# Vitamin C for COVID-19: A living systematic review

Eduard Baladia[a,*], Ana Beatriz Pizarro[b], Luis Ortiz-Muñoz[c], Gabriel Rada[c,d,e], COVID-19 L·OVE Working Group

[a] Red de Nutrición Basada en la Evidencia, Academia Española de Nutrición y Dietética, Pamplona, España
[b] Departamento de Epidemiología Clínica y Bioestadística, Pontificia Universidad Javeriana, Bogotá, Colombia
[c] UC Evidence Center, Cochrane Chile Associated Center, Pontificia Universidad Católica de Chile, Santiago, Chile
[d] Fundación Epistemonikos, Santiago, Chile
[e] Internal Medicine Department, Faculty of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile

* **Corresponding author**
e.baladia@academianutricion.org

**Citation** Baladia E, Pizarro AB, Ortiz-Muñoz L, Rada G, COVID-19 L·OVE Working Group. Vitamin C for COVID-19: A living systematic review. *Medwave* 2020;20(6):e7978

**Doi** 10.5867/medwave.2020.06.7978

**Submission date** 2/5/2020
**Acceptance date** 9/6/2020
**Publication date** 28/7/2020

**Origin** Not commissioned.

**Type of review** Externally peer-reviewed by four reviewers, double-blind.

**Keywords** COVID-19, Severe Acute Respiratory Syndrome Coronavirus 2, Coronavirus disease, Coronavirus Infections, Systematic Review, Ascorbic Acid, Vitamin C

## Abstract

### Objective

This living systematic review aims to provide a timely, rigorous, and continuously updated summary of the available evidence on the role of vitamin C in treating patients with COVID-19.

### Data sources

We conducted searches in PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), grey literature, and in a centralized repository in L·OVE (Living OVerview of Evidence). In response to the COVID-19 emergency, L·OVE was adapted to expand the range of evidence it comprises and has been customized to group all COVID-19 evidence in one place. All the searches covered the period until April 29, 2020 (one day before submission).

### Study selection and methods

We adapted an already published standard protocol for multiple parallel systematic reviews. We searched for randomized trials evaluating the effect, in patients with COVID-19, of vitamin C versus placebo or no treatment. Anticipating the lack of randomized trials directly addressing this question, we also searched for trials evaluating MERS-CoV and SARS-CoV, and non-randomized studies in COVID-19. Two reviewers independently screened each study for eligibility. A living, web-based version of this review will be openly available during the COVID-19 pandemic, and we will resubmit it to the journal whenever there are substantial updates.

### Results

We screened 95 records, but no study was considered eligible. We identified 20 ongoing studies, including 13 randomized trials evaluating vitamin C in COVID-19.

### Conclusions

We did not find any studies that met our inclusion criteria, and hence there is no evidence to support or refute the use of vitamin C in the treatment of patients with COVID-19. A substantial number of ongoing studies should provide valuable evidence to inform researchers and decision-makers soon.

**PROSPERO Registration number:** CRD42020181216.

**Main messages**

- Currently, there is no proven effective treatment against COVID-19.
- Some authors have suggested that vitamin C might play a role in improving the pro-inflammatory and pro-oxidant environment, as well as mediating in the ACE2 environment. It is thought that this receptor could be involved in the severity of disease induced by SARS-CoV-2.
- Ours is the most extensive and robust review to date on this intervention; however, the short time since the discovery of the new coronavirus may not have allowed adequate testing of the impact of vitamin C on COVID-19.
- We found 13 ongoing randomized controlled trials that include high doses of vitamin C, often combined with other vitamins and minerals, drugs, and other substances. These trials will be evaluated appropriately in this living systematic review as soon as they are published.

**Box 1 - Linked resources in this Living Systematic Review**

**Common protocol**
A standard protocol for the systematic reviews and overviews of systematic reviews being conducted by the COVID-19 L·OVE Working Group:
Available here

**Living review**
The web version of this systematic review, presented in a 'living systematic review format,' is continuously updated as soon as new evidence emerges:
Available here

**Living OVerview of Evidence - L·OVE**
An open platform that uses artificial intelligence and a broad network of contributors to identify all of the evidence relevant to this and other healthcare questions, including those related to COVID-19:
Available here

## Introduction

COVID-19 is an infection caused by the SARS-CoV-2 coronavirus[1]. It was first identified in Wuhan, China, on December 31, 2019[2]; by April 29, 2020, the number of confirmed COVID-19 cases had reached 3 139 415, with 218 456 confirmed deaths[3]. On March 11, 2020, the WHO characterized the COVID-19 outbreak as a pandemic[1].

