

# Iota-carrageenan for COVID-19: real-time meta analysis of 1 study

@CovidAnalysis, April 2024, Version 3  
<https://c19early.org/gmeta.html>

## Abstract

Statistically significant lower risk is seen for cases.

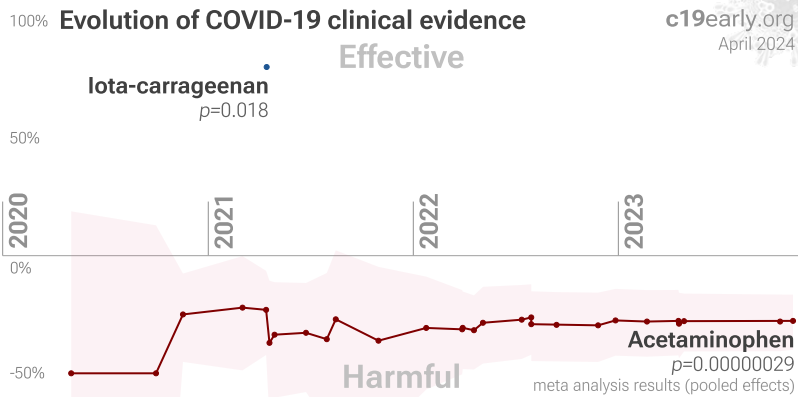
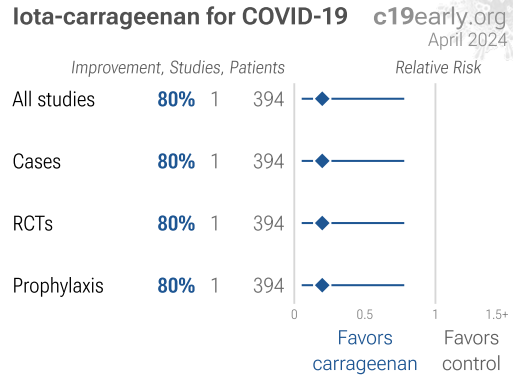
Meta analysis using the most serious outcome reported shows 80% [22-95%] lower risk.

Currently there is very limited data, with only one study to date.

1 RCT with 480 patients has not reported results (1 year late)  
*Jessop*

No treatment or intervention is 100% effective. All practical, effective, and safe means should be used based on risk/benefit analysis. Multiple treatments are typically used in combination, and other treatments may be more effective. *Carvalho et al.* has been excluded due to combined treatments that may significantly contribute to efficacy.

All data to reproduce this paper and sources are in the appendix.



## HIGHLIGHTS

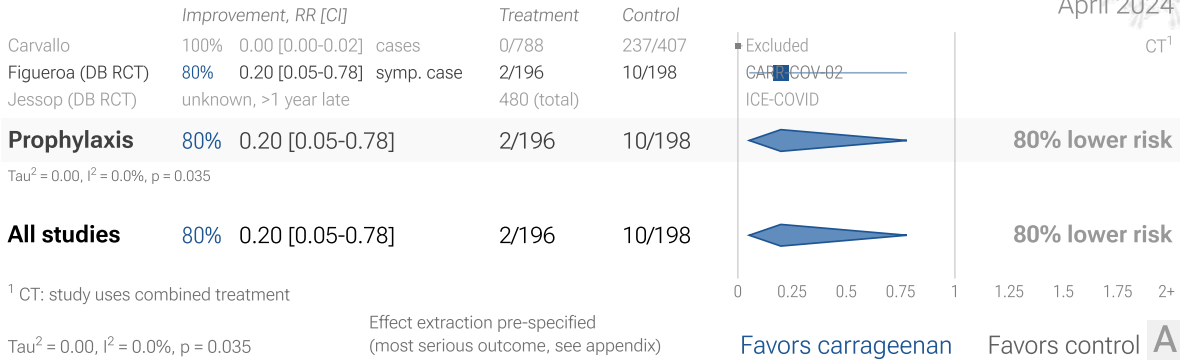
Iota-carrageenan reduces risk for COVID-19 with low confidence for cases and in pooled analysis.

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 69 treatments, outcome specific analyses and combined evidence from all studies.

# 1 iota-carrageenan COVID-19 study (+1 unreported RCT)

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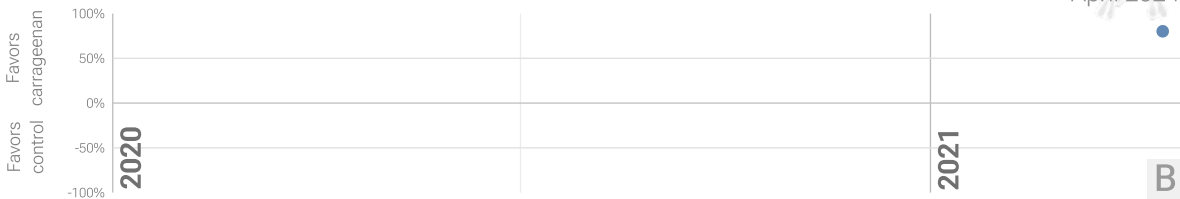
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## Timeline of COVID-19 iota-carrageenan studies (pooled effects)

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**Figure 1. A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in iota-carrageenan studies.**

## Introduction

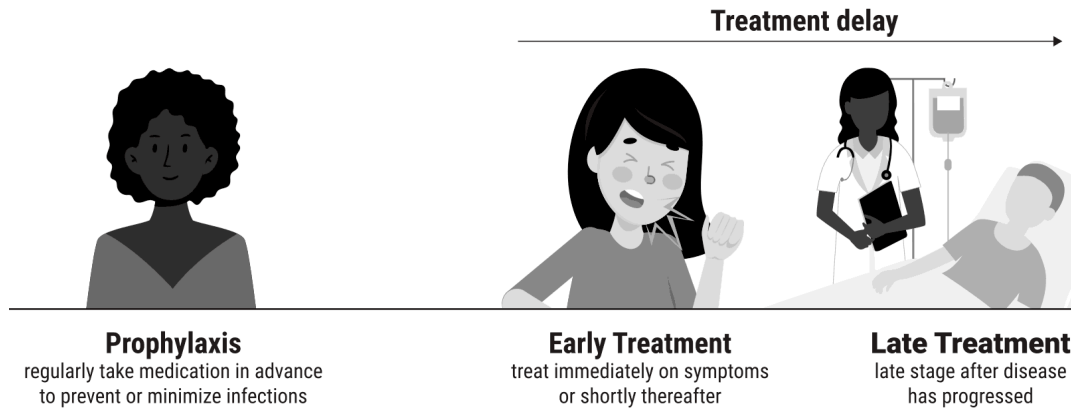
**Immediate treatment recommended.** SARS-CoV-2 infection typically starts in the upper respiratory tract, and specifically the nasal respiratory epithelium. Entry via the eyes and gastrointestinal tract is possible, but less common, and entry via other routes is rare. Infection may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems. The primary initial route for entry into the central nervous system is thought to be the olfactory nerve in the nasal cavity <sup>Dai</sup>. Progression may lead to cytokine storm, pneumonia, ARDS, neurological issues <sup>Duloquin, Hampshire, Scardua-Silva, Yang</sup>, cardiovascular complications <sup>Eberhardt</sup>, organ failure, and death. Minimizing replication as early as possible is recommended. Logically, stopping replication in the upper respiratory tract should be simpler and more effective. Early or prophylactic nasopharyngeal/oropharyngeal treatment can avoid the consequences of viral replication in other tissues, and avoid the requirement for systemic treatments with greater potential for side effects.

