Povidone-Iodine for COVID-19: real-time meta analysis of 20 studies

@CovidAnalysis, March 2024, Version 35
https://c19early.org/pmeta.html

Abstract

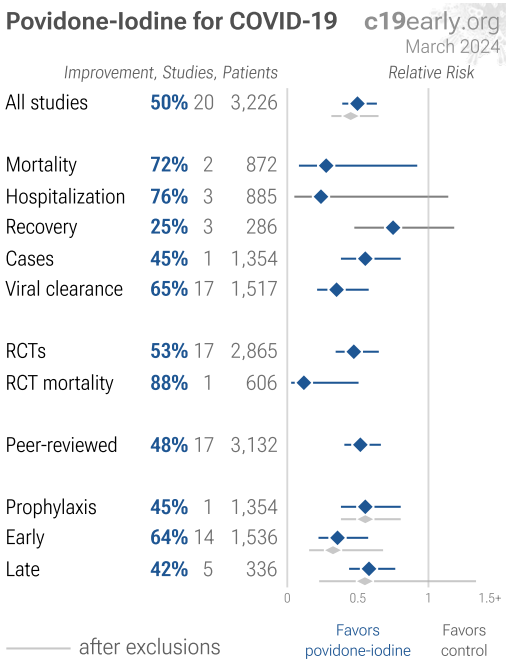
Statistically significant lower risk is seen for mortality, cases, and viral clearance. 11 studies from 11 independent teams in 9 countries show statistically significant improvements.

Meta analysis using the most serious outcome reported shows 50% [37-61%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies. Early treatment is more effective than late treatment.

Results are robust — in exclusion sensitivity analysis 15 of 20 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

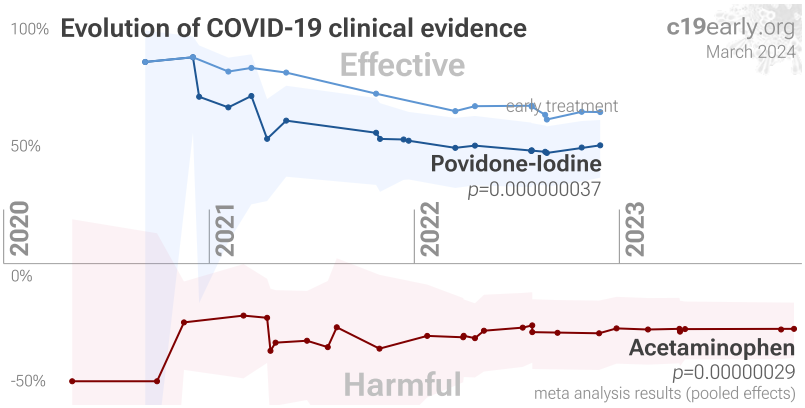
3 RCTs with 424 patients have not reported results (up to 2 years late).

Excessive use of PVP-I could affect thyroid function.



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. Povidone-Iodine may be detrimental to the natural microbiome, raising concern for side effects, especially with prolonged or excessive use.

All data to reproduce this paper and sources are in the appendix. Other meta analyses show significant improvements with povidone-iodine for viral load *Hasan, Idrees* and viral clearance *Hasan*.



HIGHLIGHTS

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

PVP-I was the 13th treatment shown effective with ≥3 clinical studies in February 2021, now known with p = 0.000000037 from 20 studies.

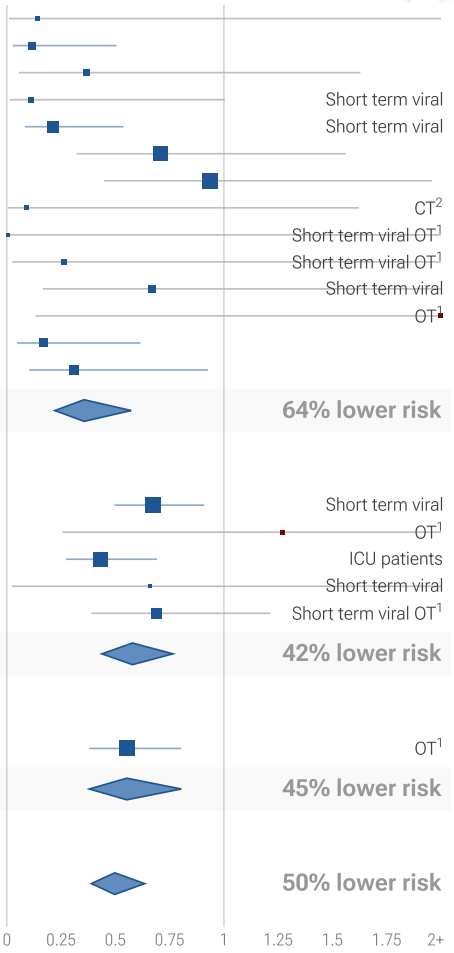
We show traditional outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor in COVID-19 studies.

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 66 treatments.

20 povidone-iodine COVID-19 studies

c19early.org
March 2024

		Improvement, RR [CI]		Treatment	Control
Mohamed (RCT)	86%	0.14 [0.01-2.21]	viral+	0/5	3/5
Choudhury (RCT)	88%	0.12 [0.03-0.50]	death	2/303	17/303
Guenezan (RCT)	63%	0.37 [0.06-1.63]	viral load	12 (n)	12 (n)
Elzein (DB RCT)	89%	0.11 [0.01-1.00]	viral load	25 (n)	9 (n)
Arefin (RCT)	79%	0.21 [0.08-0.54]	viral+	4/27	19/27
Pablo-Marcos	29%	0.71 [0.32-1.56]	viral load	31 (n)	40 (n)
Sulistyani (SB RCT)	6%	0.94 [0.45-1.96]	viral load	15 (n)	15 (n)
Elsersy (DB RCT)	91%	0.09 [0.01-1.62]	hosp.	0/100	5/100
Sevinç Gül (RCT)	99%	0.01 [0.00-439]	viral load	21 (n)	20 (n)
Natto (RCT)	74%	0.26 [0.03-2.76]	viral load	12 (n)	12 (n)
Sirijatuphat	33%	0.67 [0.17-2.67]	viral load	12 (n)	12 (n)
Baxter (RCT)	-214%	3.14 [0.13-74.7]	hosp.	1/37	0/42
Karaaltin (RCT)	83%	0.17 [0.05-0.62]	viral load	30 (n)	30 (n)
Matsuyama (RCT)	69%	0.31 [0.10-0.93]	viral+	4/139	13/140
Early treatment	64%	0.36 [0.22-0.57]		11/769	57/767
Tau² = 0.23, I² = 32.3%, p < 0.0001					
		Improvement, RR [CI]		Treatment	Control
Seneviratne (RCT)	33%	0.67 [0.50-0.91]	viral load	4 (n)	2 (n)
Zarabanda (RCT)	-27%	1.27 [0.26-6.28]	no recov.	3/13	2/11
Jamir (ICU)	57%	0.43 [0.27-0.69]	death	39/163	62/103
Ferrer (RCT)	34%	0.66 [0.02-19.0]	viral load	9 (n)	12 (n)
Fantozzi (RCT)	31%	0.69 [0.39-1.21]	viral+	5/8	10/11
Late treatment	42%	0.58 [0.44-0.76]		47/197	74/139
Tau² = 0.03, I² = 28.0%, p = 0.00014					
		Improvement, RR [CI]		Treatment	Control
Seet (CLUS. RCT)	45%	0.55 [0.38-0.80]	symp. case	42/735	64/619
Prophylaxis	45%	0.55 [0.38-0.80]		42/735	64/619
Tau² = 0.00, I² = 0.0%, p = 0.002					
All studies	50%	0.50 [0.39-0.63]		100/1,701	195/1,525



[1] OT: comparison with other treatment
[2] CT: study uses combined treatment
Tau² = 0.07, I² = 30.4%, p < 0.0001

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

A

Efficacy in COVID-19 povidone-iodine studies (pooled effects)

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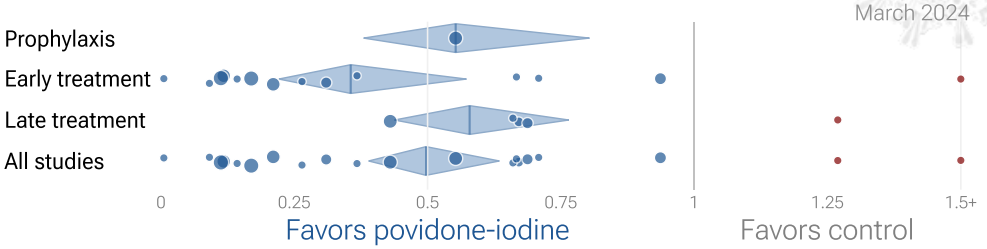

