COVID-19 and received 75-150 mg of aspirin daily [9]. The maintenance dose and disease severity were not reported in two studies [8,10]. The studies did not report thromboembolic and bleeding events. The authors reported adjusted odds ratios (ORs) (Appendix 3).

### Methodological quality

Overall quality of evidence was very low due to imprecision and inconsistency. Risk of bias assessment using the Newcastle-Ottawa Scale revealed a score of 8/9 in two studies [8,10] and 9/9/ in one study [9]. There was substantial heterogeneity in terms of the pooled effect estimates for mortality, possibly due to mixed disease severity, where it was not reported in 2 studies [8,10] and in another study, patients had severe to critical COVID-19 [9]. There was also imprecision (confidence interval crossed the null value of 1 due to small sample size in one study [9] (Appendix Table 2).

### Outcomes

Aspirin was not associated with decreased odds of mortality (pooled aOR 0.54, 95% CI 0.23, 1.29). These studies [8,9], however, showed substantial between-study heterogeneity ($I^2$ 78%). One study reported a significant increase in odds of the composite outcome of mortality or discharge to hospice (aOR 1.53, 95% CI 1.15, 2.05) [10]. The association of aspirin with thromboembolic events and bleeding was not assessed in these studies (Appendix 3).

## RECOMMENDATIONS FROM OTHER GROUPS

NIH (April 21, 2021) and EMA (March 18, 2020) recommend continuation of nonsteroidal anti-inflammatory drugs (NSAIDs) for underlying medical conditions during acute management of patients with COVID-19 unless discontinuation is otherwise warranted by their clinical condition [11].

## RESEARCH GAPS

There are no ongoing studies.

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# Appendix 1. Characteristics of included studies

| Author<br>Year<br>Country | Design | Pre-existing illnesses/<br>Risk factors | Disease Severity<br>(COVID)<br>Age<br>Sex distribution | Aspirin | No Aspirin | Outcome | Risk of bias (Newcastle-Ottawa 9/9)<br>Other sources of bias |
|---|---|---|---|---|---|---|---|
| Osborne<br>2021<br>USA | Retrospective Cohort | Prior congestive heart failure<br>diabetes and hypertension | Not reported<br>58 years<br>Males 89% | n=6,300<br>Dose not reported | n=6,300<br>Not reported | Mortality<br>aOR 0.38 (0.33–0.44)<br>propensity score matching | 8/9<br>Dosage not reported |
| Reese<br>2021<br>USA | Retrospective Cohort | Charlson comorbidity index of 2.51 | Mild to severe<br>67.5 years<br>Males 46% | n=1,133<br>Dose not reported | n=1,133<br>Not reported | Mortality/ discharge to hospice or WHO Severity 10<br>aOR 3.25 (2.76-3.83)<br>propensity score matching | 8/9<br>Not peer-reviewed<br>dosage not reported |
| Yuan<br>2021<br>China | Retrospective Cohort | Coronary artery disease - more than one of the following conditions:<br>1) existing myocardial infarction;<br>2) treated with percutaneous coronary intervention or a coronary artery bypass graft; 3) > 50% stenosis of at least 1 of the 3 major coronary arteries (left anterior descending, circumflex, or right coronary artery) demonstrated by coronary angiography. | Severe to critical<br>71 years<br>Males 50% | n=52<br>75-150 mg/day | n=131<br>Standard of care | Mortality<br>aOR 0.94 (0.41-2.17) | 9/9<br>small sample size |

# Appendix 2. GRADE Evidence Profile

| CERTAINTY ASSESSMENT | | | | | | | NO. OF PATIENTS | | EFFECT | | CERTAINTY | IMPORTANCE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Aspirin | SOC | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality** | | | | | | | | | | | | |
| 2 | Observational studies | Not serious | Not serious | Not serious | Serious [1,a] | None | 283/6352 (4.5%) | 690/6431 (10.7%) | **OR 0.54** (0.23 to 1.29) | **46 fewer per 1,000** (from 80 fewer to 27 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Composite mortality/ discharge to hospice** | | | | | | | | | | | | |
| 1 | Observational study | Not serious | Not serious | Not serious | Not serious | None | 124/1133 (10.9%) | 84/1133 (7.4%) | **OR 3.25** (2.76 to 3.83) | **132 more per 1,000** (from 107 more to 161 more) | ⨁⨁◯◯ LOW | CRITICAL |

## Q15. Should antiseptic mouthwashes/gargles be used be as adjunctive treatment for COVID-19 infection?

*As of 21 December 2021*

### RECOMMENDATIONS

**We recommend against the use of any antiseptic mouthwash as an adjunctive therapy for patients with COVID-19.** *(Very low certainty of evidence; Strong recommendation)*

**We recommend against the use of any antiseptic mouthwash to prevent COVID-19 in healthy individuals.** *(Very low certainty of evidence; Strong recommendation)*

*Consensus Issues*

The panelists voted unanimously to recommend against the use of antiseptic mouthwash as an adjunctive treatment mainly due to the unclear clinical benefit based on the surrogate outcomes and the risk of harm among patients with COVID-19 from the very low certainty evidence. The evidence of harm on using mouthwash, which came from the studies used for adjunctive treatment, led the panel to also formulate a strong recommendation against its use for the prevention of COVID-19 infection in healthy individuals. They considered the probable risk of harm from long-term exposure to particular mouthwash components if used as a preventive strategy. Their strong recommendations also took into account individuals with possible or suspected thyroid problem. A panelist expressed that mouthwashes are unnecessary because people breathe in virus-containing particles that are likely to settle in their nasal passages. Furthermore, these antiseptic gargles could result in wasteful spending.

### PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of antiseptic mouthwash or gargle to prevent covid-19 in healthy individuals*. (very low quality of evidence)*

*Consensus issues*

The panel did not provide a recommendation on the use of antiseptic mouthwashes/gargles because the indirect evidence found included COVID-19 positive patients instead of healthy individuals. Furthermore, the surrogate outcomes reported were more on the decrease in forward transmission (clearance of SARS-CoV-2 virus) rather than prevention of a healthy individual from contracting the infection. It was one completed study in Canada which involved COVID-19 negative individuals, the result of which is not yet available.

## WHAT'S NEW IN THIS VERSION?

- Revision of clinical question to focus on the evidence of antiseptic gargle as adjunctive therapy for COVID-19 infection
- Latest literature search: November 30, 2021
- Addition of five randomized trials and removal of one observational study
- Addition of Risk of Bias assessment of the seven randomized controlled trials included in the review

- Addition of GRADE Evidence Profile which summarizes the evidence on the critical outcomes rated by the consensus panel

## KEY FINDINGS

There were no studies that directly investigated antiseptic mouthwash for the prevention of COVID-19 in people without the infection. Seven randomized controlled trials (RCTs) on the use of antiseptic mouthwashes as adjunctive therapy in patients with COVID-19 were found. Of these, six RCTs studied the effect of antiseptic mouthwashes on the SARS-CoV-2 viral load or cycle threshold. The studies, which used different agents, showed no clear clinical benefit. Only one RCT, which used hydrogen peroxide mouthwash, investigated symptom relief and found no significant benefit. Increased risk of thyroid dysfunction with povidone iodine mouthwash and nasal powder exposure was reported in one RCT. Another RCT reported increased risk of burning throat sensation with hydrogen peroxide mouthwash. For both adjunctive treatment and prevention of COVID-19, there was evidence for harm and no clear benefit with the use of antiseptic mouthwash.

## INTRODUCTION

The use of a mouth-rinse for COVID-19 patients was mainly based on the general vulnerability of SARS-CoV-2 toward oxidation, and on the finding that products containing oxidizing agents such as hydrogen peroxide and povidone iodine (PI) were able to inactivate coronaviruses on inanimate surfaces [1] within a thirty-second [2] or one-minute exposure period. Another laboratory study [3] showed that povidone iodine was effective at inactivating SARS-CoV-2 at the three different concentrations after 60-second exposure times. Although cytotoxicity or cell death was not observed in the test wells, safety concerns arose from possible irritation to the oral mucosa, or allergic reactions to components of the product.[4] Moreover, local application of antimicrobials will disrupt the normal oral microbiota [1,4], which is increasingly recognized for its vital role in preventing the colonization of pathogens and supporting one’s immune system.

## REVIEW METHODS

Studies that involved administration of antiseptic mouthwash to COVID-19 patients were included in this review. Outcomes of interest were change in viral load or cycle threshold, clinical improvement, and adverse events associated with antiseptic mouthwash. Published and preprint randomized controlled trials were included in this review.

The inclusion criteria for this review were the following:

- Population: COVID-19 patients
- Intervention: any antiseptic mouthwash (povidone iodine, chlorhexidine gluconate, hydrogen peroxide, cetylpyridinium chloride, B-cyclodextrin-citrox)
- Comparator: placebo or standard of care
- Outcomes: change in viral load or cycle threshold, clinical improvement, adverse events
- Methodology**:** randomized controlled trials (RCTs)

We searched until November 30, 2021 for published and pre-print articles through MEDLINE via PubMed, Cochrane Libarary, medRxiv, guideline sites such as NICE,

Australian, WHO, the USPSTF and Canadian Task Force on Preventive Health. We used “antiseptic oral rinse”, “antiseptic mouthwash”, and “antiseptic gargle” besides the search words for COVID-19.

