Alkalinization for COVID-19: real-time meta analysis of 11 studies

@CovidAnalysis, March 2024, Version 11
https://c19early.org/phmeta.html

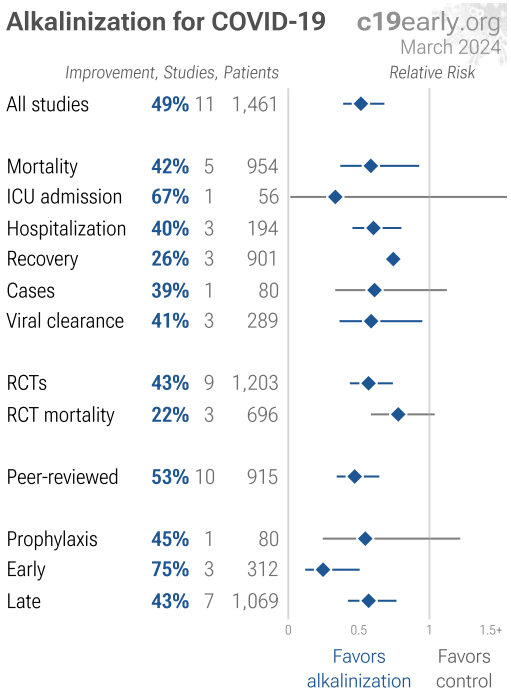
Abstract

Statistically significant lower risk is seen for mortality, hospitalization, progression, recovery, and viral clearance. 9 studies from 8 independent teams in 8 countries show statistically significant improvements.

Meta analysis using the most serious outcome reported shows 49% [32-61%] lower risk. Results are similar for Randomized Controlled Trials and peer-reviewed studies. Early treatment is more effective than late treatment.

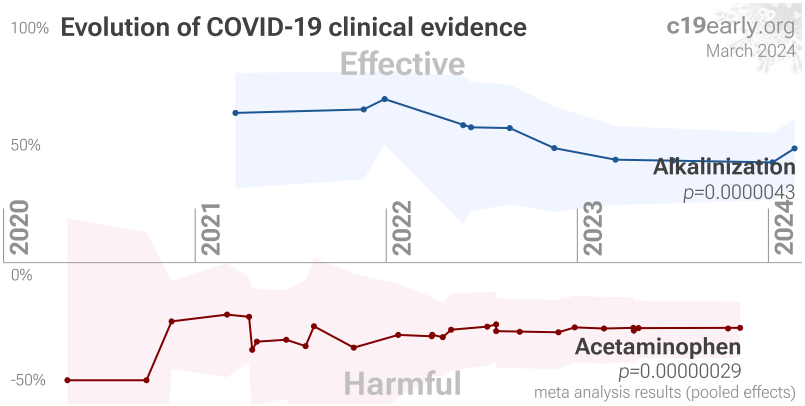
Results are robust — in exclusion sensitivity analysis 9 of 11 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

SARS-CoV-2 requires acidic pH for fusion *Kreutzberger*. Alkalinization of the respiratory mucosa may reduce risk. Treatments investigated to date typically use sodium bicarbonate.



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. Alkalinization may affect the natural microbiome, especially with prolonged use.

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



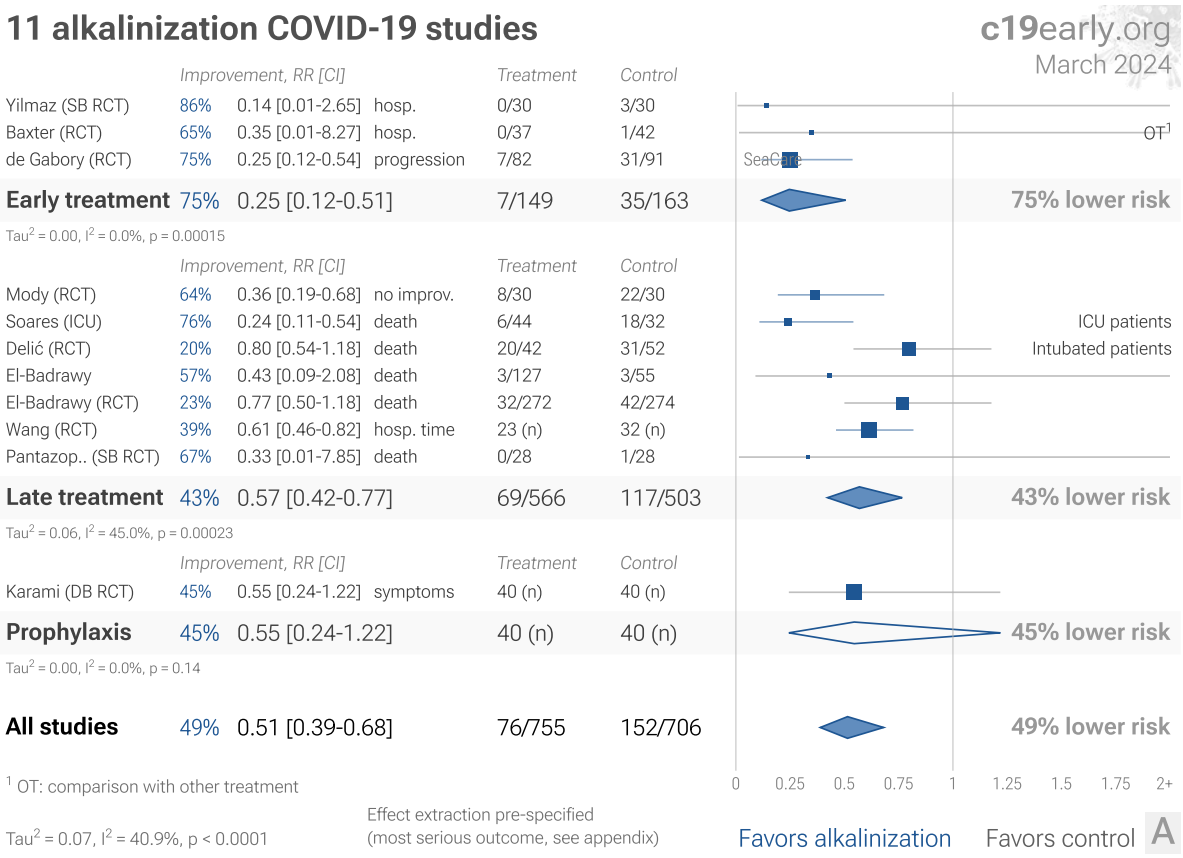
HIGHLIGHTS

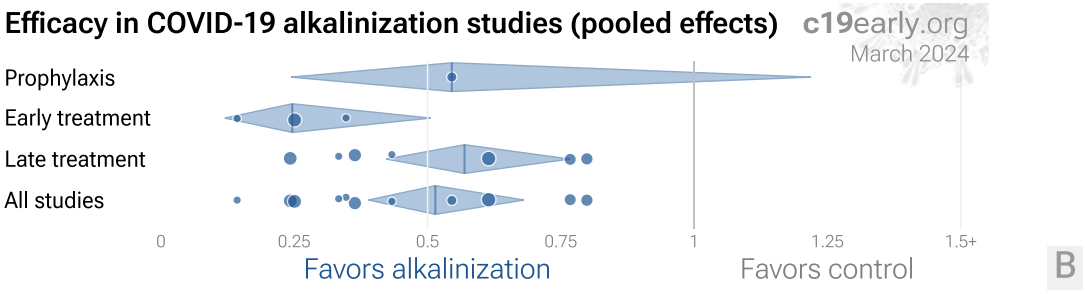
Alkalinization reduces risk for COVID-19 with very high confidence for hospitalization, progression, recovery, and in pooled analysis, high confidence for mortality and viral clearance, and low confidence for cases.

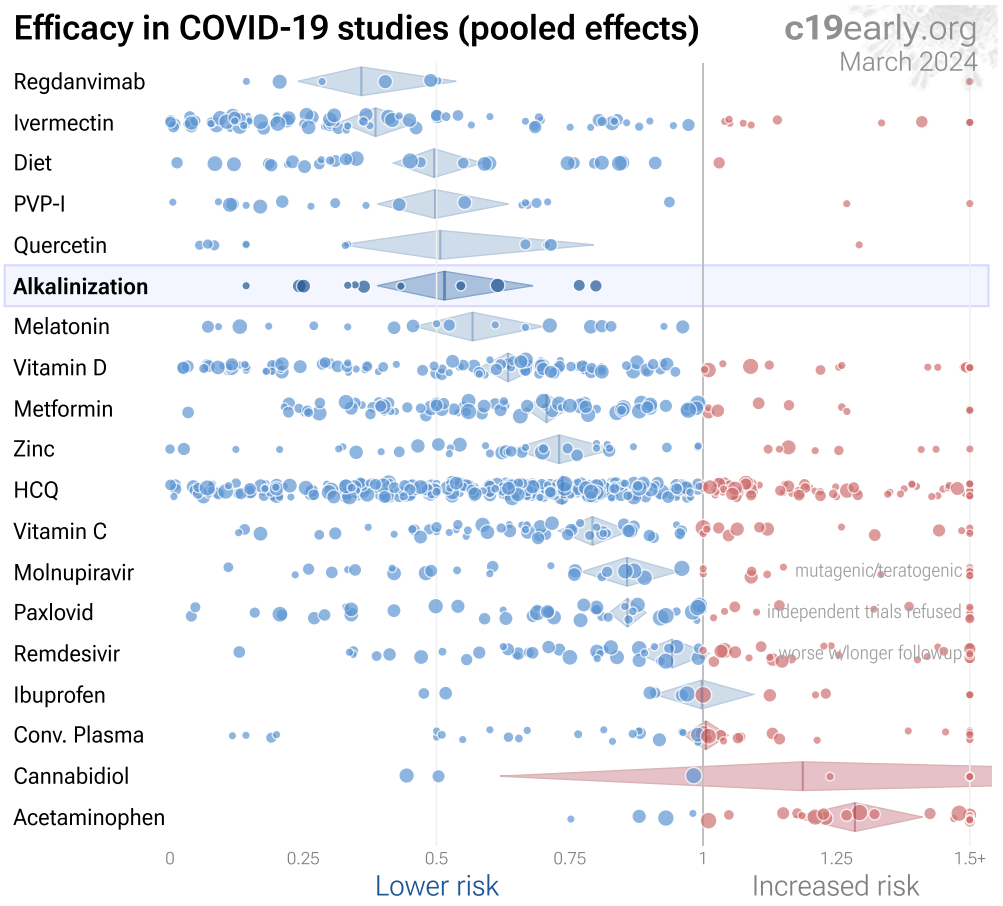
Alkalinization was the 31st treatment shown effective with ≥3 clinical studies in December 2021, now known with p = 0.0000043 from 11 studies.

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.