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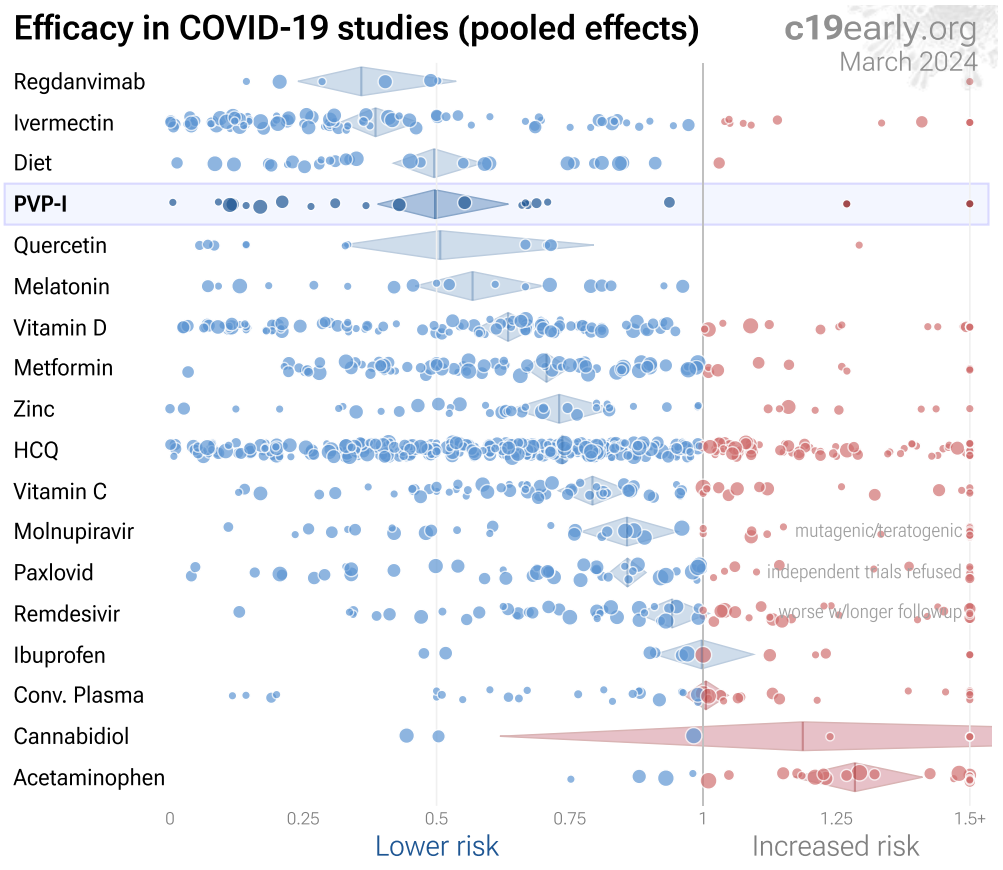


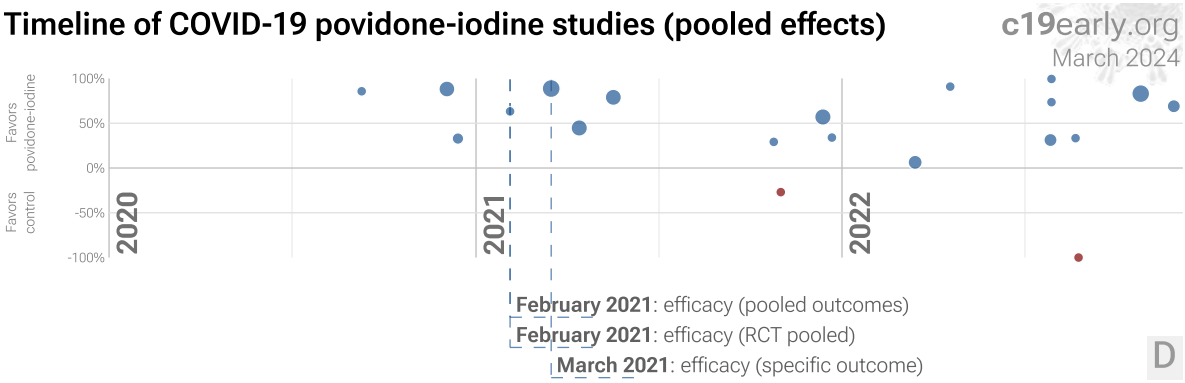


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the 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 povidone-iodine 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, and pooled outcomes in RCTs. Efficacy based on specific outcomes was delayed by 1.3 months, compared to using pooled outcomes.

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.

Analysis. We analyze all significant controlled studies of povidone-iodine 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, Randomized Controlled Trials (RCTs), and higher quality studies.

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.

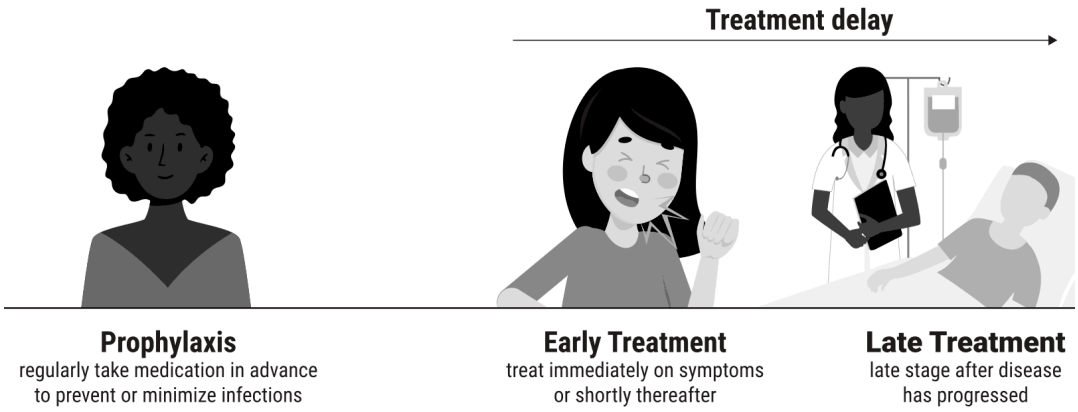


Figure 2. Treatment stages.

Preclinical Research

Several *in vitro* studies show that PVP-I is effective for SARS-CoV-2 at clinically relevant concentrations [Anderson, Bidra, Frank, Hassandarvish, Pelletier, Tucker, Xu].

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

	Improvement	*Studies*	*Patients*	*Authors*
All studies	**50%** [37-61%] ****	20	3,226	194
After exclusions	**55%** [35-69%] ****	11	2,932	112
Peer-reviewed studies	**48%** [34-60%] ****	17	3,132	158
Randomized Controlled Trials	**53%** [35-66%] ****	17	2,865	178
Mortality	**72%** [8-92%] *	2	872	12
Hospitalization	**76%** [-14-95%]	3	885	26
Recovery	**25%** [-18-53%]	3	286	33
Viral	**65%** [42-79%] ****	17	1,517	161
RCT hospitalization	**76%** [-14-95%]	3	885	26

Table 1. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes.** Results show the percentage improvement with treatment and the 95% confidence interval. ** p<0.01 *** p<0.001 **** p<0.0001.

	Early treatment	*Late treatment*	*Prophylaxis*
All studies	**64%** [43-78%] ****	**42%** [24-56%] ***	**45%** [20-62%] **
After exclusions	**68%** [32-85%] **	**45%** [-34-77%]	**45%** [20-62%] **
Peer-reviewed studies	**63%** [36-79%] ***	**42%** [24-56%] ***	**45%** [20-62%] **
Randomized Controlled Trials	**71%** [50-83%] ****	**31%** [11-47%] **	**45%** [20-62%] **
Mortality	**88%** [50-97%] **	**57%** [31-73%] ***	
Hospitalization	**76%** [-14-95%]		
Recovery	**32%** [-28-64%]	**-27%** [-528-74%]	
Viral	**73%** [49-86%] ****	**32%** [11-48%] **	
RCT hospitalization	**76%** [-14-95%]		

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<0.01 *** p<0.001 **** p<0.0001.

