Hypochlorous Acid for COVID-19: real-time meta-analysis of 3 studies

@CovidAnalysis, September 2026, Version 1, c19early.org/hoclmeta.html

Abstract

Significantly lower risk is seen for recovery, cases, and viral clearance. 3 studies from 3 independent teams in 2 countries show significant benefit.

Meta-analysis using the most serious outcome reported shows 50% [-32-81%] lower risk, without reaching statistical significance. Currently all studies are RCTs.

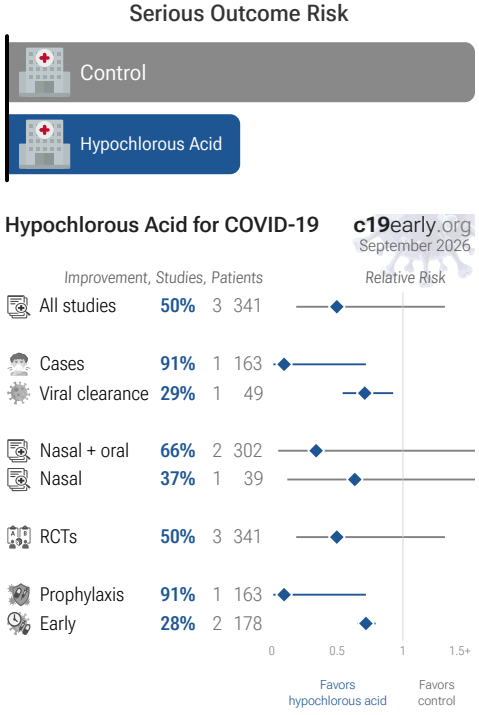
Currently there is limited data, with only 341 patients and only 13 control events for the most serious outcome in trials to date. Studies to date are from only 3 different groups.

No treatment is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. Hypochlorous Acid may affect the natural microbiome, especially with prolonged use. All data and sources to reproduce this analysis are in the appendix.

HYPOCHLOROUS ACID FOR COVID-19 — HIGHLIGHTS

Hypochlorous Acid reduces risk with low confidence for recovery, cases, and viral clearance, and very low confidence for pooled analysis.

Real-time updates and corrections with a consistent protocol for 226 treatments. Outcome specific analysis and combined evidence from all studies including treatment delay, a primary confounding factor.



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[2]. Progression may lead to cytokine storm, pneumonia, ARDS, neurological injury[3-19] and cognitive deficits[6,11], cardiovascular complications[20-26], DNA damage[27-30], organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits[31]—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Systemic treatments may be insufficient to prevent neurological damage[10]. Minimizing replication as early as possible is recommended.

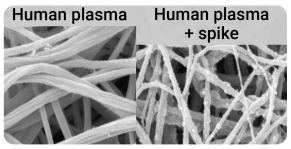


Fig. 1. SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from[1].

Targeted treatment to the primary location of initial infection

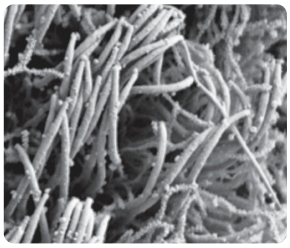


Fig. 2. SARS-CoV-2 virions attached to cilia of nasal epithelial cells, from Chien-Ting Wu[32,33].

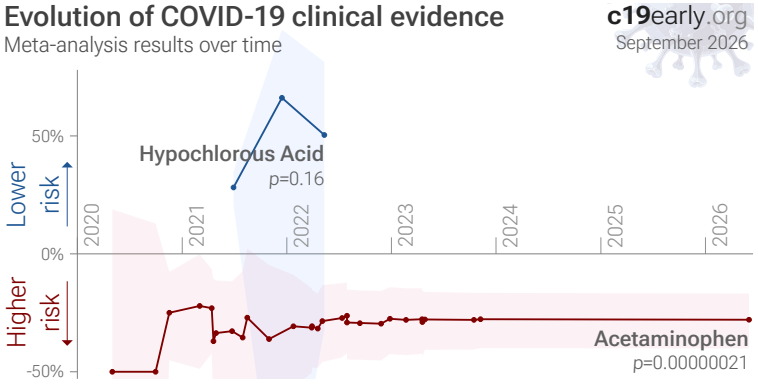
Logically, stopping replication in the upper respiratory tract should be simpler and more effective. *Wu et al.*, using an airway organoid model incorporating many *in vivo* aspects, show that SARS-CoV-2 initially attaches to cilia—hair-like structures responsible for moving the mucus layer and where ACE2 is localized in nasal epithelial cells[34]. The mucus layer and the need for ciliary transport slow down infection, providing more time for localized treatments[32,33]. Early or prophylactic nasopharyngeal/oropharyngeal treatment may 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 500+ host and viral proteins and other factors[A,35-42], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 12,000 compounds may reduce COVID-19 risk[43], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Analysis

We analyze all significant controlled studies of hypochlorous acid 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, studies within



	Relative Risk	Studies	Patients
All studies	0.50 [0.19-1.32]	3	341
RCTs	0.50 [0.19-1.32]	3	341

Table 1. **Random-effects meta-analysis for all stages combined and for Randomized Controlled Trials.** Results show the relative risk with treatment and the 95% confidence interval. * $p<0.05$ **** $p<0.0001$.

	Early treatment	Prophylaxis
All studies	0.72 [0.65-0.79] ****	0.09 [0.01-0.72] *
RCTs	0.72 [0.65-0.79] ****	0.09 [0.01-0.72] *

Table 2. **Random-effects meta-analysis results by treatment stage.** Results show the relative risk with treatment and the 95% confidence interval. * $p<0.05$ **** $p<0.0001$.

each treatment stage, individual outcomes, and Randomized Controlled Trials (RCTs).

Treatment timing

Fig. 3 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.

Preclinical Research

2 *in vitro* studies support the efficacy of hypochlorous acid [44,45].

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 stages combined and for Randomized Controlled Trials. Table 2 shows results by treatment stage. Fig. 4 shows a timeline of the results in hypochlorous acid studies. Fig. 5 plots individual results by treatment stage. Fig. 6, 7, 8, 9, 10, and 11 show forest plots for random-effects meta-analysis of all studies with pooled effects, progression, recovery, cases, viral clearance, and nasopharyngeal/oropharyngeal administration.

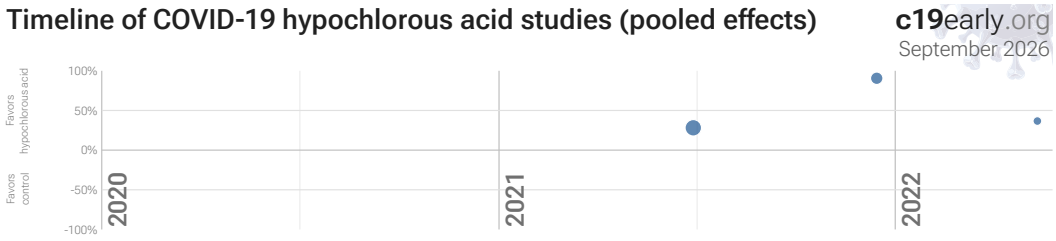


Fig. 4. Timeline of results in hypochlorous acid studies.

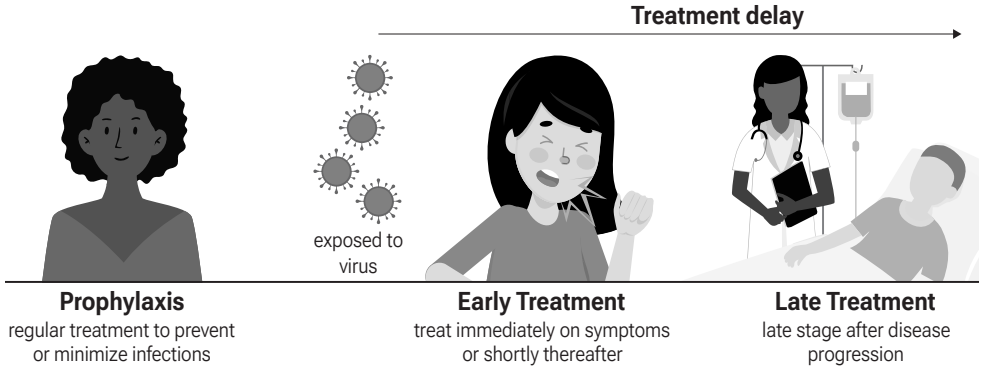


Fig. 3. Treatment stages.