While the majority of cases result in mild symptoms, some might progress to pneumonia, acute respiratory distress syndrome, and death[4-6]. The case fatality rate reported across countries, settings, and age groups is highly variable, ranging from about 0.5% to 10%[7]. In some centers, it has been reported to be higher than 10% in hospitalized patients[8].

Vitamin C is one of the most commonly used interventions to treat respiratory infections, so the interest in testing its effects in the current pandemic is not surprising. The use of vitamin C began in the early 30s, and by the 70s, after the Nobel Prize winner Linus Pauling concluded that vitamin C could relieve the common cold, its use became widespread[9]. Today, vitamin C is usually perceived as an effective, harmless, and inexpensive therapeutic alternative. It is thought to improve the functioning of the immune system through a variety of means, such as increasing the activity of phagocytes and lymphocytes, improving the response of T lymphocytes, and augmenting interferon levels[10].

When it comes to the treatment of respiratory infections, however, the evidence does not show that the intake of vitamin C translates into a clinically meaningful benefit[11]. There might exist beneficial roles in the treatment of select critical patients (severe respiratory infections, requiring mechanical ventilation), yet the mechanisms that would explain the benefits are not clear[12]. Hence, research that specifically addresses the effect of vitamin C on COVID-19 would add valuable information[13].

Among the different hypotheses on the mechanisms through which COVID-19 could aggravate the health of patients are an uncontrolled inflammatory response and cytokine storm during disease progress, possibly starting with the binding of SARS-CoV-2 with the angiotensin-converting enzyme 2 (ACE2)[14]. Some authors have been enthusiastic that vitamin C could play a role in improving the pro-inflammatory and pro-oxidant environment, and could also mediate in the ACE2 environment[15]. This living systematic review aims to provide a timely, rigorous, and continuously updated summary of the evidence available on the role of vitamin C in preventing infection or in treating patients with COVID-19. Using innovative and

agile processes, we take advantage of technological tools and tap into the collective effort of several research groups.

## Methods

This manuscript complies with the 'Preferred Reporting Items for Systematic reviews and Meta-Analyses' (PRISMA) guidelines for reporting systematic reviews and meta-analyses[16] (see Appendix 1 - PRISMA Checklist). A protocol stating the shared objectives and methodology of multiple evidence syntheses (systematic reviews and overviews of systematic reviews) to be conducted in parallel for different questions relevant to COVID-19 was previously published[17]. The review was registered in PROSPERO with the number CRD42020181216, and a detailed protocol was uploaded to a preprint server[18].

### Search strategies

We used a repository that includes searches in 34 trial registries, preprint servers, and websites specialized in COVID-19. We also conducted additional searches in three electronic databases and scanned the references of multiple guidelines, reviews, and other documents.

*Electronic searches*

Our literature search was devised by the team maintaining the L·OVE platform, using the following approach:

1. Identification of terms relevant to the population and intervention components of the search strategy, using Word2vec technology[19] to the corpus of documents available in Epistemonikos Database;
2. Discussion of terms with content and methods experts to identify relevant, irrelevant and missing terms;
3. Creation of a sensitive boolean strategy encompassing all the relevant terms;
4. Iterative analysis of articles missed by the boolean strategy, and refinement of the strategy accordingly.

Our primary search source was Epistemonikos database, a comprehensive database of systematic reviews and other types of evidence[20] that we have supplemented with information coming from 35 sources relevant to COVID-19. The list of sources that have been added to the Epistemonikos database is continuously expanded. This list of sources regularly screened by Epistemonikos for COVID-19 is updated regularly on our website[21]. We conducted additional explorations using highly sensitive searches in PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), and Embase.

The searches in Epistemonikos are continuously updated[20] but were last checked for this review the day before submission to the journal (April 29, 2020). The additional searches were updated on April 29, 2020, and covered the period from the inception date of each database.

No study design, publication status, or language restriction was applied to the searches in Epistemonikos or the additional electronic searches.