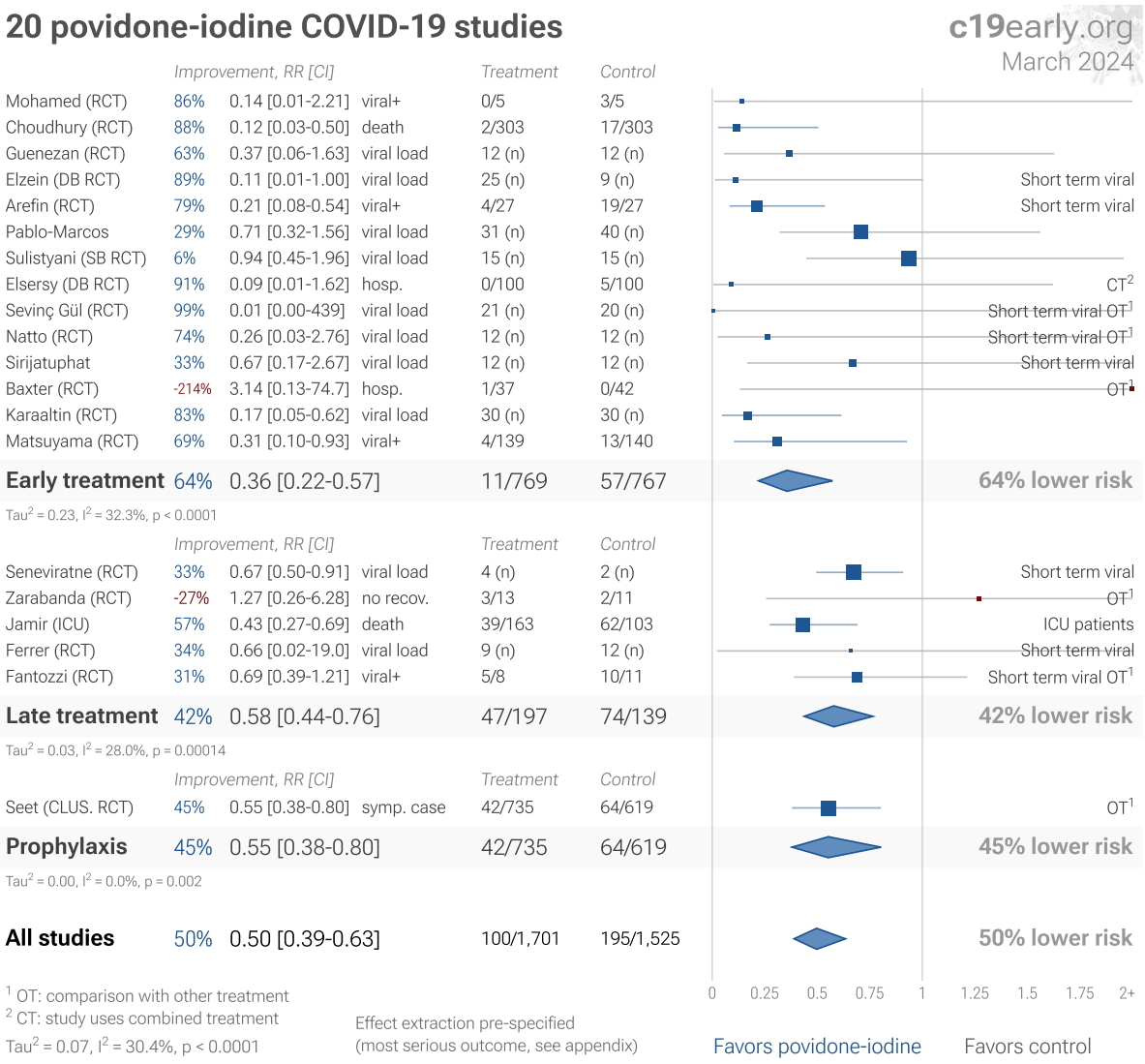


Figure 3. **Random effects meta-analysis for all studies with pooled effects.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details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

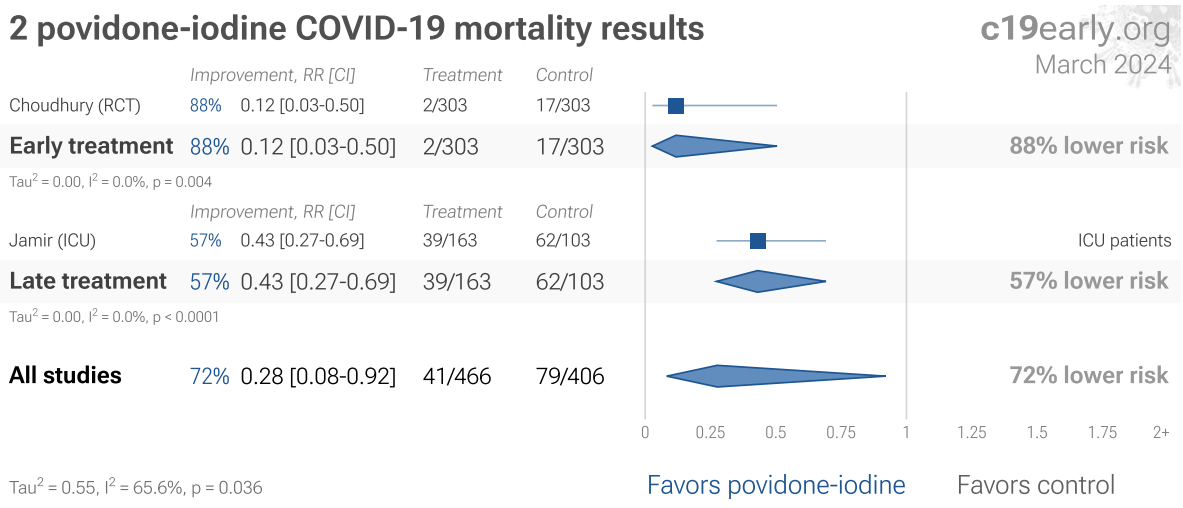


Figure 4. **Random effects meta-analysis for mortality results.**

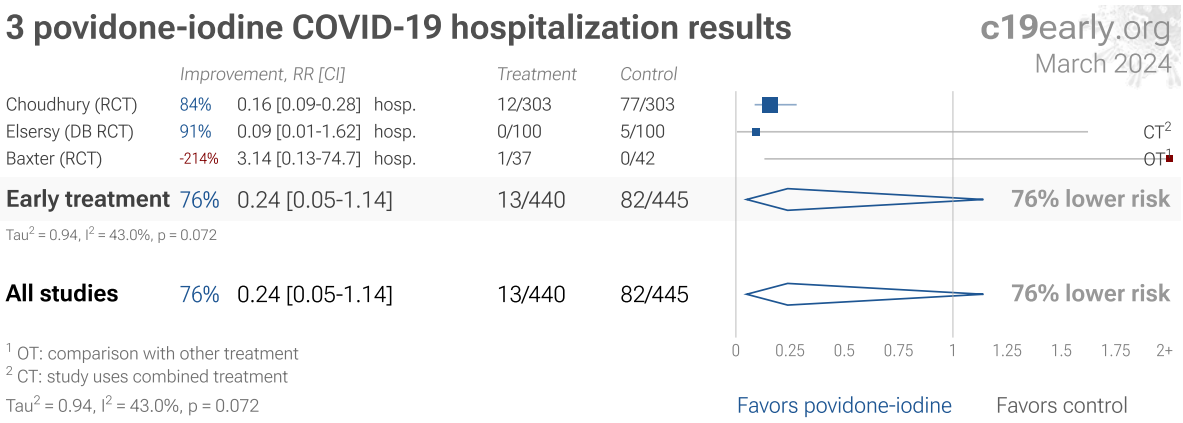


Figure 5. Random effects meta-analysis for hospitalization.