**Many treatments are expected to modulate infection.** SARS-CoV-2 infection and replication involves the complex interplay of 50+ host and viral proteins and other factors <sup>Note A, Malone, Murigneux, Lv, Lui, Niarakis</sup>, providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 7,000 compounds may reduce COVID-19 risk <sup>c19early.org</sup>, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

**Other infections.** Studies have shown efficacy with iota-carrageenan for coronavirus OC43 or 229E <sup>Hemilä</sup>, influenza A <sup>Hemilä</sup>, and rhinovirus <sup>Hemilä</sup>.

**Analysis.** We analyze all significant controlled studies of iota-carrageenan for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random effects meta-analysis results for all studies, individual outcomes, and Randomized Controlled Trials (RCTs).

**Treatment timing.** Figure 2 shows stages of possible treatment for COVID-19. Prophylaxis refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. Early Treatment refers to treatment immediately or soon after symptoms appear, while Late Treatment refers to more delayed treatment.



**Figure 2.** Treatment stages.

## Preclinical Research

4 *In Silico* studies support the efficacy of iota-carrageenan *Alsaïdi, Rohilla, Sattari, Thet,*

10 *In Vitro* studies support the efficacy of iota-carrageenan *Alsaïdi, Bansal, Bovard, Fröba, Meister, Morokutti-Kurz, Morokutti-Kurz (B), Setz, Song, Varese,*

Preclinical research is an important part of the development of treatments, however results may be very different in clinical trials. Preclinical results are not used in this paper.

## Results

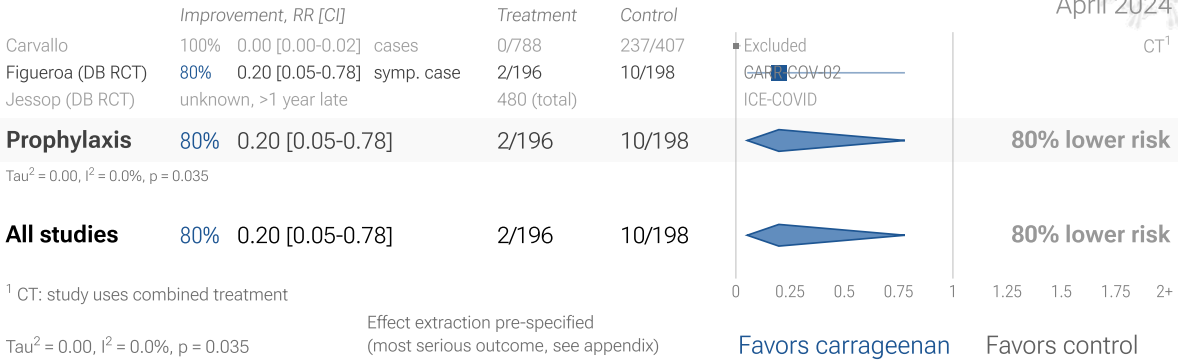
Table 1 summarizes the results for all studies and for Randomized Controlled Trials. Figure 3 and 4 show forest plots for random effects meta-analysis of all studies with pooled effects and cases.

	<i>Improvement</i>	<i>Studies</i>	<i>Patients</i>	<i>Authors</i>
All studies	80% [22-95%] *	1	394	18
Randomized Controlled Trials	80% [22-95%] *	1	394	18

**Table 1.** Random effects meta-analysis for all studies and for Randomized Controlled Trials. Results show the percentage improvement with treatment and the 95% confidence interval. \*  $p < 0.05$ .

# 1 iota-carrageenan COVID-19 study (+1 unreported RCT)

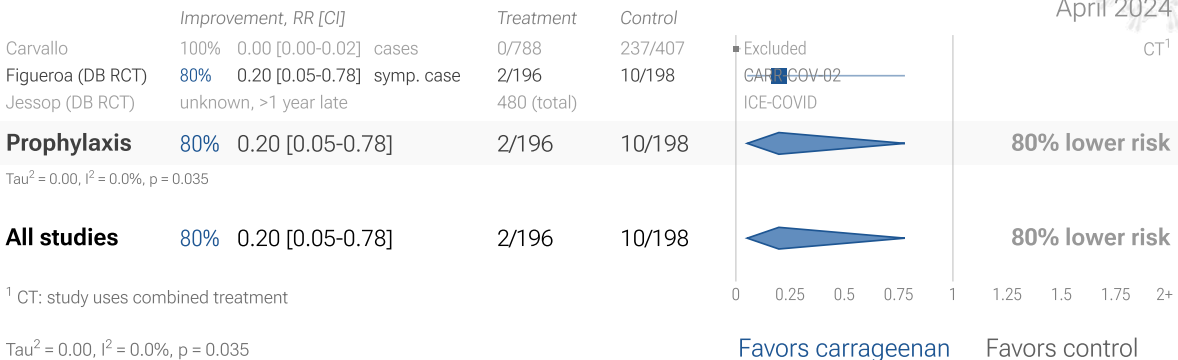
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**Figure 3. Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

# 1 iota-carrageenan COVID-19 case result

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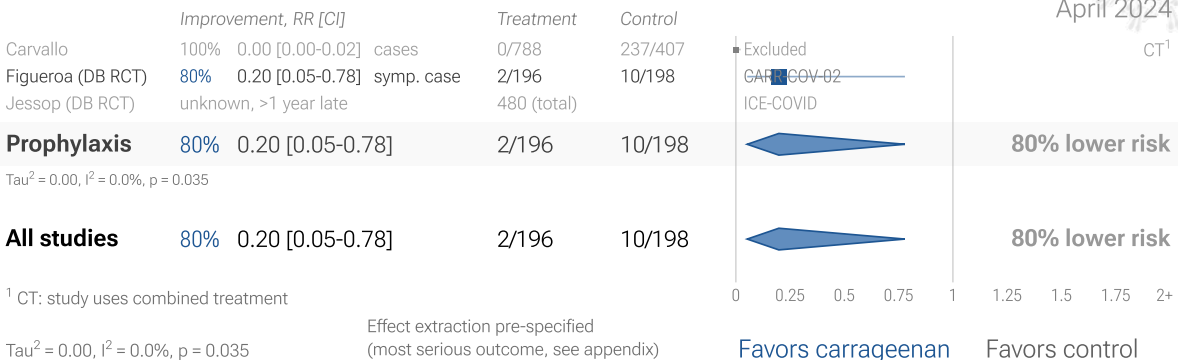
**Figure 4. Random effects meta-analysis for cases.**

## Randomized Controlled Trials (RCTs)

Figure 5 shows a forest plot for random effects meta-analysis of all Randomized Controlled Trials. RCT results are included in Table 1. Currently there is only one study which is an RCT.

# 1 iota-carrageenan COVID-19 study (+1 unreported RCT)

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**Figure 5. Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

## Unreported RCTs

1 iota-carrageenan RCT has not reported results <sup>Jessop</sup>. The trial reports total actual enrollment of 480 patients. The result is delayed over 1 year.