## RESULTS

### Efficacy

We found no studies on the use of antiseptic mouthwash as prophylaxis or prevention against COVID-19.

We found seven RCTs (n=438) on the use of antiseptic mouthwashes as adjunctive treatment for COVID-19 patients (see Appendix 2).[5-11] Six RCTs determined the effect of mouthwashes on the reduction in SARS-CoV-2 viral load [5,6,8-11], while one RCT investigated the effect on COVID-19 symptoms.[7] Antiseptics used in the RCTs were povidone iodine, chlorhexidine gluconate (CHX), cetylpyridinium chloride (CPC), B-cyclodextrin-citrox, and hydrogen peroxide. Two studies had issues with incomplete outcome data due to exclusion of withdrawals in the outcome analysis.[6,7] Two other studies had issues with allocation concealment [8,9], one of which also had unclear randomization method and possible reporting bias due to unpublished peer-reviewed results.[9] Risk of bias assessment is found in Appendix 4.

The efficacy of three commercial mouth-rinses, specifically povidone iodine, chlorhexidine gluconate and cetylpyridinium chloride, in reducing the salivary SARS-CoV-2 viral load in COVID-19 positive patients (n=16) were compared with water in a small randomized clinical trial by Seneviratne in 2020.[10] Saliva samples were collected from all patients at baseline and at 5min, 3h and 6h post-application of mouth-rinses or water, and these were subjected to SARS-CoV-2 RT-PCR analysis. Outcome measures were reported in terms of cycle threshold values (Ct, or the number of cycles needed to detect SARS-CoV-2 in a sample) and fold changes in Ct values (Ct at timepoint divided by Ct at baseline) of each substance compared to water. Results showed that Ct values detected in all 16 patients were within the range of 15.64 to 34.58, with a mean value of 27.73 ± 4.77. No statistical differences were obtained in the Ct values with regard to any time point in all the groups. A statistically significant increase in -fold change of Ct value at 5min and 6h was observed post-rinsing with cetylpyridinium chloride mouthwash compared to the water group ($p$<0.05; mean difference not mentioned). Although the -fold changes in Ct values were higher at 3h in the cetylpyridinium chloride group, no statistical significance was achieved ($p$=0.20; mean difference not mentioned). In povidone iodine mouthwash, statistically significant increase in -fold change was obtained only at 6h post rinsing in comparison with water ($p$<0.01; mean difference not mentioned). The effect of decreasing salivary load with cetylpyridinium chloride and povidone iodine mouth-rinsing was observed to be sustained at the 3h and 6h time points compared to the control group.

An open-label randomized clinical trial by Mohamed in 2020 [11] compared the effect of gargling for 30 seconds thrice daily using 1% povidone iodine, essential oils (EO, Listerine), and tap water on SARS-CoV-2 viral clearance among asymptomatic COVID-19 patients (n=20). The gargling activity lasted for 7 days, and nasopharyngeal and oropharyngeal swabs were collected on days 4, 6 and 12 of the intervention. The study reported that all patients in the povidone iodine group (5/5) had negative RT-PCR on all days of testing, and the difference compared to control was statistically significant at days 4 (p=0.048), 6 (p=0.008) and 12 (p=0.048). Similar analyses for 1%

povidone iodine vs. tap water group, essential oils vs. control group and EO vs. tap water group were stated as not significant, but the results were not shown.

Another study which investigated the efficacy of cetylpyridinium chloride + zinc lactate, hydrogen peroxide, chlorhexidine gluconate, and hydrogen peroxide + chlorhexidine gluconate reported 15.8 ± 0.08- and 20.4 ± 3.7-fold reduction in salivary viral load immediately after rinsing with hydrogen peroxide and cetylpyridinium chloride + zinc lactate, respectively.[6] Chlorhexidine mouthwash was able to meet the minimum acceptance criteria of □2-fold reduction at all timepoints (2.1 ± 1.5-fold immediately after rinsing; 6.2 ± 3.8-fold 30mins after; 4.2 ± 2.4-fold 60mins after). The combination of hydrogen peroxide + chlorhexidine gluconate did not result in acceptable viral load fold reduction.

Two studies reported the logarithmic reduction of SARS-CoV-2 viral copies in salivary samples.[5,9] A statistically significant median difference of -0.38 $\log_{10}$ copies/mL (-1.39 to 0.0; $p$<0.001) was observed from baseline at 4 hours after rinsing with B-cyclodextrin-citrox mouthwash, compared to -0.15 $\log_{10}$ copies/mL (-0.97 to 0.33; $p$=0.039) in placebo. The difference between placebo and the intervention group was statistically significant ($p$=0.036; mean difference value not mentioned).[5] On the other hand, the second study (preprint) reported partial data on mean logarithmic reduction in SARS-CoV-2 copies in both whole mouth fluid and respiratory droplet samples using povidone iodine, hydrogen peroxide, or chlorhexidine.[9] Preliminary results showed that mean viral copies collected from respiratory droplet samples were statistically reduced from baseline at 20mins (2.5 ± 0.40; $p$=0.02) and 60mins (1.58 ± 1.87; $p$=0.03) with povidone iodine, at 20mins with hydrogen peroxide (3.36 ± 3.66; $p$<0.0001), and at 90mins with chlorhexidine (1.15 ± 0.82; $p$=0.04). However, the mean differences between groups were not available in the preprint. Results were not pooled, and meta-analysis could not be performed due to very serious inconsistencies in units, observation time, specimen samples, and lack of available data. The evidence showed unclear clinical benefit given that only surrogate outcomes were presented by the studies.

Lastly, the study by Di Domenico 2021 showed no significant difference in time to clinical relief among patients given hydrogen peroxide compared to the control group in the intention-to-treat population (HR for clinical relief 0.99, 95% CI 0.60-1.63).[7]

Overall, the RCTs we found showed no clear clinical benefit: six studies measured as outcomes viral loads and showed no significant effect, and the one study that investigated improvement of symptoms reported no significant difference between those given hydrogen peroxide and those given control.

**Safety**

The RCT by Guenezan 2021 on the use of the combination of 1% aqueous povidone iodine solution mouthwash, nasal pulverization and ointment for COVID-19 patients reported thyroid dysfunction as a safety outcome.[8] All patients in the intervention group had elevation in thyroid stimulating hormone (TSH) from baseline (median [IQR], 3.4 [2.6-4.3] mIU/L vs 2.1 [1.4-3.1] mIU/L at baseline) 5 days after exposure. Five patients were reported to have TSH greater than the upper limit of normal (RR 11, 95% CI 0.675-179.3), indicating increased risk of thyroid dysfunction among patients exposed to povidone iodine. TSH values returned to baseline levels at 7 to 12

days post exposure. No changes in T3 and T4 values were observed among patients. There were also no reported hospital admissions among the participants.

The RCT by Di Domenico 2021 reported adverse events on the use of 1% hydrogen peroxide mouthwash combined with 0.5% hydrogen peroxide nasal wash as an adjunctive treatment for COVID-19 patients.[7] Increased risk for burning throat (22.2%) (RR 4.78, 95% CI 1.14-19.97; $p$=0.01) was noted in the hydrogen peroxide group compared to placebo on day 2 of exposure. Moreover, there was an increased risk for burning nose (31.7%) (RR 6.83, 95% CI 1.68-27.70; $p$<0.01) in the treatment group since the study employed a combination of hydrogen peroxide mouthwash and nasal wash intervention. Other adverse events such as burning mouth (7.9%) and ageusia (4.8%) were not statistically significant.

The safety outcomes assessed for this review showed significant risk of adverse events with the use of antispetic mouthwash (specifically, 1) povidone iodine and 2) hydrogen peroxide).

## EVIDENCE TO DECISION

There are no cost-effectiveness studies on antiseptic mouthwash as adjunctive treatment for COVID-19 patients. Prices of antiseptic mouthwash vary depending on brand, agent used and volume. In local drugstores, a 60-mL bottle of hydrogen peroxide and povidone-iodine cost approximately Php 22.00 and Php 116.00, respectively.[12,13]

## RECOMMENDATION FROM OTHER GROUPS

On the use of pre-procedural mouth rinses (PPMR), the Centers for Disease Control state that PPMRs with an antimicrobial product (chlorhexidine gluconate, essential oils, povidone-iodine or cetylpyridinium chloride) may reduce the level of oral microorganisms in aerosols and spatter generated during dental procedures.[14]

The Philippine Dental Association has recommended the use of 1% hydrogen peroxide or 0.2% povidone-iodine as pre-procedural mouth-rinse to reduce the salivary load of oral microbes, including potential SARS-CoV-2 carriage.[15]

## ONGOING STUDIES

There are nine ongoing clinical trials [16-26] and two recently completed studies [26,27] (see Appendix 6. Results of the completed trials are still pending.