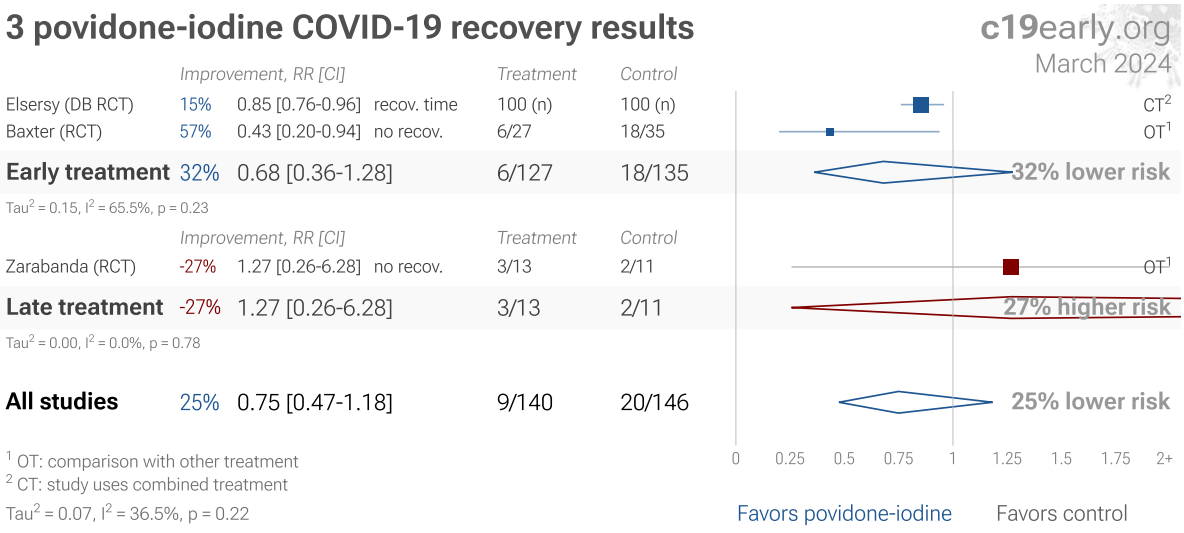


Figure 6. Random effects meta-analysis for recovery.

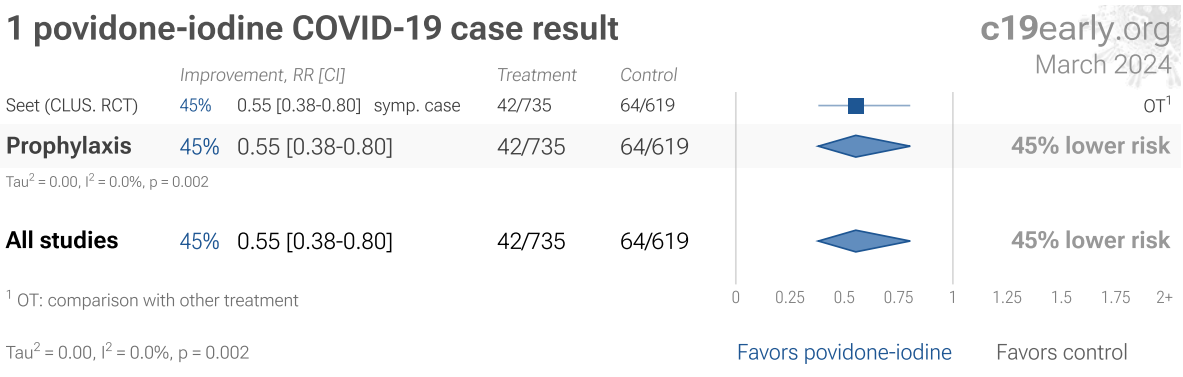


Figure 7. Random effects meta-analysis for cases.

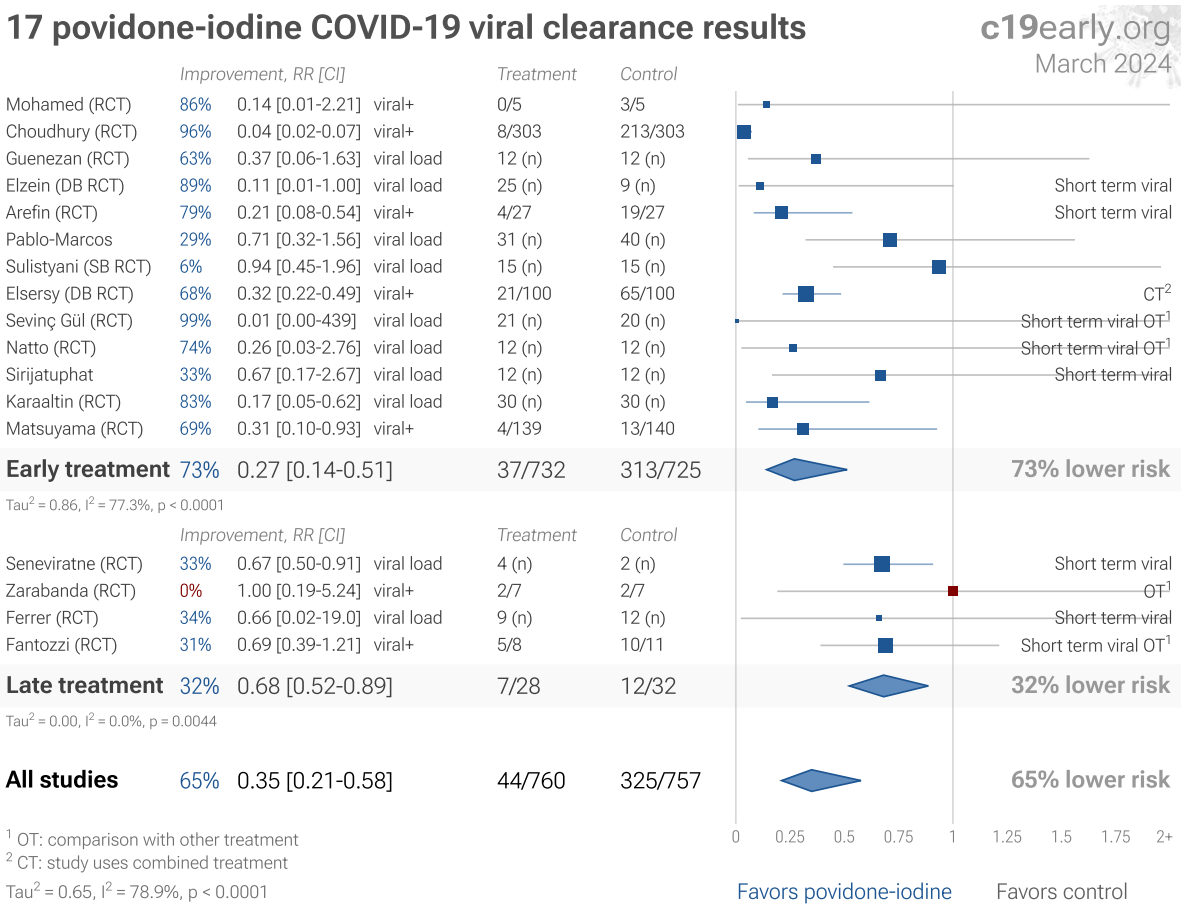


Figure 8. Random effects meta-analysis for viral clearance.