The following strategy was used to search in the Epistemonikos Database. We adapted it to the syntax of other databases (see Appendix 2 - Search strategies).

(coronavir* OR coronovirus* OR "corona virus" OR "virus corona" OR "corono virus" OR "virus corono" OR hcov* OR "covid-19" OR covid19* OR "covid 19" OR "2019-nCoV" OR cv19* OR "cv-19" OR "cv 19" OR "n-cov" OR ncov* OR "sars-cov-2" OR "sars-cov2" OR (wuhan* AND (virus OR viruses OR viral) OR coronav*) OR (covid* AND (virus OR viruses OR viral)) OR "sars-cov" OR "sars cov" OR "sars-coronavirus" OR "severe acute respiratory syndrome" OR "mers-cov" OR "mers cov" OR "middle east respiratory syndrome" OR "middle-east respiratory syndrome" OR "covid-19-related" OR "SARS-CoV-2-related" OR "SARS-CoV2-related" OR "2019-nCoV-related" OR "cv-19-related" OR "n-cov-related") AND (("vitamin c" OR "vit c" OR "vitamin-c" OR "vitamins c" OR ascorb* OR "l-ascorbic"))

*Other sources*

To identify articles that may have been missed in the online inquiry, we proceeded, if necessary, as follows to find more relevant published or unpublished (grey literature) research:

1. Screening of the reference lists of other systematic reviews;
2. Scanning the reference lists of selected guidelines, narrative reviews, and other documents;
3. Reviewing the websites specialized in COVID-19 (see Appendix 2);
4. Emails to the contact authors of all the included studies to ask for additional publications or data on their studies, and other studies on the topic;
5. Cross-citation searches in Google Scholar and Microsoft Academic, using each included study as the index reference;
6. Reviewing the reference list of each included study.

### Eligibility criteria

*Types of studies*

This living review preferentially includes randomized trials. Non-randomized studies would be included if there was no direct evidence from randomized trials, or the certainty of the evidence for the critical outcomes resulting from the randomized trials would be graded as low- or very low, and the certainty provided by the non-randomized evidence grades higher than the one provided by the randomized evidence[22]. We excluded studies evaluating the effects on animal models or *in vitro* conditions.

*Types of participants*

We included trials assessing participants with COVID-19, as defined by the authors of the trials. Whenever we found substantial clinical heterogeneity on how the condition was defined, we explored it using a sensitivity analysis.

When we did not find direct evidence from randomized trials, or whenever the evidence from randomized trials provided low- or very low-certainty evidence for critical outcomes, we considered eligible randomized trials evaluating vitamin C in other coronavirus infections, such as MERS-CoV or SARS-CoV infections[22].

*Type of interventions*

The intervention of interest is vitamin C. We did not restrict our criteria to any dosage, duration, timing, or route of administration.

The comparison of interest is placebo (vitamin C plus optimal treatment versus placebo plus optimal treatment) or no treatment (vitamin C plus optimal treatment versus optimal treatment). Trials assessing vitamin C plus other interventions were deemed eligible if the co-interventions were identical in both the intervention and the comparison groups. Trials evaluating vitamin C in combination with other active interventions versus placebo or no treatment were also deemed eligible.

*Type of outcomes*

We did not use the outcomes as an inclusion criterion during the selection process. Any article meeting all the criteria except for the outcome criterion was preliminarily included and assessed in full text.

We used the core outcome set COS-COVID[23], the existing guidelines and reviews, and the judgment of the authors of this review as an input for selecting the primary and secondary outcomes, as well as to decide upon inclusion. The review team regularly revised this list of outcomes in order to incorporate ongoing efforts to define Core Outcomes Sets (e.g., COVID-19 Core Outcomes)[24].

The primary outcome was all-cause mortality. The secondary outcomes included the following: mechanical ventilation, extracorporeal membrane oxygenation, length of hospital stay, respiratory failure, serious adverse events, and time to SARS-CoV-2 RT-PCR negativity. Other outcomes were acute respiratory distress syndrome and overall adverse events.

If we included at least one study, primary and secondary outcomes are presented in the GRADE 'Summary of Findings' tables, and a table with all the outcomes is presented as an appendix[25].

