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

Abstract

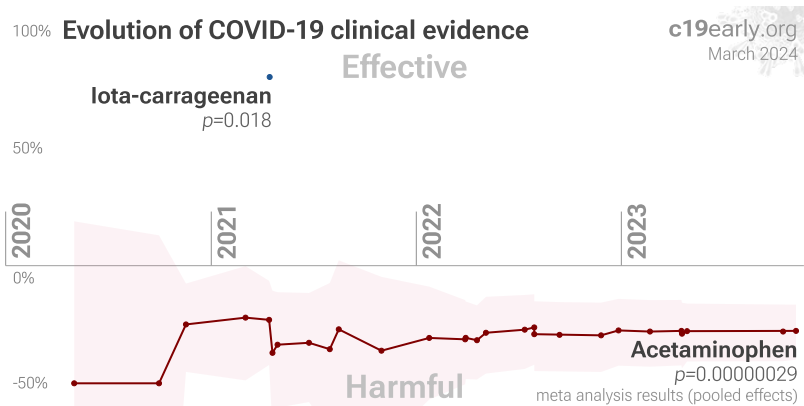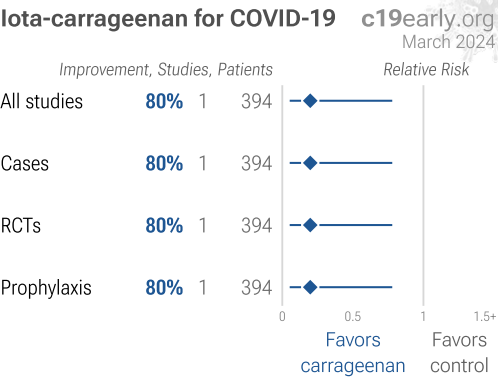Statistically significant lower risk is seen for cases.

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. *Carvallo 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.

Iota-carrageenan for COVID-19 — c19early.org — March 2024

	Improvement, Studies, Patients			Relative Risk
All studies	80%	1	394	
Cases	80%	1	394	
RCTs	80%	1	394	
Prophylaxis	80%	1	394	

Favors carrageenan — Favors control

Evolution of COVID-19 clinical evidence

Iota-carrageenan *p*=0.018

Acetaminophen *p*=0.00000029
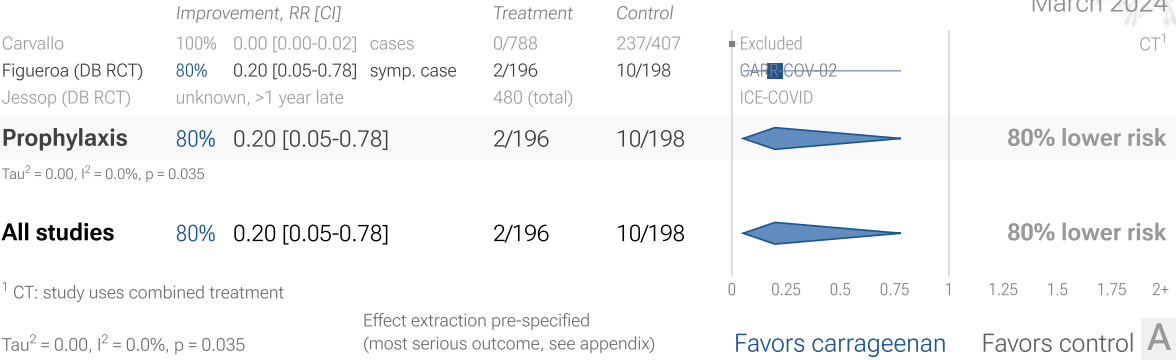
meta analysis results (pooled effects)

HIGHLIGHTS

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

We show traditional outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor in COVID-19 studies.