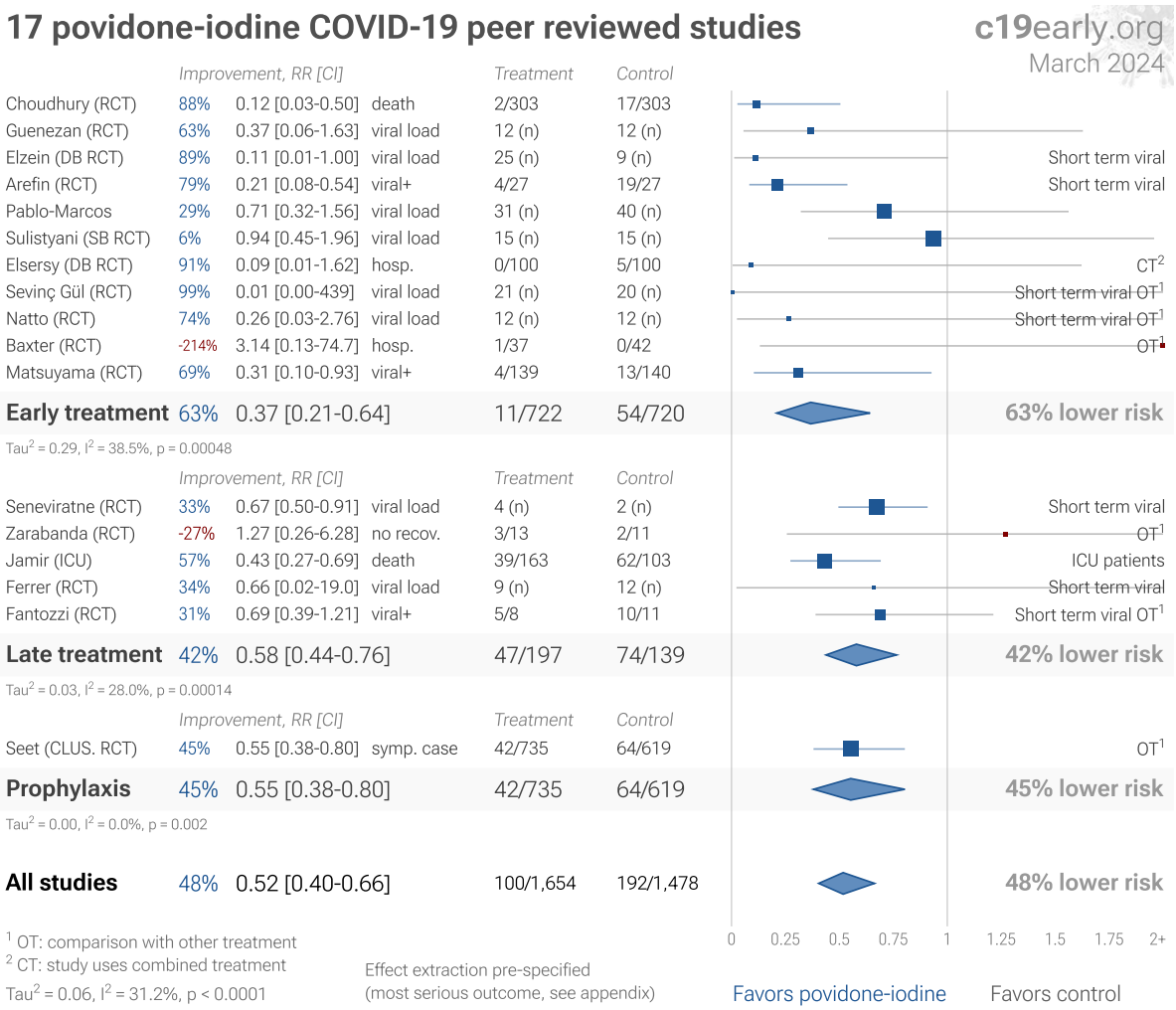


Figure 9. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with 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 10 shows a comparison of results for RCTs and non-RCT studies. The median effect size for RCTs is 69% improvement, compared to 33% for other studies. Figure 11, 12, and 13 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).

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.