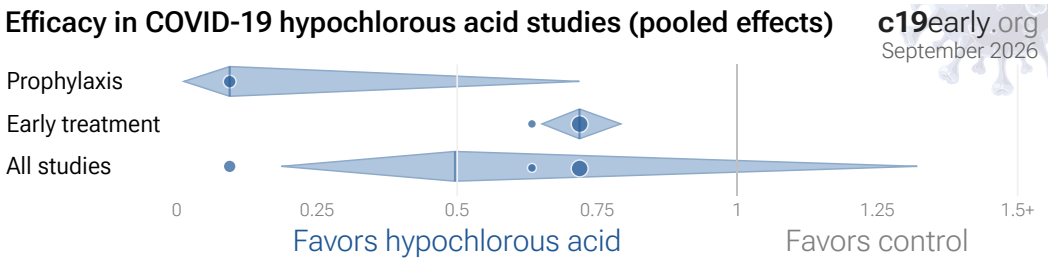


Fig. 5. Scatter plot showing the most serious outcome in all studies, and for studies within each stage. Diamonds shows the results of random-effects meta-analysis.

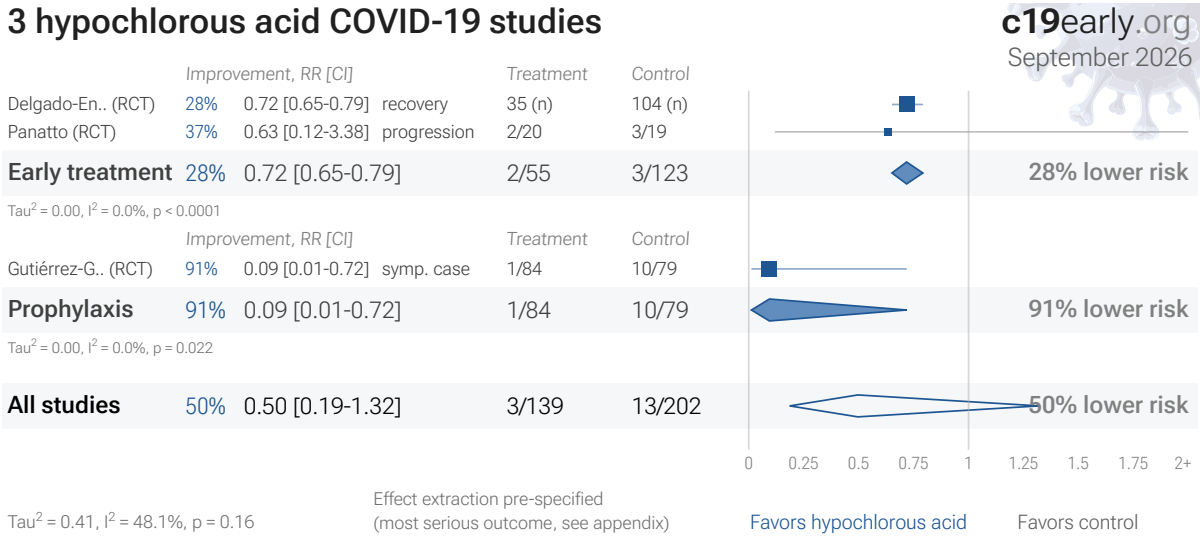


Fig. 6. **Random-effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

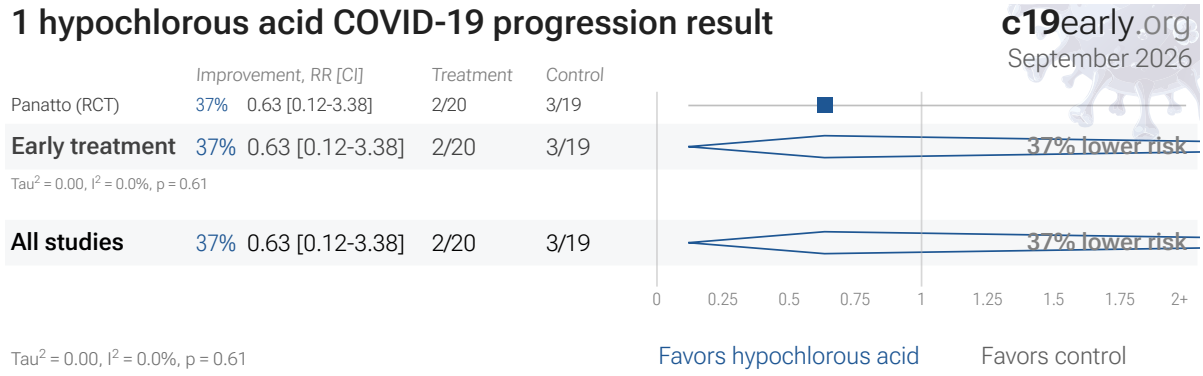


Fig. 7. Random-effects meta-analysis for progression.

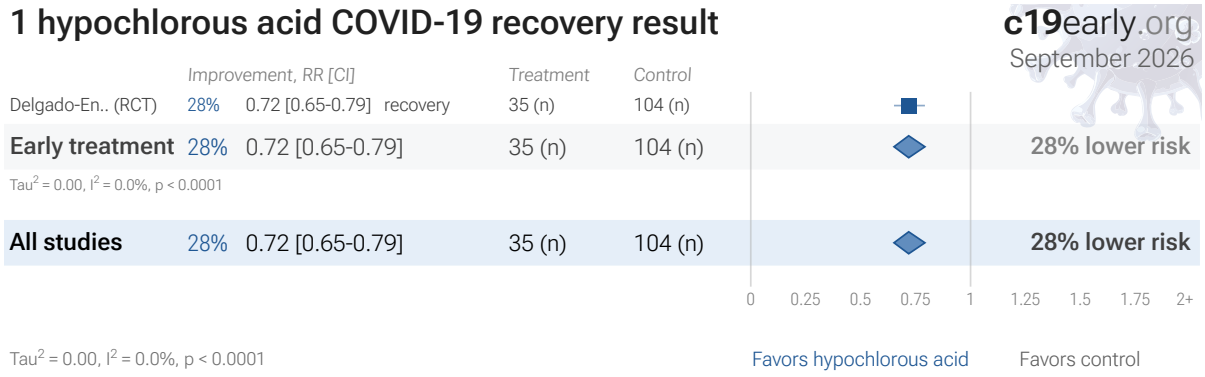


Fig. 8. Random-effects meta-analysis for recovery.

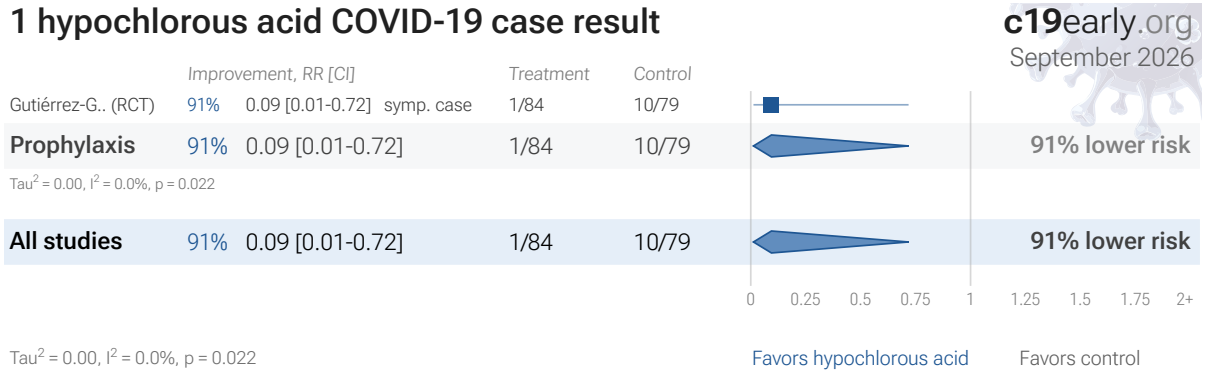


Fig. 9. Random-effects meta-analysis for cases.