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 66 treatments.
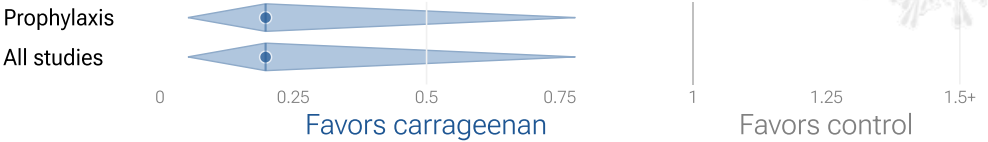
1 iota-carrageenan COVID-19 study (+1 unreported RCT)

	Improvement, RR [CI]			Treatment	Control		
Carvallo	100%	0.00 [0.00-0.02]	cases	0/788	237/407	Excluded	CT[1]
Figueroa (DB RCT)	80%	0.20 [0.05-0.78]	symp. case	2/196	10/198	CARR-COV-02	
Jessop (DB RCT)	unknown, >1 year late			480 (total)		ICE-COVID	
Prophylaxis	**80%**	0.20 [0.05-0.78]		2/196	10/198		**80% lower risk**

Tau^2 = 0.00, I^2 = 0.0%, p = 0.035

All studies	**80%**	0.20 [0.05-0.78]	2/196	10/198	**80% lower risk**

[1] CT: study uses combined treatment

Tau^2 = 0.00, I^2 = 0.0%, p = 0.035

Effect extraction pre-specified
(most serious outcome, see appendix)

Favors carrageenan   Favors control   A

Efficacy in COVID-19 iota-carrageenan studies (pooled effects)

Favors carrageenan   Favors control   B

Efficacy in COVID-19 studies (pooled effects)

Lower risk   Increased risk   C

Timeline of COVID-19 iota-carrageenan studies (pooled effects)
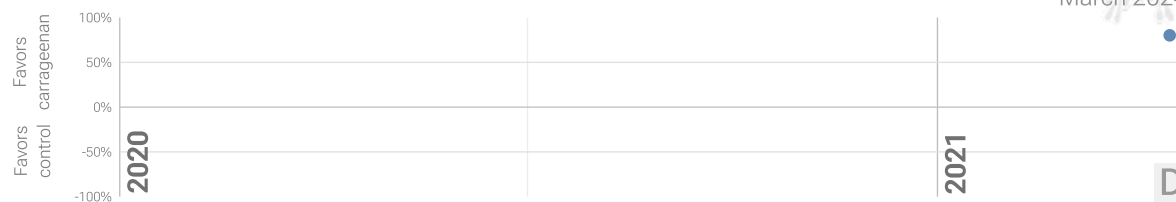
Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix. **B. Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis. **C. Results within the context of multiple COVID-19 treatments.** 0.6% of 6,686 proposed treatments show efficacy [c19early.org]. **D. Timeline of results in iota-carrageenan studies.**
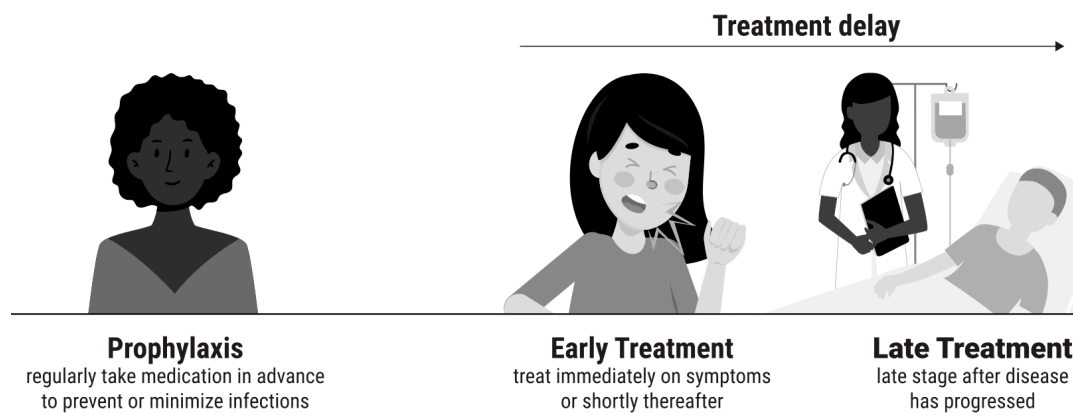
Introduction