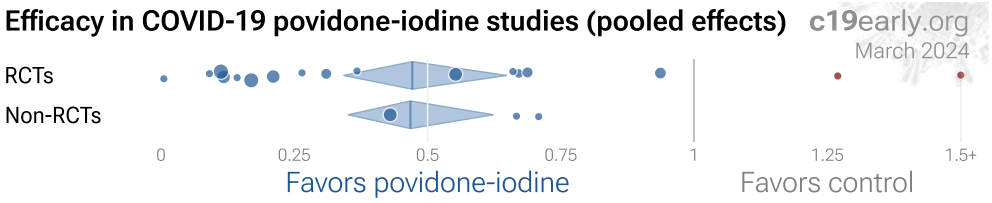


Figure 10. **Results for RCTs and non-RCT studies.**

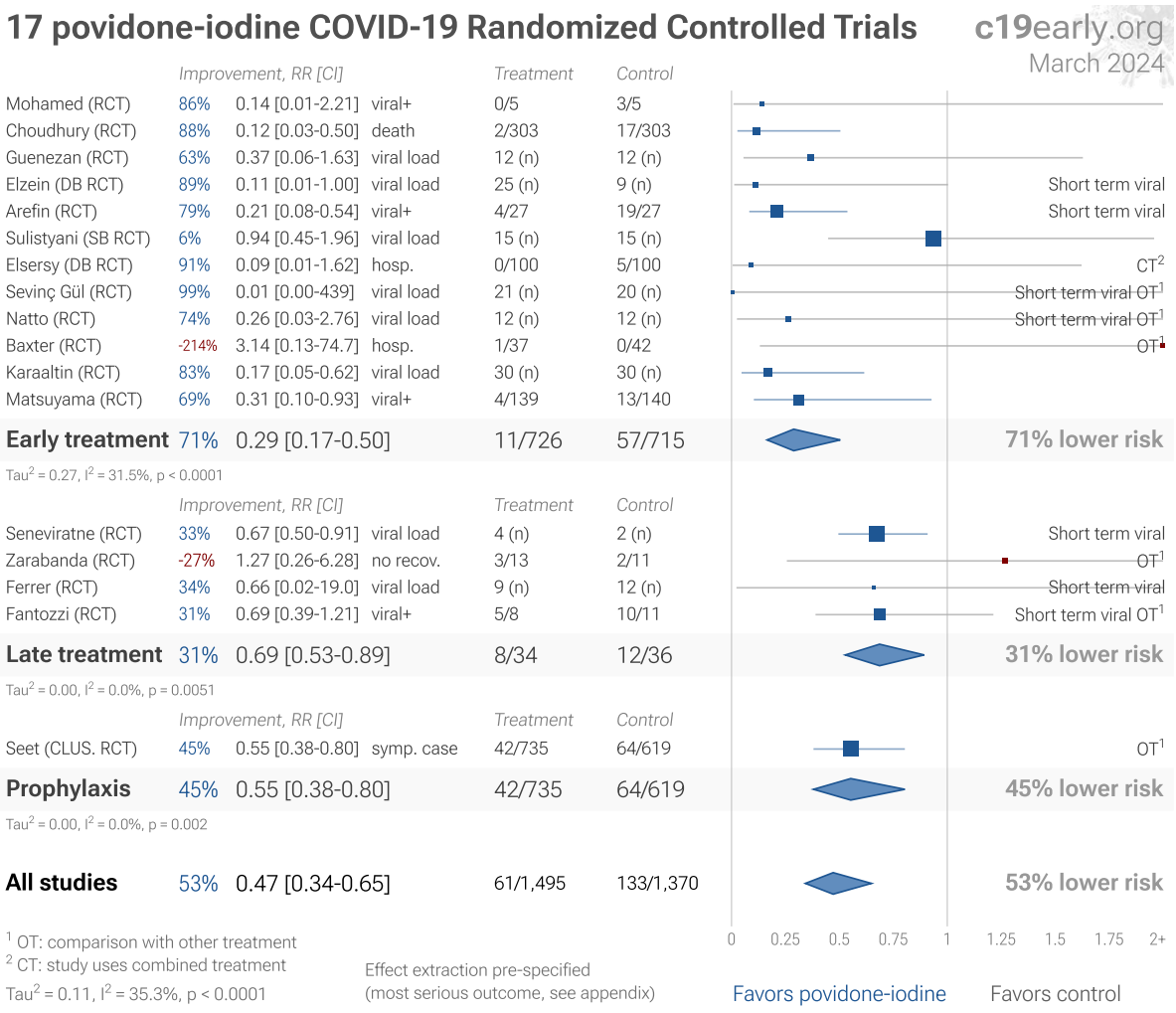


Figure 11. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

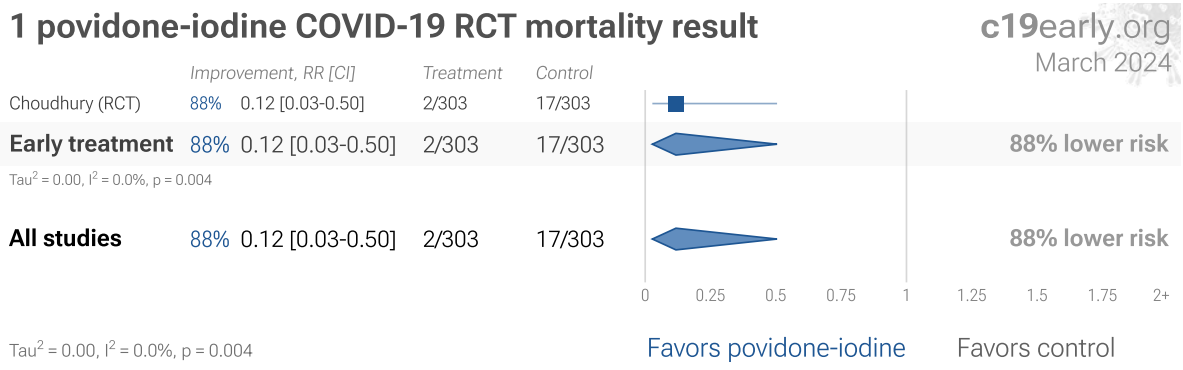


Figure 12. **Random effects meta-analysis for RCT mortality results.**

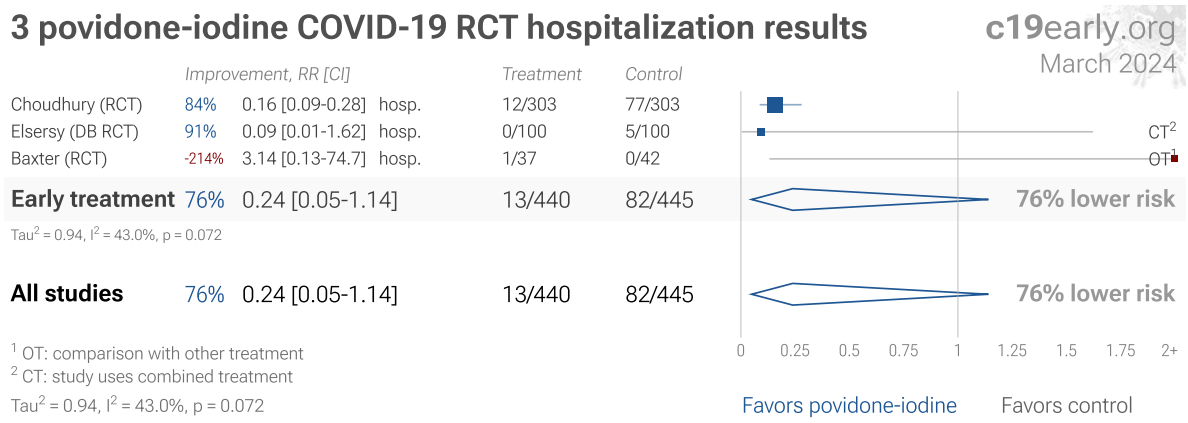


Figure 13. Random effects meta-analysis for RCT hospitalization results.

Unreported RCTs

3 povidone-iodine RCTs have not reported results *Jacox, Keating, Khan*. The trials report a total of 424 patients, with 2 trials having actual enrollment of 374, and the other estimated. The results are delayed from 1.5 years to over 2 years.

Exclusions

To avoid bias in the selection of studies, we analyze all non-retracted studies. Here we show the results after excluding studies with major issues likely to alter results, non-standard studies, and studies where very minimal detail is currently available. Our bias evaluation is based on analysis of each study and identifying when there is a significant chance that limitations will substantially change the outcome of the study. We believe this can be more valuable than checklist-based approaches such as Cochrane GRADE, which may underemphasize serious issues not captured in the checklists, overemphasize issues unlikely to alter outcomes in specific cases (for example, lack of blinding for an objective mortality outcome, or certain specifics of randomization with a very large effect size), and can be easily influenced by potential bias.

The studies excluded are as below. Figure 14 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Arefin, study only provides short-term viral load results.

Elzein, study only provides short-term viral load results.

Fantozzi, study only provides short-term viral load results.

Ferrer, study only provides short-term viral load results.

Natto, study only provides short-term viral load results.

Pablo-Marcos, unadjusted results with no group details.

Seneviratne, study only provides short-term viral load results.

Sevinç Gül, study only provides short-term viral load results.

Sirijatuphat, study only provides short-term viral load results.

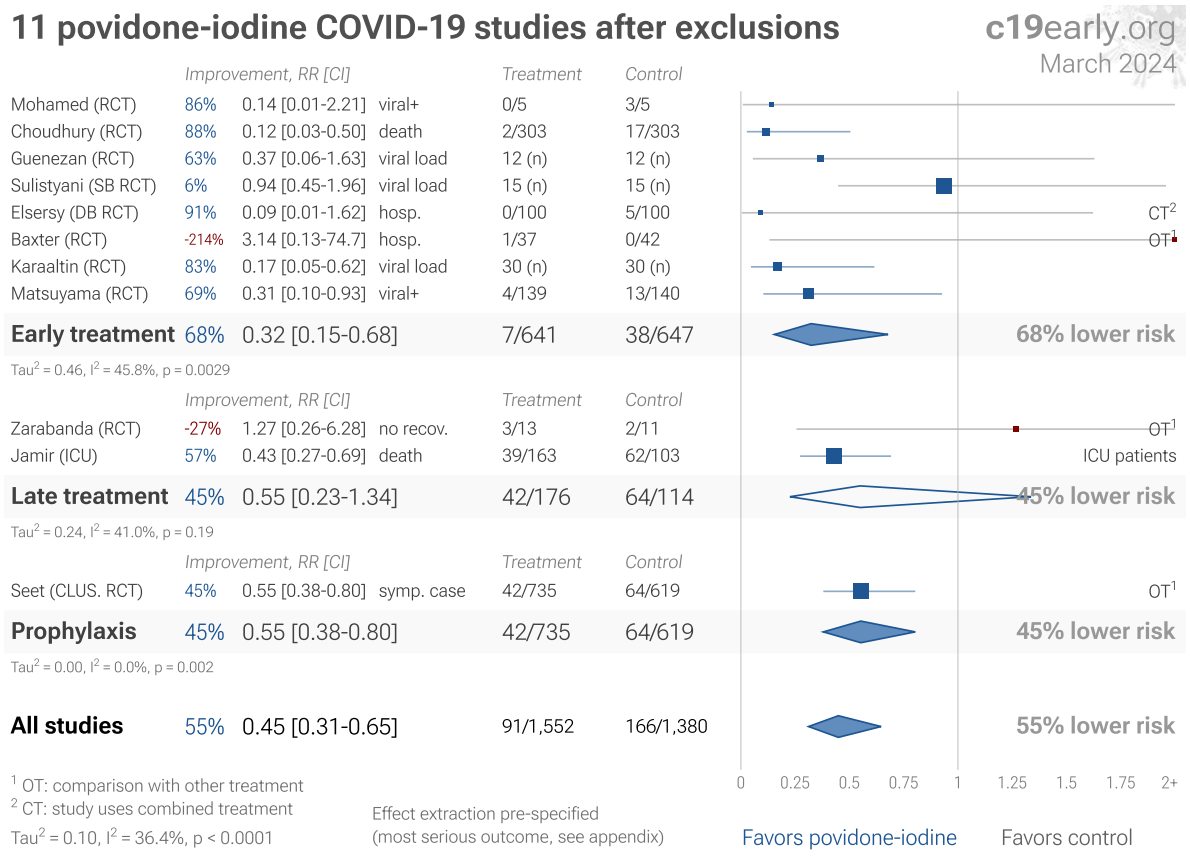


Figure 14. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

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 15 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.

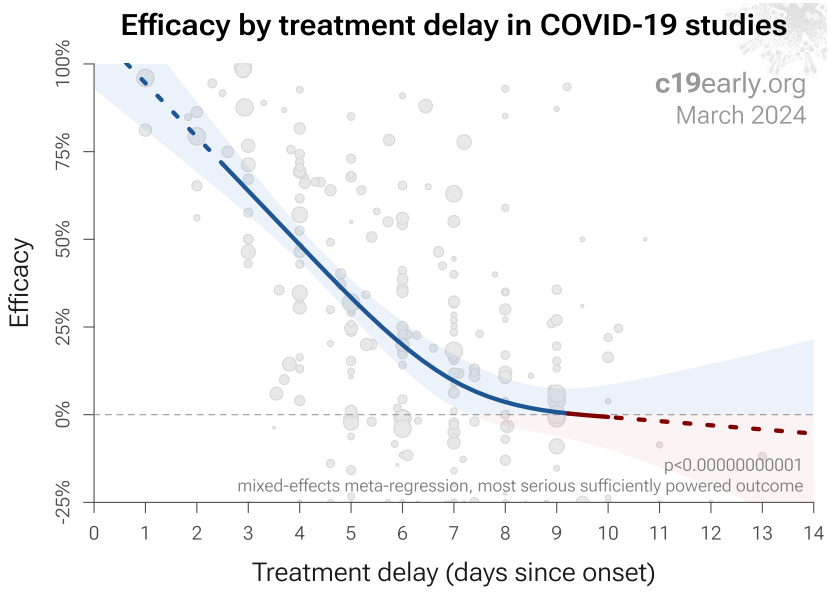


Figure 15. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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 (B)* 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 16. 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.