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# Appendix 1. Evidence to Decision

Table 1. Summary of initial judgments prior to the actual panel meeting (n = 9)

| FACTORS | JUDGMENT | | | | | | RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS |
|---|---|---|---|---|---|---|---|
| **Problem** | No (1) | Yes (8) | | | | | • Hypothesis that mouthrinse (hydripgen peroxide and povidone-iodine) for COVID-19 can inactivate coronaviruses on inanimate surfaces within a thirty-second or one-minute exposure period |
| **Benefits** | Large | Moderate (1) | Small | Uncertain (8) | | | • Clinical benefits remain unclear based on the studies that focused on quantifying the reduction in viral load among patients with COVID-19<br>• One RCT showed no statistically significant benefit in symptom relief if hydrogen peroxide-based mouthwash is used. |
| **Harm** | Large (8) | Small (1) | Uncertain | Varies | | | • Increased risk of thyroid dysfunction with povidone iodine mouthwash and nasal powder exposure was reported in one RCT.<br>• Another RCT reported increased risk of burning throat sensation with hydrogen peroxide mouthwash. |
| **Certainty of Evidence** | High | Moderate | Low (1) | Very low (8) | | | • The overall certainty of evidence is very low due to serious risk of bias and very serious imprecision. |
| **Balance of effects** | Favors antiseptic mouthwash/ gargles | Does not favor antiseptic mouthwash/ gargles (7) | Uncertain (2) | Varies | | | • Clinical benefits remain unclear based on the studies that focused on quantifying the reduction in viral load among patients with COVID-19<br>• One RCT showed no statistically significant benefit in symptom relief if hydrogen peroxide-based mouthwash is used.<br>• Increased risk of thyroid dysfunction with povidone iodine mouthwash and nasal powder exposure was reported in one RCT.<br>• Another RCT reported increased risk of burning throat sensation with hydrogen peroxide mouthwash. |
| **Values** | Important uncertainty or variability (2) | Possibly important uncertainty or variability (6) | Possibly NO important uncertainty or variability (1) | No important uncertainty or variability | | | • *Panel: Possibly if used in specific occupations that are high risk for exposure to COVID-19, perform aerosol generating procedures, and with uncertainty on the effectiveness of PPE used during the exposure.* |
| **Resources Required** | Uncertain (2) | Large cost | Moderate Costs (7) | Negligible costs or savings | Moderate savings | Large savings | • No cost-effectiveness studies on antiseptic gargles specifically for COVID-19. Local prices of commercial mouthwash vary depending on brand, content and volume.60 mL of hydrogen peroxide – Php 22 (Watsons)60 mL of povidone-iodine – Php 116 (Watsons) |
| **Certainty of evidence of required resources** | No included studies (8) | Very low (1) | Low | Moderate | High | | • No cost-effectiveness studies on antiseptic gargles specifically for COVID-19. |
| **Cost effectiveness** | No included studies (9) | Favors the comparison | Does not favor either the intervention or the comparison | Favors the intervention | | | • No cost-effectiveness studies on antiseptic gargles specifically for COVID-19. |
| **Equity** | Uncertain (8) | Reduced | Probably no impact (1) | Increased | | | • No research evidence found. |
| **Acceptability** | Uncertain (4) | No (1) | Yes (4) | Varies | | | • No research evidence found. |
| **Feasibility** | Uncertain (4) | No | Yes (5) | Varies | | | • No research evidence found. |

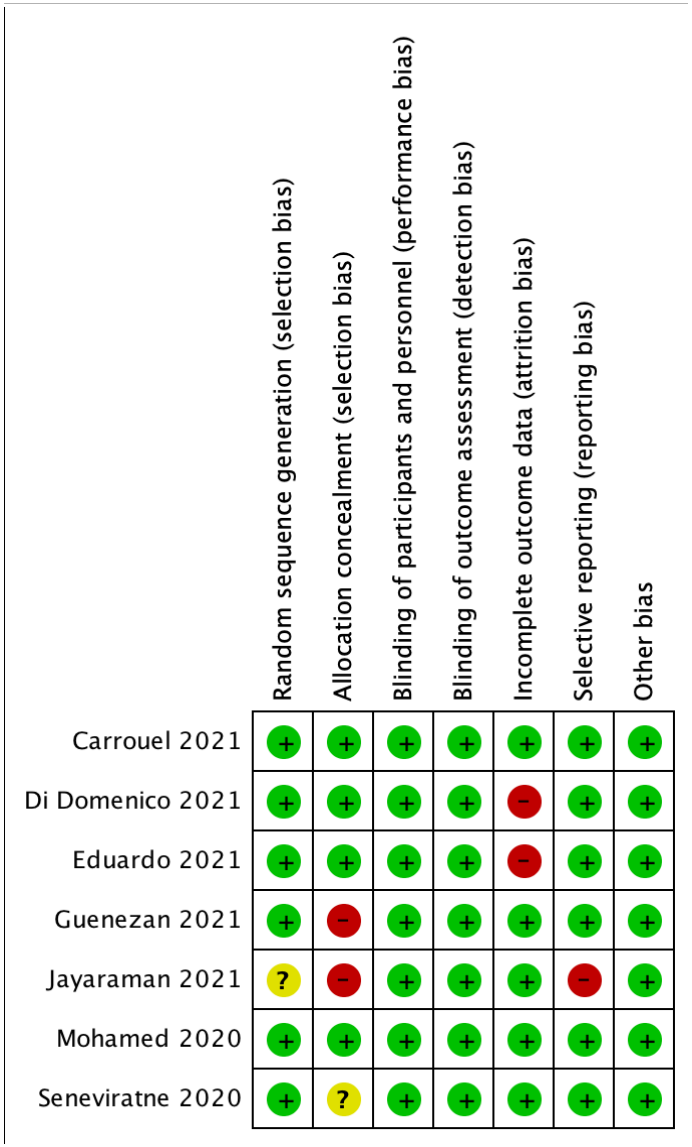
## Appendix 2. Search Strategy and Yield

| Database | Date of Last Search | Search Strategy | Yield | Hit |
|---|---|---|---|---|
| PubMed | September 21, 2021 | ((((((((((((((((povidone-iodine[MeSH Terms]) OR (chlorhexidine gluconate[MeSH Terms])) OR (antiseptic [MeSH Terms])) OR (antiseptic formulation* [tiab])) OR (cetylpyridinium chloride [MeSH Terms])) OR (Listerine [tiab])) OR (mouthwash [tiab])) OR (mouthwash [tiab])) OR (mouth rinse [tiab])) OR (mouth rinse [tiab])) OR (pre-procedural mouth rinses)) OR (pre-procedural mouth rinse* [tiab])) OR (gargle* [tiab])) OR (povidone-iodine [tiab])) OR (chlorhexidine gluconate [tiab])) OR (antiseptic [tiab])) OR (cetylpyridinium chloride [tiab])) AND ((((((((((COVID-19 [MeSH Terms]) OR (coronavirus [MeSH Terms])) OR (SARS-COV-2 [MeSH Terms])) OR (novel coronavirus [MeSH Terms])) OR (n-CoV)) OR (n-COV [tiab])) OR (COVID* [tiab])) OR (COVID-19 [tiab])) OR (coronavirus [tiab])) OR (SARS-COV-2 [tiab])) | 339 | 10 |
| Epistemonikos | November 30, 2021 | ((((((((((((((((povidone-iodine[MeSH Terms]) OR (chlorhexidine gluconate[MeSH Terms])) OR (antiseptic [MeSH Terms])) OR (antiseptic formulation* [tiab])) OR (cetylpyridinium chloride [MeSH Terms])) OR (Listerine [tiab])) OR (mouthwash [tiab])) OR (mouthwash [tiab])) OR (mouth rinse [tiab])) OR (mouth rinse [tiab])) OR (pre-procedural mouth rinses)) OR (pre-procedural mouth rinse* [tiab])) OR (gargle* [tiab])) OR (povidone-iodine [tiab])) OR (chlorhexidine gluconate [tiab])) OR (antiseptic [tiab])) OR (cetylpyridinium chloride [tiab])) AND ((((((((((COVID-19 [MeSH Terms]) OR (coronavirus [MeSH Terms])) OR (SARS-COV-2 [MeSH Terms])) OR (novel coronavirus [MeSH Terms])) OR (n-CoV)) OR (n-COV [tiab])) OR (COVID* [tiab])) OR (COVID-19 [tiab])) OR (coronavirus [tiab])) OR (SARS-COV-2 [tiab])) | 4 | 2 |
| Cochrane Library | November 30, 2021 | ((((((((((((((((povidone-iodine[MeSH Terms]) OR (chlorhexidine gluconate[MeSH Terms])) OR (antiseptic [MeSH Terms])) OR (antiseptic formulation* [tiab])) OR (cetylpyridinium chloride [MeSH Terms])) OR (Listerine [tiab])) OR (mouthwash [tiab])) OR (mouthwash [tiab])) OR (mouth rinse [tiab])) OR (mouth rinse [tiab])) OR (pre-procedural mouth rinses)) OR (pre-procedural mouth rinse* [tiab])) OR (gargle* [tiab])) OR (povidone-iodine [tiab])) OR (chlorhexidine gluconate [tiab])) OR (antiseptic [tiab])) OR (cetylpyridinium chloride [tiab])) AND ((((((((((COVID-19 [MeSH Terms]) OR (coronavirus [MeSH Terms])) OR (SARS-COV-2 [MeSH Terms])) OR (novel coronavirus [MeSH Terms])) OR (n-CoV)) OR (n-COV [tiab])) OR (COVID* [tiab])) OR (COVID-19 [tiab])) OR (coronavirus [tiab])) OR (SARS-COV-2 [tiab])) | 49 | 4 |
| medRxiv | November 30, 2021 | (COVID-19 OR SARS-CoV-2) AND antiseptic gargle | 7 | 1 |
| covid-nma | November 30, 2021 | Povidone-iodine, nasal rinse, oral rinse, antiseptic formulations, chlorhexidine gluconate, cetylpyridinium chloride | 0 | 0 |