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 [Dai]. Progression may lead to cytokine storm, pneumonia, ARDS, neurological issues [Scardua-Silva, Yang], cardiovascular complications [Eberhardt], 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 [Note A, Malone, Murigneux, Lv, Lui], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 6,000 compounds may reduce COVID-19 risk [c19early.org (B)], 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 [Hemilä], influenza A [Hemilä], and rhinovirus [Hemilä].

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.

Treatment delay →

Prophylaxis
regularly take medication in advance
to prevent or minimize infections

Early Treatment
treat immediately on symptoms
or shortly thereafter

Late Treatment
late stage after disease
has progressed

Figure 2. Treatment stages.

Preclinical Research

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

10 *In Vitro* studies support the efficacy of iota-carrageenan *Alsaidi, 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.
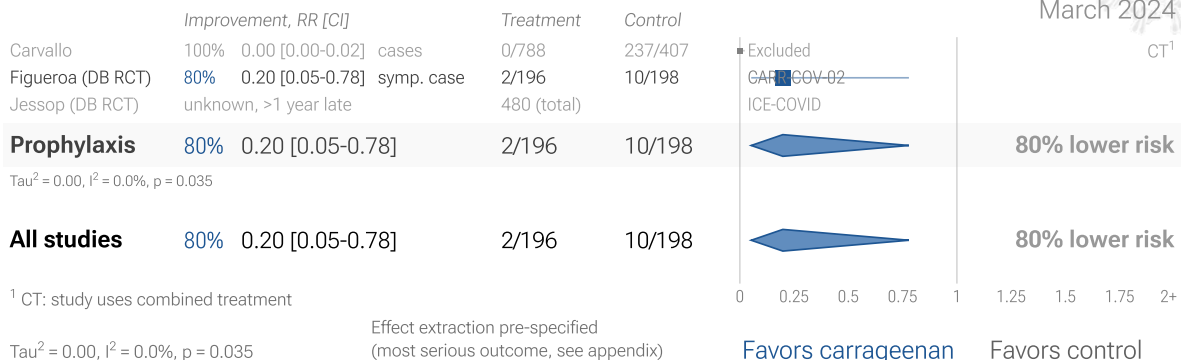
Results

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.

	Improvement	Studies	Patients	Authors
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. * $p < 0.05$.
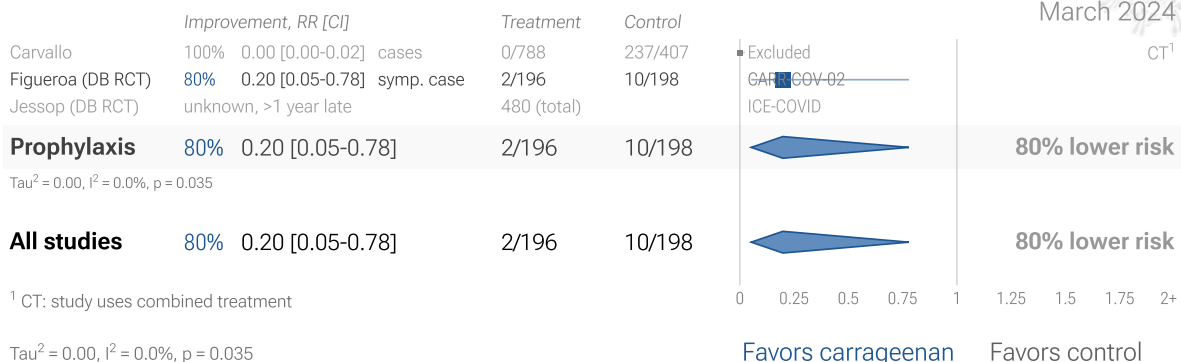
1 iota-carrageenan COVID-19 study (+1 unreported RCT)