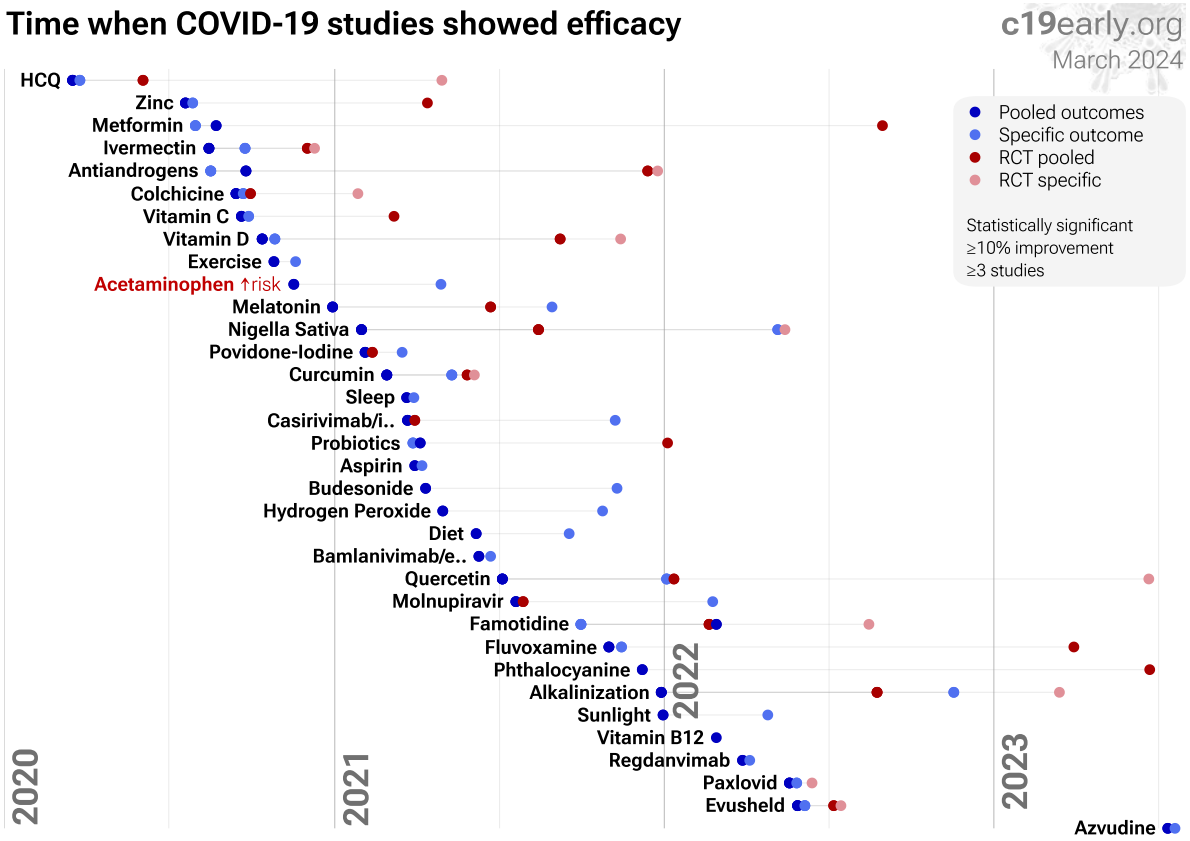


Figure 16. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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

Safety. Safety analysis can be found in *Frank (B), Frank (C), Khan (B)*. *Frank (B)* conclude that PVP-I can safely be used in the nose at concentrations up to 1.25% and in the mouth at concentrations up to 2.5% for up to 5 months.

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 povidone-iodine, there is currently not enough data to evaluate publication bias with high confidence.

One method to evaluate bias is to compare prospective vs. retrospective studies. Prospective studies are more likely to be published regardless of the result, while retrospective studies are more likely to exhibit bias. For example, researchers may perform preliminary analysis with minimal effort and the results may influence their decision to continue. Retrospective studies also provide more opportunities for the specifics of data extraction and adjustments to influence results.

Figure 17 shows a scatter plot of results for prospective and retrospective studies. Prospective studies show 49% [33-62%] improvement in meta analysis, compared to 57% [31-73%] for retrospective studies, showing no significant difference. However, there has only been one retrospective study to date.

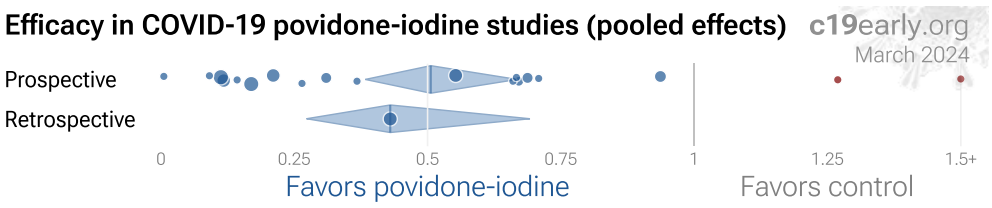


Figure 17. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

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 18 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.

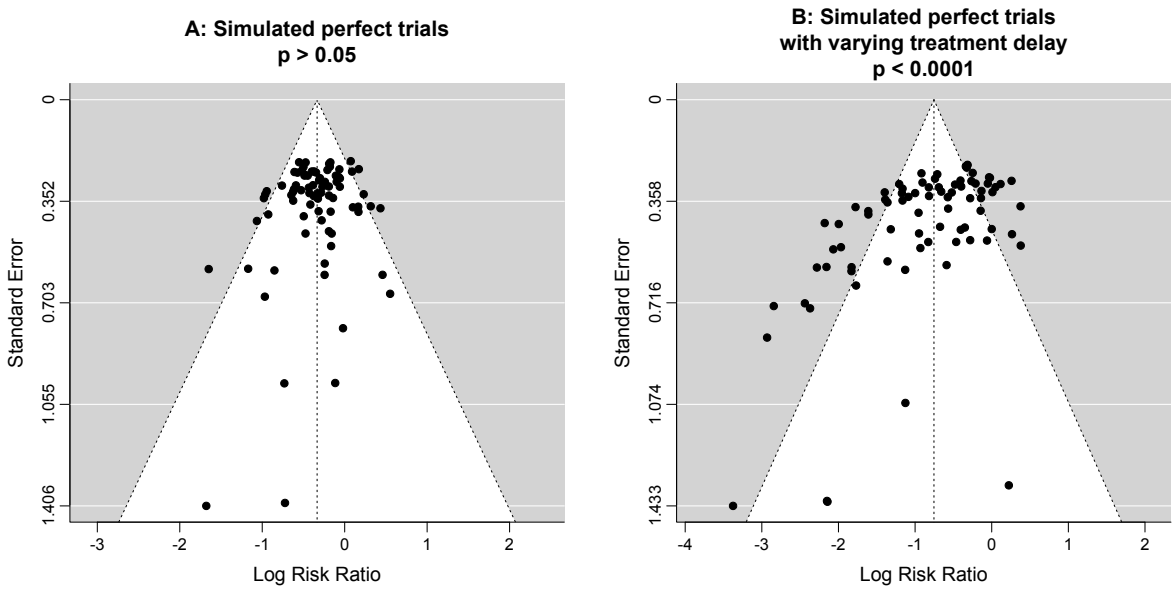


Figure 18. **Example funnel plot analysis for simulated perfect trials.**

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. PVP-I for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 povidone-iodine 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 povidone-iodine 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. 6 of the 20 studies compare against other treatments, which may reduce the effect seen. 1 of 20 studies combine treatments. The results of povidone-iodine alone may differ. 1 of 17 RCTs use combined treatment. Other meta analyses show significant improvements with povidone-iodine for viral load *Hasan, Idrees* and viral clearance *Hasan*.

Reviews. Multiple reviews cover povidone-iodine for COVID-19, presenting additional background on mechanisms and related results, including *Chavda, Chopra, Lim, O'Donnell, Ting*.

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.

PVP-I is an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality, cases, and viral clearance. 11 studies from 11 independent teams in 9 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 50% [37-61%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies. Early treatment is more effective than late treatment. Results are robust — in exclusion sensitivity analysis 15 of 20 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

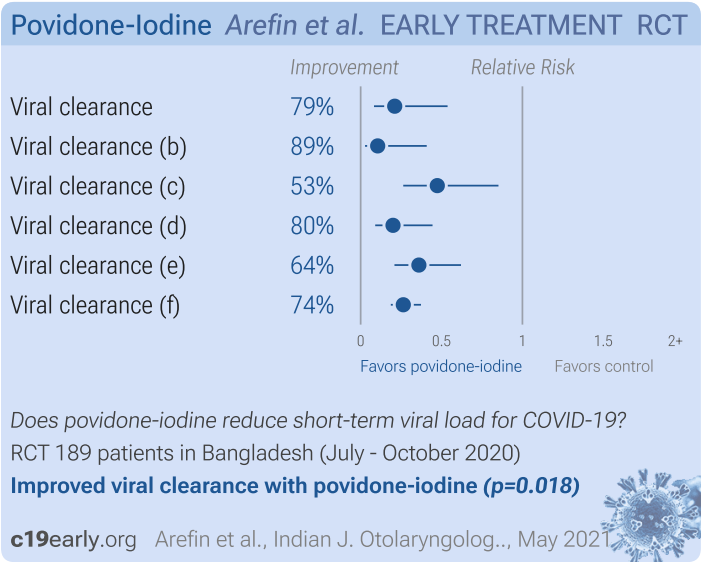
Excessive use of PVP-I could affect thyroid function.