**Selection of studies**

The results of the literature search in the Epistemonikos database were automatically incorporated into the L·OVE platform (automated retrieval) where duplicates were removed by an algorithm that compares unique identifiers (database ID, DOI, trial registry ID), and citation details (i.e., author names, journal, year of publication, volume, number, pages, article title, and article abstract). The additional searches were uploaded to the screening software Collaboratron™[26].

In both L·OVE platform and Collaboratron™, two researchers independently screened the titles and abstracts yielded by the search against the inclusion criteria. We obtained the full reports for all titles that appeared to meet the inclusion criteria or required further analysis, and then decided on their inclusion. We recorded the reasons for excluding trials in any stage of the search and outline the study selection process in a PRISMA flow diagram that we adapted for this project.

**Strategy for data synthesis**

The results of the search and the selection of the studies are presented with the corresponding flow chart according to recommendations of the PRISMA statement[14].

**Living evidence synthesis**

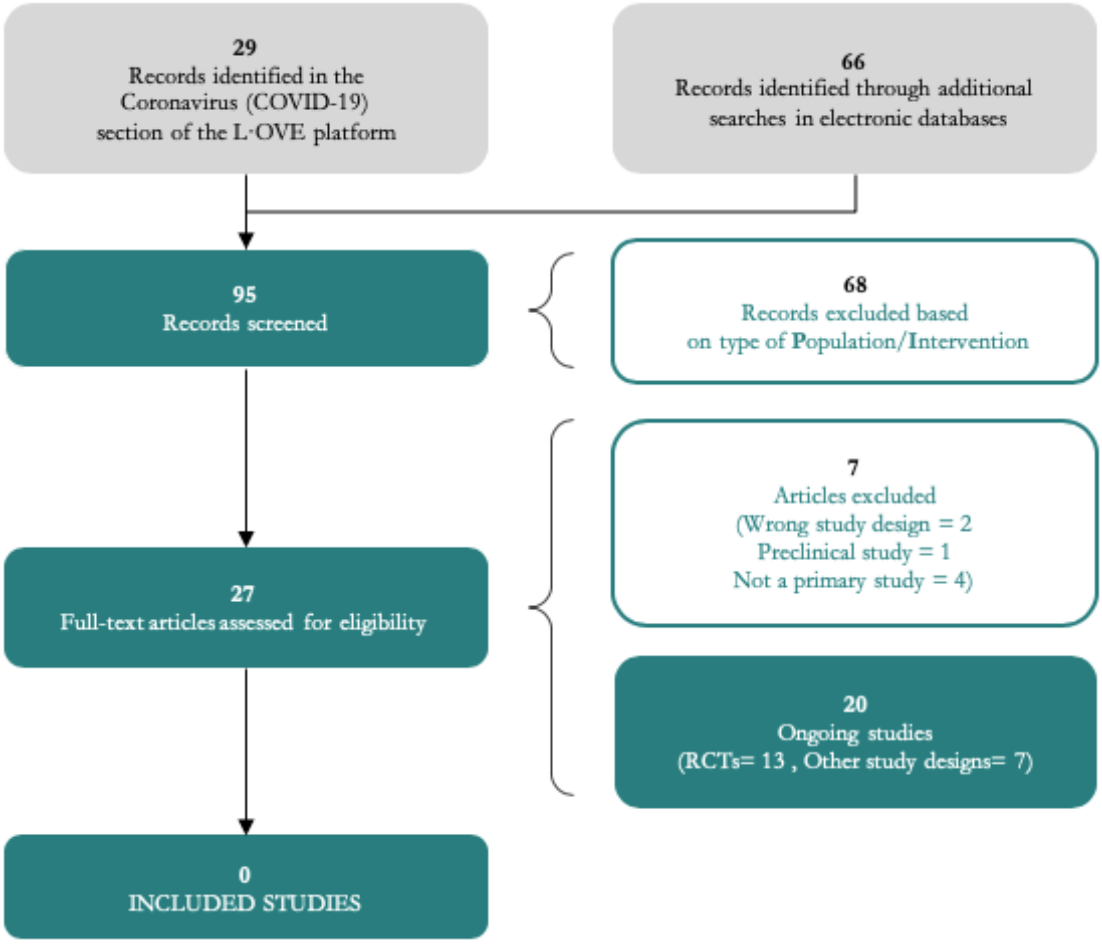
An artificial intelligence algorithm deployed in the Coronavirus/COVID-19 topic of the L·OVE platform provides instant notification of articles with a high likelihood of being eligible. The authors review them, decide upon inclusion, and update the living web version of the review accordingly. We expect to resubmit to the journal anytime there is a change in the direction of the effect on the critical outcomes or a substantial modification to the certainty of the evidence. This review is part of a larger project set up to produce multiple parallel systematic reviews relevant to COVID-19[17].