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Jessop (DB RCT)	unknown, >1 year late			480 (total)		ICE-COVID	
Prophylaxis	**80%**	**0.20 [0.05-0.78]**		**2/196**	**10/198**		**80% lower risk**
Tau² = 0.00, I² = 0.0%, p = 0.035							
All studies	**80%**	**0.20 [0.05-0.78]**		**2/196**	**10/198**		**80% lower risk**

$Tau^2 = 0.00$, $I^2 = 0.0\%$, p = 0.035

[1] CT: study uses combined treatment

Effect extraction pre-specified
(most serious outcome, see appendix)

Favors carrageenan — Favors control

Figure 3. Random effects meta-analysis for all studies with pooled effects. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

1 iota-carrageenan COVID-19 case result

	Improvement, RR [CI]			Treatment	Control		
Carvallo	100%	0.00 [0.00-0.02]	cases	0/788	237/407	Excluded	CT[1]
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Prophylaxis	**80%**	**0.20 [0.05-0.78]**		**2/196**	**10/198**		**80% lower risk**
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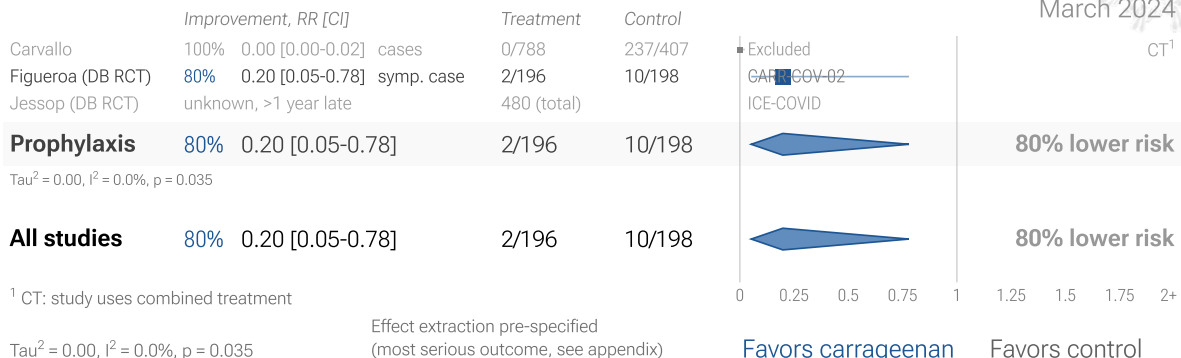
Favors carrageenan — Favors control

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)

	Improvement, RR [CI]			Treatment	Control		
Carvallo	100%	0.00 [0.00-0.02]	cases	0/788	237/407	Excluded	CT[1]
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(most serious outcome, see appendix)

Favors carrageenan — Favors control

Figure 5. Random effects meta-analysis for all Randomized Controlled Trials. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

Unreported RCTs

1 iota-carrageenan RCT has not reported results *Jessop*. 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 *McLean, Treanor*. Baloxavir studies for influenza also show that treatment delay is critical — *Ikematsu* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden* 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* report only 2.5 hours improvement for inpatient treatment.