## Heterogeneity

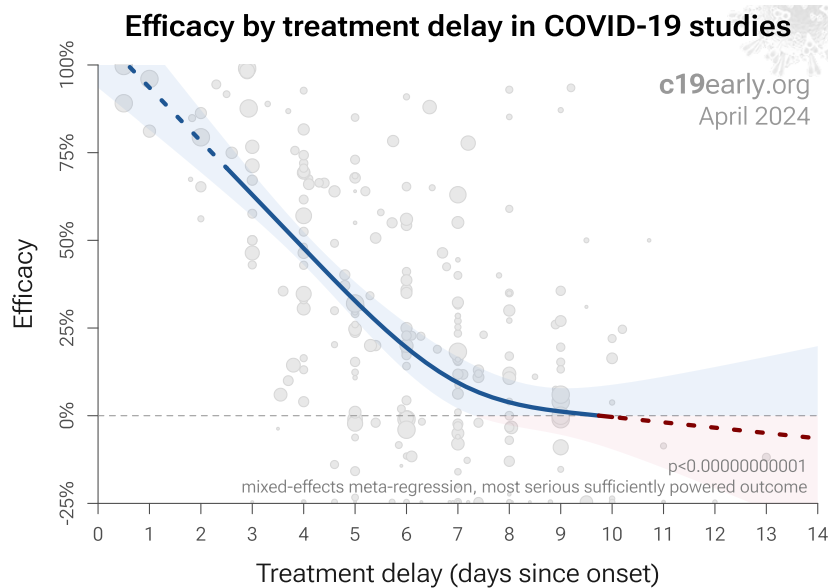
Heterogeneity in COVID-19 studies arises from many factors including:

**Treatment delay.** The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours <sup>McLean, Treanor</sup>. Baloxavir studies for influenza also show that treatment delay is critical – *Ikematsu et al.* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden et al.* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and *Kumar et al.* report only 2.5 hours improvement for inpatient treatment.

<i>Treatment delay</i>	<i>Result</i>
Post-exposure prophylaxis	<b>86% fewer cases</b> <i>Ikematsu</i>
<24 hours	<b>-33 hours symptoms</b> <i>Hayden</i>
24-48 hours	<b>-13 hours symptoms</b> <i>Hayden</i>
Inpatients	<b>-2.5 hours to improvement</b> <i>Kumar</i>

**Table 2.** Studies of baloxavir for influenza show that early treatment is more effective.

Figure 6 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 69 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.



**Figure 6.** Early treatment is more effective. Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 69 treatments.

**Patient demographics.** Details of the patient population including age and comorbidities may critically affect how well a treatment works. For example, many COVID-19 studies with relatively young low-comorbidity patients show all patients recovering quickly with or without treatment. In such cases, there is little room for an effective treatment to improve results, for example as in *López-Medina et al.*

**Variants.** Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants <sup>Korves</sup>, for example the Gamma variant shows significantly different characteristics *Faria, Karita, Nonaka, Zavascki*. Different mechanisms of action may be more or less effective depending on variants, for example the degree to which TMPRSS2 contributes to viral entry can differ across variants *Peacock, Willett*.

**Regimen.** Effectiveness may depend strongly on the dosage and treatment regimen.

**Other treatments.** The use of other treatments may significantly affect outcomes, including supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic *Alsaïdi, Andreani, De Forni, Fiaschi, Jeffreys, Jitobaom, Jitobaom (B), Ostrov, Said, Thairu, Wan*, therefore efficacy may depend strongly on combined treatments.

**Medication quality.** The quality of medications may vary significantly between manufacturers and production batches, which may significantly affect efficacy and safety. *Williams et al.* analyze ivermectin from 11 different sources, showing highly variable antiparasitic efficacy across different manufacturers. *Xu et al.* analyze a treatment from two different manufacturers, showing 9 different impurities, with significantly different concentrations for each manufacturer.

**Effect measured.** Across all studies there is a strong association between different outcomes, for example improved recovery is strongly associated with lower mortality. However, efficacy may differ depending on the effect measured, for example a treatment may be more effective against secondary complications and have minimal effect on viral clearance.

**Meta analysis.** The distribution of studies will alter the outcome of a meta analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though early treatment is very effective. All meta analyses combine heterogeneous studies, varying in population, variants, and potentially all factors above, and therefore may obscure efficacy by including studies where treatment is less effective. Generally, we expect the estimated effect size from meta analysis to be less than that for the optimal case. Looking at all studies is

valuable for providing an overview of all research, important to avoid cherry-picking, and informative when a positive result is found despite combining less-optimal situations. However, the resulting estimate does not apply to specific cases such as early treatment in high-risk populations. While we present results for all studies, we also present treatment time and individual outcome analyses, which may be more informative for specific use cases.

## Pooled Effects

**Combining studies is required.** For COVID-19, delay in clinical results translates into additional death and morbidity, as well as additional economic and societal damage. Combining the results of studies reporting different outcomes is required. There may be no mortality in a trial with low-risk patients, however a reduction in severity or improved viral clearance may translate into lower mortality in a high-risk population. Different studies may report lower severity, improved recovery, and lower mortality, and the significance may be very high when combining the results. "*The studies reported different outcomes*" is not a good reason for disregarding results.

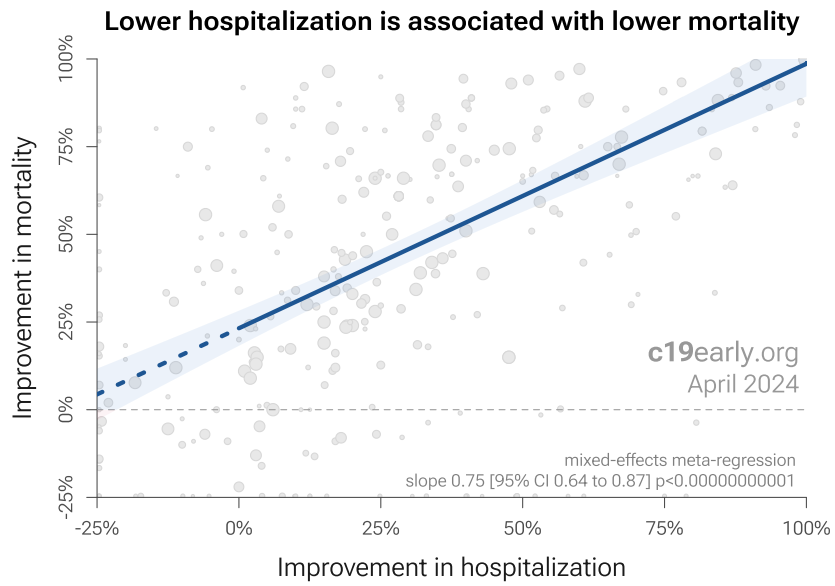
**Specific outcome and pooled analyses.** We present both specific outcome and pooled analyses. In order to combine the results of studies reporting different outcomes we use the most serious outcome reported in each study, based on the thesis that improvement in the most serious outcome provides comparable measures of efficacy for a treatment. A critical advantage of this approach is simplicity and transparency. There are many other ways to combine evidence for different outcomes, along with additional evidence such as dose-response relationships, however these increase complexity.

**Using more information.** Another way to view pooled analysis is that we are using more of the available information. Logically we should, and do, use additional information. For example dose-response and treatment delay-response relationships provide significant additional evidence of efficacy that is considered when reviewing the evidence for a treatment.

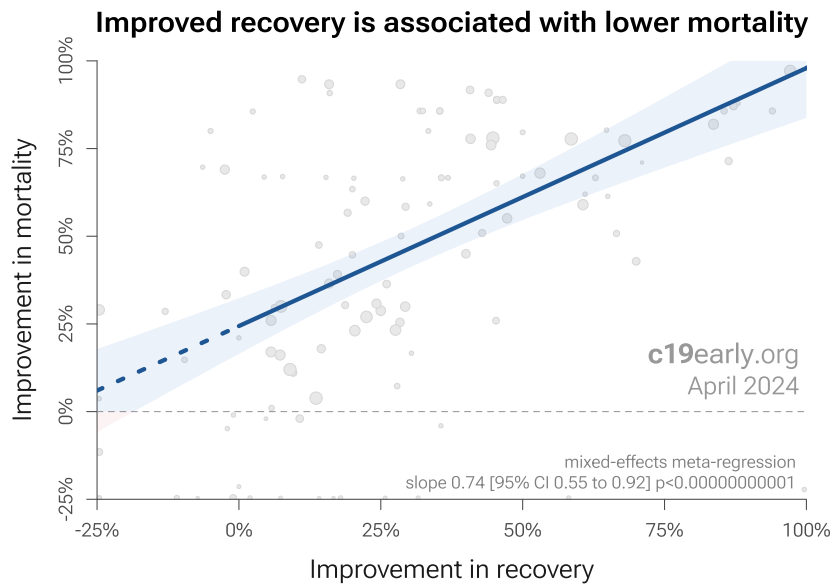
**Ethical and practical issues limit high-risk trials.** Trials with high-risk patients may be restricted due to ethics for treatments that are known or expected to be effective, and they increase difficulty for recruiting. Using less severe outcomes as a proxy for more serious outcomes allows faster collection of evidence.