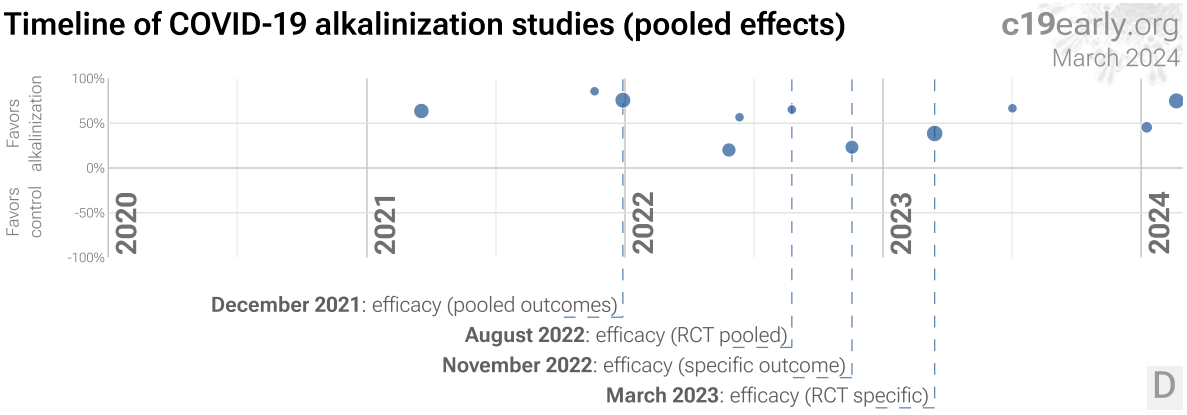


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the 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 alkalinization studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes, one or more specific outcome, pooled outcomes in RCTs, and one or more specific outcome in RCTs. Efficacy based on RCTs only was delayed by 7.9 months, compared to using all studies. Efficacy based on specific outcomes was delayed by 10.6 months, compared to using pooled outcomes. Efficacy based on specific outcomes in RCTs was delayed by 6.6 months, compared to using pooled outcomes in RCTs.

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.

SARS-CoV-2 requires acidic pH for fusion [Kreutzberger]. The mean pH of the airway-facing surface of the nasal cavity was 6.6 in [Kreutzberger], compatible with fusion. pH is neutral in other parts of the nasopharyngeal cavity and in the lung [Effros], suggesting no viral fusion in those locations prior to endocytic uptake. Treatments formulated to increase the pH of respiratory mucosa may inhibit fusion and reduce risk for COVID-19. Studies to date typically use sodium bicarbonate.

Analysis. We analyze all significant controlled studies of alkalinization 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 each treatment stage, individual outcomes, peer-reviewed studies, and Randomized Controlled Trials (RCTs).

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

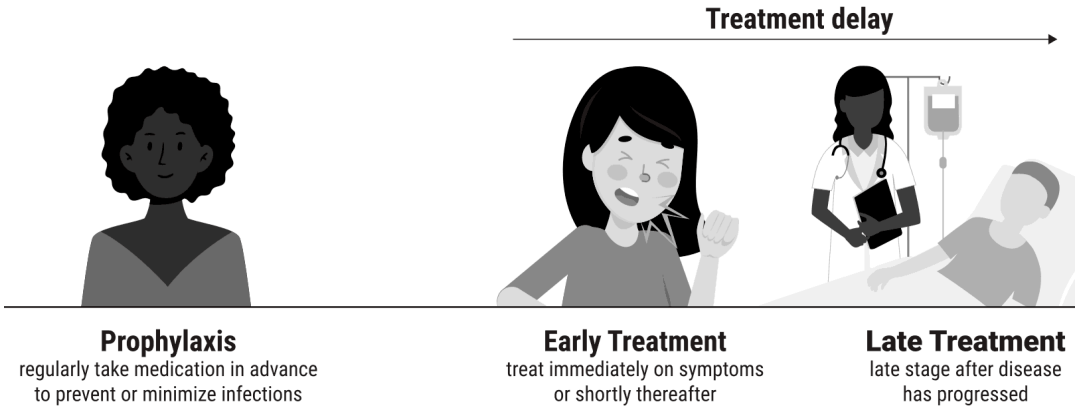


Figure 2. Treatment stages.

Preclinical Research

2 *In Vitro* studies support the efficacy of alkalinization *Jimenez, Kreutzberger (B)*.

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, for Randomized Controlled Trials, for peer-reviewed studies, and for specific outcomes. Table 2 shows results by treatment stage. Figure 3, 4, 5, 6, 7, 8, 9, 10, and 11 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ICU admission, hospitalization, progression, recovery, cases, viral clearance, and peer reviewed studies.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	**49%** [32-61%] ****	11	1,461	92
Peer-reviewed studies	**53%** [35-66%] ****	10	915	85
Randomized Controlled Trials	**43%** [26-56%] ****	9	1,203	68
Mortality	**42%** [7-63%] *	5	954	50
Hospitalization	**40%** [20-55%] ***	3	194	33
Recovery	**26%** [20-31%] ****	3	901	18
Viral	**41%** [5-64%] *	3	289	19
RCT mortality	**22%** [-4-41%]	3	696	26
RCT hospitalization	**40%** [20-55%] ***	3	194	33

Table 1. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, and for specific outcomes.** Results show the percentage improvement with treatment and the 95% confidence interval. * $p<0.05$ *** $p<0.001$ **** $p<0.0001$.

	Early treatment	*Late treatment*	*Prophylaxis*
All studies	**75%** [49-88%] ***	**43%** [23-58%] ***	**45%** [-22-76%]
Peer-reviewed studies	**75%** [49-88%] ***	**48%** [26-64%] ***	**45%** [-22-76%]
Randomized Controlled Trials	**75%** [49-88%] ***	**35%** [18-49%] ***	**45%** [-22-76%]
Mortality		**42%** [7-63%] *	
Hospitalization	**79%** [-84-97%]	**39%** [18-54%] ***	
Recovery	**24%** [4-40%] *	**25%** [18-32%] ****	
Viral	**37%** [-106-81%]	**42%** [2-66%] *	
RCT mortality		**22%** [-4-41%]	
RCT hospitalization	**79%** [-84-97%]	**39%** [18-54%] ***	

Table 2. **Random effects meta-analysis results by treatment stage.** Results show the percentage improvement with treatment, the 95% confidence interval, and the number of studies for the stage. * $p<0.05$ *** $p<0.001$ **** $p<0.0001$.

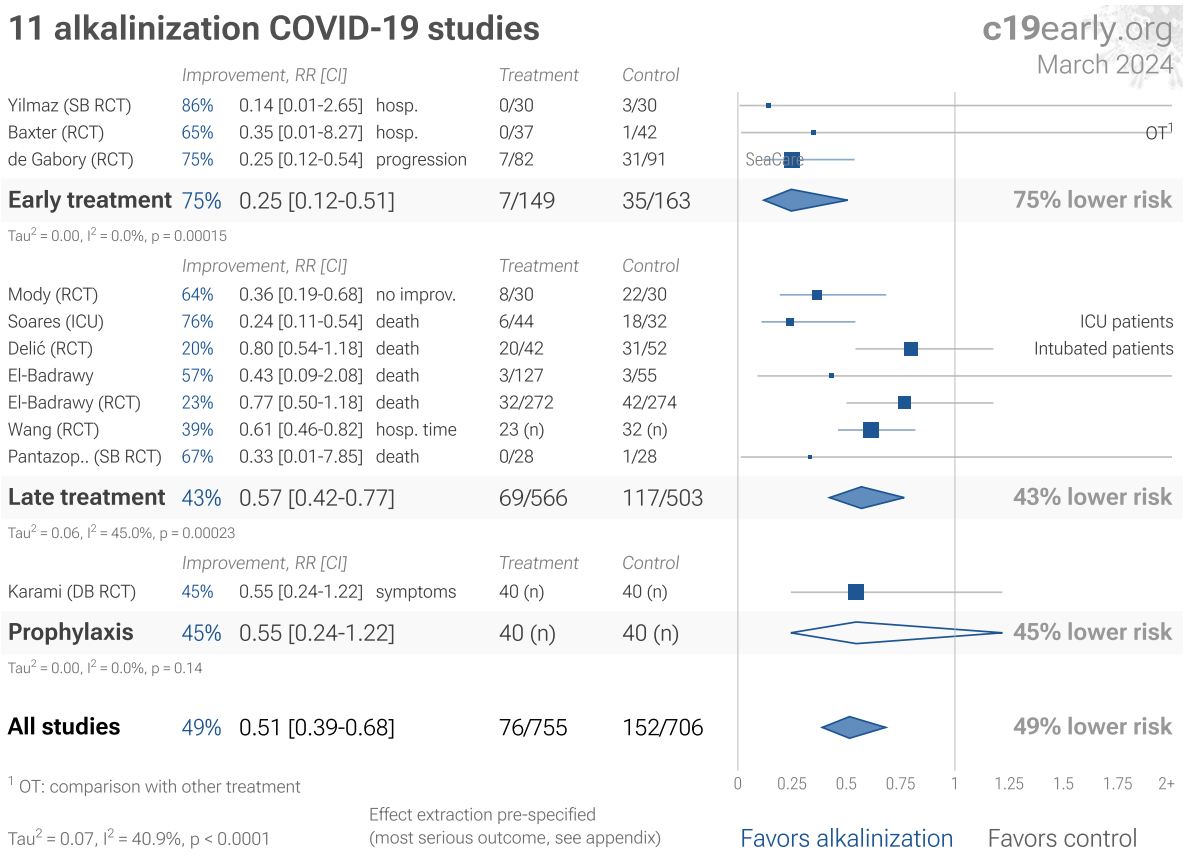


Figure 3. **Random effects meta-analysis for all studies with pooled effects.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details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

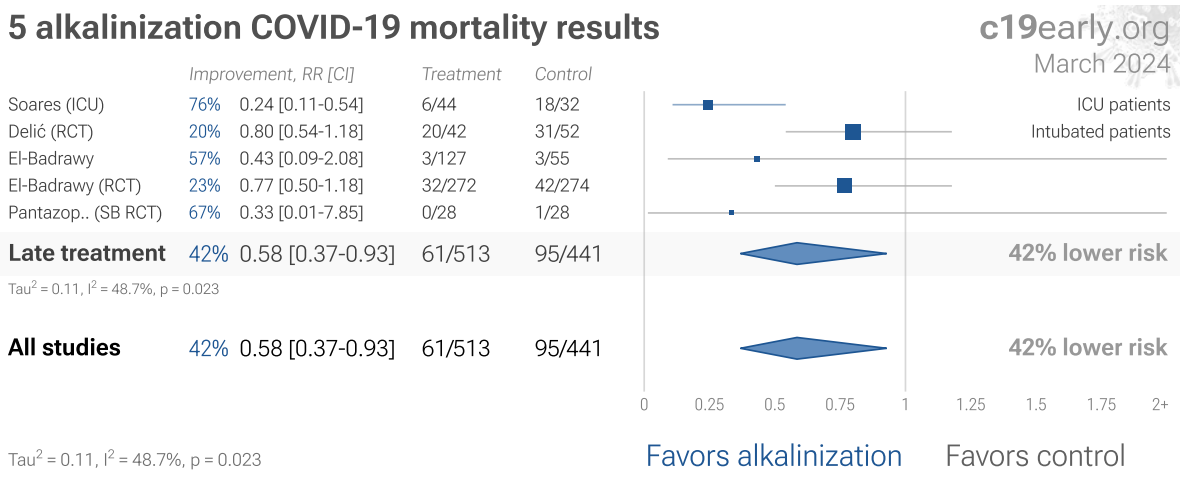


Figure 4. Random effects meta-analysis for mortality results.