## Appendix 3. Characteristics of Included Studies

| Author/Country | Population (n) | Interventions | Comparator | Outcomes |
|---|---|---|---|---|
| Carrouel 2021<br><br>France | Asymptomatic and mild COVID-19 patients<br>n = 176 | B-cyclodextrin-citrox mouthwash (CDCM) (n=88): 200 mL antiviral components (b-cyclodextrin (0.1%) and citrox (0.01%)) | Placebo (n=88) | Reduction in SARS-CoV 2 viral load in salivary samples |
| Eduardo 2021<br><br>Brazil | Hospitalized adults aged 18-90 years with COVID-19<br><br>n = 60 | ● Arm 1 (n=12): 0.075% Cetylpyridinium chloride + 0.28% Zinc lactate (20 mL for 30 s)<br>● Arm 2 (n=12): 1.5% Hydrogen Peroxide (10 mL for 1 min)<br>● Arm 3 (n=12): 0.12% Chlorhexidine gluconate (15 mL for 30s)<br>● Arm 4 (n=12): 1.5% Hydrogen peroxide + 0.12% chlorhexidine<br>(10 mL of HP for 1 min, followed by 15 mL of CHX for 30 s) | Placebo (n=12): distilled water 20 mL for 1 min | Reduction in SARS-CoV 2 viral load in salivary sample, Ct values (only figures available) |
| Di Domenico 2021<br><br>Brazil | Patients positive for SARS-CoV 2<br><br>n = 106 (from 193 recruited) | 1% $H_2O_2$ for gargling, 3x/day for 7 days. Plus 0.5% $H_2O_2$ for a nasal wash, 2x/day for 7 days (n=63) | Placebo (n=43): distilled water and mint essence | Improvement of COVID-19 symptoms,<br>adverse events |
| Guenezan 2021<br><br>France | Adult outpatients aged 18 years and above with highly positive (cycle threshold ≤20) for SARSCoV-2 NP swabs<br>n = 24 | Povidone iodine (n=12): 4 successive mouthwashes and gargles with 25 mL of 1% aqueous PI solution + 2.5-mL nasal pulverization of the same solution into each nostril + 1 application on each nasal mucosa of a dab of 10% PI ointment | No intervention (n=12) | SARS-CoV 2 RNA quantification, viral titer, adverse events (only figure/plot box available), hospital admission |
| Jayaraman 2021 (preprint)<br><br>India | SARS-CoV 2 positive inpatients<br>n = 36 | ● Arm 1: 20 and 60 mins 1% povidone iodine<br>● Arm 2: 20 and 60 mins 1.5% hydrogen peroxide;<br>● Arm 3: 90 and 180 minutes after 1.5% hydrogen peroxide<br>● Arm 4: 90 and 180 minutes after 0.2% chlorhexidine | - | Reduction in SARS-CoV 2 viral copies from whole mouth fluid and respiratory droplets |
| Mohamed 2020 (preprint)<br><br>Malaysia | adults aged 18 years and above, asymptomatic COVID-19 patients (Stage 1)<br>less than 5 days from diagnosis (first positive swab sample)<br>n = 20 | EXPERIMENTAL 1 (n=5):<br>Povidone iodine<br>EXPERIMENTAL 2:<br>Essential oils<br>EXPERIMENTAL 3:<br>water | no mouthwash | No. of cases with viral clearance at days 4, 6, 12 |
| Seneviratne 2020<br><br>Singapore | COVID-19 positive patients laboratory confirmed<br><br>n =16 (from 36 recruited) | EXPERIMENTAL 1 (n=6):<br>15 mL undiluted chlorhexidine gluconate<br>EXPERIMENTAL 2 (n=4):<br>5 mL povidone iodine diluted with 5mL water<br>EXPERIMENTAL 3 (n=4):<br>20 mL of 0.075% cetylpyridinium chloride | CONTROL (n=2): water | Cycle threshold (Ct), Ct fold change (only figure/plot box available) |

## Appendix 4. Risk of Bias Table



# Appendix 5. GRADE Evidence Profile

**Should antiseptic mouthwashes/gargles compared to placebo for COVID-19 as adjunctive treatment**

| CERTAINTY ASSESSMENT | | | | | | | SUMMARY OF FINDINGS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates | | Relative effect (95% CI) | Anticipated absolute effects | |
| | | | | | | | With placebo | With antiseptic | | Risk with placebo | Risk difference with antiseptic |
| **SARS-CoV-2 Viral Load** | | | | | | | | | | | |
| 176 (1 RCT) | Serious[a,b] | Not serious | Not serious | Not serious | None | ⨁⨁⨁◯ Moderate | Statistically significant median difference of -0.38 (-1.39 to 0.0, $p$ <0.001) from baseline at 4 hrs after rinsing with B-cyclodextrin-citrox mouthwash, compared to -0.15 (-0.97 to 0.33, $p$ = 0.039) in placebo. The difference between placebo and the intervention group was statistically significant ($p$ = 0.036, mean difference between groups not indicated). | | | | |
| **Clinical Improvement** | | | | | | | | | | | |
| 106 (1 RCT) | Serious[b] | Not serious | Not serious | Serious[c] | None | ⨁⨁◯◯ Low | No significant difference was seen in time to clinical relief among patients given hydrogen peroxide compared to the control group by intention to treat analysis (HR for clinical relief, 0.99; 95% CI 0.60 to 1.63). | | | | |
| **Adverse Events with Povidone Iodine (TSH elevation)** | | | | | | | | | | | |
| 24 (1 RCT) | Serious[a] | Not serious | Not serious | Very serious[d] | None | ⨁◯◯◯ Very low | 5/12 (41.7%) | 0/12 (0.0%) | **RR 11.0** (0.675 to 179.302) | 417 per 1,000 | **1,000 more per 1,000** (from 135 fewer to 1,000 more) |
| **Adverse Events with Hydrogen Peroxide** | | | | | | | | | | | |
| 106 (1 RCT) | Serious[b] | Not serious | Not serious | Not serious | None | ⨁⨁⨁◯ Moderate | Incidence of burning throat (22.2%) (RR 4.78, 95% CI 1.14 to 19.97, $p$ = 0.01) and burning nose (31.7%) (RR 6.83, 95% CI 1.68 to 27.70, $p$ < 0.01) observed on day 2 of exposure were statistically significant compared to placebo. Other adverse events such as burning mouth (7.9%) and ageusia (4.8%) were not statistically significant. | | | | |

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

**Explanations**

[a] Lack of allocation concealment
[b] Incomplete outcome data (attrition bias)
[c] Different interventions, timeframe, specimens used in studies
[d] Crossed the point of no benefit
[e] Small sample size, optimal information size (OIS) not reached, single study