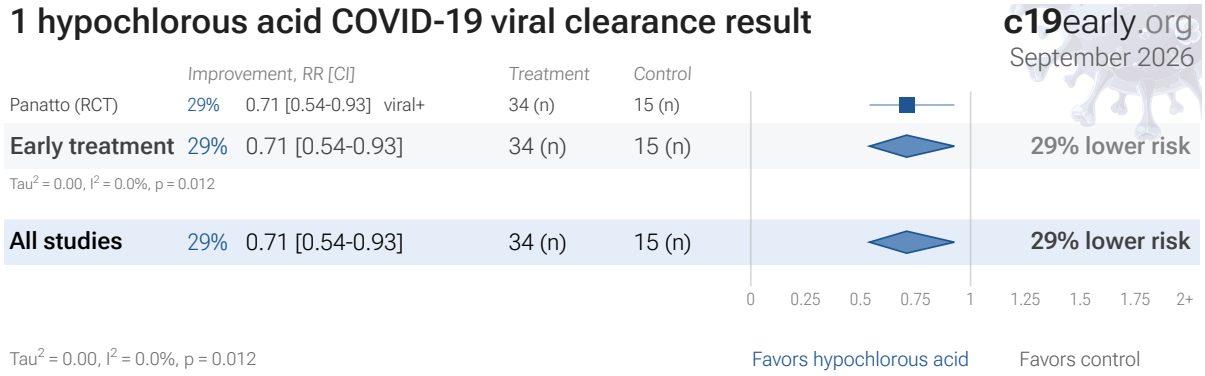


Fig. 10. Random-effects meta-analysis for viral clearance.

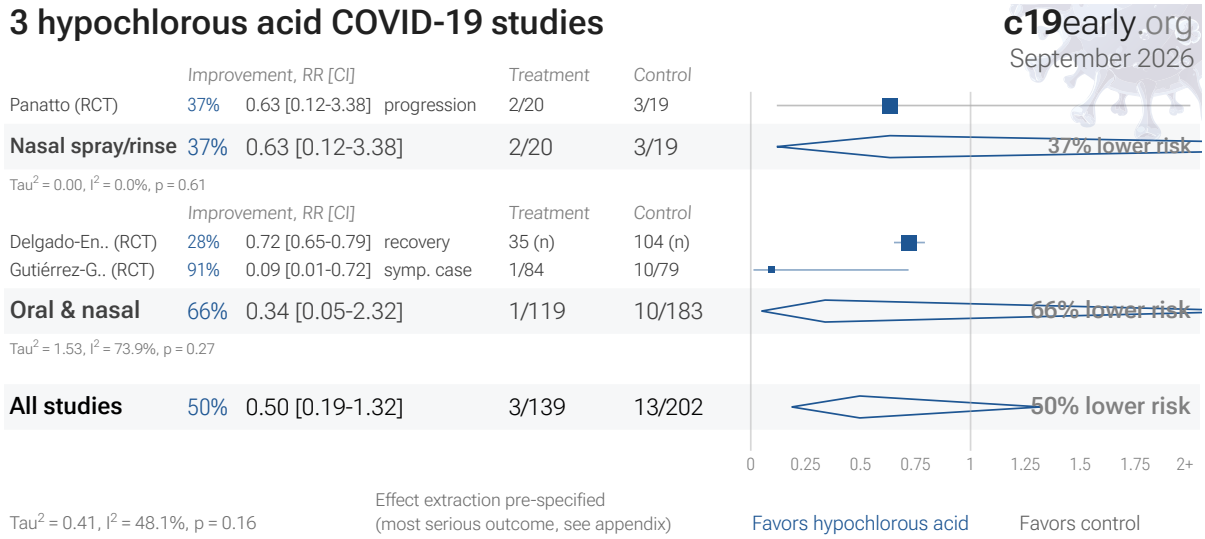


Fig. 11. **Random-effects meta-analysis for nasopharyngeal/oropharyngeal administration.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below.

Randomized Controlled Trials (RCTs)

Currently all studies are RCTs.

Application

In addition to the dosage and frequency of administration, efficacy for nasopharyngeal/oropharyngeal treatments may depend on many other details. For example considering sprays, viscosity, mucoadhesion, sprayability, droplet size[46,47], dispersion[47], and application angle[46] are important.

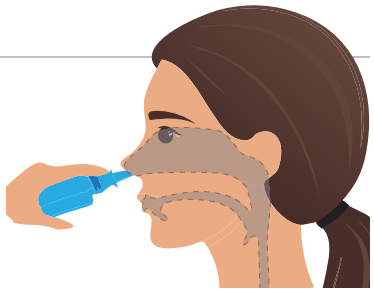


Fig. 12. Optimal spray angle may increase nasopharyngeal drug delivery 100x for nasal sprays, adapted from *Akash et al.*

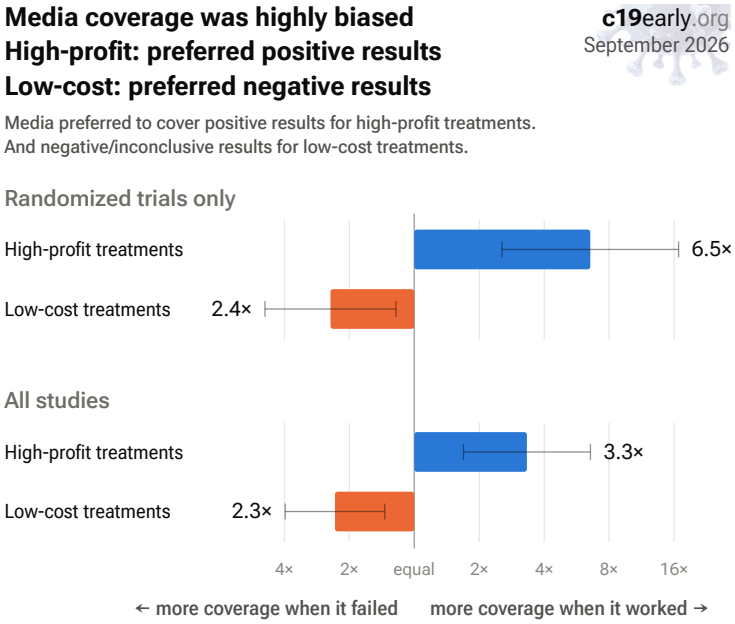
Akash et al. performed a computational fluid dynamics study of nasal spray administration showing 100x improvement in nasopharyngeal drug delivery using a new spray placement protocol, which involves holding the spay nozzle close to horizontal at the nostril, with a slight tilt towards the cheeks. The study also found the optimal droplet size range for nasopharyngeal deposition was ~7-17μm.

Media Censorship

Low-cost treatments were subject to bias and censorship during the pandemic. Scientific bias is seen in the design, analysis, presentation, and selective reporting of studies, which often favored negative results. A similar bias is seen in the media coverage for low-cost treatments. While broadly seen, bias was particularly notable for ivermectin and hydroxychloroquine, e.g., Scott Alexander noted that *"if you say anything in favor of ivermectin you will be cast out of civilization and thrown into the circle of social hell reserved for Klan members and 1/6 insurrectionists. All the health officials in the world will shout 'horse dewormer!' at you and compare you to Josef Mengele."*[48].

We analyze media coverage for the 226 treatments we cover using Altmetric[49], which reports the number of ~12,000 tracked news outlets that covered each study[50]. Studies are considered to have received significant media coverage if they were covered by at least 0.5% of the tracked news outlets. Fig. 13, 14, and 15 show the bias toward negative results for low-cost treatments, in contrast to the opposite bias for high-profit treatments. This may result in widespread incorrect perceptions on the relative efficacy of high-profit and low-cost treatments. The impact is significant—increased cost limits the use of high-profit treatments and treatment equity, and high-profit treatments were also more difficult to access, especially for earlier treatment which improves efficacy and minimizes community transmission.

The mainstream media did not cover any of the positive studies for hypochlorous acid.



Many studies show lower risk with low-cost treatments 98% of these were not covered by the media

Coverage of positive vs. negative/inconclusive results; whiskers are 95% confidence intervals.
Data from Altmetric. Log scale. See: c19early.org/msm.html

Fig. 13. Media was more likely to cover negative or inconclusive results for low-cost treatments, and positive results for high-profit treatments.

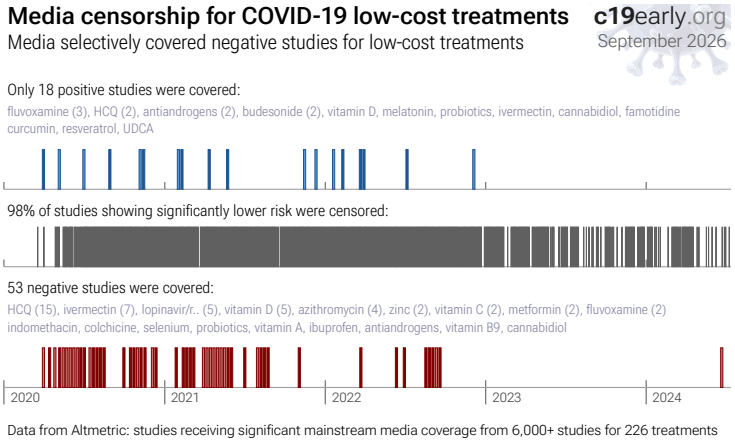


Fig. 14. Mainstream media was biased against positive results for low-cost treatments.