## Results

**Results of the search**

The search in the L·OVE platform retrieved 29 records, and the additional searches retrieved 66 records (total records screened = 95). We considered 27 as potentially eligible and retrieved and evaluated their full texts. However, none of the studies were eligible for inclusion. The reasons for exclusion are described in Appendix 3 - List of included, excluded, and ongoing studies. The study selection process is summarized in Figure 1 - PRISMA Flowchart.

**Figure 1:** PRISMA Flowchart.




### Description of the studies

No study was considered eligible.

### Ongoing studies

We identified 20 ongoing studies (13 randomized trials and seven non-randomized studies). See Appendix 3 - List of relevant studies.

## Discussion

We performed a comprehensive search of the literature and did not find any randomized trials evaluating the effect of vitamin C in patients with COVID-19. Anticipating this lack of randomized trials, we also searched for non-randomized, comparative studies in COVID-19, and for randomized trials evaluating other coronavirus infections, such as MERS-CoV and SARS-CoV. These additional searches provided no relevant studies either. In sum, we did not find any studies fulfilling the minimum requirements to inform decisions.

Systematic reviews are the gold standard to collect and summarize the available evidence regarding a scientific question. However, the traditional model for conducting reviews has several limitations, including high demand for time and resources[33] and rapid obsolescence[34]. Amid the COVID-19 crisis, researchers should make their best effort to answer the urgent needs of health decision-makers without giving up scientific accuracy. Information is being produced at a dizzying speed[35], so alternative models are needed.

One potential solution to these shortcomings is the use of rapid review methods, a form of knowledge synthesis that streamlines or omits specific methods of a traditional systematic review in order to move faster. Unfortunately, in many cases, this speed comes at the cost of quality[36]. Furthermore, they do not solve the issue of obsolescence. In contrast, living systematic reviews do address that issue[37] as they are continuously updated by incorporating relevant new evidence as it becomes available, at a substantial effort. So, an approach combining these two models might prove more successful in providing the scientific community and other interested parties with evidence that is actionable, rapidly and efficiently produced, up to date, and of the highest quality[38][.

This review is part of a larger project set up to put such an approach into practice. This project aims to produce multiple parallel living systematic reviews relevant to COVID-19 following the higher standards of quality in evidence synthesis production[17]. We believe that our methods are well suited to handle the abundance of evidence that is to come, including evidence on the role of vitamin C for COVID-19. We have identified multiple ongoing studies addressing this question, including 13 randomized trials, which will

provide valuable evidence to inform researchers and decision-makers shortly.

To the best of our knowledge, this is the first published systematic review addressing this question. The main limitation of our review results from the absence of any evidence to inform decisions. We hope that the substantial number of studies that are expected to be completed in the next months will shed some light on the role of vitamin C in the treatment of COVID-19.

During the COVID-19 pandemic, we will maintain a living, web-based, openly available version of this review, and we will resubmit the review any time the conclusions change or whenever there are substantial updates. Our systematic review aims to provide high-quality, up-to-date synthesis of the evidence that is useful for clinicians and other decision-makers.

## Notes

**Authorship contributions**
GR conceived the standard protocol for all the reviews being conducted by the COVID-19 L·OVE Working Group. GR drafted the manuscript, and all other authors contributed to it. ABP, LOM, and EB performed the initial title/abstract screening in Collaboratron™ and L·OVE platform and maintained the live screening until submission. ABP and EB performed complementary searches through reference list screening, the scanning reference list of grey literature and narrative reviews, and conducting cross-citation. ABP and EB performed full-text screening. All authors participated in writing the discussion section and conclusions and reviewed the final version. The corresponding author is the guarantor and declares that all authors meet authorship criteria and that no other authors meeting the criteria have been omitted.

**Collaborators**
The COVID-19 L·OVE Working Group was created by Epistemonikos and several expert teams to provide decision-makers with the best evidence related to COVID-19. Up-to-date information about the group and its member organizations is available here: epistemonikos.cl/working-group.