# Appendix 6. Table of Ongoing Studies

| | Clinical Trial ID / Title | Status | Dates | Study design | Country | Population | Intervention Group(s) | Comparison Group(s) | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Evaluation of the Effectiveness of an Oral Antiseptic in Improving the Clinical Status, Decreasing Viral Load and Substantivity in Patients with SARS-CoV-2<br>UTN code: U1111-1255-3454<br>Registration Code: RBR-58ftdj<br><br>Author: Oncina | Recruiting | Start: 10/28/2020 | Interventional, randomized-controlled, parallel, triple blind, with two arms | Brazil | Patients 18-80 yo, with mild to moderate SARS-COV2 | N=20<br>Mouthwash/gargle (30 sec/30 sec) plus active toothpaste, 5x/day, | N=20<br>Mouthwash/gargle (30 sec/30 sec) plus control toothpaste | Viral load; coronavirus infections in saliva (collected in posterior oropharynx) on D0, D2 and D5 |
| 2 | Effectiveness of a mouthwash and toothpaste containing PHTALOX in controlling symptoms of COVID-19 and flu<br>UTN code: U1111-1260-4839<br>Registration Code: RBR-8x8g36<br><br>Author: Poleti | Not yet recruiting | Start: 01/11/2020 | Clinical safety / efficacy trial, randomized, parallel, with triple concealment, with two arms, phase 3 | Londrina, Brazil | Patients 18-70 yo, with symptoms of SARS-COV2 | N=250<br>Oral care kit PLUS mouthwash and dental gel containing PHTALOX<br>Rinse/gargle for 1 min, 5x/day | N=250<br>Oral care kit PLUS mouthwash and dental gel WITHOUT PHTALOX<br>Rinse/gargle for 1 min, 5x/day | Improvement of clinical symptoms in 14 days, measured via self-administered questionnaire<br>At least 30% reduction of respiratory symptoms |
| 3 | Evaluation of the effectiveness of an oral antiseptic and nasal spray in improving the clinical picture, decreasing viral load and its substantivity in patients with Sars-cov-2<br>UTN code: U1111-1260-7525<br>Registration Code: RBR-8tygcz7<br><br>Author: Oncina | Recruiting | Start: 01/16/2020 | Clinical trial of treatment, randomized-controlled, parallel, triple-blind, with three arms, phase 1 | Brazil | Patients 18-70 yo, volunteers; infected with SARS-CoV-2; both sexes; age between 18 to 70 years; be able to gargle. | N=15<br>Active oral antiseptic (0.010% active ingredient) with active nasal spray (fluocyanine)<br><br>N=15<br>Oral antiseptic with 0.010% active ingredient and placebo nasal spray Gargle (30 sec/30 sec), 5x/day | N=15<br>Placebo mouthwash (30 sec/30 sec), 5x/day) and placebo nasal spray | It is expected to find a reduction in the SARS-CoV-2 viral load in the naso-oropharyngeal samples through the RT-PCR method |
| 4 | Povidone-Iodine Intranasal Prophylaxis in Front-line Healthcare Personnel and Inpatients (PIIPPI)<br>NCT04364802<br><br>Author: Kejner | Recruiting | Start: 04/28/2020<br>Est. completion May 2021 | Non-randomized, parallel, open label, phase II clinical trial | USA | Total target N= 300<br><br>Healthcare workers<br><br>Inpatients with >7 days hospitalization or will undergo significant surgical procedure<br><br>Community participants who are (-) COVID-19 | Community: pre- and post-study nasal swab COVID19 test PLUS povidone-iodine spray and gargle (10% diluted 1:30)<br><br>Inpatients: Community PLUS standard care<br><br>HCW:Community PLUS PPE; (PI) nasal spray and gargle at beginning, middle and end of shift | HCW: standard PPE, pre- and post-study test for COVID-19<br><br>Inpatient: standard care, pre- and post-study test for COVID-19<br><br>Community: pre- and post-study test for COVID-19 | % HCW (+) COVID-19 in 3 weeks<br><br>% inpatients (+) COVID-19 in 2 weeks<br><br>% community participants (+) COVID-19 in 3 weeks |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 5 | Mouth Rinses for Inactivation of COVID-19 (MOR) NCT04584684<br><br>Author: Jacox | Active, Not Recruiting | Start: Dec 18, 2020 Estimated Study Completion Date: Sept 2023G Ott | Randomized, double-blind, triple mask, prospective, Phase II trial | USA | Total target N= 480 18 to 65 years<br><br>Diagnosed COVID+ status by physician<br><br>In good oral health. No known allergies to commercial dental products or cosmetics<br><br>Non-pregnant | Drug: 1.5-2% w/v Hydrogen Peroxide<br><br>Drug: 0.12% Chlorhexidine Gluconate<br><br>Drug: 21% Ethanol plus essential oils<br><br>Drug: 1% w/v Povidone-iodide<br><br>Drug: 0.075% Cetylpyridinium Chloride | Saline solution | Change in quantitative polymerase chain reaction (qPCR) from baseline to 15, 30, 45, 60 minutes |
| 6 | Nitric Oxide Releasing Solutions to Prevent and Treat Mild/Moderate COVID-19 Infection (NOCOVID) NCT04337918<br><br>Author: Road | Completed Study, posting of results pending | Start: May 8, 2020 End: Jan 31, 2021 | Multi-center, prospective, randomized, controlled, phase II, parallel group | Canada | COVID-19 (-) at baseline | Standard screening and protection for COVID-19 PLUS Nitric Oxide Releasing Solution (NORS) treatment for 14 days | Standard screening and protection for COVID-19 | Proportion of subjects with either swab positive COVID-19 or presentation of clinical symptoms as measured by fatigue with either fever >37.2 (oral)and/or a persistent cough. |
| 7 | Efficacy of Mouthwash in Reducing Salivary Carriage of COVID-19 NCT04603794<br><br>Author: Hall | Recruiting | Published: Oct 27, 2020 | Randomized, cross-sectional, double blinded, negative controlled, four armed, prospective, interventional study | US | Total target N=60 | Povidone iodine<br><br>Hydrogen peroxide<br><br>CLorhexidine | Normal saline | Real time reverse transcriptase quantitative PCR |
| 8 | Antiseptic Mouth Rinses to Reduce Salivary Viral Load in COVID-19 Patients (BUCOSARS) NCT04707742<br><br>Author: Mira | Completed | Start: June 15, 2020 | Multicentre, randomized, triple-blind, five-parallel-group, placebo-controlled trial | Spain | N=84<br>18 years and above <7 days from the positive SARS-COV-2 PCR test of a nasopharyngeal sample | PVI, Hydrogen peroxide, chlorhexidine, Cetylpyridinium chloride | Distilled water | SARS-Cov2 viral load. [Time Frame: Minute 0 (before mouthwash) - Minute 30 (after mouthwash) - Minute 60 (after mouthwash) - Minute 120 (after mouthwash) ] |
| 9 | A Clinical Trial of Gargling Agents in Reducing Intraoral Viral Load Among COVID-19 Patients (GARGLES) NCT04341688<br><br>Author: Kazmi | Not yet recruiting | Estimated start: Feb 1, 2021 | Quadruple blind randomized controlled trial followed by laboratory based analysis | Pakistan | N=50<br>laboratory confirmed Covid-19, 18-65 years, within seven days of the onset of mild to moderate symptoms of viral infection, already | Gargles and nasal lavages: PVI, hydrogen peroxide, Neem extract, hypertonic saline | Positive control: distilled water Negative control: no gargles or nasal lavages | Primary: Intraoral viral load as deciphered by RT-PCR Secondary: Salivary cytokine profiles of IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ and IL-17 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | admitted in the hospital. | | | |
| 10 | The Efficacy of Pre-procedural Mouth Rinses on SARS-CoV-2 Saliva Viral Load: A Randomized Control Clinical Trial<br>NCT04721457<br><br>Author: Alzahrani | Recruiting | Start: Jan 3, 2021<br>Est. study completion: June 30, 2021 | randomized, cross-sectional, triple-blinded, five-armed, interventional study | Jeddah, Saudi Arabia | Target N=120<br>18 years and above<br>COVID-19 (+) with RT-PCR within 2 days of oral or nasopharyngeal swab<br>Asymptomatic or within 7 days of symptoms<br>Able to rinse and expectorate | Gargles and nasal lavages: 1% PVI, 1.5% hydrogen peroxide, 0.075% cetylpyridinium chloride (CPC), 0.1% sodium hypochlorite | Distilled water | Saliva load was expressed in copies x 10 8 of COVID-19 RNA Cycle thresholds |
| 11 | Reduction of Sars-CoV-2 Oral Viral Load With Prophylactic Mouth Rinse<br>NCT04719208<br><br>Author: Bloomquist | Recruiting | Start: Oct 6, 2020<br>Est. study completion: June 2021 | Randomized, parallel assignment, double blind, interventional study | US | Target N = 60 | Povidone iodine<br>1.5% Hydrogen peroxide<br>0.2% Clorhexedine gluconate<br>Alcohol mouthwash | Water | Change in oral SARS-CoV-2 load in oral cavity of COVID-19 patient using prophylactic mouth rinse |

## Q16. Should nasal sprays be used in the prevention and treatment of COVID-19 infection?

*As of 03 December 2021*

### RECOMMENDATIONS

**We suggest against the use of nasal spray as an adjunct to treatment of COVID-19 infection.** *(Low certainty of evidence; Weak recommendation)*

**There was no consensus on the use of nasal spray in addition to other preventive interventions such as vaccination, proper use of personal protective equipment, and adherence to quarantine and isolation protocols to prevent COVID-19 infection.**

*Consensus Issues*

The statement suggesting against the use of nasal spray as an adjunct to treatment was unanimously approved by the panel members due to the high certainty of the risk of adverse events and the uncertain benefits from the use of glycerol- and hydrogen-peroxide-based nasal sprays. For the panel, the statement warranted a weak recommendation because (1) it is not a primary intervention and (2) despite the risk of harm, it may not necessarily result in overuse, unlike other drugs such as antibiotics.

The decision regarding the statement on the use of nasal spray as an adjunctive to other preventive interventions reached an impasse. The panel members who were inclined towards its use despite possible added costs based their arguments on the risk reduction of developing COVID-19, its availability in the local market, and its authorization from the Philippine Food and Drug Administration as a medical device intended for short-term use. They also claimed that it could be a weak recommendation and that it would not be a replacement for any existing recommended intervention. However, other panel members who voted against its use placed a greater value on the benefit of vaccinations. A panel member also voiced opposition because the word “suggest” implied a strong recommendation for use despite the fact that only two small trials demonstrated benefit and several clinical trials are still underway. Another posited that glycerol-based sprays, which can be oily, might obstruct breathing when used with masks.

### KEY FINDINGS

As an adjunct to prevention, two randomized controlled trials on healthy asymptomatic healthcare workers providing direct care to COVID-19 patients showed that the use of iota-carrageenan or dimethylsulfoxide ethanol nasal spray provided significant benefit in reducing the risk of COVID-19 infection compared to routine care with or without saline placebo. The risk of adverse events and discontinuation of the intervention due to intolerance, comparing treatment and control groups, was inconclusive. Nasal sprays in these trials were used as an adjunct to proper personal protective equipment and universal precautions. Overall certainty of evidence was low.

As an adjunct to treatment, nine randomized controlled trials on patients with mild and moderate COVID-19 showed that the use of nasal sprays containing different active agents (one study each for glycerol, hydrogen peroxide, nitric oxide, ivermectin, momethasone and triamcinolone; povidone iodine in three studies) did not result in significant benefit in terms of viral clearance and showed inconsistent benefit in terms of symptomatic relief. Furthermore, the risk for adverse events (mostly minor, such as sensation of nasal and throat burning, frequent sneezing, altered taste sensation, and minor epistaxis) was significantly higher in the nasal spray arm compared to placebo. Overall certainty of evidence was low.