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

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 66 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.
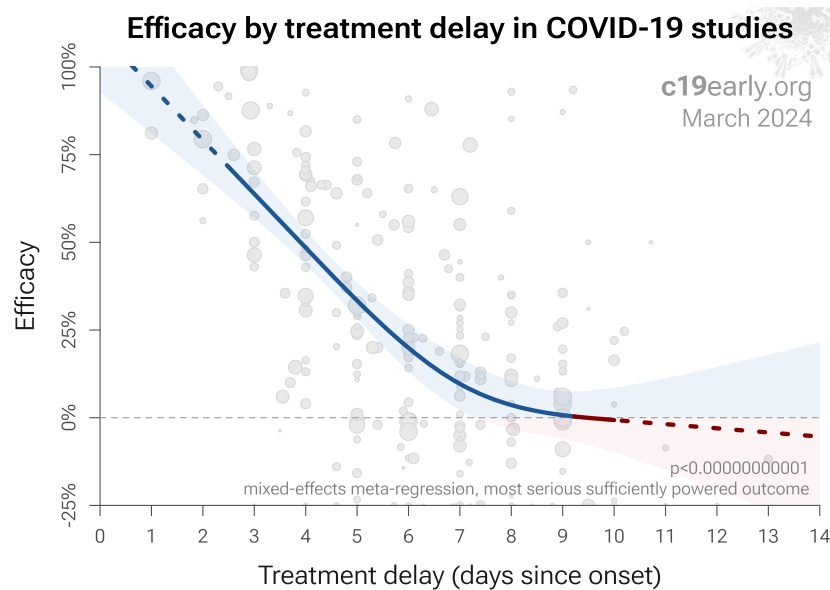
Figure 6. Early treatment is more effective. Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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 (as in *López-Medina*).

Effect measured. Efficacy may differ significantly depending on the effect measured, for example a treatment may be very effective at reducing mortality, but less effective at minimizing cases or hospitalization. Or a treatment may have no effect on viral clearance while still being effective at reducing mortality.

Variants. There are many different variants of SARS-CoV-2 and efficacy may depend critically on the distribution of variants encountered by the patients in a study. 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 viral entry process for the omicron variant has moved towards TMPRSS2-independent fusion, suggesting that TMPRSS2 inhibitors may be less effective *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 anything from supplements, other medications, or other kinds of treatment such as prone positioning.

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

Pooled outcome analysis. We present both pooled analyses and specific outcome analyses. Notably, pooled analysis often results in earlier detection of efficacy as shown in Figure 7. For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, etc. An antiviral tested with a low-risk population may report zero mortality in both arms, however a reduction in severity and improved viral clearance may translate into lower mortality among a high-risk population, and including these results in pooled analysis allows faster detection of efficacy. Trials with high-risk patients may also be restricted due to ethical concerns for treatments that are known or expected to be effective.

Pooled analysis enables using more of the available information. While there is much more information available, for example dose-response relationships, the advantage of the method used here is simplicity and transparency. Note that pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral replication or early stage disease could show no efficacy in pooled analysis if most studies only examine viral clearance. While we present pooled results, we also present individual outcome analyses, which may be more informative for specific use cases.