**Improvement across outcomes.** For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, which follows from a reduction in PCR positivity. We can directly test this for COVID-19.

**Validating pooled outcome analysis for COVID-19.** Analysis of the the association between different outcomes across studies from all 69 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 7 shows that lower hospitalization is very strongly associated with lower mortality ( $p < 0.00000000001$ ). Similarly, Figure 8 shows that improved recovery is very strongly associated with lower mortality ( $p < 0.00000000001$ ). Considering the extremes, *Singh et al.* show an association between viral clearance and hospitalization or death, with  $p = 0.003$  after excluding one large outlier from a mutagenic treatment, and based on 44 RCTs including 52,384 patients. Figure 9 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to *Singh et al.*, with higher confidence due to the larger number of studies. As with *Singh et al.*, the confidence increases when excluding the outlier treatment, from  $p = 0.0000045$  to  $p = 0.000000067$ .

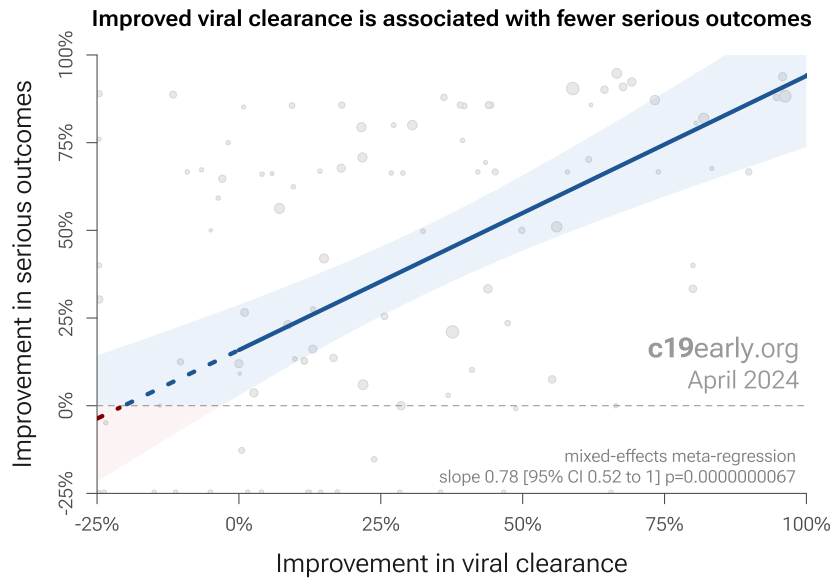


**Figure 7.** Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.



**Figure 8.** Improved recovery is associated with lower mortality, supporting pooled outcome analysis.



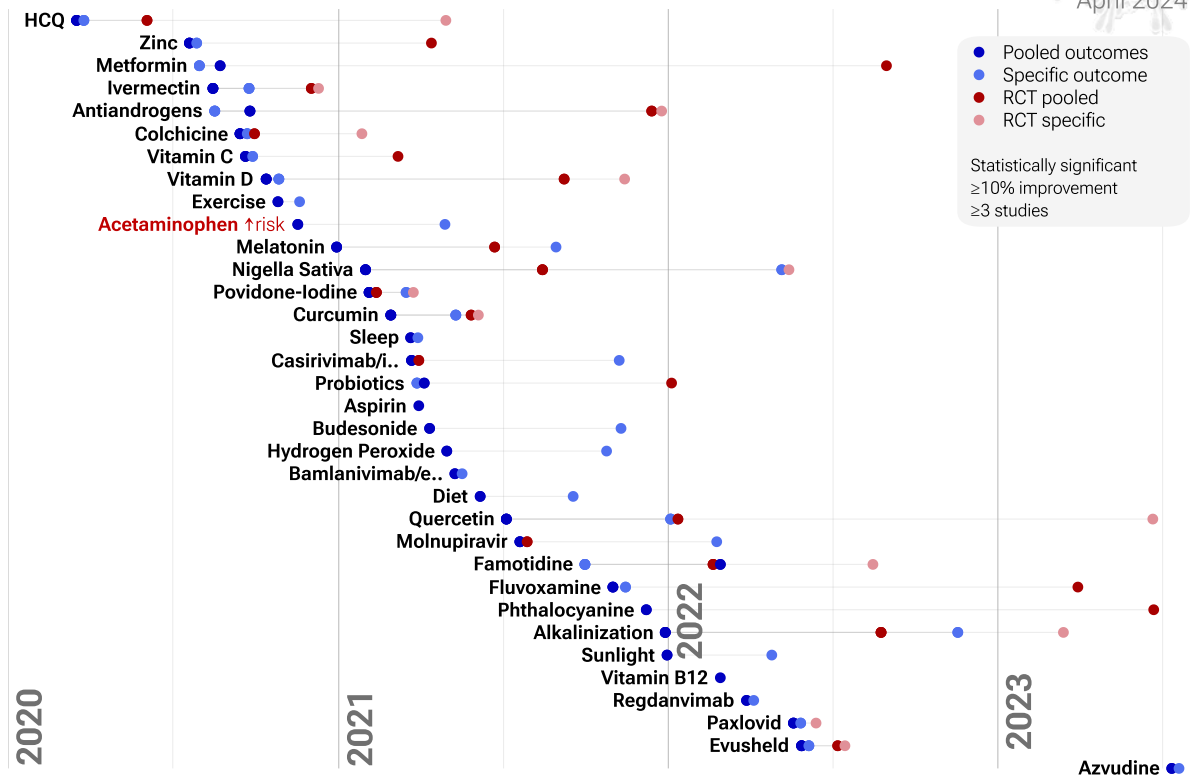


**Figure 7.** Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.

**Pooled outcomes identify efficacy 4 months faster (6 months for RCTs).** Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as  $\geq 10\%$  decreased risk or  $>0\%$  increased risk from  $\geq 3$  studies. 85% of these have been confirmed with one or more specific outcomes, with a mean delay of 3.7 months. When restricting to RCTs only, 54% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 5.8 months. Figure 10 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

## Time when COVID-19 studies showed efficacy

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**Figure 10.** The time when studies showed that treatments were effective, defined as statistically significant improvement of  $\geq 10\%$  from  $\geq 3$  studies. Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

**Limitations.** Pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral clearance may show no efficacy if most studies only examine viral clearance. In practice, it is rare for a non-antiviral treatment to report viral clearance and to not report clinical outcomes; and in practice other sources of heterogeneity such as difference in treatment delay is more likely to hide efficacy.

**Summary.** Analysis validates the use of pooled effects and shows significantly faster detection of efficacy on average. However, as with all meta analyses, it is important to review the different studies included. We also present individual outcome analyses, which may be more informative for specific use cases.

## Discussion

**Results for other viruses.** Studies have also shown efficacy with iota-carrageenan for coronavirus OC43 or 229E Hemilä, influenza A Hemilä, and rhinovirus Hemilä.

**Nasal/oral administration.** Studies to date use a variety of administration methods to the respiratory tract, including nasal and oral sprays, nasal irrigation, oral rinses, and inhalation. Table 3 shows the relative efficacy for nasal, oral, and combined administration. Combined administration shows the best results, and nasal administration is more effective than oral. Precise efficacy depends on the details of administration, e.g., mucoadhesion and sprayability for sprays.