**Acknowledgments**
The members of the COVID-19 L·OVE Working Group and Epistemonikos Foundation have made possible the building of systems and the compiling of information needed by this project. Epistemonikos is a collaborative effort, based on the ongoing volunteer work of over a thousand contributors since 2012.

**Competing interest**
All authors declare no financial relationships with any organization that might have a real or perceived interest in this work. There are no other relationships or activities that might have influenced the submitted work.

**Funding**
This project was not commissioned by any organization and did not receive external funding. Epistemonikos Foundation is providing training, support, and tools at no cost for all the members of the COVID-19 L·OVE Working Group.

**Differences between protocol and review**
In this review, there several methods that could not be implemented because no article met the eligibility criteria. Methods that could not be implemented are described in detail below and should be implemented when relevant studies are included to maintain consistency between the initial protocol and each version of this review.

**Extraction and management of data**
Using standardized forms, two reviewers independently would extract data from each included and ongoing study. We would collect the following information: study design, setting, participant characteristics (including disease severity and age) and study eligibility criteria; details about the administered intervention and comparison, including administration route, dose, duration and timing (i.e., the time after diagnosis); the outcomes assessed and the time they were measured; the source of funding of the study and the conflicts of interest disclosed by the investigators; the risk of bias assessment for each study. We would resolve disagreements by discussion, and one arbiter adjudicated unresolved disagreements.

**Risk of bias assessment**
The risk of bias for each randomized trial would be assessed by using the 'risk of bias' tool (RoB 2.0: a revised tool to assess the risk of bias in randomized trials)[27]. We would consider the effect of the assignment to the intervention for this review. Two reviewers independently would assess five domains of bias for each outcome result of all reported outcomes and time points. These five domains would be (1) bias due to the randomization process, (2) deviations from intended interventions (effects of assignment to interventions at baseline), (3) missing outcome data, (4) measurement of the outcome, and (5) selection of reported results. Answers to signaling questions and collectively supporting information will lead to a domain-level judgment in the form of 'Low risk of bias,' 'Some concerns,' or 'High risk of bias.' These domain-level judgments would inform an overall 'risk of bias' judgment for each result. Discrepancies between review authors would be resolved by discussion to reach consensus. If necessary, a third review author will be consulted to reach a decision.
We would assess the risk of bias of other study designs with the ROBINS-I tool (ROBINS-I: Risk Of Bias In Non-randomized Studies of Interventions)[28]. We would address the following domains: bias due to confounding, bias in the selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions (effect of assignment to intervention), bias due to missing data, bias in the measurement of outcomes and bias in the selection of the reported result. We will judge each domain as low risk, moderate risk, serious risk, critical risk, or no information, and evaluated individual bias items as described in ROBINS-I guidance. We will not consider time-varying confounding, as these confounders are not relevant in this setting[28].
We will consider the following factors as potential baseline confounders: age, comorbidities (e.g., cardiovascular disease, renal disease, eye disease, liver disease), co-interventions, severity as defined by the authors (i.e., respiratory failure versus respiratory distress syndrome versus intensive care requirement).

**Measures of treatment effect**
For dichotomous outcomes, we would express the estimate of the treatment effect of an intervention as risk ratios or odds ratios along with 95% confidence intervals. For continuous outcomes, we will use the mean difference and standard deviation to summarise the data using a 95% confidence interval. Whenever continuous outcomes will be measured using different scales, the treatment effect will be expressed as a standardized mean difference with 95% confidence interval. When possible, we will multiplied the standardized mean difference by a standard deviation that is representative from the pooled studies, for example, the standard deviation from a well-known scale used by several of the studies included in the analysis on which the result is based. In cases where the minimally important difference is known, we will present continuous outcomes as minimally important difference units or inform the results as the difference in the proportion of patients achieving a minimal important effect between intervention and control[29].

Then, these results would be displayed on the 'Summary of Findings' table as mean differences[29].