## INTRODUCTION

As the primary sites of infection and replication of SARS-CoV-2 are through the nasal cavity, it has been theorized that early and targeted treatment of the nasal mucosa may block viral entry and interfere locally with the cascade of viral replication and host infection.[1] In vitro and pre-clinical studies have shown that the effectiveness of various active compounds in nasal sprays against SARS-CoV-2 is mainly based on the creation of a film barrier [1] and the general vulnerability of SARS-CoV-2 to osmotic [2,3], chemical [4], cytokine-regulated [5,6], free-radical membrane [7] disruption, and oxidative damage [8,9]. However, safety and tolerability concerns that arise from potential irritation of nasal mucosa, and allergic reactions to components of the products are major concerns. This systematic review aimed to estimate the effectiveness of nasal sprays as an adjunctive intervention in the prevention and treatment of COVID-19.

## REVIEW METHODS

The Pubmed for Medline database, ClinicalTrials.gov, and WHO International Clinical Trials Registry Platform were searched on 18 November 2021 using the search terms “nasal spray” and “COVID-19” or “SARS-COV-2.” The medRxiv and bioRxiv databases were also searched for pre-publication articles. Full texts were reviewed to determine which studies would be included in the final analysis. When randomized controlled trials were available, we excluded brief communications, reviews, cohort studies, case-control studies, case series, and case reports in the final screening of studies.

## RESULTS

### As Adjunct to Treatment of COVID-19 Infection

A total of nine randomized controlled trials [3, 7, 9-15] were reviewed and analyzed to determine the efficacy of nasal sprays as an adjunct to the routine treatment of mild to moderate COVID-19. The trials investigated nasal sprays containing seven different ingredients namely glycerol [3] nitric oxide [7], povidone iodine [9,11,12], hydrogen peroxide [10], ivermectin [13], momethasone [14], and triamcinolone [15]. Nasal sprays together with routine care were compared to routine care with placebo. Clinically important outcomes were viral clearance, forward transmission of SARS-CoV-2 to household contacts, symptomatic relief of COVID-19 symptoms, and adverse events. Characteristics of studies included in this review are shown in Appendix 3A.

*Outcome: Viral Clearance*

Two studies [11,13] on two different active agents provided data on viral clearance, which was defined as a negative SARS-CoV-2 RT-PCR after the use of nasal spray. The first study, which utilized a povidone iodine-based nasal spray, showed statistically significant viral clearance (RR 10.00, 95% CI 2.61-38.31; Low Certainty) after only one application of the nasal spray.[11] Another study, which utilized ivermectin-based nasal spray, also showed statistically significant viral clearance (RR 1.26, 95% CI 1.07-1.47; Low Certainty).[13] In the latter study, viral clearance was defined as two consecutive negative SARS-CoV-2 RT-PCR. Certainty of evidence in both studies were low due to very serious risk of bias. Both studies had unclear to high risk of bias in terms of participant and outcome assessor blinding, and allocation concealment. An attempt to do pooled analysis further downgraded the certainty of evidence to very low due to very serious risk of bias, highly significant heterogeneity resulting in very serious inconsistency, and overall imprecision (RR 3.40, 95% CI 0.13-91.80; $I^2$=88.9%; Very Low Certainty).

*Outcome: Forward Transmission*

One study, which utilized hydrogen peroxide-based nasal spray, investigated the incidence of forward transmission of SARS-CoV-2 among family members of 106 study participants. In this study, the risk for forward transmission of SARS-CoV-2 between intervention and placebo groups was inconclusive (RR 0.69, 95% CI 0.24-1.95; Moderate Certainty).[10] Certainty of evidence was downgraded to moderate due to imprecision of risk estimates.

*Outcome: Symptomatic Relief of COVID-19 Symptoms*

Relief of COVID-19 symptoms was reported in three trials which utilized three different types of nasal sprays. The trial on glycerol-based nasal spray [3] reported statistically significant benefits in the relief of sore throat (RR 2.50, 95% CI 1.24-5.05; High Certainty), fever (RR 1.12, 95% CI 1.04-1.20; High Certainty), and ageusia (RR 3.50, 1.92-6.27; High Certainty) but inconclusive benefit on the relief of headache (RR 1.24, 95% CI 1.00-1.54; Moderate Certainty). Length of follow-up for relief of symptoms ranged from 7 to 14 days. Certainty of evidence on relief of loss of headache was downgraded to moderate certainty due to imprecision of risk interval estimates.

In another trial which compared hydrogen peroxide-based nasal spray versus control [10], there were inconclusive results for the relief of cough (RR 1.23, 95% 0.50-3.02; Moderate Certainty), ageusia (RR 2.50, 95% 0.78-7.97; Moderate Certainty), anosmia (RR 1.73, 95% 0.62-4.82; Moderate Certainty), dyspnea (RR 2.50, 95% CI 0.57-11.05; Moderate Certainty), and sore throat (RR 0.51, 95% 0.10-2.51; Moderate Certainty). Length of follow-up for relief of symptoms ranged from 4 to 6 days. Certainty of evidence were all downgraded to moderate certainty due to the imprecision of risk interval estimates. One small trial, which utilized a povidone iodine-based nasal spray [12], also reported inconclusive effect in terms of relief of the loss of sense of smell (RR 3.25, 95% 0.93-11.40; Moderate Certainty) between the intervention and the placebo. This finding was in agreement with the results from the study which used hydrogen peroxide-based nasal

spray.[10] Certainty of evidence was downgraded to moderate due to imprecision of risk interval estimates.

*Outcome: Adverse Events*

The risk of developing adverse events associated with the use of nasal sprays was reported in four trials that utilized three different types of nasal sprays, and the pooled risk was found to be significantly higher in the nasal spray arm compared to control (RR 6.18, 95%CI 1.79-21.37). The nasal spray with highest risk for developing adverse events when compared to placebo was found in the glycerol-based nasal spray (RR 81.70, 95% CI 5.10-1309.53; High Certainty) [3] followed by the hydrogen peroxide-based nasal spray (RR 5.87, 95% CI 2.53-13.61; High Certainty) [10], and lastly in the povidone iodine-based nasal sprays (RR 2.91, 95% CI 0.88-9.63; $I^2$=0%; Moderate Certainty).[11,12] All reported adverse events were considered minor. Most common adverse events observed were burning sensation in the nose and throat, frequent sneezing, altered sense of taste, altered tongue sensation, and minor epistaxis. No life-threatening adverse events were observed in all four trials. Certainty of evidence was downgraded to moderate certainty because of the serious risk of bias from the lack of blinding in one of the trials that utilized povidone iodine-based nasal sprays.[11,12]

**As Adjunct to Prevention of COVID-19 Infection**

We found two randomized controlled trials that enrolled a total of 626 healthcare workers providing direct care to COVID-19 patients from Argentina [1] and Iran [4]. Healthcare workers included in these studies were healthy physicians, nurses, kinesiologists and other medical professionals providing direct care to COVID-19 patients. Study participants were asymptomatic [1,4] and IgG and IgM seronegative [4] at the beginning of the study to confirm that they were not infected with COVID-19. In both studies, participants in treatment and control groups had similar baseline characteristics. Only the Argentine study specified that study participants were still unvaccinated during the trial implementation. The study further specified that the trial was carried out during the time when Argentina was experiencing sustained community transmission of SARS-CoV-2. Thus, even though the study participants were healthcare workers, there was still significant participant community exposure. Two different active interventions were analyzed in this evidence review. The Argentine study used iota-carrageenan (IC) 1 puff per nostril (delivering 0.17mg of IC) compared to routine care with saline solution placebo. Meanwhile, the Iranian study used dimethylsulfoxide ethanol (3% dimethylsulfoxide with 20% ethanol; DMSO-ethanol) 1 puff per nostril every 8 hours compared to routine care without placebo. Clinically important outcomes measured in the studies were incidence of COVID-19 infection in 21-28 days, development of adverse events, and discontinuation of the intervention due to intolerance. Characteristics of studies included in this review are shown in Appendix 3B.

*Outcome: Risk of Developing COVID-19*

The use of IC-based nasal spray [1] as an additional preventive measure significantly reduced the risk of developing COVID-19 among healthcare workers within 21 days (RR 0.20, 95% CI 0.04-0.91; Moderate Certainty). No death or hospitalization for any cause was observed in either the intervention and control groups. Likewise, the use of DMSO-

ethanol-based nasal spray [2] significantly reduced the risk of developing COVID-19 among healthcare workers within 28 days (RR 0.13, 95% CI 0.02-0.98; Moderate Certainty). Certainty of evidence in this outcome was downgraded to moderate certainty due incomplete outcome assessment [1] and lack of participant blinding.[4]

*Outcome: Adverse Events*

The risk of adverse events (RR 1.14, 95% CI 0.73-1.79; Low Certainty) and discontinuation of the intervention due to intolerance (RR 0.67, 95% CI 0.11-3.99; Low Certainty), comparing treatment with IC spray and control groups, was inconclusive. No significant difference was found in the occurrence of commonly observed adverse events, namely, headache (RR 1.32, 95% CI 0.66-2.65) and rhinorrhea (RR 0.50, 95% CI 0.13-1.99) between the use of IC-based nasal spray compared to placebo [1]. No data on adverse events were provided in the DMSO-ethanol-based nasal spray study. Certainty of evidence in this outcome was downgraded to low certainty due to incomplete outcome assessment and imprecision of risk estimates.