Pooled outcomes identify efficacy faster. Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 88% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 3.6 months. When restricting to RCTs only, 50% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.1 months.
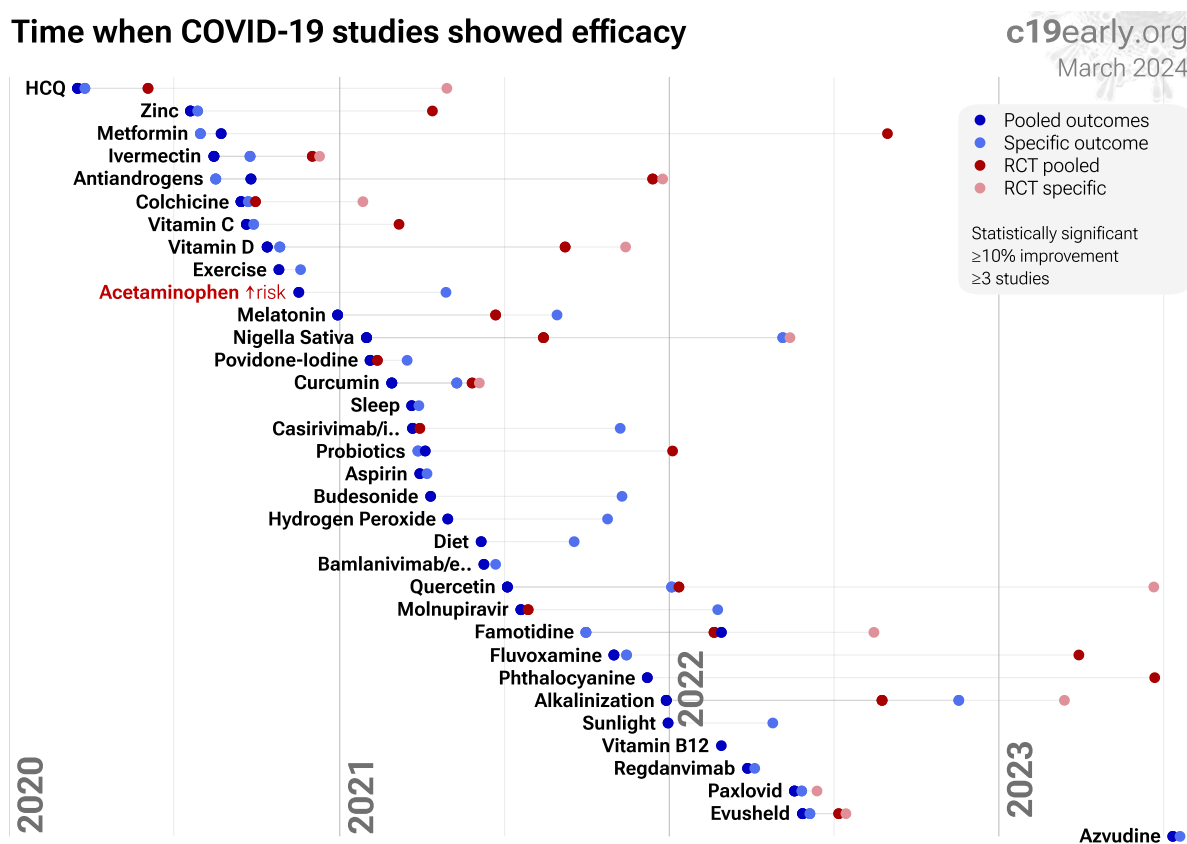
Figure 7. The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies. Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

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. This may have a greater effect than pooling different outcomes such as mortality and hospitalization. For example a treatment may have 50% efficacy for mortality but only 40% for hospitalization when used within 48 hours. However efficacy could be 0% when used late.

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.

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.

Nasal/oral administration to the respiratory tract	Improvement	Studies
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, alkalinization, 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.
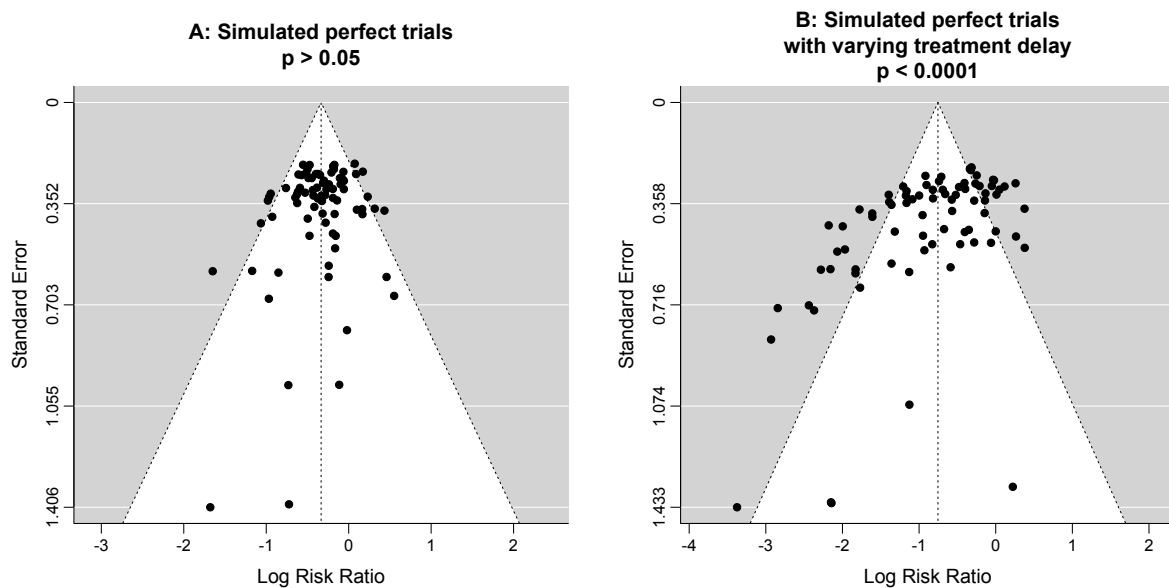
Impact on the microbiome. Nasopharyngeal/oropharyngeal treatments may not be highly selective. In addition to inhibiting or disabling SARS-CoV-2, they may also be harmful to beneficial microbes, disrupting the natural microbiome in the oral cavity and nasal passages that have important protective and 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.