<i>Nasal/oral administration to the respiratory tract</i>	<i>Improvement</i>	<i>Studies</i>
Oral spray/rinse	38% [25-49%]	8
Nasal spray/rinse	54% [42-63%]	11
Nasal & oral	94% [74-99%]	6

**Table 3.** Respiratory tract administration efficacy. Relative efficacy of nasal, oral, and combined nasal/oral administration for treatments administered directly to the respiratory tract, based on studies for povidone-iodine, iota-carrageenan, alkalization, hydrogen peroxide, nitric oxide, chlorhexidine, cetylpyridinium chloride, and phthalocyanine. Results show random effects meta analysis for the most serious outcome reported for all prophylaxis and early treatment studies.

**Impact on the microbiome.** Nasopharyngeal/oropharyngeal treatments may not be highly selective. In addition to inhibiting or disabling SARS-CoV-2, they may also be harmful to beneficial microbes, disrupting the natural microbiome in the oral cavity and nasal passages that have important protective and metabolic roles. This may be especially important for prolonged use or overuse. Table 4 summarizes the potential for common nasopharyngeal/oropharyngeal treatments to affect the natural microbiome.

<i>Treatment</i>	<i>Microbiome disruption potential</i>	<i>Notes</i>
Iota-carrageenan	Low	Primarily antiviral, however extended use may mildly affect the microbiome
Nitric Oxide	Low to moderate	More selective towards pathogens, however excessive concentrations or prolonged use may disrupt the balance of bacteria
Alkalinization	Moderate	Increases pH, negatively impacting beneficial microbes that thrive in a slightly acidic environment
Cetylpyridinium Chloride	Moderate	Quaternary ammonium broad-spectrum antiseptic that can disrupt beneficial and harmful bacteria
Phthalocyanine	Moderate to high	Photodynamic compound with antimicrobial activity, likely to affect the microbiome
Chlorhexidine	High	Potent antiseptic with broad activity, significantly disrupts the microbiome
Hydrogen Peroxide	High	Strong oxidizer, harming both beneficial and harmful microbes
Povidone-Iodine	High	Potent broad-spectrum antiseptic harmful to beneficial microbes

**Table 4.** Potential effect of treatments on the nasopharyngeal/oropharyngeal microbiome.

**Publication bias.** Publishing is often biased towards positive results, however evidence suggests that there may be a negative bias for inexpensive treatments for COVID-19. Both negative and positive results are very important for COVID-19, media in many countries prioritizes negative results for inexpensive treatments (inverting the typical

incentive for scientists that value media recognition), and there are many reports of difficulty publishing positive results *Boulware, Meeus, Meneguesso, twitter.com*. For iota-carrageenan, there is currently not enough data to evaluate publication bias with high confidence.

**Conflicts of interest.** Pharmaceutical drug trials often have conflicts of interest whereby sponsors or trial staff have a financial interest in the outcome being positive. Iota-carrageenan for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 iota-carrageenan trials have been run by physicians on the front lines with the primary goal of finding the best methods to save human lives and minimize the collateral damage caused by COVID-19. While pharmaceutical companies are careful to run trials under optimal conditions (for example, restricting patients to those most likely to benefit, only including patients that can be treated soon after onset when necessary, and ensuring accurate dosing), not all iota-carrageenan trials represent the optimal conditions for efficacy.

**Limitations.** Summary statistics from meta analysis necessarily lose information. As with all meta analyses, studies are heterogeneous, with differences in treatment delay, treatment regimen, patient demographics, variants, conflicts of interest, standard of care, and other factors. We provide analyses for specific outcomes and by treatment delay, and we aim to identify key characteristics in the forest plots and summaries. Results should be viewed in the context of study characteristics.

Some analyses classify treatment based on early or late administration, as done here, while others distinguish between mild, moderate, and severe cases. Viral load does not indicate degree of symptoms — for example patients may have a high viral load while being asymptomatic. With regard to treatments that have antiviral properties, timing of treatment is critical — late administration may be less helpful regardless of severity.

Details of treatment delay per patient is often not available. For example, a study may treat 90% of patients relatively early, but the events driving the outcome may come from 10% of patients treated very late. Our 5 day cutoff for early treatment may be too conservative, 5 days may be too late in many cases.

Comparison across treatments is confounded by differences in the studies performed, for example dose, variants, and conflicts of interest. Trials with conflicts of interest may use designs better suited to the preferred outcome.

In some cases, the most serious outcome has very few events, resulting in lower confidence results being used in pooled analysis, however the method is simpler and more transparent. This is less critical as the number of studies increases. Restriction to outcomes with sufficient power may be beneficial in pooled analysis and improve accuracy when there are few studies, however we maintain our pre-specified method to avoid any retrospective changes.

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone *Alsaïdi, Andreani, De Forni, Fiaschi, Jeffreys, Jitobaom, Jitobaom (B), Ostrov, Said, Thairu, Wan*. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

This real-time analysis is constantly updated based on submissions. Accuracy benefits from widespread review and submission of updates and corrections from reviewers. Less popular treatments may receive fewer reviews.

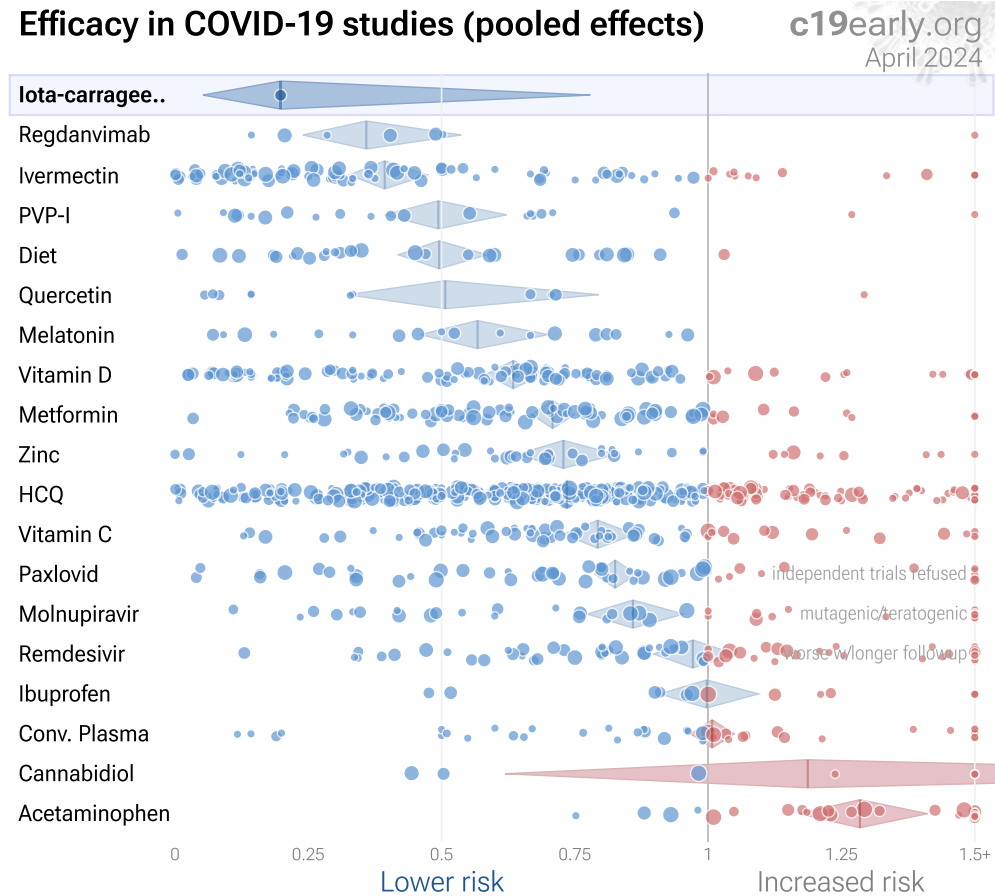
No treatment or intervention is 100% available and effective for all current and future variants. Efficacy may vary significantly with different variants and within different populations. All treatments have potential side effects. Propensity to experience side effects may be predicted in advance by qualified physicians. We do not provide medical advice. Before taking any medication, consult a qualified physician who can compare all options, provide personalized advice, and provide details of risks and benefits based on individual medical history and situations.