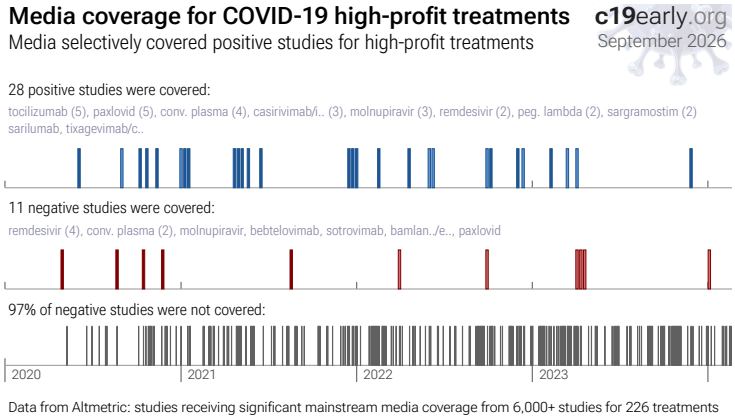


Fig. 15. In contrast to the results for low-cost treatments, mainstream media was biased towards positive results for high-cost treatments.

A combination of factors may have led to the media's suppression of low-cost treatments:

- Politicization led to a media environment where coverage was often framed to support a political narrative rather than to provide objective scientific information. As Scott Alexander said: *"if you say anything in favor of ivermectin you will be cast out of civilization and thrown into the circle of social hell reserved for Klan members and 1/6 insurrectionists. All the health officials in the world will shout 'horse dewormer!' at you and compare you to Josef Mengele."* There was strong social pressure to discredit low-cost treatments.
- Censorship of information conflicting with selected authorities. For example, individuals and organizations presenting conflicting science were often banned on Twitter and YouTube.
- FDA requires *"no adequate, approved, and available alternatives"* in order to grant an EUA for novel high-profit interventions, creating a strong incentive for authorities to ignore or downplay existing low-cost treatments.
- Regulatory capture biases authorities towards high-profit interventions.
- Authorities ignored most evidence for low-cost treatments, for example the NIH references only 2% of studies in delayed, rarely-updated, biased commentaries with no quantitive analysis.
- Media coverage of science is often not very accurate, e.g., misunderstanding confounding issues. For example the media widely considered the RECOVERY HCQ RCT to be conclusive on efficacy, but very late treatment of late stage patients (mostly on oxygen already) with an excessive toxic dose (shown dangerous in a dose comparison RCT) provides no information on the recommended early/prophylactic treatment. With difficulting in understanding basic confounders like treatment delay and dose, the media may favor deferring to authorities. Many studies for low-cost treatments require greater expertise to analyze. Relatively few journalists have a strong ability to analyze clinical trials and are outnumbered by the rest.
- Substantial funding from pharmaceutical advertising biases editorial decisions towards high-profit interventions.
- PR power - companies/teams with strong PR presence are favored in the media, which correlates with high-profit and high conflict of interest studies.
- The media was very negative in general, inflating risk, fear, and anxieties. A negative bias may improve ratings and revenue, increasing motivation to continue watching coverage. A combination of low-cost treatments greatly reducing risk conflicts with the negative narrative.

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 [51,52]. Baloxavir marboxil 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.

Treatment delay	*Result*
Post-exposure prophylaxis	86% fewer cases [53]
<24 hours	-33 hours symptoms [54]
24-48 hours	-13 hours symptoms [54]
Inpatients	-2.5 hours to improvement [55]

Table 3. Studies of baloxavir marboxil for influenza show that early treatment is more effective.

Fig. 16 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 226 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

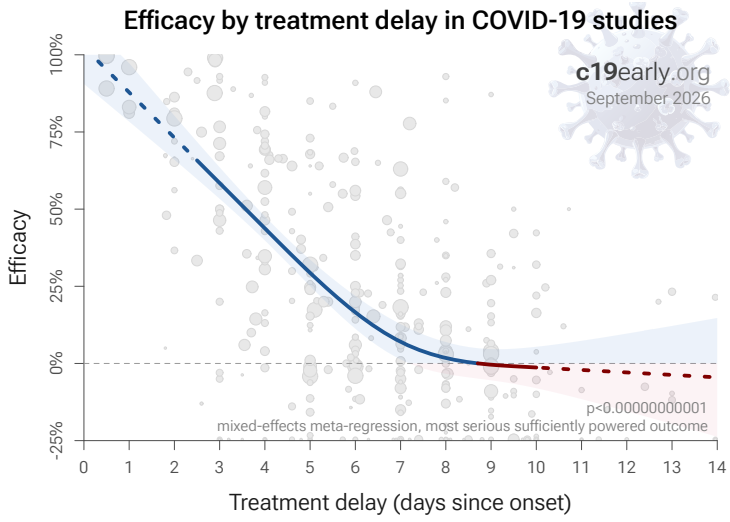


Fig. 16. Early treatment is more effective. Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 226 treatments.

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.*

SARS-CoV-2 variants

Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants [57], for example the Gamma variant shows significantly different characteristics [58-61]. 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 [62,63].

Treatment regimen

Effectiveness may depend strongly on the dosage and treatment regimen.

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.

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 [66-90], therefore efficacy may depend strongly on combined treatments.

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. Pooling the results of studies reporting different outcomes allows us to use more of the available information. Logically we should, and do, use additional information when evaluating treatments—for example dose-response and treatment delay-response relationships provide additional evidence of efficacy that is considered when reviewing the evidence for a treatment.

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.

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 and safer collection of evidence.

Validating pooled outcome analysis for COVID-19

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.

Analysis of the the association between different outcomes across studies from all 226 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Fig. 17 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.0000000001$). Similarly, Fig. 18 shows that improved recovery is very strongly associated with lower mortality ($p < 0.0000000001$). 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. Fig. 19 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 $p = 0.0000000074$ to $p = 0.00000000015$.

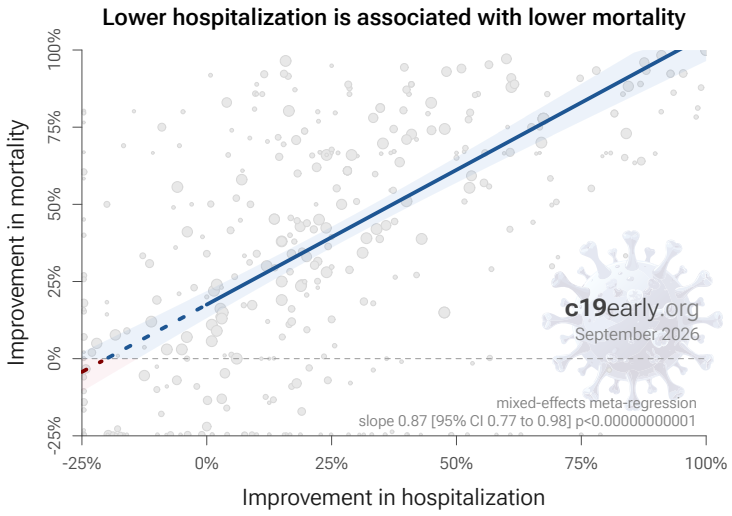


Fig. 17. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

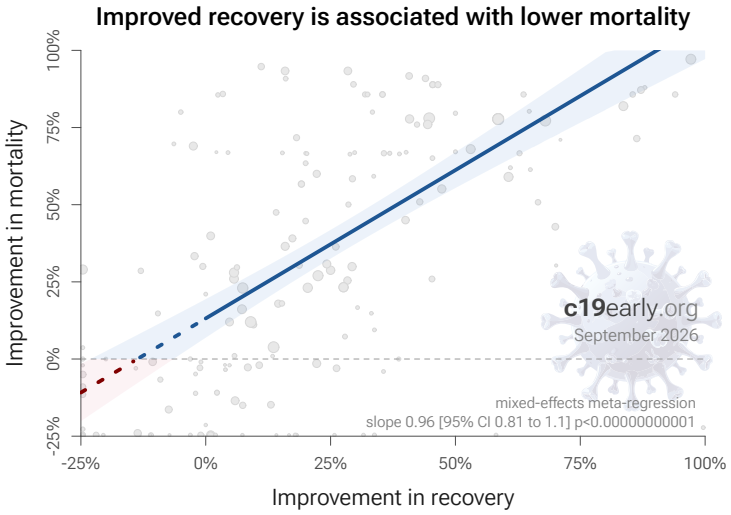


Fig. 18. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

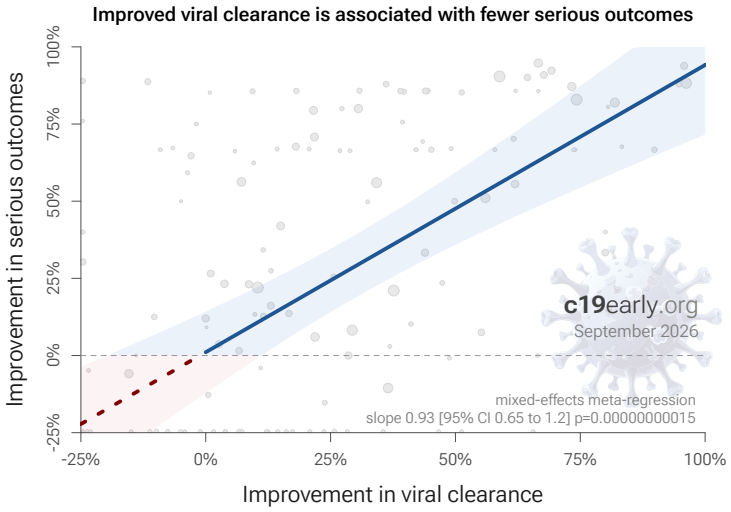


Fig. 17. Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.