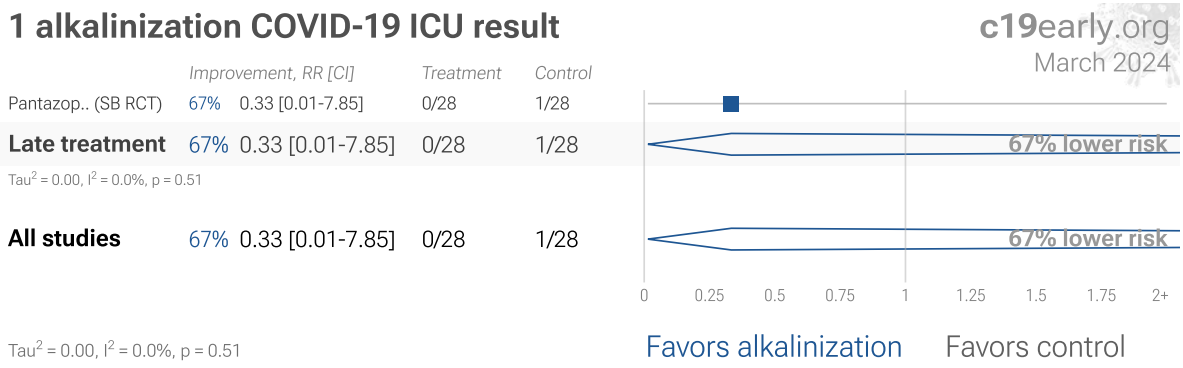


Figure 5. Random effects meta-analysis for ICU admission.

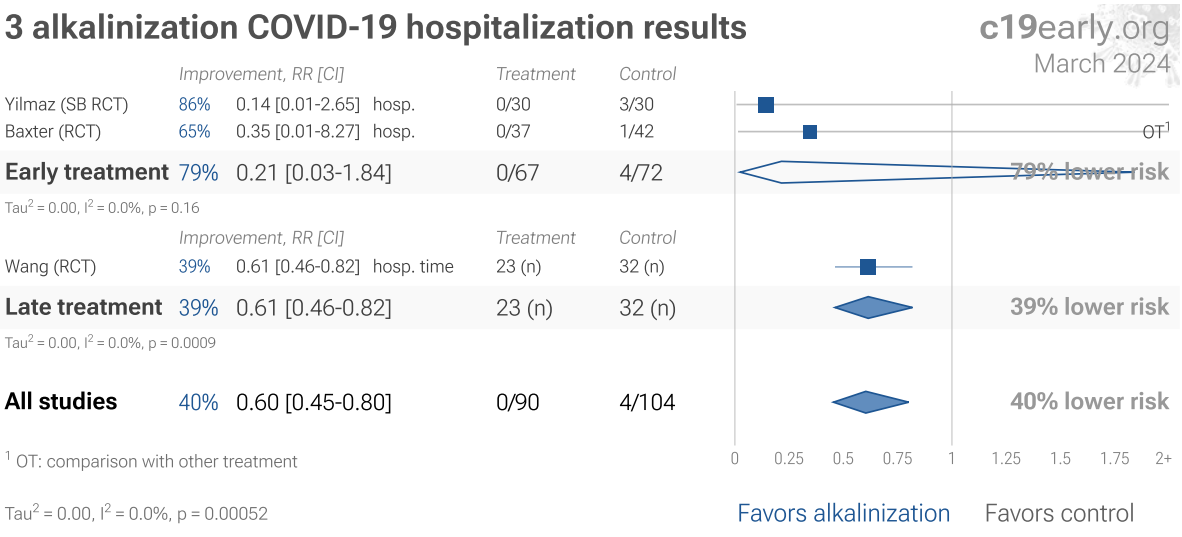


Figure 6. Random effects meta-analysis for hospitalization.

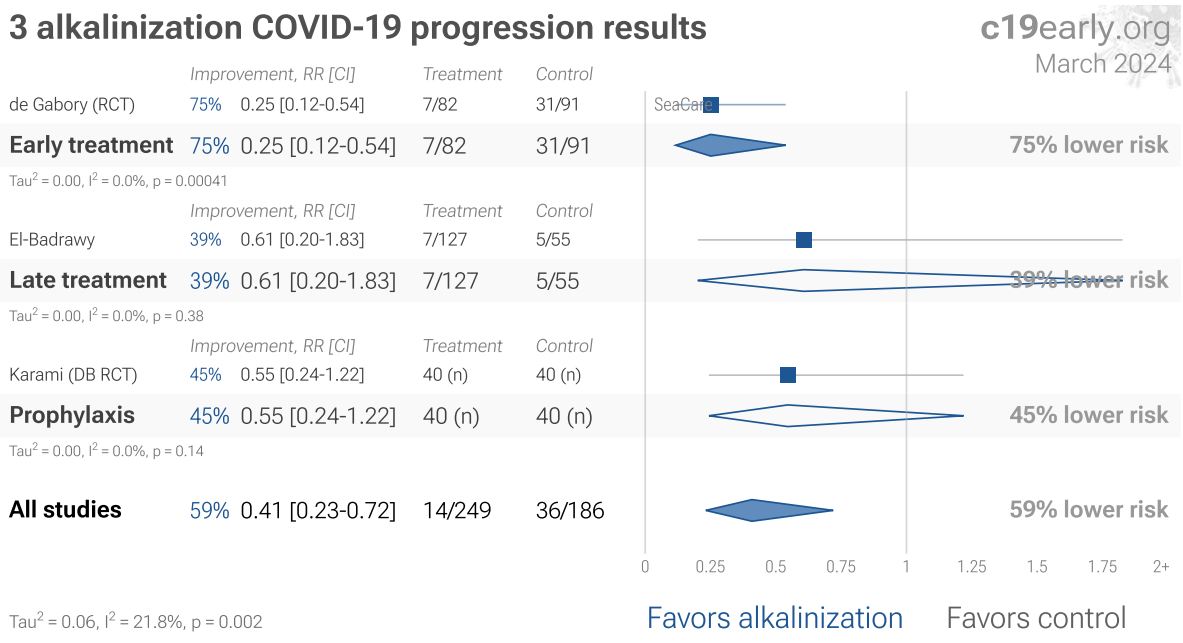


Figure 7. Random effects meta-analysis for progression.

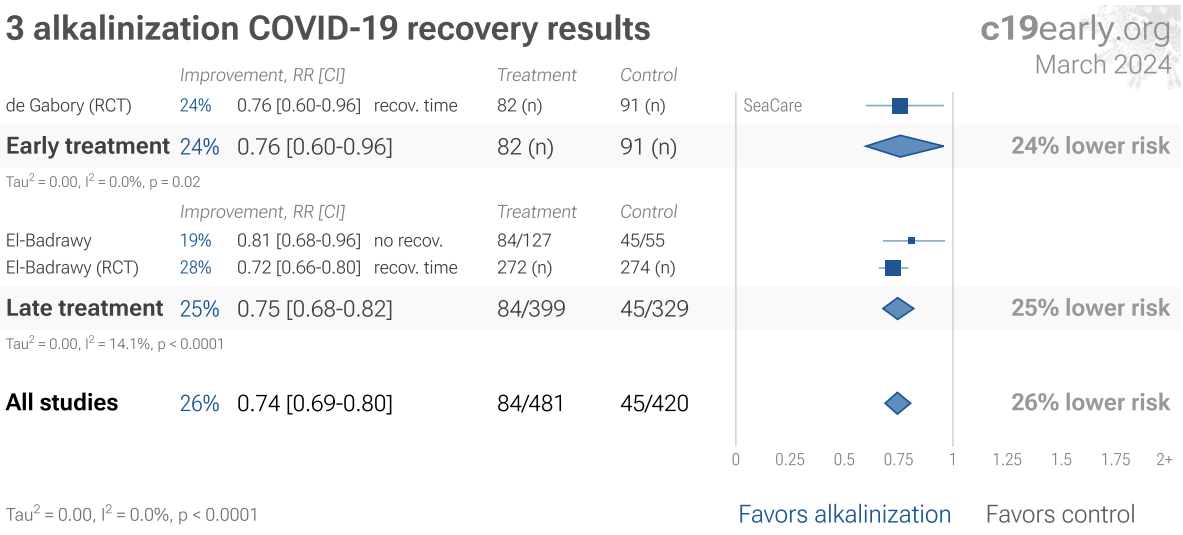


Figure 8. Random effects meta-analysis for recovery.

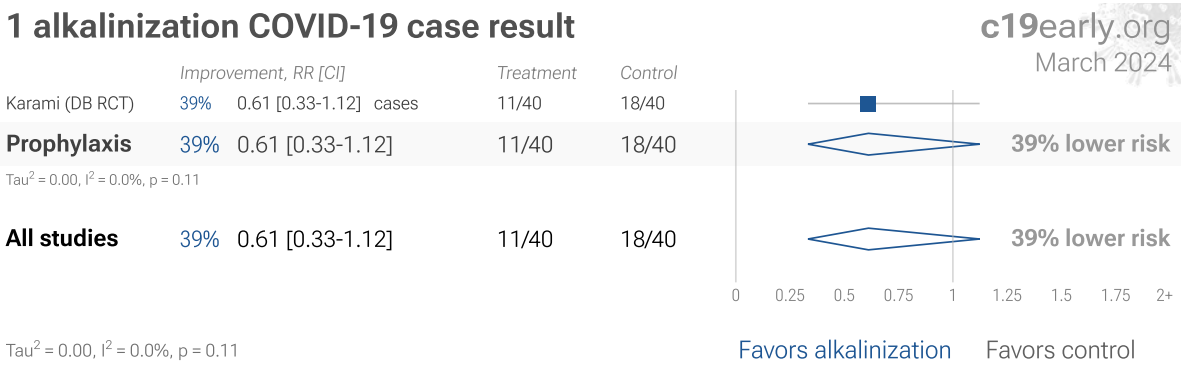


Figure 9. Random effects meta-analysis for cases.