**Strategy for data synthesis**

For any outcomes where data would be insufficient to calculate an effect estimate, a narrative synthesis will be presented, describing the studies in terms of the direction and the size of effects, and any available measure of precision. For the main comparisons and outcomes, we will prepare Summary of Findings tables[29,30], and also an interactive Summary of Findings tables. A Summary of Findings table with all the comparisons and outcomes will be presented as an appendix. For any outcomes where data is available from more than one trial, we will conduct a formal quantitative synthesis (meta-analysis) for studies clinically homogeneous using RevMan 5[31], using the inverse variance method with the random-effects model. All forest-plots of all evaluated comparisons will be generated. The $I^2$ index would be used to assess heterogeneity, which will be classified according to the following cut-off points: <40% low; 30-60% moderate; 50-90% substantial, 75-100% considerable. Any level of heterogeneity greater than 40% should be explained according to the covariates collected, by sensitivity analysis (elimination of a study), and by subgroup analysis and meta-regression. If heterogeneity cannot be explained, the results of the meta-analysis performed will not be offered.

**Subgroup and sensitivity analysis**

We would perform subgroup analysis according to the definition of severe COVID-19 infection (i.e., respiratory failure vs respiratory distress syndrome vs ICU requirement). In case we identify significant differences between subgroups (test for interaction < 0.05), we will report the results of individual subgroups separately. We would perform sensitivity analysis excluding studies with high risk of bias, and if non-randomized studies are used, excluding studies that do not report adjusted estimates. In cases where the primary analysis effect estimates and the sensitivity analysis effect estimates differ significantly, we will either present the low risk of bias—adjusted sensitivity analysis estimates—or present the primary analysis estimates but downgrading the certainty of the evidence because of risk of bias.

**Assessment of certainty of evidence**

The certainty of the evidence for all outcomes would be judged using the Grading of Recommendations Assessment, Development, and Evaluation working group methodology (GRADE Working Group)[30], across the domains of risk of bias, consistency, directness, precision and reporting bias. Certainty will be adjudicated as high, moderate, low, or very low. For the main comparisons and outcomes, we will prepare Summary of Findings tables[29,30], and also interactive Summary of Findings tables. A Summary of Findings table with all the comparisons and outcomes would be presented as an appendix.

**PROSPERO registration**

CRD42020181216

**Ethics**

As researchers will not access information that could lead to the identification of an individual participant, obtaining ethical approval was waived.

**Data sharing**

All data related to the project will be available. Epistemonikos Foundation will grant access to data.

**Appendix**

Appendix 1
Appendix 2
Appendix 3

## References


1. World Health Organization. Director-General's remarks at the media briefing on 2019-nCoV on February 11 2020. World Health Organization; 2020 [Accessed on April 8, 2020 ]. [Internet] | Link |
2. Hui DS, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020 Feb;91:264-266. | CrossRef | PubMed |
3. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020 May;20(5):533-534. | CrossRef | PubMed |
4. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708-1720. | CrossRef | PubMed |
5. Tavakoli A, Vahdat K, Keshavarz M. Novel Coronavirus Disease 2019 (COVID-19): An Emerging Infectious Disease in the 21st Century. Iran South Med J 2020, 22(6): 432-450. | CrossRef |
6. Li LQ, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol. 2020 Jun;92(6):577-583. | CrossRef | PubMed |
7. Global Covid-19 Case Fatality Rates. UK: Centre for Evidence-Based Evidence. [Accessed on April 8, 2020 ]. [Internet] | Link |
8. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020 Mar-Apr;34:101623. | CrossRef | PubMed |
9. Heikkinen T, Järvinen A. The common cold. The Lancet. 2003 Jan 4;361 (9351): 51-9. | CrossRef |
10. Hemilä H. Vitamin C intake and susceptibility to the common cold. Br J Nutr. 1997 Jan;77(1):59-72. | CrossRef | PubMed |
11. Gómez E, Quidel S, Bravo-Soto G, Ortigoza Á. Does vitamin C prevent the common cold?. Medwave. 2018 Aug 6;18(4):e7235. | CrossRef | PubMed |
12. Hemilä H, Chalker E. Vitamin C Can Shorten the Length of Stay in the ICU: A Meta-Analysis. Nutrients. 2019 Mar 27;11(4):708. | CrossRef | PubMed |
13. Carr AC. A new clinical trial to test high-dose vitamin C in patients with COVID-19. Version 2. Crit Care. 2020 Apr 7;24(1):133. | CrossRef | PubMed |
14. Zabetakis I, Lordan R, Norton C, Tsoupras A. COVID-19: The Inflammation Link and the Role of Nutrition in Potential Mitigation. Nutrients. 2020 May 19;12(5):1466. | CrossRef | PubMed |
15. Cheng RZ. Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)?. Med Drug Discov. 2020 Mar;5:100028. | CrossRef | PubMed |
16. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009 Oct;62(10):1006-12. | CrossRef | PubMed |
17. Rada G, Verdugo-Paiva F, Ávila C, Morel-Marambio M, Bravo-Jeria R, Pesce F, et al. Evidence synthesis relevant to COVID-19: a protocol for multiple systematic reviews and overviews of systematic reviews. Medwave. 2020 Apr 1;20(3):e7868. | CrossRef | PubMed |
18. Baladía E, Pizarro A, Rada G. Vitamin C for COVID-19: A living systematic review protocol. medRxiv. 2020.04.28.20083360 | CrossRef |
19. Github repository [Accessed 2020 April 12]. [Internet] | Link |
20. Epistemonikos Database Methods. Santiago: Epistemonikos Foundation [Accessed 2020 April 12]. [Internet] | Link |
21. Methods for the special L·OVE of Coronavirus infection. Santiago: Epistemonikos Foundation [Accessed 2020 April 12]. [Internet] | Link |