**Notes.** 1 of 1 studies combine treatments. The results of iota-carrageenan alone may differ. None of the RCTs use combined treatment. Currently all studies are peer-reviewed.

**Reviews.** Multiple reviews cover iota-carrageenan for COVID-19, presenting additional background on mechanisms and related results, including *Chavda, Hans*.

## Perspective

**Results compared with other treatments.** SARS-CoV-2 infection and replication involves a complex interplay of 50+ host and viral proteins and other factors *Lui, Lv, Malone, Murigneux, Niarakis*, providing many therapeutic targets. Over 7,000 compounds have been predicted to reduce COVID-19 risk *c19early.org*, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 11 shows an overview of the results for iota-carrageenan in the context of multiple COVID-19 treatments, and Figure 12 shows a plot of efficacy vs. cost for COVID-19 treatments.



**Figure 11.** Scatter plot showing results within the context of multiple COVID-19 treatments. Diamonds shows the results of random effects meta-analysis. 0.6% of 7,400 proposed treatments show efficacy *c19early.org* (B).

## Efficacy vs. cost for COVID-19 treatments

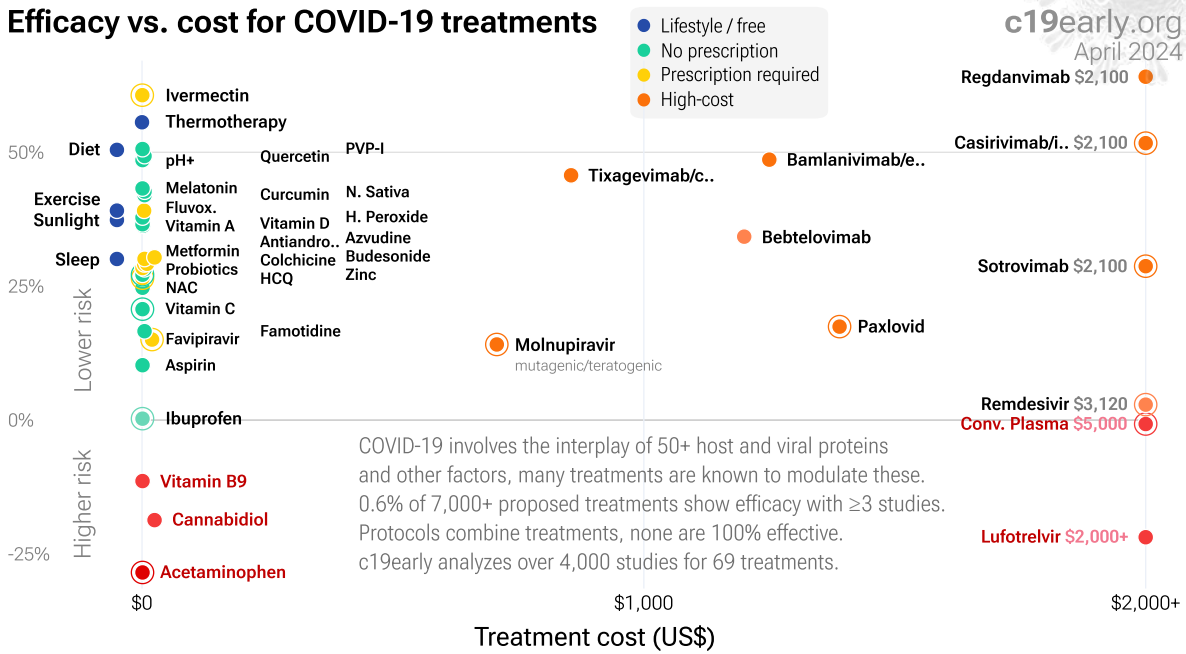


Figure 12. Efficacy vs. cost for COVID-19 treatments.

## Conclusion

SARS-CoV-2 infection typically starts in the upper respiratory tract. Progression may lead to cytokine storm, pneumonia, ARDS, neurological issues, organ failure, and death. Stopping replication in the upper respiratory tract, via early or prophylactic nasopharyngeal/oropharyngeal treatment, can avoid the consequences of progression to other tissues, and avoid the requirement for systemic treatments with greater potential for side effects.

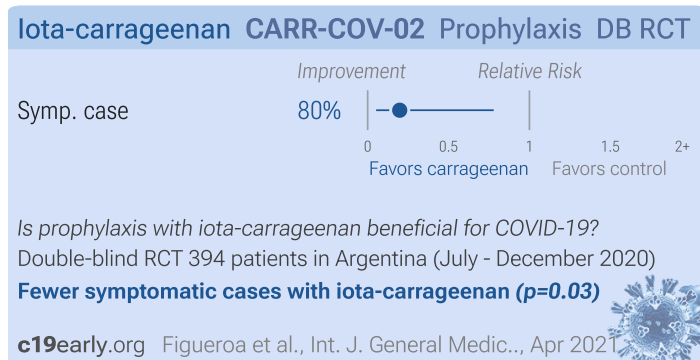
Studies to date show that iota-carrageenan is an effective treatment for COVID-19. Statistically significant lower risk is seen for cases. Meta analysis using the most serious outcome reported shows 80% [22-95%] lower risk.

Currently there is very limited data, with only one study to date.

Carvalho et al. has been excluded due to combined treatments that may significantly contribute to efficacy.

## Study Notes

### Figuroa



*Figuroa*: Prophylaxis RCT with 394 healthcare workers, 196 treated with iota-carrageenan, showing significantly lower symptomatic cases with treatment. There were no deaths or hospitalizations. There was a significant number of PCR- symptomatic cases (7.6% treatment and 8.6% control). The two treatment cases occurred shortly after randomization - infection may have occurred before the start of treatment.

## Jessop

*Jessop*: 480 participant iota-carrageenan prophylaxis RCT with results not reported over 1 year after completion.

## Appendix 1. Methods and Data

We perform ongoing searches of PubMed, medRxiv, Europe PMC, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19early.org. Search terms are iota-carrageenan and COVID-19 or SARS-CoV-2. Automated searches are performed twice daily, with all matches reviewed for inclusion. All studies regarding the use of iota-carrageenan for COVID-19 that report a comparison with a control group are included in the main analysis. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral test status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO<sub>2</sub> is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to *Zhang*. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 *Sweeting*. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.12.2) with scipy (1.12.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.1), and plotly (5.20.0).

Forest plots are computed using PythonMeta *Deng* with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the I<sup>2</sup> statistic. Mixed-effects meta-regression results are computed with R (4.1.2) using the metafor (3.0-2) and rms (6.2-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a *p*-value less than 0.05 was considered statistically significant. Grobid 0.8.0 is used to parse PDF documents.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment (for example based on oxygen status or lung involvement), and treatment started within 5 days of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of

patients contributing most to the events (for example, consider a study where most patients are treated early but late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective *McLean, Treanor*.

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A summary of study results is below. Please submit updates and corrections at <https://c19early.org/gmeta.html>.