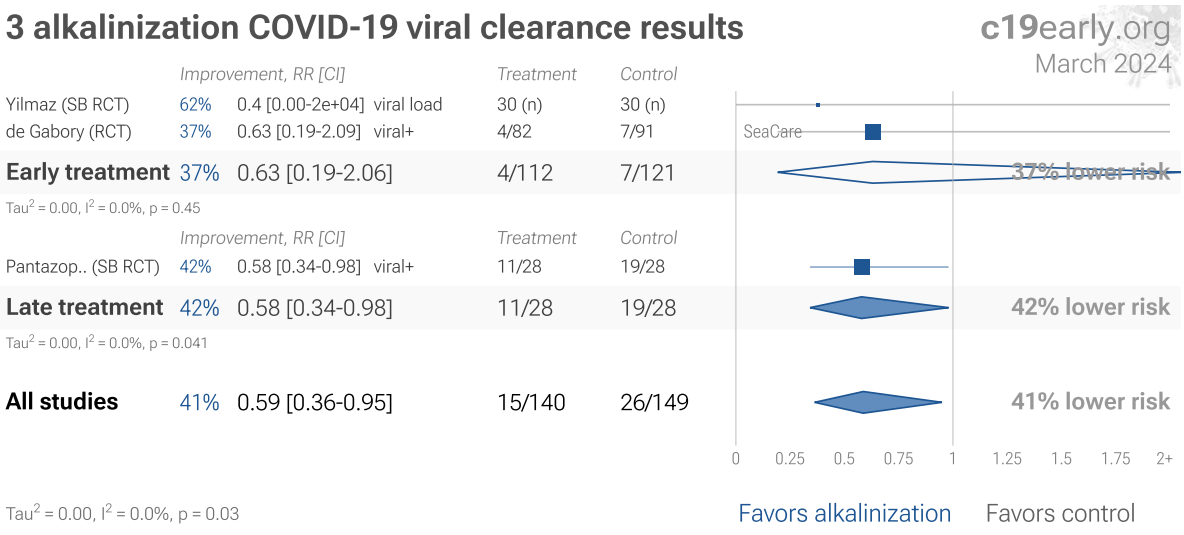


Figure 10. Random effects meta-analysis for viral clearance.

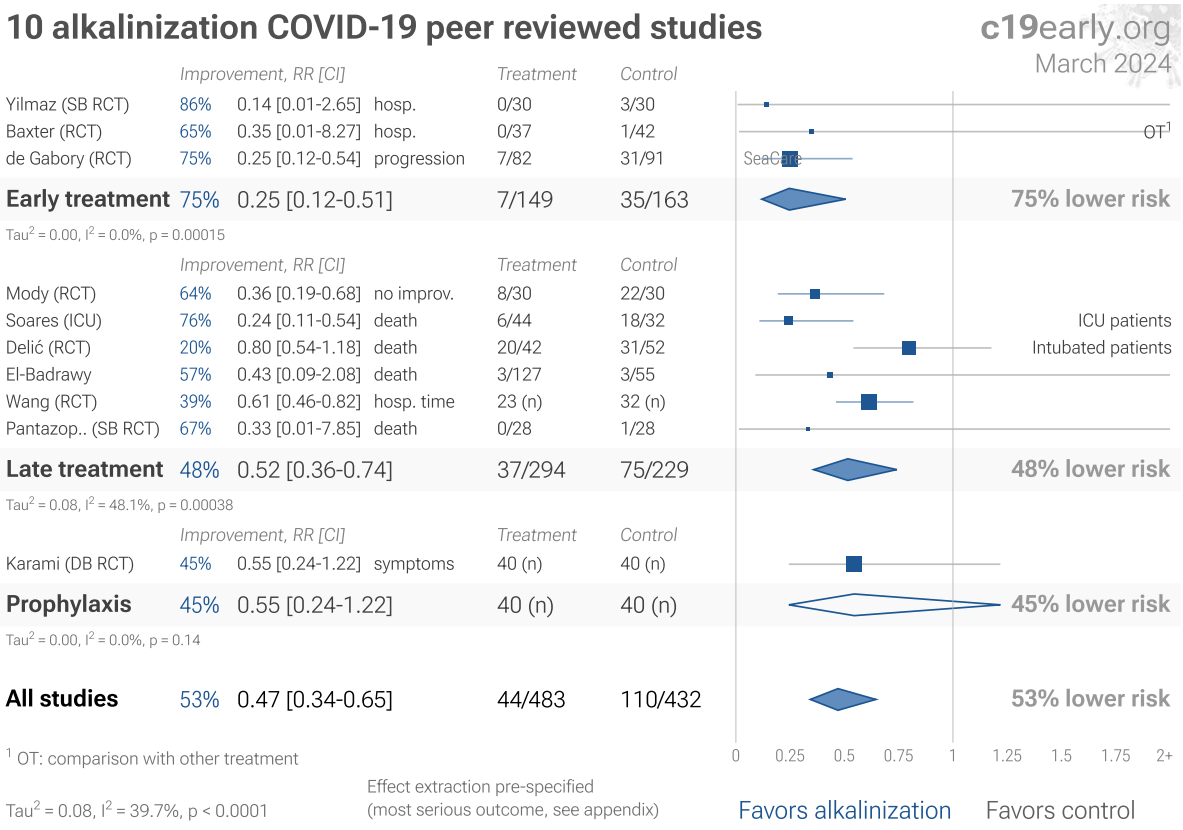


Figure 11. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. *Davidson et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

Randomized Controlled Trials (RCTs)

Figure 12 shows a comparison of results for RCTs and non-RCT studies. Figure 13, 14, and 15 show forest plots for random effects meta-analysis of all Randomized Controlled Trials, RCT mortality results, and RCT hospitalization results. RCT results are included in Table 1 and Table 2.

RCTs have many potential biases. Bias in clinical research may be defined as something that tends to make conclusions differ systematically from the truth. RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases Jadad, and analysis of double-blind RCTs has identified extreme levels of bias Gøtzsche. For COVID-19, the overhead may delay treatment, dramatically compromising efficacy; they may encourage monotherapy for simplicity at the cost of efficacy which may rely on combined or synergistic effects; the participants that sign up may not reflect real world usage or the population that benefits most in terms of age, comorbidities, severity of illness, or other factors; standard of care may be compromised and unable to evolve quickly based on emerging research for new diseases; errors may be made in randomization and medication delivery; and investigators may have hidden agendas or vested interests influencing design, operation, analysis, and the potential for fraud. All of these biases have been observed with COVID-19 RCTs. There is no guarantee that a specific RCT provides a higher level of evidence.

Conflicts of interest for COVID-19 RCTs. RCTs are expensive and many RCTs are funded by pharmaceutical companies or interests closely aligned with pharmaceutical companies. For COVID-19, this creates an incentive to show efficacy for patented commercial products, and an incentive to show a lack of efficacy for inexpensive treatments. The bias is expected to be significant, for example *Als-Nielsen et al.* analyzed 370 RCTs from Cochrane reviews, showing that trials funded by for-profit organizations were 5 times more likely to recommend the experimental drug compared with those funded by nonprofit organizations. For COVID-19, some major philanthropic organizations are largely funded by investments with extreme conflicts of interest for and against specific COVID-19 interventions.

RCTs for novel acute diseases requiring rapid treatment. High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way. Every treatment RCT to date involves delayed treatment. Among the 66 treatments we have analyzed, 63% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments (they may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration).

RCT bias for widely available treatments. RCTs have a bias against finding an effect for interventions that are widely available — patients that believe they need the intervention are more likely to decline participation and take the intervention. RCTs for alkalinization are more likely to enroll low-risk participants that do not need treatment to recover, making the results less applicable to clinical practice. This bias is likely to be greater for widely known treatments, and may be greater when the risk of a serious outcome is overstated. This bias does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable.

Non-RCT studies have been shown to be reliable. Evidence shows that non-RCT trials can also provide reliable results. *Concato et al.* found that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. *Anglemyer et al.* summarized reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. *Lee et al.* showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or Internet survey bias could have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see Deaton, Nichol.

Using all studies identifies efficacy 5.7+ months faster for COVID-19. 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. Of the 44 treatments with statistically significant efficacy/harm, 28 have been confirmed in RCTs, with a mean delay of 5.7 months. When considering only low cost treatments, 23 have been confirmed with a delay of 6.9 months. For the 16 unconfirmed treatments, 3 have zero RCTs to date. The point estimates for the remaining 13 are all consistent with the overall results (benefit or harm), with 10 showing >20%. The only treatments showing >10% efficacy for all studies, but <10% for RCTs are sotrovimab and aspirin.

Summary. We need to evaluate each trial on its own merits. RCTs for a given medication and disease may be more reliable, however they may also be less reliable. For off-patent medications, very high conflict of interest trials may be more likely to be RCTs, and more likely to be large trials that dominate meta analyses.