Pooled outcomes identify efficacy 5 months faster (7 months for RCTs)

Currently, 59 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 85% of these have been confirmed with one or more specific outcomes, with a mean delay of 4.6 months. When restricting to RCTs only, 53% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 7.5 months. Fig. 20 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

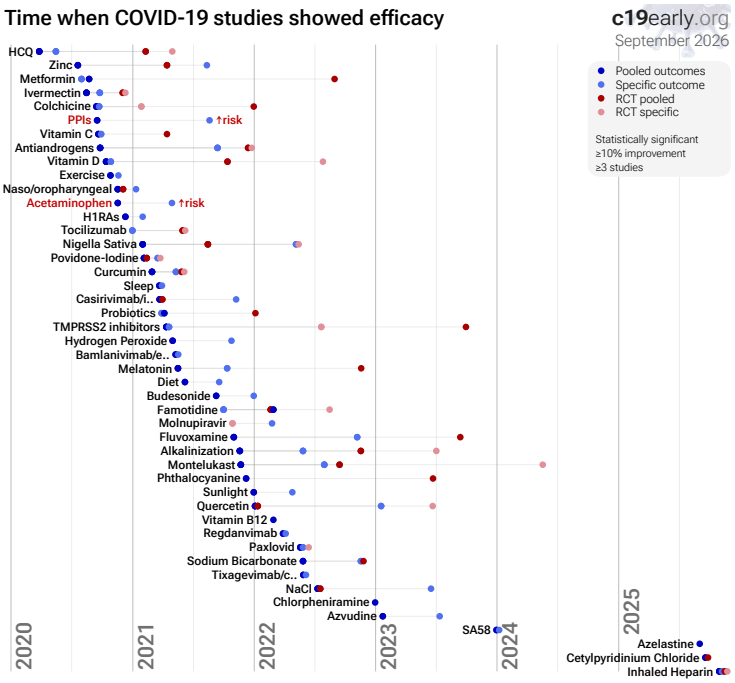


Fig. 20. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

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 differences in treatment delay are 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

PCR viral load

Analysis of short-term changes in viral load using PCR may not detect effective treatments because PCR is unable to differentiate between intact infectious virus and non-infectious or destroyed virus particles. For example *Tarragó-Gil, Alemany* perform RCTs with cetylpyridinium chloride (CPC) mouthwash that show no difference in PCR viral load, however there was significantly increased detection of SARS-CoV-2 nucleocapsid protein, indicating viral lysis. CPC inactivates SARS-CoV-2 by degrading its membrane, exposing the nucleocapsid of the virus. To better estimate changes in viral load and infectivity, methods like viral culture that can differentiate intact vs. degraded virus are preferred.

Nasopharyngeal/oropharyngeal 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 4 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.

Combined nasal and oral administration is most effective

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Across all nasopharyngeal/oropharyngeal treatments we cover, combined nasal and oral administration shows the highest efficacy, followed by nasal administration, with oral administration alone showing the lowest efficacy.

ADMINISTRATION	IMPROVEMENT	STUDIES
Nasal & oral	88% [72-95%]	10
Nasal spray/rinse	59% [50-66%]	21
Oral spray/rinse	38% [25-49%]	11

Table 4. **Respiratory tract administration efficacy. Relative efficacy of nasal, oral, and combined nasal/oral administration for treatments administered directly to the respiratory tract. Results show random-effects meta-analysis for the most serious outcome reported for all prophylaxis and early treatment studies.**

Nasopharyngeal/oropharyngeal treatment mechanisms of action

Nasopharyngeal/oropharyngeal treatments work via different methods. Some are drugs with other primary uses and have a greater potential for side effects and drug interactions, for example azelastine and chlorpheniramine are antihistamines. Table 5 summarizes the primary classes of mechanisms of action, and Table 6 shows mechanisms of action for specific treatments.

Nasal/oral sprays and rinses—primary mechanisms

Primary mechanisms of action for nasopharyngeal/oropharyngeal sprays and rinses. Note: sequenced application is possible to maximize efficacy—for example, using a virucidal spray/wash first (to clean), followed by a barrier spray (to protect), with a 5-10 minute drying window in between.

Virucidal action	Chemically inactivating or destroying the structure of viral particles
Blocking attachment	Binding to the virus or host cells to prevent viral attachment to host cells
Physical barrier	Forming a physical layer over the nasal mucosa preventing viral access to host cells
Physical removal	Mechanical washout/flushing of viral particles and mucus (e.g., large volume irrigation)
Mucociliary clearance	Stimulating the natural beating of nasal cilia to accelerate the clearing of trapped pathogens

Table 5. Primary classes for mechanisms of action for nasopharyngeal/oropharyngeal treatments.

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 [106,107]. This may be especially important for prolonged use or overuse. Table 7 summarizes the potential for common nasopharyngeal/oropharyngeal treatments to affect the natural microbiome.

Nasal/oral sprays and rinses may affect the microbiome

Nasopharyngeal/oropharyngeal treatments may significantly alter the microbiome. These effects may be more important with longer-term prophylaxis.

TREATMENT	MICROBIOME DISRUPTION POTENTIAL	NOTES
Iota-carrageenan [100]	Low	Primarily antiviral, however extended use may mildly affect the microbiome
Nitric Oxide [102]	Low to moderate	More selective towards pathogens, however excessive concentrations or prolonged use may disrupt the balance of bacteria
Alkalinization [108]	Moderate	Increases pH, negatively impacting beneficial microbes that thrive in a slightly acidic environment
Cetylpyridinium Chloride [95]	Moderate	Quaternary ammonium broad-spectrum antiseptic that can disrupt beneficial and harmful bacteria
Hypochlorous Acid	Moderate	Broad-spectrum oxidizing antiseptic that may affect beneficial and harmful bacteria
Phthalocyanine [103]	Moderate to high	Photodynamic compound with antimicrobial activity, likely to affect the microbiome
Chlorhexidine [96]	High	Potent antiseptic with broad activity, significantly disrupts the microbiome
Hydrogen Peroxide [98]	High	Strong oxidizer, harming both beneficial and harmful microbes
Povidone-Iodine [104]	High	Potent broad-spectrum antiseptic harmful to beneficial microbes

Table 7. Potential effect of nasopharyngeal/oropharyngeal treatments on the 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 [109-112]. For hypochlorous acid, there is currently not enough data to evaluate publication bias with high confidence.

Nasal/oral sprays and rinses—mechanisms of action

Nasopharyngeal/oropharyngeal treatments have many different mechanisms of action. Specific treatments may have significant systemic effects or significantly alter the microbiome.