Treatment	Microbiome disruption potential	Notes
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 nasophyrngeal/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]. For iota-carrageenan, there is currently not enough data to evaluate publication bias with high confidence.

Funnel plot analysis. Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 8 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ($p > 0.05$). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, $p < 0.0001$, with six variants of Egger's test all showing p < 0.05 [Egger, Harbord, Macaskill, Moreno, Peters, Rothstein, Rücker, Stanley]. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.

A: Simulated perfect trials
p > 0.05

B: Simulated perfect trials
with varying treatment delay
p < 0.0001

Figure 8. Example funnel plot analysis for simulated perfect trials.

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 by 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 affiliated with special interests 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 *Alsaidi, 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, vaccine, 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*.

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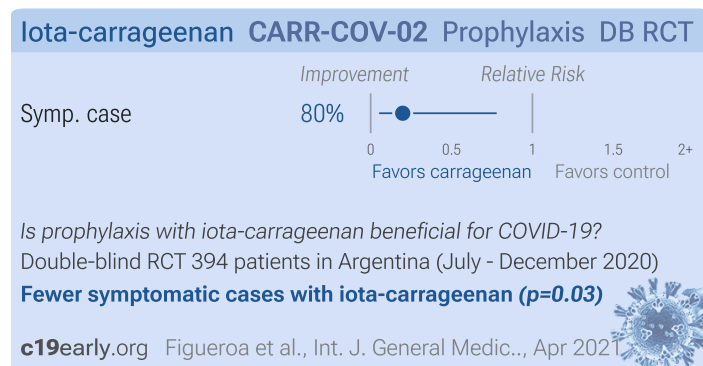
Studies to date show that iota-carrageenan is an effective treatment for COVID-19. Statistically significant lower risk is seen for cases. Meta analysis using the most serious outcome reported shows 80% [22-95%] lower risk.

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

Study Notes

Figueroa

Iota-carrageenan CARR-COV-02 Prophylaxis DB RCT

Improvement — 80% Symp. case — Relative Risk

Is prophylaxis with iota-carrageenan beneficial for COVID-19?
Double-blind RCT 394 patients in Argentina (July - December 2020)
Fewer symptomatic cases with iota-carrageenan *(p=0.03)*

c19early.org   Figueroa et al., Int. J. General Medic.., Apr 2021

Figueroa: 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_2 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 (5.19.0).

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^2 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].

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.

Carvallo (B), 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.	risk of case, 99.9% lower, RR 0.001, *p* < 0.001, 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).
Figueroa, 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).	risk of symptomatic case, 80.2% lower, RR 0.20, *p* = 0.03, treatment 2 of 196 (1.0%), control 10 of 198 (5.1%), NNT 25, odds ratio converted to relative risk.
Jessop, 11/18/2022, Double Blind Randomized Controlled Trial, placebo-controlled, United Kingdom, trial NCT04590365 (history) (ICE-COVID).	480 patient RCT with results unknown and over 1 year late.

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.

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