22. Schünemann HJ, Cuello C, Akl EA, Mustafa RA, Meerpohl JJ, Thayer K, et al. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. J Clin Epidemiol. 2019 Jul;111:105-114. | CrossRef | PubMed |
23. Jin X, Pang B, Zhang J, Liu Q, Yang Z, Feng J, et al. Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (COS-COVID). Engineering (Beijing). 2020 Mar 18. | CrossRef| PubMed |
24. COVID-19 Core Outcomes. [Accessed 2020 April 12]. [Internet] | Link |
25. Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol. 2013 Feb;66(2):158-72. | CrossRef | PubMed |
26. Collaboratron [Software]. Santiago: Epistemonikos Foundation, 2017.
27. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019 Aug 28;366:l4898. | CrossRef | PubMed |
28. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016 Oct 12;355:i4919. | CrossRef | PubMed |
29. Guyatt GH, Thorlund K, Oxman AD, Walter SD, Patrick D, Furukawa TA, et al. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. J Clin Epidemiol. 2013 Feb;66(2):173-83. | CrossRef | PubMed |
30. Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol. 2013 Feb;66(2):158-72. | CrossRef | PubMed |
31. Review Manager (RevMan) [Software]. Version 5.3.5 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
32. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008 Apr 26;336(7650):924-6. | CrossRef | PubMed |
33. Borah R, Brown AW, Capers PL, Kaiser KA. Analysis of the time and workers needed to conduct systematic reviews of medical interventions using data from the PROSPERO registry. BMJ Open. 2017 Feb 27;7(2):e012545. | CrossRef | PubMed |
34. Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med. 2007 Aug 21;147(4):224-33. | CrossRef | PubMed |
35. Coronavirus and the risks of 'speed science' Reuters; 2020 [Accessed 2020 April 12]. [Internet] | Link |
36. Kelly SE, Moher D, Clifford TJ. Quality of conduct and reporting in rapid reviews: an exploration of compliance with PRISMA and AMSTAR guidelines. Syst Rev. 2016 May 10;5:79. | CrossRef | PubMed |
37. Elliott JH, Synnot A, Turner T, Simmonds M, Akl EA, McDonald S, et al. Living systematic review: 1. Introduction-the why, what, when, and how. J Clin Epidemiol. 2017 Nov;91:23-30. | CrossRef | PubMed |
38. Akl EA, Haddaway NR, Rada G, Lotfi T. Future of Evidence Ecosystem Series: Evidence synthesis 2.0: when systematic, scoping, rapid, living, and overviews of reviews come together. J Clin Epidemiol. 2020 Jul;123:162-165. | CrossRef| PubMed |
39. Neumann I, Schünemann HJ. Guideline groups should make recommendations even if the evidence is considered insufficient. CMAJ. 2020 Jan 13;192(2):E23-E24. | CrossRef | PubMed |
40. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ. 2016 Jun 28;353:i2016. | CrossRef | PubMed |

**Postal address**
C/ Consell de Cent 314, pral B 08007
Barcelona, España