## EVIDENCE TO DECISION

Presently, at least ten different [1-10] active agents are being investigated as potential prophylactic and treatment interventions against COVID-19 infection. However, current studies providing moderate to high certainty of evidence are still very limited. Among the active agents presented in this evidence base, IC- and glycerol-based nasal sprays are currently available commercially with regulatory approval for use for prevention and symptomatic relief of common viral respiratory infections but not yet for COVID-19. Certain limitations of currently available data should be taken into careful consideration. In both analyses, the studies had relatively short lengths of follow up ranging from 21 to 28 days for prevention studies and 14 to 60 days for symptomatic treatment studies. Thus, long-term effectiveness and adverse events in prolonged use could not be established at this time. Most importantly, clinical effectiveness of nasal sprays was intended as an adjunct to vaccination, proper use of personal protective equipment like masking, hand hygiene, physical distancing, and adherence to quarantine and isolation protocols for the prevention and as an adjunct to routine treatment of COVID-19.

Currently, no cost-effectiveness study on nasal sprays in the prevention of COVID-19 is available for review. The price of nasal spray in local market ranges from Php 297 (20 mL with each mL containing 1.2 mg of Carrageenan) to Php 1,050 (COVISPRAY).

## RECOMMENDATIONS FROM OTHER GROUPS

Currently, there are no published recommendations from the World Health Organization, US National Institutes of Health, and the Centers of Disease Control regarding the use of nasal sprays in preventing COVID-19 infection.

In September 2021, the Philippine Food and Drug Administration released FDA Advisory No. 2021-2289 to notify the public that nasal spray products have been authorized as medical devices with non-specific effect against pathogens. The advisory further emphasized that nasal sprays should not be used as substitutes to vaccines and interventions to prevent or treat SARS-CoV-2 infection.[16]

IC-based nasal sprays have been approved in USA (FDA Medical Devices Databases Establishment Registration & Device & Listing D 441354)[1], Latin America [1], Europe [1], France [3], Asia[1], and Australia [1] as over-the-counter products for common cold and related diseases.

## RESEARCH GAPS

Despite the significant reduction in the risk of COVID-19 infection, findings in these trials should be replicated with longer follow-up periods to ascertain long term effectiveness, safety, and tolerability. Furthermore, effect of nasal sprays on viral clearance and symptomatic relief should still be established. At present, seven randomized controlled trials are investigating iota-carrageenan (2 studies), ivermectin + carrageenan (1 study), GLS-1200 which is a quinine-based agent (1 study), hypochlorous acid (1 study), and nitrous oxide (2 studies) as prophylactic and therapeutic nasal spray against COVID-19 infection.

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# Appendix 1. Evidence to Decision

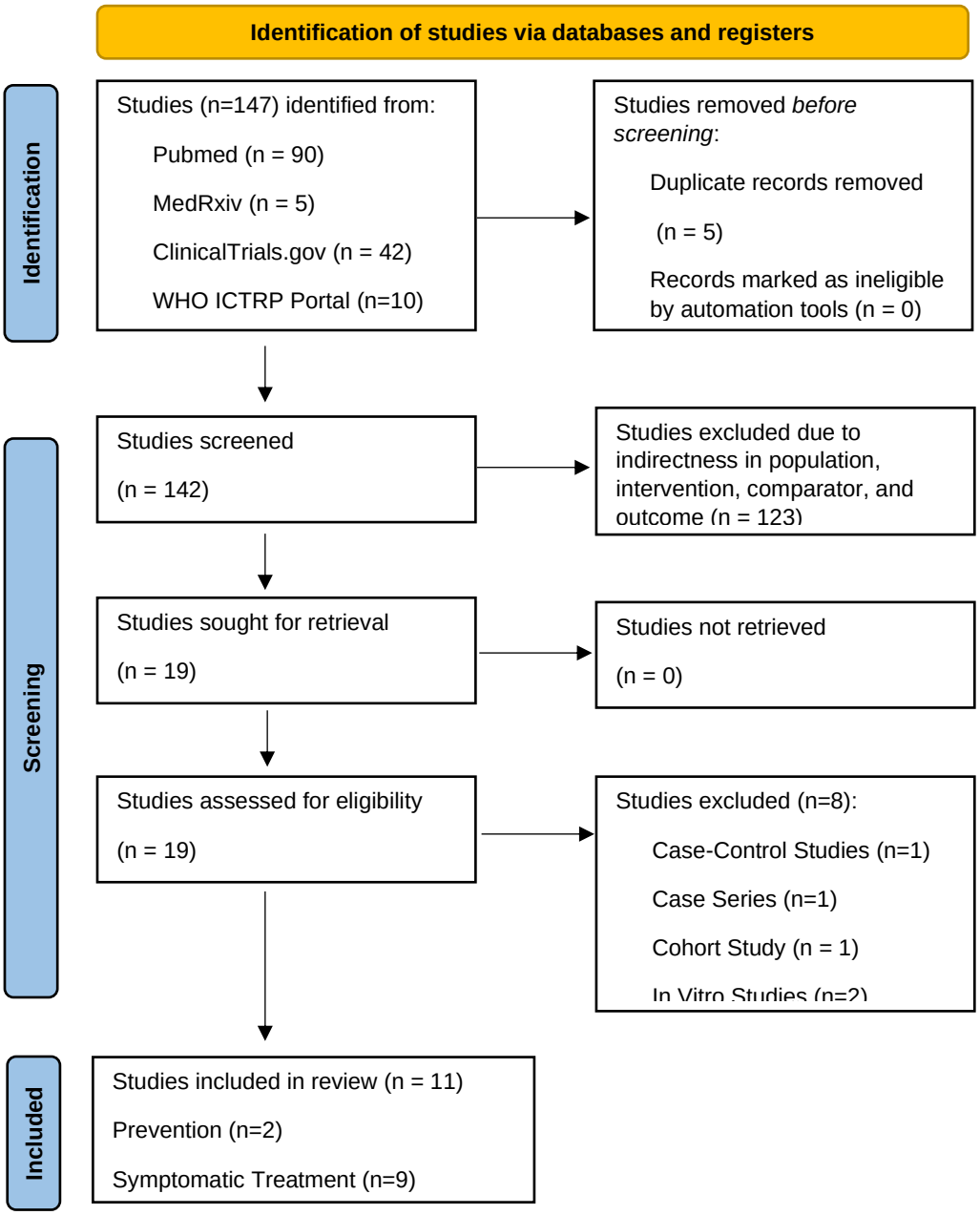
Table 1. Summary of initial judgments prior to the actual panel meeting (n = 5)

| FACTORS | JUDGMENT | | | | | RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS |
|---|---|---|---|---|---|---|
| **Problem** | No | Yes (5) | | | | • Especially in instances when an individual is not yet fully protected by vaccine immunity and in instances when personal protective equipment like masks are temporarily being removed. [1,4] |
| **Benefits** | Large (1) | Moderate (4) | Small | Uncertain | | • As an adjunct to prevention, two randomized controlled trials on healthy asymptomatic healthcare workers providing direct care to COVID-19 patients showed that the use of iota-carrageenan or dimethylsulfoxide ethanol nasal spray provided significant benefit in reducing the risk of COVID-19 infection compared to routine care with or without saline placebo. Nasal sprays in these trials were used as adjunct to proper personal protective equipment and universal precautions. Overall certainty of evidence was low.<br>• As an adjunct to treatment, nine randomized controlled trials on patients with mild and moderate COVID-19 showed that the use of nasal sprays containing different active agents (one study each for glycerol, hydrogen peroxide, nitric oxide, ivermectin, momethasone and triamcinolone; povidone iodine in three studies) did not result in significant benefit in terms of viral clearance and showed inconsistent benefit in terms of symptomatic relief. |
| **Harm** | Large | Small (4) | Uncertain (1) | Varies | | • The risk of adverse events and discontinuation due to intolerance, comparing adjunctive treatment to prevention and control groups, was inconclusive.<br>• As adjunct to treatment, the risk for adverse events (mostly minor, such as sensation of nasal and throat burning, frequent sneezing, altered taste sensation, and minor epistaxis) was significantly higher in the nasal spray arm compared to placebo. |
| **Certainty of Evidence** | High | Moderate | Low (5) | Very low | | • Overall certainty of evidence for nasal spray as adjunct to prevention and treatment was low due to serious risk of bias and imprecision. |
| **Balance of effects** | Favors nasal spray (4) | Does not favor nasal spray | Uncertain (1) | Varies | | • As an adjunct to prevention, two randomized controlled trials on healthy asymptomatic healthcare workers providing direct care to COVID-19 patients showed that the use of iota-carrageenan or dimethylsulfoxide ethanol nasal spray provided significant benefit in reducing the risk of COVID-19 infection compared to routine care with or without saline placebo. As an adjunct to treatment, nine randomized controlled trials on patients with mild and moderate COVID-19 showed that the use of nasal sprays containing different active agents (one study each for glycerol, hydrogen peroxide, nitric oxide, ivermectin, momethasone and triamcinolone; povidone iodine in three studies) did not result in significant benefit in terms of viral clearance and showed inconsistent benefit in terms of symptomatic relief.<br>• The risk of adverse events and discontinuation due to intolerance, comparing adjunctive treatment to prevention and control groups, was inconclusive. As adjunct to treatment, the risk for adverse events (mostly minor, such as sensation of nasal and throat burning, frequent sneezing, altered taste sensation, and minor epistaxis) was significantly higher in the nasal spray arm compared to placebo |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability (4) | Possibly NO important uncertainty or variability (1) | No important uncertainty or variability | | • Lack of studies investigating long-term effectiveness, safety, and tolerability |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Resources Required** | Uncertain (4) | Large cost | Moderate Costs | Negligible costs or savings | Moderate savings (1) | Large savings | • Currently, no cost-effectiveness study on nasal sprays in the prevention of COVID-19 is available for review.<br>• The price of nasal spray in local market ranges from Php 297[1] (each mL with 1.2 mg of Carrageenan) to Php 1050[2] (COVISPRAY) (without shipping fee). |
| **Certainty of evidence of required resources** | No included studies (4) | Very low (1) | Low | Moderate | High | | • Currently, no cost-effectiveness study on nasal sprays in the prevention of COVID-19 is available for review. |
| **Cost effectiveness** | No included studies (5) | Favors the comparison | Does not favor either the intervention or the comparison | Favors the intervention | | | • Currently, no cost-effectiveness study on nasal sprays in the prevention of COVID-19 is available for review.<br>• *Cost is probably one of the important considerations. However, if the spray will indeed prevent many infections, the intervention will likely be deemed extremely cost-effective. (n = 1)* |
| **Equity** | Uncertain (2) | Reduced | Probably no impact (2) | Increased (1) | | | • No research evidence found. |
| **Acceptability** | Uncertain (1) | No | Yes (4) | Varies | | | • Nasal sprays have been authorized as medical devices by the FDA of the Philippines. (FDA Advisory 2021-2289) |
| **Feasibility** | Uncertain (1) | No | Yes (4) | Varies | | | • Nasal sprays are available in local drugstores. |