## Prophylaxis

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

<p><i>Carvalho (B)</i>, 11/17/2020, prospective, Argentina, peer-reviewed, 4 authors, this trial uses multiple treatments in the treatment arm (combined with ivermectin) - results of individual treatments may vary, excluded: combined treatment may significantly contribute to efficacy, concern about potential data issues.</p>	<p>risk of case, 99.9% lower, RR 0.001, <math>p &lt; 0.001</math>, treatment 0 of 788 (0.0%), control 237 of 407 (58.2%), NNT 1.7, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).</p>
<p><i>Figueroa</i>, 4/15/2021, Double Blind Randomized Controlled Trial, Argentina, peer-reviewed, 18 authors, study period 24 July, 2020 - 20 December, 2020, trial NCT04521322 (history) (CARR-COV-02).</p>	<p>risk of symptomatic case, 80.2% lower, RR 0.20, <math>p = 0.03</math>, treatment 2 of 196 (1.0%), control 10 of 198 (5.1%), NNT 25, odds ratio converted to relative risk.</p>
<p><i>Jessop</i>, 11/18/2022, Double Blind Randomized Controlled Trial, placebo-controlled, United Kingdom, trial NCT04590365 (history) (ICE-COVID).</p>	<p>480 patient RCT with results unknown and over 1 year late.</p>

## Supplementary Data

Supplementary Data

## Footnotes

- a. Viral infection and replication involves attachment, entry, uncoating and release, genome replication and transcription, translation and protein processing, assembly and budding, and release. Each step can be disrupted by therapeutics.

## References

1. **Alsaidi** et al., *Griffithsin and Carrageenan Combination Results in Antiviral Synergy against SARS-CoV-1 and 2 in a Pseudoviral Model*, Marine Drugs, doi:10.3390/md19080418.
2. **Altman**, D., *How to obtain the P value from a confidence interval*, BMJ, doi:10.1136/bmj.d2304.
3. **Altman (B)** et al., *How to obtain the confidence interval from a P value*, BMJ, doi:10.1136/bmj.d2090.



4. **Andreani** et al., *In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect*, Microbial Pathogenesis, doi:10.1016/j.micpath.2020.104228.
5. **Bansal** et al., *Iota-carrageenan and xylitol inhibit SARS-CoV-2 in Vero cell culture*, PLoS ONE, doi:10.1371/journal.pone.0259943.
6. **Boulware**, D., *Comments regarding paper rejection*, twitter.com/boulware\_dr/status/1311331372884205570.
7. **Bovard** et al., *Iota-carrageenan extracted from red algae is a potent inhibitor of SARS-CoV-2 infection in reconstituted human airway epithelia*, Biochemistry and Biophysics Reports, doi:10.1016/j.bbrep.2021.101187.
8. **c19early.org**, c19early.org/treatments.html.
9. **c19early.org (B)**, c19early.org/timeline.html.
10. **Carvallo** et al., *Safety and Efficacy of the Combined Use of Ivermectin, Dexamethasone, Enoxaparin and Aspirina against COVID-19 the I.D.E.A. Protocol*, Journal of Clinical Trials, 11:459 (preprint 9/15/20), www.longdom.org/open-access/safety-and-efficacy-of-the-combined-use-of-ivermectin-dexamethasone-enoxaparin-and-aspirina-against-covid19-the-idea-protocol-70290.html.
11. **Carvallo (B)** et al., *Study of the Efficacy and Safety of Topical Ivermectin + Iota-Carrageenan in the Prophylaxis against COVID-19 in Health Personnel*, Journal of Biomedical Research and Clinical Investigation, doi:10.31546/2633-8653.1007.
12. **Chavda** et al., *Nasal sprays for treating COVID-19: a scientific note*, Pharmacological Reports, doi:10.1007/s43440-023-00463-7.
13. **Dai** et al., *Neurological complications of COVID-19*, QJM: An International Journal of Medicine, doi:10.1093/qjmed/hcac272.
14. **De Forni** et al., *Synergistic drug combinations designed to fully suppress SARS-CoV-2 in the lung of COVID-19 patients*, PLoS ONE, doi:10.1371/journal.pone.0276751.
15. **Deng**, H., *PyMeta*, Python module for meta-analysis, www.pymeta.com/.
16. **Duloquin** et al., *Is COVID-19 Infection a Multiorganic Disease? Focus on Extrapulmonary Involvement of SARS-CoV-2*, Journal of Clinical Medicine, doi:10.3390/jcm13051397.
17. **Eberhardt** et al., *SARS-CoV-2 infection triggers pro-atherogenic inflammatory responses in human coronary vessels*, Nature Cardiovascular Research, doi:10.1038/s44161-023-00336-5.
18. **Faria** et al., *Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil*, Science, doi:10.1126/science.abh2644.
19. **Fiaschi** et al., *In Vitro Combinatorial Activity of Direct Acting Antivirals and Monoclonal Antibodies against the Ancestral B.1 and BQ.1.1 SARS-CoV-2 Viral Variants*, Viruses, doi:10.3390/v16020168.
20. **Figueroa** et al., *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 A pragmatic multicenter, randomized, double-blind, placebo-controlled trial (CARR-COV-02)*, International Journal of General Medicine, doi:10.2147/IJGM.S328486.
21. **Fröba** et al., *Iota-Carrageenan Inhibits Replication of SARS-CoV-2 and the Respective Variants of Concern Alpha, Beta, Gamma and Delta*, International Journal of Molecular Sciences, doi:10.3390/ijms222413202.
22. **Hampshire** et al., *Cognition and Memory after Covid-19 in a Large Community Sample*, New England Journal of Medicine, doi:10.1056/NEJMoa2311330.
23. **Hans** et al., *Antiviral activity of sulfated polysaccharides from marine algae and its application in combating COVID-19: Mini review*, Bioresource Technology Reports, doi:10.1016/j.biteb.2020.100623.
24. **Hayden** et al., *Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents*, New England Journal of Medicine, doi:10.1056/NEJMoa1716197.
25. **Hemilä** et al., *Carrageenan nasal spray may double the rate of recovery from coronavirus and influenza virus infections: Re-analysis of randomized trial data*, Pharmacology Research and Perspectives, doi:10.1002/prp2.810.