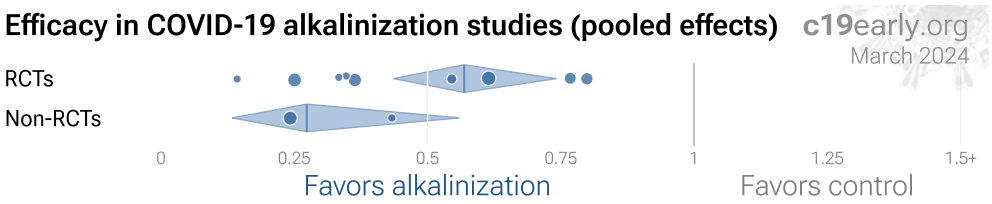


Figure 12. **Results for RCTs and non-RCT studies.**

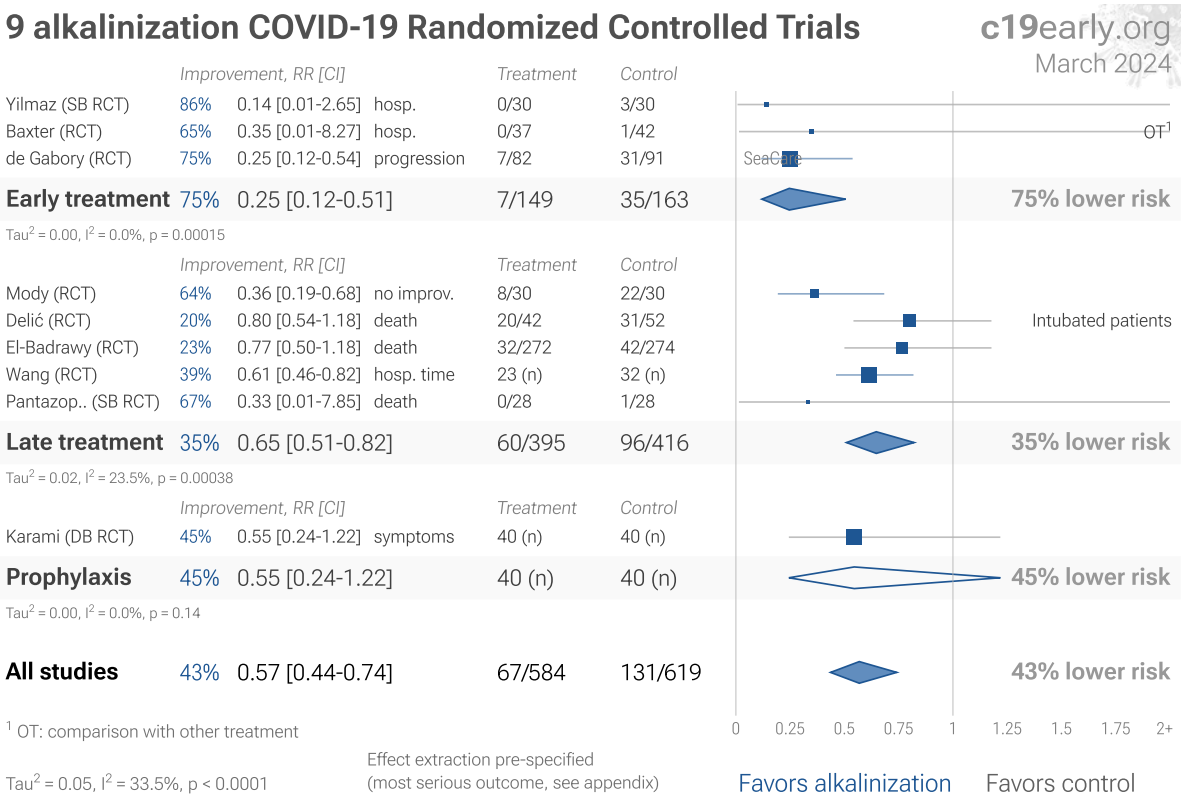


Figure 13. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

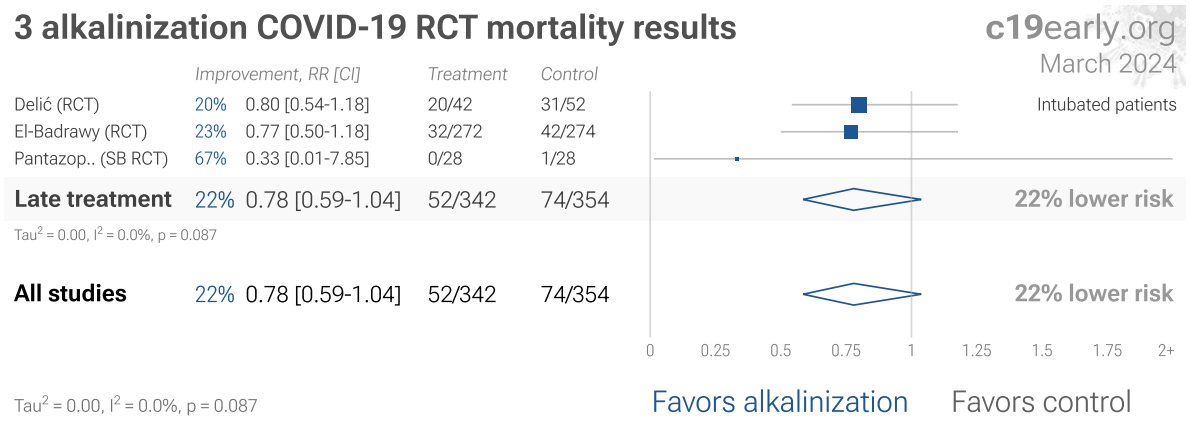


Figure 14. Random effects meta-analysis for RCT mortality results.

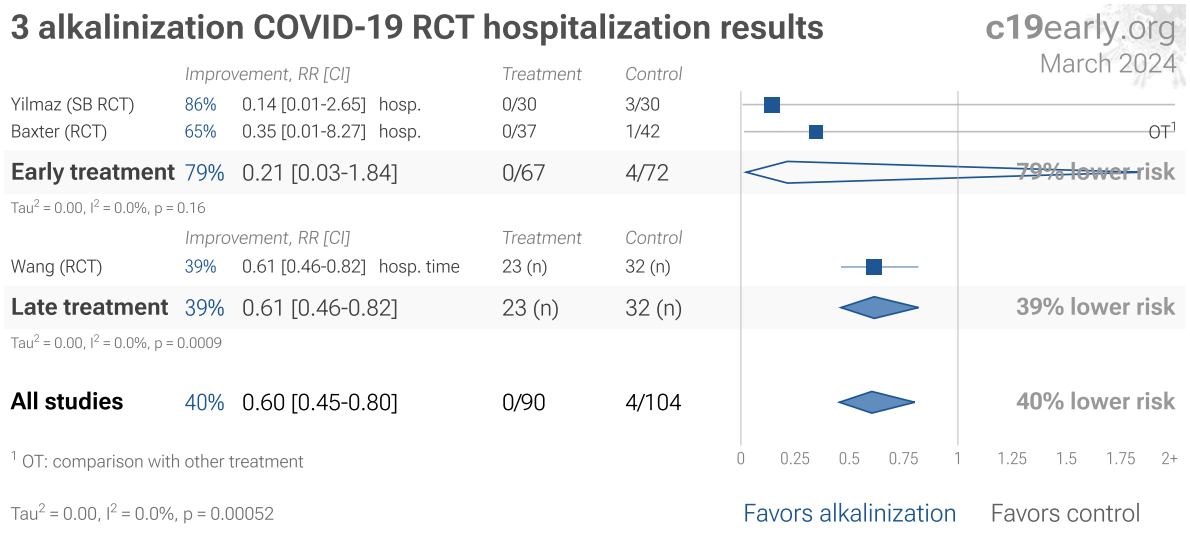


Figure 15. Random effects meta-analysis for RCT hospitalization results.

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

Figure 16 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.

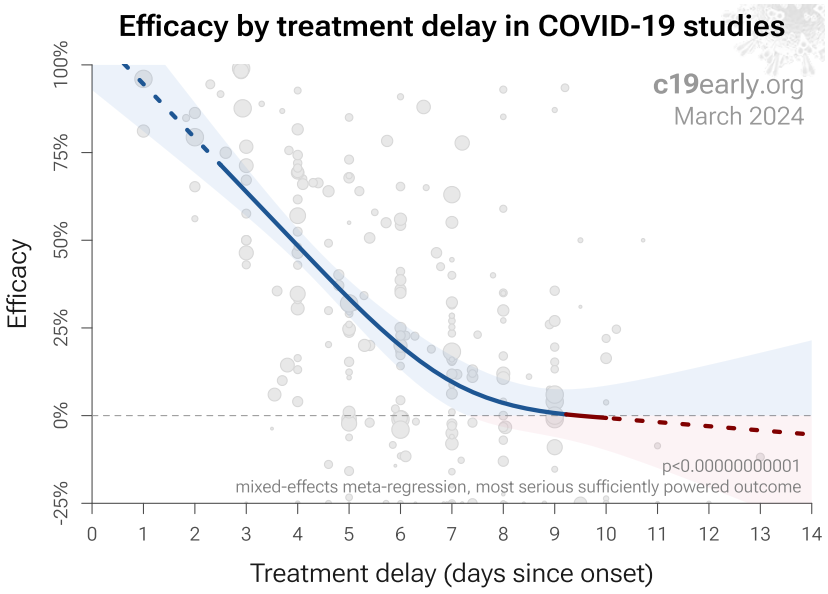


Figure 16. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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 17. 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.

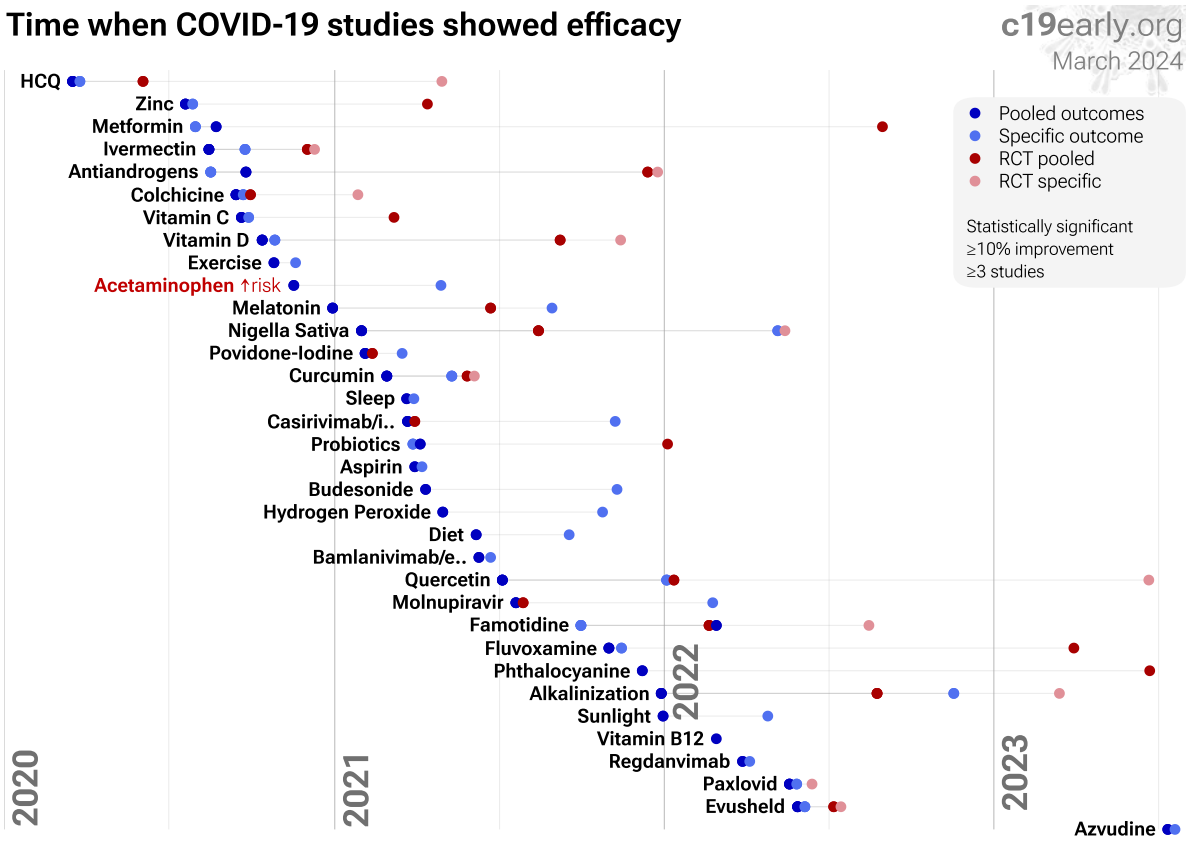


Figure 17. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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

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 *Alemany, Tarragó-Gil* 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 or antigen detection that can differentiate intact vs. degraded virus are preferred.

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 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.

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 4. **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 5 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 5. **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 alkalinization, there is currently not enough data to evaluate publication bias with high confidence.