[1] https://www.mims.com/philippines/company/info/mono%20chem-pharm
[2] https://www.lazada.com.ph/products/preventia-covispray-i2448793605.html

# Appendix 2. Search Yield and Results



# Appendix 3A. Table of Included Studies for Nasal Spray as Adjunct to Treatment of COVID-19

| Study ID<br>Title<br>Author | Study Design | Setting/<br>Country | Total number of Patients Included | Population | Intervention | Comparator/<br>Control | Outcomes |
|---|---|---|---|---|---|---|---|
| **Aref et. Al., 2021 [13]**<br><br>Clinical, Biochemical and Molecular Evaluations of Ivermectin Mucoadhesive Nanosuspension Nasal Spray in Reducing Upper Respiratory Symptoms of Mild COVID-19 | Randomized Controlled Trial | Egypt | 114 | Mild COVID-19 | Ivermectin Nanosuspension Nasal Spray + Routine Care (n=57) | Routine Care included paracetamol 500 mg IV every 6 hours, hydroxychloroquine 500 mg every 12 hours, azithromycin 1g on day 1 then 500 mg per 3 days or clarithromycin 500 mg every 12 h for 7-14 days, oseltamivir 150 mg every 12 hours for 5 days, ascorbic acid 500 mg every 12 hours 1(n=57) | Viral Clearance defined as 2 consecutive negative RT-PCR (54/57 vs 43/57; p=0.004)<br><br>Symptom duration:<br>fever, cough, dyspnea, anosmia, GIT*, PCR conversion<br>*NS<br><br>Duration taken for nasopharyngeal swab to be negative<br><br>Improvement of the abnormal routine laboratory parameters 7 days after treatment: NLR, CRP, d-dimer, ferritin |
| **Arefin, et. Al, 2021 [11]**<br><br>Virucidal effect of povidone iodine on COVID-19<br>in the nasopharynx: an open-label randomized clinical trial | Randomized Controlled Trial | Iran | 81 | Mild, Moderate, Severe COVID-19 | Povidone Iodine 0.5%, 0.6% Nasal Spray (n=54) | Normal Saline (n=27) | Viral clearance after one application<br><br>Number of adverse events |
| **DiDomenico et. Al., 2021 [10]**<br><br>Hydrogen peroxide as an auxiliary treatment for COVID-19 in Brazil: a randomized double-blind clinical trial | Randomized Controlled Trial | Brazil | 106 | Mild and Moderate COVID-19 | Hydrogen peroxide 0.5%, 1.0% Nasal Wash (n=63) | Deionized water with Mint Essence + Routine Care (n=43) | Forward transmission<br><br>Improvement<br><br>Adverse Events |
| **Guenezan et. Al., 2021 [19]**<br><br>Povidone Iodine Mouthwash, Gargle, and Nasal Spray to Reduce Nasopharyngeal Viral Load in Patients With COVID-19: A Randomized Clinical Trial | Randomized Controlled Trial | 9842 | 24 | Mild COVID-19 in the Outpatient | Povidone Iodine 1% Mouthwash + Gargle + Nasal Spray (n=12) | Routine Care (n=12) | Mean Difference in Viral Titer at Day 0 |
| **Kasiri et al., 2021 [14]**<br><br>Mometasone furoate nasal spray in the treatment of patients with | Randomized Controlled Trial<br><br>Prospective double-blind trial | Iran | 77 | Mild and Moderate COIVD-19 | Mometasone furoate 0.05% nasal spray BID for four weeks (n=39) | Saline spray + Routine Care (n=38) | Olfactory dysfunction |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| COVID-19 olfactory dysfunction: A randomized, double blind clinical trial | | | | | | | |
| **Shrivastava et. Al., 2021** [3]<br><br>Clinical Efficacy of an Osmotic, Antiviral and Anti-Inflammatory Polymeric Nasal Film to Treat Covid-19 Early-Phase Respiratory Symptoms | Randomized Controlled Trial | France | 200 | Mild and Moderate COVID-19 | Glycerol (COVISPRAY) + Symptomatic Treatment (n=98) | Symptomatic Treatment (n=102) | Overall Clinical Improvement<br><br>Adverse Events |
| **Winchester et. Al., 2021** [7]<br><br>Clinical efficacy of nitric oxide nasal spray (NONS) for the treatment of mild COVID-19 infection | Randomized Controlled Trial | United Kingdom | 80 | Mild COVID-19 | Nitric oxide Nasal Spray (NONS) 5-6x/day, two s[rays per nostril per dose, 120-140 microliter of solution per spray) for 9 days (n=20) | Placebo (n=20) | Overall Clinical Improvement<br><br>Adverse Events |
| **Yildiz et. Al., 2021** [15]<br><br>Comparison of the Healing Effect of Nasal Saline Irrigation with Triamcinolone Acetonide Versus Nasal Saline Irrigation alone in COVID-19 Related Olfactory Dysfunction:<br>A Randomized Controlled Study | Randomized Controlled Trial | India | 100 | Mild COVID-19 Olfactory Dysfunction | Triamcinolone acetonide nasal spray + Nasal irrigation (n=50) | Nasal Irrigation (n=50) | Self-rating Olfactory Score<br><br>Duration of Olfactory Dysfunction<br>NI: 12.2 ± 2.2<br>NS+NI: 5.6 ± 3.2<br>MD -6.6 days; 95% CI -7.68, -5.52 |
| **Zarabanda et. Al., 2021** [12]<br><br>The Effect of Povidone-Iodine Nasal Spray on Nasopharyngeal SARSCoV-<br>2 Viral Load: A Randomized Control Trial | Randomized Controlled Trial | USA | 35 | Mild COVID-19 | Povidone Iodine 0.5%, 2% in water (n=24) | Saline Solution (n=11) | Mean Cycle Threshold value:<br><br>Conversion to RT-PCR Negative From Detectable Minus-strand SARS-CoV-<br><br>Overall Clinical Improvement<br><br>Adverse Event |

# Appendix 3B. Table of Included Studies for Nasal Spray as Adjunct to Prevention of COVID-19

## Study Characteristics of Included Studies

| Study ID<br>Title<br>Author | Study Design | Setting/<br>Country | Total number of Patients Included | Population | Intervention | Comparator/<br>Control | Outcomes |
|---|---|---|---|---|---|---|---|
| **Figueroa and the CARR-CoV-2 Trial, 2021**<br><br>Efficacy of a nasal spray containing Iota-Carrageenan in the prophylaxis of COVID-19 in hospital personnel dedicated to patients care with COVID-19 disease. | Randomized Controlled Trial | Argentina | 394 | Healthcare Workers handling COVID-19 Patients | Iota-carrageenan 0.10 mL (0.17 mg) per puff 4 times a day (n=196) | Routine care with saline solution as placebo (n=198) | Incidence of SARS-CoV-2 Infection in 28 days<br><br>Symptomatic SARS-CoV-2 Negative Infection<br><br>Any Adverse Events<br><br>Discontinuation due to Intolerance |
| **Hosseinzadeh et al., 2021 (Pre-print)**<br><br>Application of nasal spray containing dimethyl sufoxide (DMSO) and ethanol during the COVID-19 pandemic may protect healthcare workers: A randomized controlled trial. | Randomized Controlled Trial | Iran | 232 | Healthcare Workers handling COVID-19 Patients | Dimethylsulfoxide ethanol 1 puff every 8 hours (n=116) | Routine care without placebo (n=116) | Incidence of SARS-CoV-2 Infection in 21 days |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