26. **Ikematsu** et al., *Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts*, New England Journal of Medicine, doi:10.1056/NEJMoa1915341.
27. **Jeffreys** et al., *Remdesivir-ivermectin combination displays synergistic interaction with improved in vitro activity against SARS-CoV-2*, International Journal of Antimicrobial Agents, doi:10.1016/j.ijantimicag.2022.106542.
28. **Jessop** et al., *Efficacy of Carrageenan Nasal and Throat Spray for COVID-19 Prophylaxis - A Double Blind Randomised Placebo-controlled Trial*, NCT04590365, clinicaltrials.gov/study/NCT04590365.
29. **Jitobaom** et al., *Favipiravir and Ivermectin Showed in Vitro Synergistic Antiviral Activity against SARS-CoV-2*, Research Square, doi:10.21203/rs.3.rs-941811/v1.
30. **Jitobaom (B)** et al., *Synergistic anti-SARS-CoV-2 activity of repurposed anti-parasitic drug combinations*, BMC Pharmacology and Toxicology, doi:10.1186/s40360-022-00580-8.
31. **Karita** et al., *Trajectory of viral load in a prospective population-based cohort with incident SARS-CoV-2 G614 infection*, medRxiv, doi:10.1101/2021.08.27.21262754.
32. **Korves** et al., *SARS-CoV-2 Genetic Variants and Patient Factors Associated with Hospitalization Risk*, medRxiv, doi:10.1101/2024.03.08.24303818.
33. **Kumar** et al., *Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza (FLAGSTONE): a randomised, parallel-group, double-blind, placebo-controlled, superiority trial*, The Lancet Infectious Diseases, doi:10.1016/S1473-3099(21)00469-2.
34. **López-Medina** et al., *Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial*, JAMA, doi:10.1001/jama.2021.3071.
35. **Lui** et al., *Nsp1 facilitates SARS-CoV-2 replication through calcineurin-NFAT signaling*, Virology, doi:10.1128/mbio.00392-24.
36. **Lv** et al., *Host proviral and antiviral factors for SARS-CoV-2*, Virus Genes, doi:10.1007/s11262-021-01869-2.
37. **Malone** et al., *Structures and functions of coronavirus replication–transcription complexes and their relevance for SARS-CoV-2 drug design*, Nature Reviews Molecular Cell Biology, doi:10.1038/s41580-021-00432-z.
38. **McLean** et al., *Impact of Late Oseltamivir Treatment on Influenza Symptoms in the Outpatient Setting: Results of a Randomized Trial*, Open Forum Infect. Dis. September 2015, 2:3, doi:10.1093/ofid/ofv100.
39. **Meeus**, G., *Online Comment*, twitter.com/gertmeeus\_MD/status/1386636373889781761.
40. **Meister** et al., *Virucidal activity of nasal sprays against severe acute respiratory syndrome coronavirus-2*, Journal of Hospital Infection, doi:10.1016/j.jhin.2021.10.019.
41. **Menegusso**, A., *Médica defende tratamento precoce da Covid-19*, www.youtube.com/watch?v=X5FCrIm\_19U.
42. **Morokutti-Kurz** et al., *lota-carrageenan neutralizes SARS-CoV-2 and inhibits viral replication in vitro*, PLoS ONE, doi:10.1371/journal.pone.0237480.
43. **Morokutti-Kurz (B)** et al., *Amylmetacresol/2,4-dichlorobenzyl alcohol, hexylresorcinol, or carrageenan lozenges as active treatments for sore throat*, International Journal of General Medicine, doi:10.2147/IJGM.S120665.
44. **Murigneux** et al., *Proteomic analysis of SARS-CoV-2 particles unveils a key role of G3BP proteins in viral assembly*, Nature Communications, doi:10.1038/s41467-024-44958-0.
45. **Niarakis** et al., *Drug-target identification in COVID-19 disease mechanisms using computational systems biology approaches*, Frontiers in Immunology, doi:10.3389/fimmu.2023.1282859.
46. **Nonaka** et al., *SARS-CoV-2 variant of concern P.1 (Gamma) infection in young and middle-aged patients admitted to the intensive care units of a single hospital in Salvador, Northeast Brazil, February 2021*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2021.08.003.
47. **Ostrov** et al., *Highly Specific Sigma Receptor Ligands Exhibit Anti-Viral Properties in SARS-CoV-2 Infected Cells*, Pathogens, doi:10.3390/pathogens10111514.

48. **Peacock** et al., *The SARS-CoV-2 variant, Omicron, shows rapid replication in human primary nasal epithelial cultures and efficiently uses the endosomal route of entry*, bioRxiv, doi:10.1101/2021.12.31.474653.
49. **Rohilla** et al., *Algae Polysaccharides (Carrageenan and Alginate)—A Treasure-Trove of Antiviral Compounds: An In Silico Approach to Identify Potential Candidates for Inhibition of S1-RBD Spike Protein of SARS-CoV-2*, *Stresses*, doi:10.3390/stresses3030039.
50. **Said** et al., *The effect of Nigella sativa and vitamin D3 supplementation on the clinical outcome in COVID-19 patients: A randomized controlled clinical trial*, *Frontiers in Pharmacology*, doi:10.3389/fphar.2022.1011522.
51. **Sattari** et al., *Repositioning Therapeutics for COVID-19: Virtual Screening of the Potent Synthetic and Natural Compounds as SARS-CoV-2 3CLpro Inhibitors*, *Research Square*, doi:10.21203/rs.3.rs-37994/v1.
52. **Scardua-Silva** et al., *Microstructural brain abnormalities, fatigue, and cognitive dysfunction after mild COVID-19*, *Scientific Reports*, doi:10.1038/s41598-024-52005-7.
53. **Setz** et al., *Iota-Carrageenan Inhibits Replication of the SARS-CoV-2 Variants of Concern Omicron BA.1, BA.2 and BA.5*, *Nutraceuticals*, doi:10.3390/nutraceuticals3030025.
54. **Singh** et al., *The relationship between viral clearance rates and disease progression in early symptomatic COVID-19: a systematic review and meta-regression analysis*, *Journal of Antimicrobial Chemotherapy*, doi:10.1093/jac/dkac045.
55. **Song** et al., *Inhibitory activities of marine sulfated polysaccharides against SARS-CoV-2*, *Food & Function*, doi:10.1039/D0FO02017F.
56. **Sweeting** et al., *What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data*, *Statistics in Medicine*, doi:10.1002/sim.1761.
57. **Thairu** et al., *A Comparison of Ivermectin and Non Ivermectin Based Regimen for COVID-19 in Abuja: Effects on Virus Clearance, Days-to-discharge and Mortality*, *Journal of Pharmaceutical Research International*, doi:10.9734/jpri/2022/v34i44A36328.
58. **Thet, H.**, *The potential of carrageenan for the drug discovery of COVID-19 via molecular docking with angiotensin-converting enzyme 2 (ACE2) and the main protease (Mpro) of SARS-CoV-2*, *Journal of Bioinformatics and Genomics*, doi:10.18454/jbg.2022.18.2.001.
59. **Treanor** et al., *Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza: A Randomized Controlled Trial*, *JAMA*, 2000, 283:8, 1016-1024, doi:10.1001/jama.283.8.1016.
60. **twitter.com**, [twitter.com/KashPrime/status/1768487878454124914](https://twitter.com/KashPrime/status/1768487878454124914).
61. **Varese** et al., *Iota-carrageenan prevents the replication of SARS-CoV-2 on an in vitro respiratory epithelium model*, bioRxiv, doi:10.1101/2021.04.27.441512.
62. **Wan** et al., *Synergistic inhibition effects of andrographolide and baicalin on coronavirus mechanisms by downregulation of ACE2 protein level*, *Scientific Reports*, doi:10.1038/s41598-024-54722-5.
63. **Willett** et al., *The hyper-transmissible SARS-CoV-2 Omicron variant exhibits significant antigenic change, vaccine escape and a switch in cell entry mechanism*, medRxiv, doi:10.1101/2022.01.03.21268111.
64. **Williams, T.**, *Not All Ivermectin Is Created Equal: Comparing The Quality of 11 Different Ivermectin Sources*, *Do Your Own Research*, [doyourownresearch.substack.com/p/not-all-ivermectin-is-created-equal](https://doyourownresearch.substack.com/p/not-all-ivermectin-is-created-equal).
65. **Xu** et al., *A study of impurities in the repurposed COVID-19 drug hydroxychloroquine sulfate by UHPLC-Q/TOF-MS and LC-SPE-NMR*, *Rapid Communications in Mass Spectrometry*, doi:10.1002/rcm.9358.
66. **Yang** et al., *SARS-CoV-2 infection causes dopaminergic neuron senescence*, *Cell Stem Cell*, doi:10.1016/j.stem.2023.12.012.
67. **Zavascki** et al., *Advanced ventilatory support and mortality in hospitalized patients with COVID-19 caused by Gamma (P.1) variant of concern compared to other lineages: cohort study at a reference center in Brazil*, *Research Square*, doi:10.21203/rs.3.rs-910467/v1.
68. **Zhang** et al., *What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes*, *JAMA*, 80:19, 1690, doi:10.1001/jama.280.19.1690.