Late treatment bias. Studies for alkalinization were primarily late treatment studies, in contrast with typical patented treatments that were tested with early treatment as recommended.

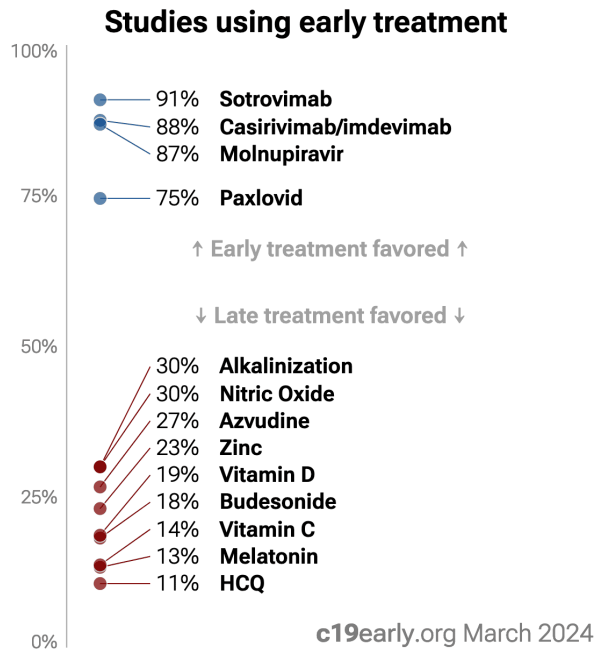


Figure 18. **Patented treatments received mostly early treatment studies, while low cost treatments were typically tested for late treatment.**

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 19 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.

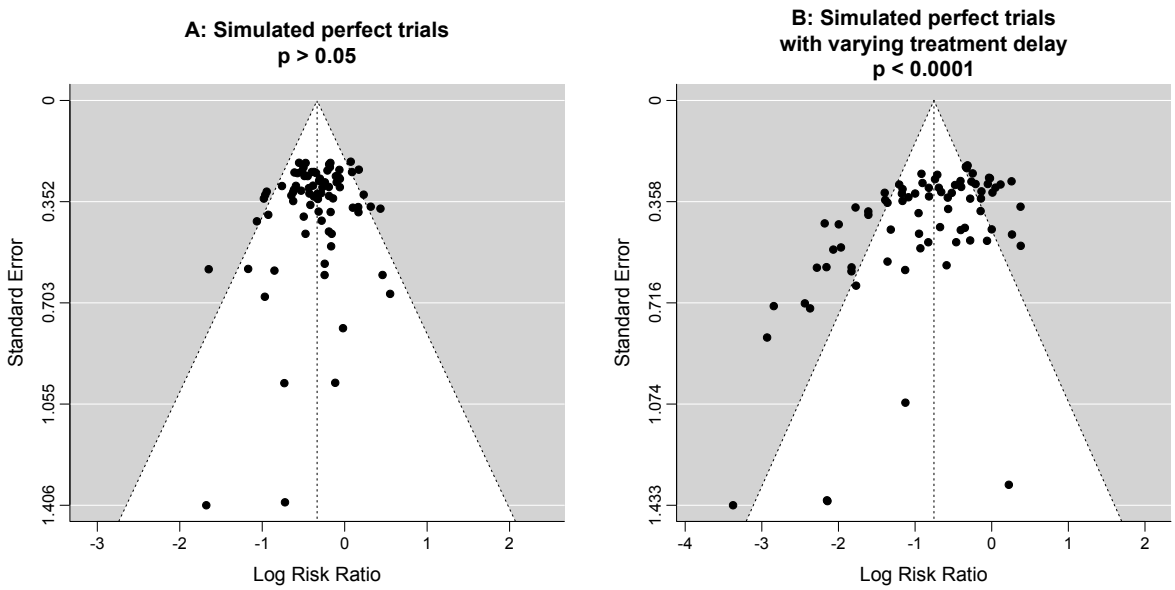


Figure 19. Example funnel plot analysis for simulated perfect trials.

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. Alkalinization for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 alkalinization 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 alkalinization 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 the 11 studies compare against other treatments, which may reduce the effect seen.

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.

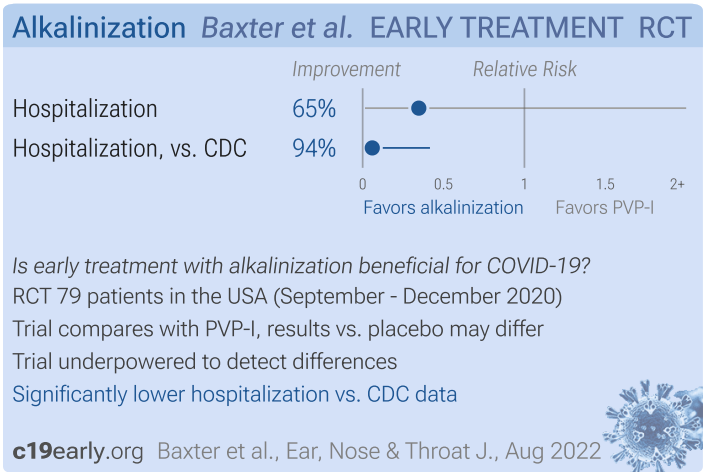
Studies to date show that alkalinization is an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality, hospitalization, progression, recovery, and viral clearance. 9 studies from 8 independent teams in 8 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 49% [32-61%] lower risk. Results are similar for Randomized Controlled Trials and peer-reviewed studies. Early treatment is more effective than late treatment. Results are robust — in exclusion sensitivity analysis 9 of 11 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

SARS-CoV-2 requires acidic pH for fusion *Kreutzberger*. Alkalinization of the respiratory mucosa may reduce risk. Treatments investigated to date typically use sodium bicarbonate.

Alkalinization may affect the natural microbiome, especially with prolonged use.

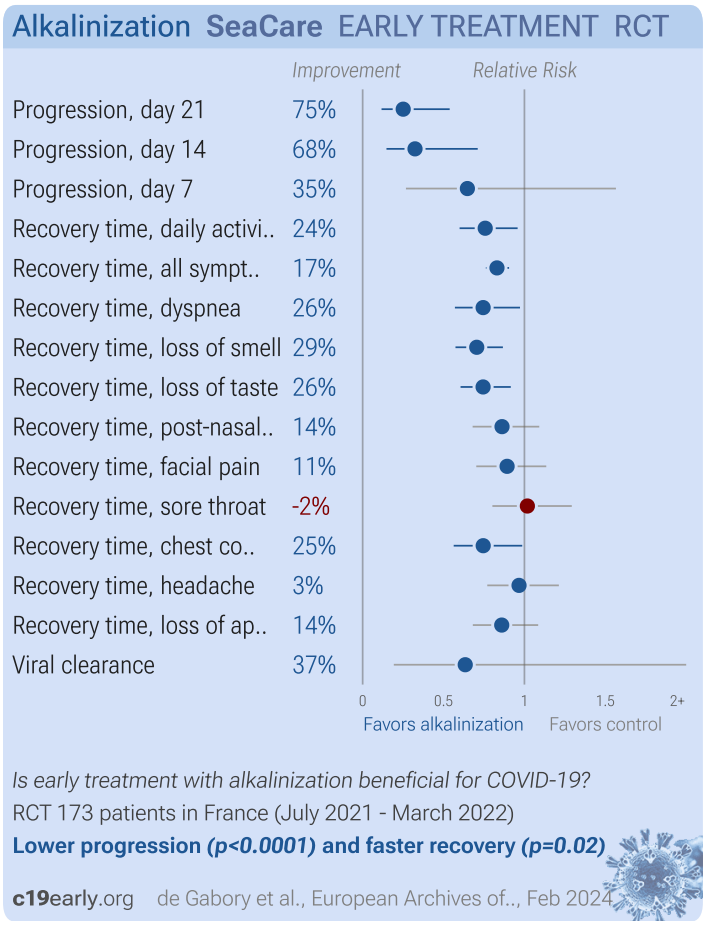
Study Notes

Baxter



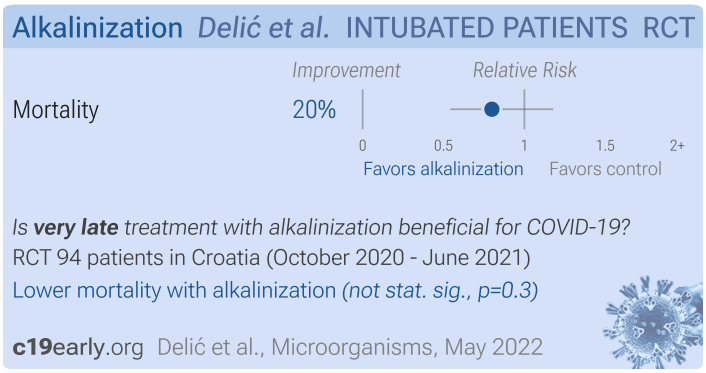
Baxter: Small RCT 79 PCR+ patients 55+ comparing pressure-based nasal irrigation with povidone-iodine and sodium bicarbonate, showing significantly lower hospitalization when compared with CDC data.

de Gabory



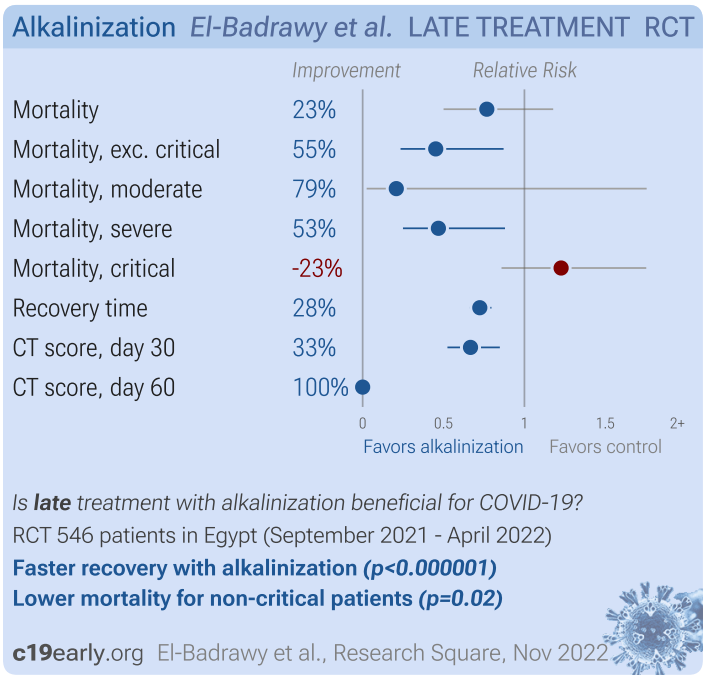
de Gabory: RCT 355 adults with COVID-19 or other upper respiratory tract infections (URTIs). For COVID-19 patients there was lower progression and faster symptom resolution with alkaline seawater nasal wash (pH ~8) 4 times daily for 21 days. There was significantly lower transmission for patients with the delta variant and for patients with high viral load. The seawater nasal wash was safe and well-tolerated.