TREATMENT	MECHANISMS	NOTES
Azelastine [94]	Antiviral: inhibits interaction between spike protein and ACE2 Antiviral: potential inhibition of viral protease (Mpro) Other: H1-receptor antagonist (antihistamine) Other: mast cell stabilizer	Antihistamine. Designed to affect human receptors. Risks include dysgeusia, drowsiness, and nasal burning.
Cetylpyridinium Chloride [95]	Virucidal: disrupts viral lipid envelope Antiseptic: quaternary ammonium compound	Chemical virucide. Common in mouthwashes. Can cause temporary staining of teeth or tongue irritation if used frequently.
Chlorhexidine [96]	Virucidal: disrupts viral lipid membranes Antiseptic: cationic polybiguanide	Chemical virucide. May cause tooth staining and altered taste.
Chlorpheniramine [97]	Antiviral: binds to viral spike protein to block entry Antiviral: high affinity for viral transport proteins Other: H1-receptor antagonist (1st generation antihistamine) Other: anticholinergic activity	Antihistamine. Stronger systemic risks than azelastine. Known to cause significant sedation/drowsiness and cognitive impairment.
Hydrogen Peroxide [98]	Virucidal: oxidizing agent that destroys viral parts Other: tissue debridement	Chemical virucide. Can be toxic to healthy tissue if concentration is too high (>1%). Long-term safety on nasal mucosa is debated.
Hypochlorous Acid	Virucidal: oxidizes viral proteins, causing aggregation and loss of function. Impairs spike-ACE2 binding Antiseptic: broad-spectrum antimicrobial activity via oxidative damage to microbial proteins and membranes	Chemical virucide. Activity depends on concentration, pH, and contact time. Saliva may reduce activity.
Inhaled Heparin [99]	Antiviral: acts as a decoy receptor (mimics heparan sulfate) Antiviral: anti-inflammatory effects on lung tissue Other: Anticoagulant	Anticoagulant. Use requires caution regarding bleeding risks.
Iota-carrageenan [100]	Barrier: forms a viscous physical layer on mucosa Trap: electrostatistically traps virus particles (mimics cell surface)	Physical barrier. High safety profile for daily use.
NaCl [101]	Cleaning: physically washes away viral particles Support: moisturizes mucosa to support natural immune barrier	Physical wash. High degree of safety, reduces viral load via physical removal.
Nitric Oxide [102]	Virucidal: physically damages viral structure via nitrosylation Other: vasodilator (relaxes blood vessels) in systemic use	Virucide/drug hybrid. In nasal spray form, it acts primarily as a topical disinfectant. Rapidly cleared, so systemic vasodilation risks are low but present.
Phthalocyanine [103]	Virucidal: generates reactive oxygen species (ROS) when exposed to light to kill virus Other: photosensitizer	Chemical virucide. A synthetic compound often used in photodynamic therapy. Works by creating an oxidative environment hostile to the virus.
Povidone-Iodine [104]	Virucidal: oxidizes viral proteins and destabilizes membrane structures Antiseptic: broad-spectrum bacterial/fungal killer	Chemical virucide. Highly effective but risk of thyroid absorption with chronic use. Can be irritating to mucous membranes.
Sodium Bicarbonate [105]	Environment: raises pH to inhibit viral fusion Cleaning: improves mucociliary clearance (washing)	Physical/chemical environment. Changes the environment rather than attacking the virus directly. High degree of safety.

Table 6. Mechanisms of action for nasopharyngeal/oropharyngeal treatments.

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. Hypochlorous Acid for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 hypochlorous acid 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 hypochlorous acid 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 [66-90]. 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.

Reviews

Multiple reviews cover hypochlorous acid for COVID-19, presenting additional background on mechanisms and related results, including [113-117].

Other studies

Additional preclinical or review papers suggesting potential benefits of hypochlorous acid for COVID-19 include [121-123]. We have not reviewed these studies in detail.

Perspective

Results compared with other treatments

SARS-CoV-2 infection and replication involves a complex interplay of 500+ host and viral proteins and other factors [35-42], providing many therapeutic targets. Over 12,000 compounds have been predicted to reduce COVID-19 risk [43], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Fig. 21 shows an overview of the results for hypochlorous acid in the context of multiple COVID-19 treatments, and Fig. 22 shows a plot of efficacy vs. cost for COVID-19 treatments.

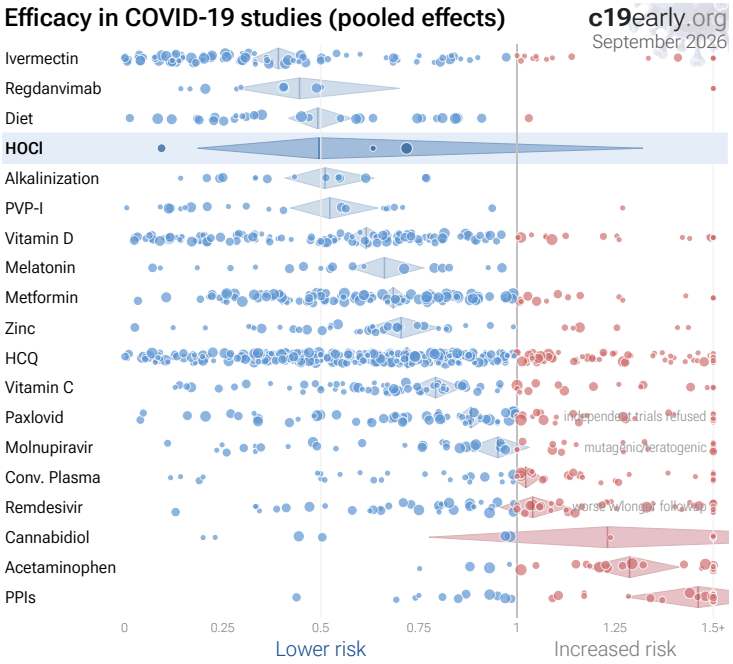


Fig. 21. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random-effects meta-analysis. 0.5% of 12,000+ proposed treatments show efficacy [124].

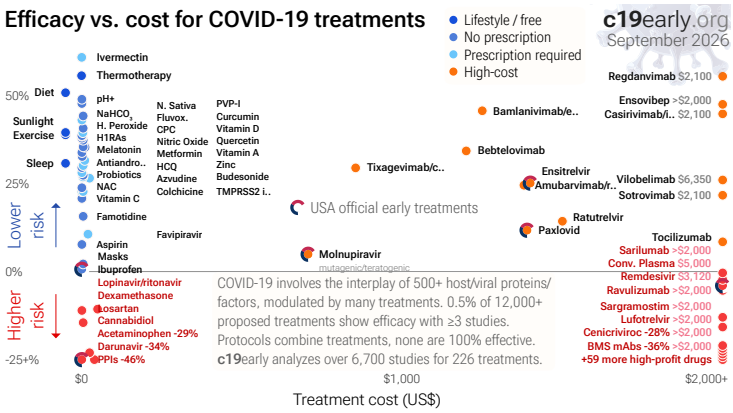


Fig. 22. Efficacy vs. cost for COVID-19 treatments.

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.

Significantly lower risk is seen for recovery, cases, and viral clearance. 3 studies from 3 independent teams in 2 countries show significant benefit. Meta-analysis using the most serious outcome reported shows 50% [-32-81%] lower risk, without reaching statistical significance. Currently all studies are RCTs.

Currently there is limited data, with only 341 patients and only 13 control events for the most serious outcome in trials to date. Studies to date are from only 3 different groups.

Hypochlorous Acid may affect the natural microbiome, especially with prolonged use.

Contact. Contact us on X at @CovidAnalysis.

Funding. We have received no funding or compensation in any form, and do not accept donations. This is entirely volunteer work.

Conflicts of interest. We have no conflicts of interest. We have no affiliation with any pharmaceutical companies, supplement companies, governments, political parties, or advocacy organizations.

Disclaimer. We do not provide medical advice. No treatment is 100% effective, and all may have side effects. Protocols combine multiple treatments. Consult a qualified physician for personalized risk/benefit analysis.

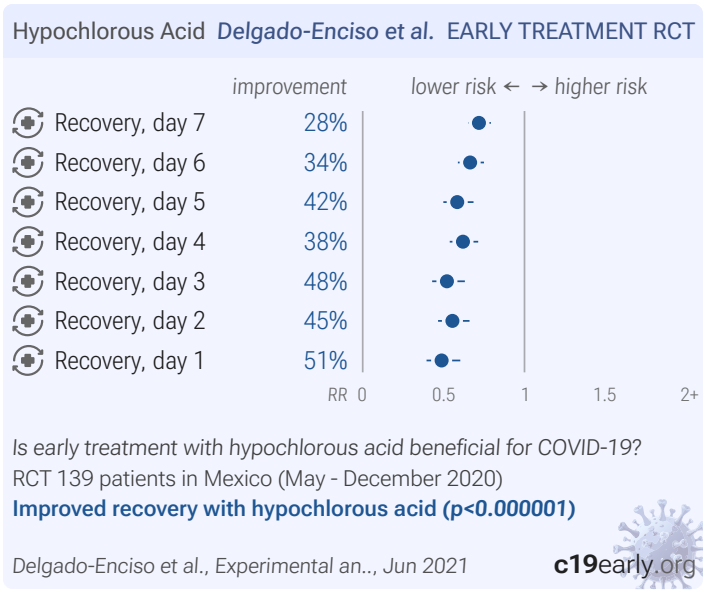
AI. We use AI models (Gemini, Grok, Claude, and ChatGPT) tasked with functioning as additional peer-reviewers to check for errors, suggest improvements, and review spelling and grammar. Any corrections are manually verified. Our preference for em dashes is independent of AI.