Delić



Delić: RCT mechanically ventilated patients in Croatia, 42 treated with sodium bicarbonate inhalation, and 52 control patients, showing no significant difference in mortality with treatment. Treated patients showed a lower incidence of gram-positive or MRSA-caused ventilator-associated pneumonia.

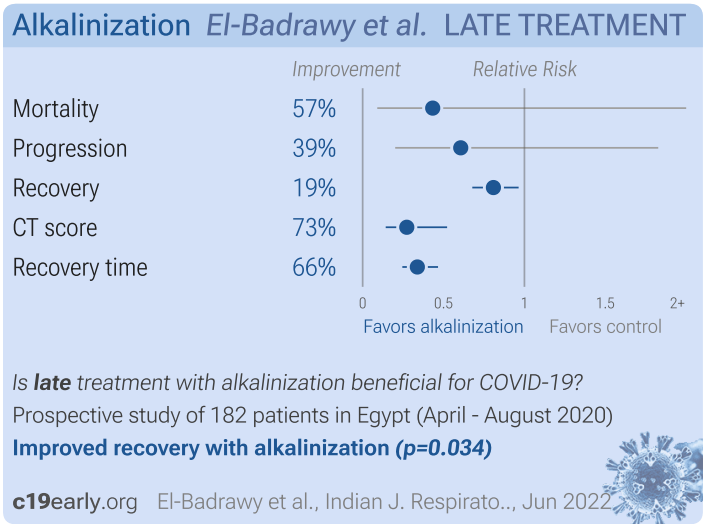
El-Badrawy



El-Badrawy: RCT 546 patients showing significantly faster recovery and lower mortality with sodium bicarbonate (inhaled and nasal drops). The reduction in mortality is only statistically significant when excluding baseline critical cases.

Inhalation of nebulized sodium bicarbonate 8.4% (5ml every 4h) 7:00am to 23:00pm every day for 30 days together with 8.4% nasal drops 4 times daily (three drops for each nostril).

El-Badrawy

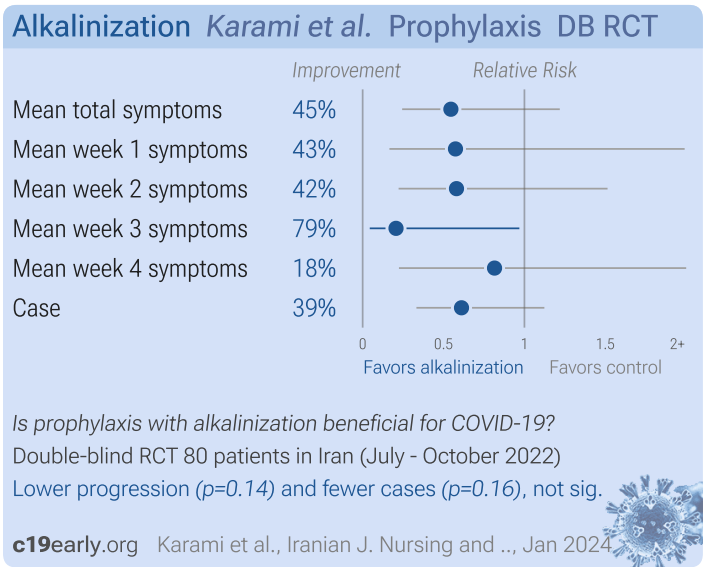


El-Badrawy (B): Prospective study of 182 COVID-19 pneumonia patients, 127 treated with sodium bicarbonate inhalation and nasal drops, showing significantly faster recovery and improved CT scores with treatment.

Authors note that contacts of index cases also received sodium bicarbonate treatment, with none reporting COVID-19.

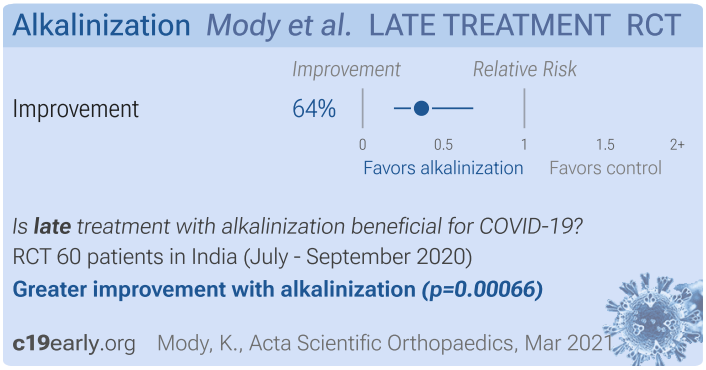
Inhalation of nebulized sodium bicarbonate 8.4% (5ml every 4h) 7:00am to 23:00pm every day for 30 days together with 8.4% nasal drops 4 times daily (three drops for each nostril).

Karami



Karami: RCT 116 healthcare workers comparing 0.2% chlorhexidine mouthwash (n=36), 7.5% sodium bicarbonate mouthwash (n=40), and placebo (n=40) twice daily for 2 weeks, with symptoms followed for 4 weeks. There were lower symtoms and cases in both treatment groups, with statistical significance for chlorhexidine only. The treatments were stopped after two weeks, results may be better with continued use, more frequent use, and with the addition of nasal use.

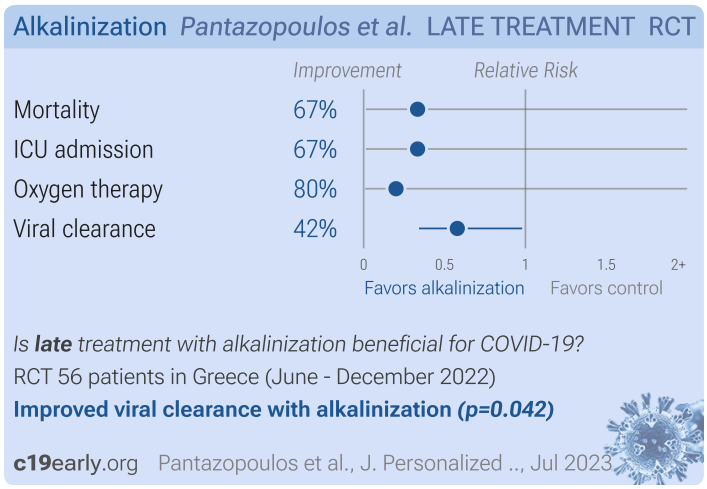
Mody



Mody: RCT 60 hospitalized patients in India, showing significantly greater clinical improvement with inhaled sodium bicarbonate.

Nasal and oral inhalation of nebulized 50ml 8.4% sodium bicarbonate for 5 minutes twice daily for 5 days.

Pantazopoulos

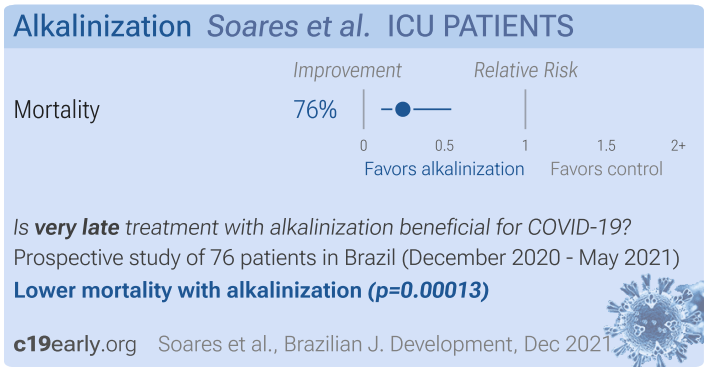


Pantazopoulos: RCT 56 severe COVID-19 patients, showing significantly decreased viral load with Sinomarin Plus Algae nasal irrigation. Sinomarin Plus Algae is a hypertonic seawater solution with algal and herbal natural ingredients with a pH of 7.5-8 *sinomarin.com*.

The treatment group received nasal irrigation every 4 hours, 16 hours per day, for 2 days. Nasopharyngeal swabs were taken at baseline and 48 hours later to measure viral load. The treatment group showed a significant increase in cycle threshold values, indicating decreased viral load, while no difference was seen in the control group. The treatment was well tolerated with only mild adverse effects.

Alkalinization is one possible mechanism of action - SARS-CoV-2 requires acidic pH for infection *Kreutzberger* and the solution has pH 7.5-8. Other possible mechanisms include antiviral activity of ingredients (e.g., fucoidan from Undaria pinnatifida) and physical removal of viral particles.

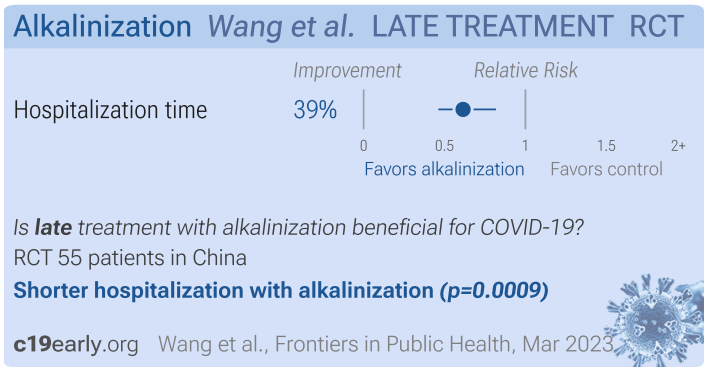
Soares



Soares: Analysis of 76 ICU patients in Brazil, 44 treated with bronchoalveolar lavage using 3% sodium bicarbonate, showing significantly lower mortality with treatment.

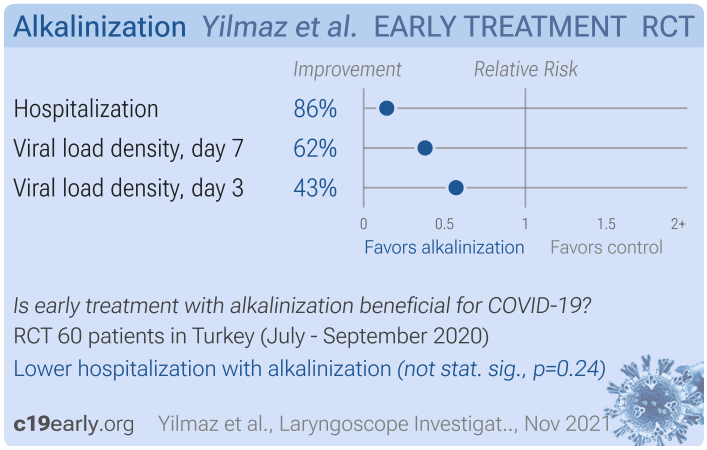
Bronchoalveolar lavage with 10ml of sodium bicarbonate solution directly into the tube (closed circuit), 500µl for each lung segment, followed by aspiration of the solution, performed every 6 hours for 7 days.

Wang



Wang: RCT 55 mild/moderate patients in China, showing shorter hospitalization with sodium bicarbonate nasal irrigation and oral rinsing. Oral rinse with 5% sodium bicarbonate solution three times daily. Nasal irrigation two times with the solution entering through one nostril and exiting from the other. 30–40mL of solution was used every time and irrigation was performed for at least 30s. Details of randomization are not provided.

Yilmaz



Yilmaz: RCT 60 outpatients with mild COVID-19 showing improved viral clearance with hypertonic alkaline (pH 9.3) nasal irrigation. All patients received HCQ. The nasal irrigation group had no hospitalizations, while 3 patients in the control group required hospitalization, associated with viral load increase at day 3.

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 alkalinization 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 alkalinization 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*.

We received no funding, this research is done in our spare time. We have no affiliations with any pharmaceutical companies or political parties.

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

Baxter, 8/25/2022, Randomized Controlled Trial, USA, peer-reviewed, 12 authors, study period 24 September, 2020 - 21 December, 2020, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04559035 (history).	risk of hospitalization, 65.3% lower, RR 0.35, $p = 1.00$, treatment 0 of 37 (0.0%), control 1 of 42 (2.4%), NNT 42, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), vs. PVP-I.
de Gabory, 2/20/2024, Randomized Controlled Trial, France, peer-reviewed, 4 authors, study period July 2021 - March 2022, trial NCT04916639 (history)	risk of progression, 74.9% lower, RR 0.25, $p < 0.001$, treatment 7 of 82 (8.5%), control 31 of 91 (34.1%), NNT 3.9, day 21.

(SeaCare).	risk of progression, 67.6% lower, RR 0.32, *p* = 0.003, treatment 7 of 82 (8.5%), control 24 of 91 (26.4%), NNT 5.6, day 14.
	risk of progression, 35.3% lower, RR 0.65, *p* = 0.47, treatment 7 of 82 (8.5%), control 12 of 91 (13.2%), NNT 22, day 7.
	recovery time, 24.2% lower, relative time 0.76, *p* = 0.02, treatment mean 5.0 (±4.1) n=82, control mean 6.6 (±4.8) n=91, time to resume daily activities.
	recovery time, 17.0% lower, relative time 0.83, *p* < 0.001, treatment 82, control 91, all symptoms combined.
	recovery time, 25.5% lower, relative time 0.74, *p* = 0.03, treatment mean 3.5 (±2.8) n=82, control mean 4.7 (±4.2) n=91, dyspnea.
	recovery time, 29.5% lower, relative time 0.71, *p* < 0.001, treatment mean 6.7 (±5.2) n=82, control mean 9.5 (±5.7) n=91, loss of smell.
	recovery time, 25.6% lower, relative time 0.74, *p* = 0.005, treatment mean 6.7 (±5.6) n=82, control mean 9.0 (±5.1) n=91, loss of taste.
	recovery time, 13.8% lower, relative time 0.86, *p* = 0.22, treatment mean 5.6 (±5.0) n=82, control mean 6.5 (±4.6) n=91, post-nasal drip.
	recovery time, 10.7% lower, relative time 0.89, *p* = 0.36, treatment mean 5.0 (±4.7) n=82, control mean 5.6 (±3.9) n=91, facial pain.
	recovery time, 1.8% higher, relative time 1.02, *p* = 0.89, treatment mean 5.6 (±5.0) n=82, control mean 5.5 (±4.6) n=91, sore throat.
	recovery time, 25.5% lower, relative time 0.75, *p* = 0.04, treatment mean 3.8 (±3.5) n=82, control mean 5.1 (±4.6) n=91, chest congestion.
	recovery time, 3.3% lower, relative time 0.97, *p* = 0.78, treatment mean 5.8 (±5.0) n=82, control mean 6.0 (±4.5) n=91, headache.
	recovery time, 14.0% lower, relative time 0.86, *p* = 0.20, treatment mean 4.9 (±3.8) n=82, control mean 5.7 (±4.4) n=91, loss of appetite.
	risk of no viral clearance, 36.6% lower, RR 0.63, *p* = 0.54, treatment 4 of 82 (4.9%), control 7 of 91 (7.7%), NNT 36, day 21.
Yilmaz, 11/19/2021, Single Blind Randomized Controlled Trial, Turkey, peer-reviewed, 8 authors, study period July 2020 - September 2020.	risk of hospitalization, 85.7% lower, RR 0.14, *p* = 0.24, treatment 0 of 30 (0.0%), control 3 of 30 (10.0%), NNT 10.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).

	relative viral load density, 62.0% better, RR 0.38, *p* = 0.87, treatment median 15.0 IQR 43.0 n=30, control median 39.51 IQR 1085.1 n=30, day 7.
	relative viral load density, 42.9% better, RR 0.57, *p* = 0.95, treatment median 1747.0 IQR 5863.5 n=30, control median 3058.0 IQR 145568.9 n=30, day 3.

Late 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.

Delić, 5/28/2022, Randomized Controlled Trial, Croatia, peer-reviewed, 12 authors, study period October 2020 - June 2021, trial NCT04755972 (history).	risk of death, 20.1% lower, RR 0.80, *p* = 0.30, treatment 20 of 42 (47.6%), control 31 of 52 (59.6%), NNT 8.3.
El-Badrawy, 11/18/2022, Randomized Controlled Trial, Egypt, preprint, 7 authors, study period 1 September, 2021 - 30 April, 2022, trial NCT05035524 (history).	risk of death, 23.2% lower, RR 0.77, *p* = 0.26, treatment 32 of 272 (11.8%), control 42 of 274 (15.3%), NNT 28, all cases.
	risk of death, 54.8% lower, RR 0.45, *p* = 0.02, treatment 12 of 247 (4.9%), control 27 of 251 (10.8%), NNT 17, mild/moderate/severe cases.
	risk of death, 79.2% lower, RR 0.21, *p* = 0.21, treatment 1 of 125 (0.8%), control 5 of 130 (3.8%), NNT 33, moderate cases.
	risk of death, 53.2% lower, RR 0.47, *p* = 0.02, treatment 11 of 63 (17.5%), control 22 of 59 (37.3%), NNT 5.0, severe cases.
	risk of death, 22.7% higher, RR 1.23, *p* = 0.33, treatment 20 of 25 (80.0%), control 15 of 23 (65.2%), critical cases.
	recovery time, 27.6% lower, relative time 0.72, *p* < 0.001, treatment mean 4.2 (±2.5) n=272, control mean 5.8 (±3.1) n=274, time to clinical improvement.
	CT score, 33.3% lower, RR 0.67, *p* = 0.001, treatment 238, control 229, CT score, day 30.
El-Badrawy (B), 6/12/2022, prospective, Egypt, peer-reviewed, 7 authors, study period 15 April, 2020 - 31 August, 2020, trial NCT04374591 (history).	risk of death, 56.7% lower, RR 0.43, *p* = 0.37, treatment 3 of 127 (2.4%), control 3 of 55 (5.5%), NNT 32.
	risk of progression, 39.4% lower, RR 0.61, *p* = 0.52, treatment 7 of 127 (5.5%), control 5 of 55 (9.1%), NNT 28, deterioration or death, day 30.
	risk of no recovery, 19.2% lower, RR 0.81, *p* = 0.03, treatment 84 of 127 (66.1%), control 45 of 55 (81.8%), NNT 6.4, day 30.
	relative CT score, 72.7% better, RR 0.27, *p* < 0.001, treatment 127, control 55, day 30.

	recovery time, 66.2% lower, relative time 0.34, $p < 0.001$, treatment mean 3.31 (±0.99) n=127, control mean 9.79 (±6.288) n=55, time to clinical improvement.
Mody, 3/19/2021, Randomized Controlled Trial, India, peer-reviewed, 1 author, study period July 2020 - September 2020, trial CTRI/2020/07/026535.	risk of no improvement, 63.6% lower, RR 0.36, $p < 0.001$, treatment 8 of 30 (26.7%), control 22 of 30 (73.3%), NNT 2.1.
Pantazopoulos, 7/3/2023, Single Blind Randomized Controlled Trial, Greece, peer-reviewed, mean age 63.6, 7 authors, study period June 2022 - December 2022, trial NCT05729204 (history).	risk of death, 66.7% lower, RR 0.33, $p = 1.00$, treatment 0 of 28 (0.0%), control 1 of 28 (3.6%), NNT 28, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of ICU admission, 66.7% lower, RR 0.33, $p = 1.00$, treatment 0 of 28 (0.0%), control 1 of 28 (3.6%), NNT 28, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of oxygen therapy, 80.0% lower, RR 0.20, $p = 0.49$, treatment 0 of 28 (0.0%), control 2 of 28 (7.1%), NNT 14, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), high flow nasal cannula or non-invasive ventilation.
	risk of no viral clearance, 42.1% lower, RR 0.58, $p = 0.04$, treatment 11 of 28 (39.3%), control 19 of 28 (67.9%), NNT 3.5.
Soares, 12/29/2021, prospective, Brazil, peer-reviewed, 17 authors, study period December 2020 - May 2021.	risk of death, 75.8% lower, RR 0.24, $p < 0.001$, treatment 6 of 44 (13.6%), control 18 of 32 (56.2%), NNT 2.3.
Wang, 3/15/2023, Randomized Controlled Trial, China, peer-reviewed, 13 authors.	hospitalization time, 38.5% lower, relative time 0.61, $p < 0.001$, treatment mean 7.7 (±4.15) n=23, control mean 12.53 (±5.56) n=32.

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.

Karami, 1/9/2024, Double Blind Randomized Controlled Trial, Iran, peer-reviewed, 4 authors, study period July 2022 - October 2022, trial IRCT20220328054364N1.	relative mean total symptoms, 45.5% better, RR 0.55, $p = 0.14$, treatment mean 2.52 (±4.99) n=40, control mean 4.62 (±7.37) n=40.
	relative mean week 1 symptoms, 42.6% better, RR 0.57, $p = 0.39$, treatment mean 0.7 (±1.84) n=36, control mean 1.22 (±3.14) n=40.
	relative mean week 2 symptoms, 42.0% better, RR 0.58, $p = 0.27$, treatment mean 0.87 (±2.26) n=36, control mean 1.5 (±2.63) n=40.

	relative mean week 3 symptoms, 79.4% better, RR 0.21, p = 0.045, treatment mean 0.2 (±0.72) n=36, control mean 0.97 (±2.16) n=40.
	relative mean week 4 symptoms, 18.5% better, RR 0.82, p = 0.77, treatment mean 0.75 (±2.43) n=36, control mean 0.92 (±2.58) n=40.
	risk of case, 38.9% lower, RR 0.61, p = 0.16, treatment 11 of 40 (27.5%), control 18 of 40 (45.0%), NNT 5.7.

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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