Updates. Our COVID-19 meta-analyses involve the extraction of over 227,000 datapoints from thousands of papers for 226 treatments. We thank the thousands of scientists, physicians, and other contributors that have provided updates, suggestions, feedback, and corrections. These are all welcome and can be submitted at https://c19early.org/hoclmeta.html.

Dedication. This work is dedicated to top evidence-based physicians that worked tirelessly to analyze evidence and greatly reduce mortality and morbidity during the pandemic. In alphabetical order: Dr. Thomas J. Borody, Dr. Mary Talley Bowden, Dr. Flavio Cadegiani, Dr. Shankara Chetty, Dr. Ryan Cole, Dr. George Fareed, Dr. Sabine Hazan, Dr. Pierre Kory, Dr. Tess Lawrie, Dr. Robert Malone, Dr. Paul Marik, Dr. Peter McCullough, Dr. Didier Raoult, Dr. Harvey Risch, Dr. Jackie Stone, Dr. Brian Tyson, Dr. Joseph Varon, and Dr. Vladimir Zelenko.

Study Notes

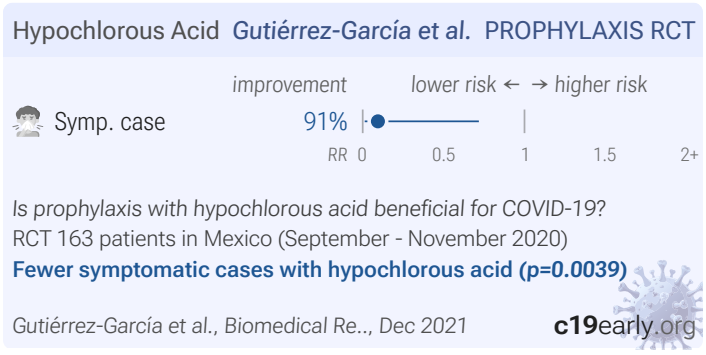
Delgado-Enciso



RCT 214 ambulatory COVID-19 patients showing significant benefit with nebulized and/or intravenous neutral electrolyzed saline. The treatment group had reduced risk of hospitalization, lower mortality, and faster time to an acceptable symptom state. The benefit was most pronounced in moderate/severe patients. HOCl is the primary active component of neutral electrolyzed saline.

This study includes nebulized and IV use which have different mechanisms of action. Nebulized treatment directly destroys the viral lipid envelope, whereas IV use may be beneficial via immunomodulation to minimize cytokine storm. For meta-analysis, we currently only include nebulized treatment. In this study, the only results provided for patients receiving nebulized treatment only is the change in symptom severity shown in Figure 2.

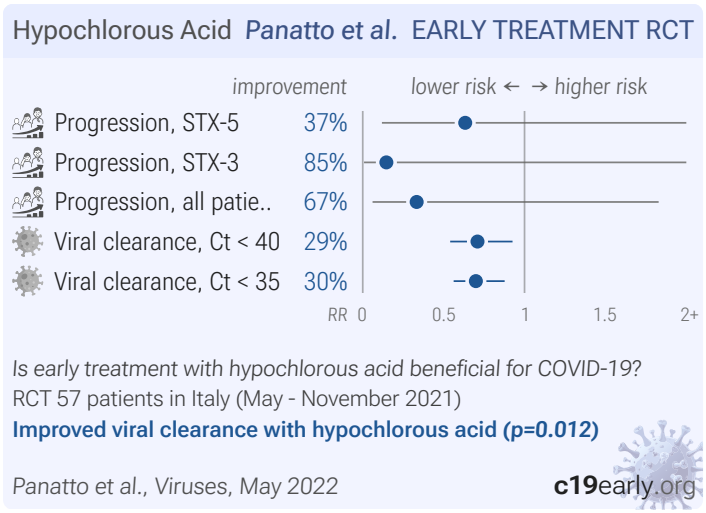
Gutiérrez-García



RCT 170 front-line healthcare workers in Mexico showing significantly lower COVID-19 cases with neutral electrolyzed water (SES) nasal and oral rinses. Authors hypothesize that SES inactivates viral particles through its oxidizing potential, reducing viral load in the upper respiratory tract where SARS-CoV-2

initially establishes infection. HOCl is the primary active component of neutral electrolyzed saline.

Panatto



RCT 57 mild COVID-19 patients showing non-significant viral load reduction with Sentinox (STX), a hypochlorous acid nasal spray. The proportion of COVID negative patients by day 5 was significantly higher in the STX-3 group than controls. Authors note that the results were likely driven by outliers with extreme baseline viral loads. When considering subjects with baseline cycle threshold values of 20-30, STX-3 showed a significant 2.01 log10 reduction.

A complementary in vitro study demonstrated STX had ≥99.9% virucidal activity against various respiratory viruses including influenza, RSV, rhinovirus, adenovirus, parainfluenza, and seasonal coronavirus.

Appendix 1. Methods and Data

Search methods

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, which regularly receives notification of studies upon publication. Search terms are hypochlorous acid 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 hypochlorous acid for COVID-19 that report a comparison with a control group are included in the main analysis. Studies with major unexplained data issues, for example major outcome data that is impossible to be correct with no response from the authors, are excluded.

Effect extraction

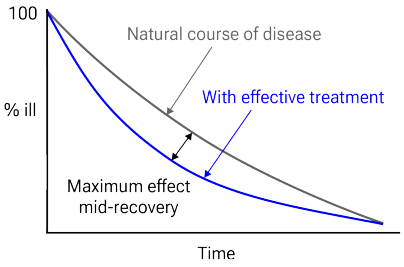


Fig. 23. Mid-recovery results can more accurately reflect efficacy when almost all patients recover. *Mateja et al.* confirm that intermediate viral load results more accurately reflect hospitalization/death.

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 reported then they are both used in specific outcome analyses, while mortality is used for pooled analysis. If symptomatic results are reported at multiple times, we use 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 outcomes. 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. An IPD meta-analysis confirms that intermediate viral load reduction is more closely associated with hospitalization/death than later viral load reduction [125]. 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.

Statistical methods

Forest plots are computed using PythonMeta [126] 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. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to *Zhang et al.* Reported confidence intervals and *p*-values are used when available, and adjusted values are used 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 [130]. 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 (3.14.7) with scipy (1.18.1), pythonmeta (1.26), numpy (2.5.3), statsmodels (0.15.0), and plotly (6.9.0). Mixed-effects meta-regression results are computed with R (4.4.0) using the metafor (4.6-0) and rms (6.8-0) 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 0.8.2 is used to parse PDF documents.

When evaluating potential effect modification across groups, we use an interaction test as described by *Altman (C) et al.* We compared the log-transformed relative risks using a *z*-test, deriving the standard error of the difference from

the 95% confidence intervals. A two-sided interaction p-value of < 0.05 was considered a statistically significant difference in treatment effect between the groups.

Quality evaluation

Cochrane RoB 2/ROBINS-I are often used to evaluate studies, and have the advantage of providing standardized rules that can be applied with minimal understanding of the domain and study. However, the rules do not account for many real-world issues, often overemphasize or underemphasize others, and studies show low inter-rater reliability[138]. Certain domains are more applicable for these tools, however the time-sensitive nature of a pandemic, with significant mortality for every day of delay in evidence assessment, and the characteristics of COVID-19 make them inappropriate for this domain. This can be demonstrated with examples where expert RoB 2/ROBINS-I ratings do not match reality for COVID-19. *Popp et al.* use RoB 2 to classify *Reis et al.* as low risk of bias, however this is the opposite of reality—the trial not only has very high risk of bias, but has very high actual known bias, refusing to release data despite pledging to, reporting multiple impossible numbers, having blinding and randomization failure, and many other issues[140]. *Axfors et al.* use RoB 2 to classify *Horby et al.* as low risk of bias, however this is the opposite of reality—the very late treatment and excessive dosage used produces results with no relevance to recommended usage. HCQ shows poor results with late treatment and excessive dosage, and the combination shows harm[B]. *Hempenius et al.* use ROBINS-I to classify 33 studies for HCQ. The two rated as having the lowest risk of bias[136,137] are far from the most informative. Both involve very late treatment, providing no information on recommended usage, and ROBINS-I does a very poor job of accounting for the impact of confounding factors[C].

Our quality evaluation focuses on known issues and bias, and the potential impact on outcomes, rather than just the risk of bias. The estimated potential impact of each confounding factor, and the direction of the impact is considered. For example, consider a study that shows significantly lower risk, the value of the study varies significantly if confounding points to an underestimate or an overestimate of efficacy. In one case, the real effect may be null, while the other case provides stronger evidence of efficacy (which may be greater than the study shows). Analysis focusing on the risk of bias, while simpler, may penalize studies for theoretical or technical issues that have no or minimal impact on outcomes. Analysis also depends on the outcome, for example certain issues are less relevant for objective outcomes such as mortality. Inaccurate penalization, and inaccurate high-quality evaluation in the face of known major issues affecting outcomes, increases in significance during a pandemic when immediate recognition of new evidence is critical, and when considering all global studies, as required during a pandemic. Investigators in other countries may have different customs for design, analysis, and reporting, and different English language skills, however they may not be less diligent or have greater bias. Investigators in lower-pharmaceutical-profit countries may have lower bias towards profitable interventions.

Treatment time

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[51,52].

Living analysis

This is a living analysis and is updated regularly. We received no funding, this research is done in our spare time. We have no affiliation with any pharmaceutical companies, supplement companies, governments, political parties, or advocacy organizations.

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

Early treatment

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.

Delgado-Enciso, 6/29/2021, Randomized Controlled Trial, Mexico, peer-reviewed, mean age 43.7, 44 authors, study period May 2020 - December 2020.	**risk of no recovery, 28.1% lower, RR 0.72, $p < 0.001$**, treatment mean 5.16 (±0.35) n=35, control mean 3.7 (±0.45) n=104, relative reduction in symptom severity, day 7.
	risk of no recovery, 33.6% lower, RR 0.66, $p < 0.001$, treatment mean 4.83 (±0.37) n=35, control mean 3.21 (±0.42) n=104, relative reduction in symptom severity, day 6.
	risk of no recovery, 41.6% lower, RR 0.58, $p < 0.001$, treatment mean 4.32 (±0.4) n=35, control mean 2.52 (±0.37) n=104, relative reduction in symptom severity, day 5.
	risk of no recovery, 38.0% lower, RR 0.62, $p < 0.001$, treatment mean 3.97 (±0.4) n=35, control mean 2.46 (±0.32) n=104, relative reduction in symptom severity, day 4.
	risk of no recovery, 47.9% lower, RR 0.52, $p < 0.001$, treatment mean 3.28 (±0.31) n=35, control mean 1.71 (±0.26) n=104, relative reduction in symptom severity, day 3.
	risk of no recovery, 44.5% lower, RR 0.55, $p < 0.001$, treatment mean 2.74 (±0.22) n=35, control mean 1.52 (±0.22) n=104, relative reduction in symptom severity, day 2.
	risk of no recovery, 51.2% lower, RR 0.49, $p < 0.001$, treatment mean 2.05 (±0.18) n=35, control mean 1.0 (±0.15) n=104, relative reduction in symptom severity, day 1.
Panatto, 5/12/2022, Randomized Controlled Trial, Italy, peer-reviewed, mean age 40.1, 10 authors, study period 20 May, 2021 - 9 November, 2021, trial NCT04909996 (history).	**risk of progression, 36.7% lower, RR 0.63, $p = 0.66$**, treatment 2 of 20 (10.0%), control 3 of 19 (15.8%), NNT 17, STX-5.
	risk of progression, 85.4% lower, RR 0.15, $p = 0.23$, treatment 0 of 18 (0.0%), control 3 of 19 (15.8%), NNT 6.3, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), STX-3.
	risk of progression, 66.7% lower, RR 0.33, $p = 0.32$, treatment 2 of 38 (5.3%), control 3 of 19 (15.8%), NNT 9.5, all patients.
	risk of no viral clearance, 29.1% lower, RR 0.71, $p = 0.01$, treatment 34, control 15, inverted to make RR<1 favor treatment, Ct < 40, day 5.
	risk of no viral clearance, 30.1% lower, RR 0.70, $p = 0.002$, treatment 34, control 15, inverted to make RR<1 favor treatment, Ct < 35, day 5.

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.

Gutiérrez-García, 12/15/2021, Randomized Controlled Trial, Mexico, peer-reviewed, mean age 38.1, 6 authors, study period September 2020 - November 2020.	risk of symptomatic case, 90.6% lower, RR 0.09, $p = 0.004$, treatment 1 of 84 (1.2%), control 10 of 79 (12.7%), NNT 8.7.

Evaluation Notes

Analyzing the data from first principles is always important, and may be especially important for COVID-19. Bias in the design, analysis, and reporting of clinical studies has long been reported, and may be increased for COVID-19 due to politicization. For example, Scott Alexander noted that *"if you say anything in favor of ivermectin you will be cast out of civilization and thrown into the circle of social hell reserved for Klan members and 1/6 insurrectionists. All the health officials in the world will shout 'horse dewormer!' at you and compare you to Josef Mengele."*[48] Social pressure to report politically acceptable results was very strong. There may therefore be unusually strong bias in design, analysis, and reporting. For example, Prof. Greenland reports that *Hayward et al.* applied an unjustified and undisclosed extremely tight, null-centered Bayesian prior that biases towards more politically acceptable results[145]. While the politicization focused on certain treatments, it was not limited to them. For example, media coverage was highly biased against positive results for low-cost treatments[146] across the 226 treatments we cover. Studies should be evaluated from first principles, incorporating the treatment delay, treatment regimen, patient population, and other confounding factors. For COVID-19, there is no significant difference in the results of RCTs compared to observational studies, RR 0.97 [0.91-1.03][147]—in both cases bias varies from minimal to extreme, and all studies must be evaluated individually.

US authorities claim only three high-profit drugs from companies with strong US lobbying are beneficial for early treatment (2 repurposed drugs - remdesivir and molnupiravir, and one novel drug - nirmatrelvir)[D]. COVID-19 involves the interplay of many viral and host proteins and factors, providing over 500 therapeutic targets[148]. Given the 12,000+ proposed treatments[43], existing results for many treatments with overlapping secondary complications and therapeutic targets, and the combination of known safety and pharmocokinetics for certain treatments along with strong mechanistic evidence, the probability of only 3 high-profit drugs from top lobbying companies being beneficial is extremely low. This likely reflects a bias toward evaluation of drugs with strong financial resources and efforts devoted to passing the US approval process, and very limited or non-existing evaluation of low-cost treatments. Indeed, official recommendations varied widely between countries[149]. Some countries evaluated limited low-cost treatments early and 25 low-cost treatments were approved in one or more countries[149].

Contrary to claims found online, we analyze both all studies and higher-quality studies (with evaluation focusing on known issues and bias, and the potential impact on outcomes, rather than just the risk of bias), we analyze specific outcomes and pooled outcomes (with extensive analysis and validation of pooled outcomes), and we do not include preclinical studies or retracted studies in meta-analysis. Pooled outcomes can detect efficacy earlier but do not bias towards efficacy—the inclusion of less appropriate designs such as very late treatment may hide efficacy for appopriate use.

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.

b. When administered late in infection, HCQ may enhance viral egress by further increasing lysosomal pH beyond the effect of ORF3a's water channel activity, thereby promoting lysosomal exocytosis, inactivating degradative enzymes, and facilitating the release of SARS-CoV-2 particles into the extracellular environment[132,133]. Research also suggests potential cardioprotective effects at lower doses, but cardiotoxicity with excessive dosage[134]. *Bobrowski et al.* also indicate negative effects if HCQ and remdesivir are combined.

c. *Peters et al.* is subject to confounding by calendar-time (SOC evolved rapidly early in the pandemic, the linear covariate does not reflect non-linear SOC changes and hospital specific effects), hospital type (non-treatment hospitals were tertiary university centers), confounding by indication (4/7 hospitals initiated treatment on deterioration), immortal-time bias for as-treated (exposure assigned after baseline), significant differences for other experimental treatments, potential overadjustment from collider bias (steroid use and indication bias), limited baseline severity information, differences in hospice referral propensity across hospitals, unadjusted difference in time from onset to admission, difference in PCR positivity, and other factors. *Mahévas et al.* is subject to confounding by hospital (treatment highly dependent on the hospital, different SOC/ICU transfer practices, not included in PS), immortal time (only partly addressed in sensitivity analysis), co-treatment differences, calendar-time (SOC evolved rapidly early in the pandemic), binary coding for age (age ≥65 despite steep age-risk gradient), residual imbalance (variables dropped from PS), a composite outcome dependent on hospital triage/capacity, and other factors.

d. Monoclonal antibodies were previously included. Other treatments such as dexamethasone, tocilizumab, and baricitinib were recommended for late stage hospitalized patients.

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