Other meta analyses show significant improvements with povidone-iodine for viral load *Hasan, Idrees* and viral clearance *Hasan*.

Povidone-Iodine may be detrimental to the natural microbiome, raising concern for side effects, especially with prolonged or excessive use.

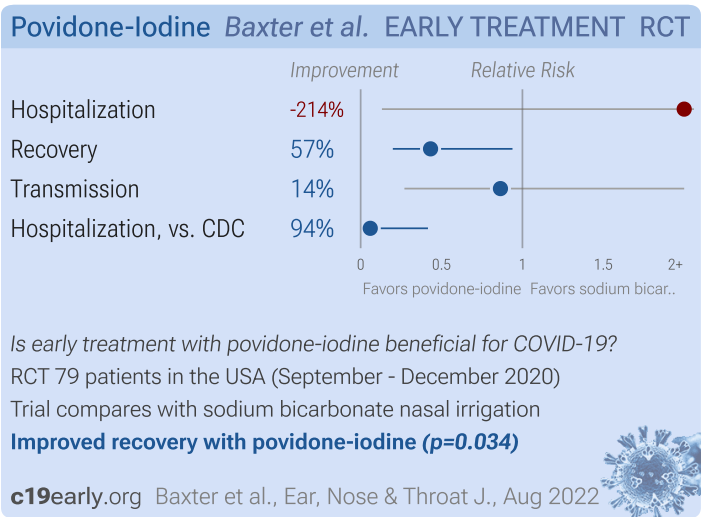
Study Notes

Arefin



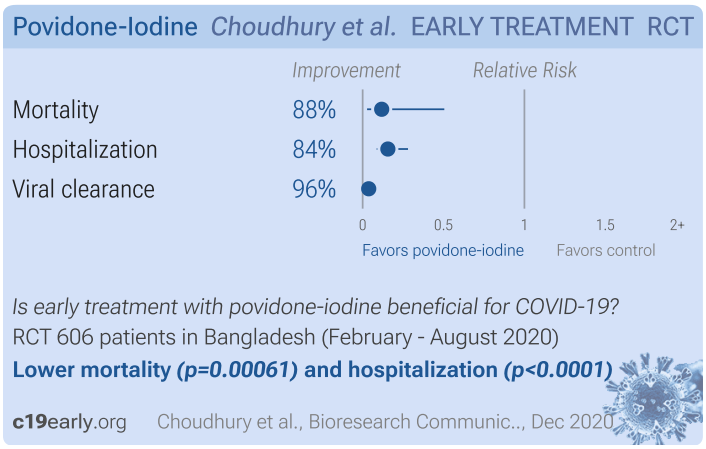
Arefin: RCT with 189 patients showing significantly greater viral clearance with a single application of PVP-I. Authors recommend using PVP-I prophylactically in the nasopharynx and oropharynx. NCT04549376 *trialsjournal.biomedcentral.com*.

Baxter



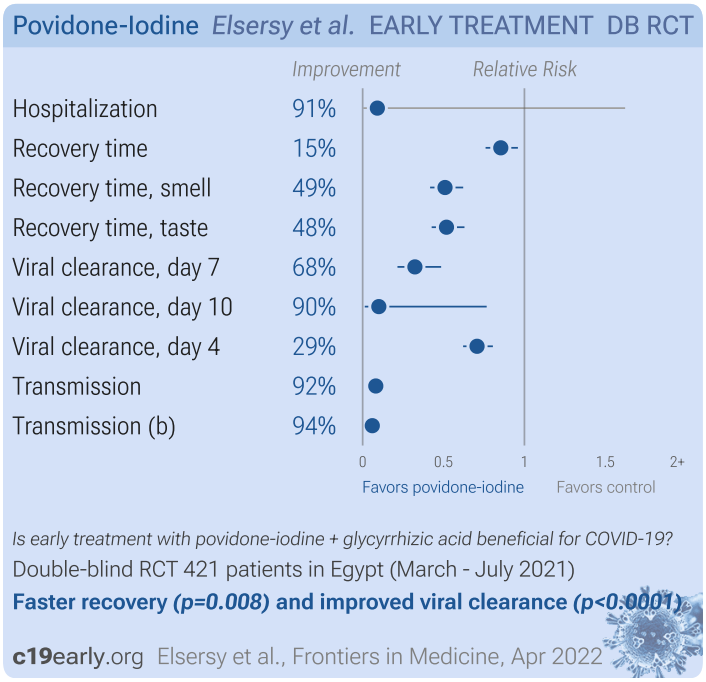
Baxter: Small RCT 79 PCR+ patients 55+ comparing pressure-based nasal irrigation with povidone-iodine and sodium bicarbonate, showing improved recovery with povidone-iodine. Not all results comparing povidone-iodine and sodium bicarbonate are in the journal version, as authors focus on the comparison with CDC data. Earlier versions can be found at *medrxiv.org*. The reported hospitalization switched groups between the preprint and the journal version.

Choudhury



Choudhury: RCT 606 patients in Bangladesh for povidone iodine mouthwash/gargle, nasal drops and eye drops showing significantly lower death, hospitalization, and PCR+ at day 7.

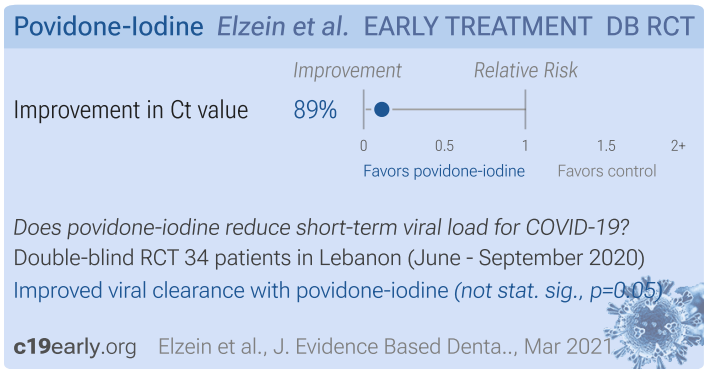
Elsersy



Elsersy: RCT with 200 patients and 421 contacts in Egypt, with 100 patients and their contacts treated with nasal and oropharyngeal sprays containing povidone-iodine and glycyrrhizic acid, showing significantly faster viral clearance and recovery, and significantly lower transmission.

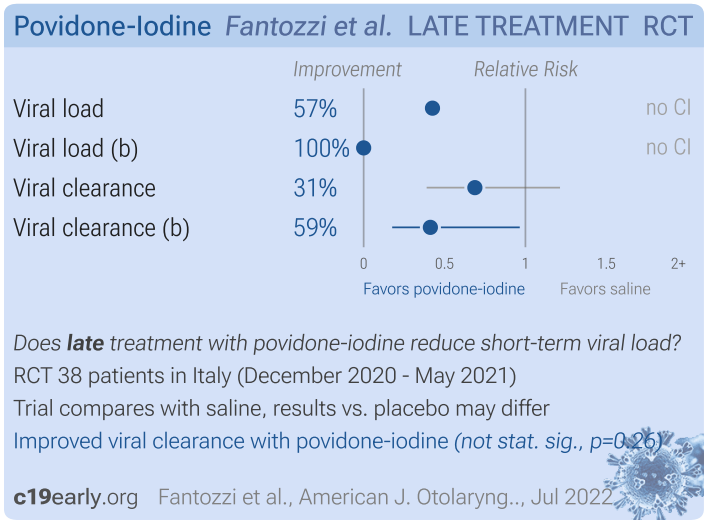
SOC included vitamin C and zinc. The spray active ingredients included a compound of glycyrrhizic acid in the form of ammonium glycyrrhizate 2.5 mg/ml plus PVI 0.5% for oropharyngeal and dipotassium glycyrrhizinate 2.5 mg/ml plus PVI 0.5% for nasal spray. Patients were advised to concomitantly use oropharyngeal and nasal sprays 6 times per day. They were instructed to abstain from food, drink, and smoke for 20min, particularly after oropharyngeal spray. The oropharyngeal spray bottle contains an atomizer that ends with a long arm applicator to insert inside the mouth cavity and can be directed up, down, right, or left to cover the entire pharyngeal area.

Elzein



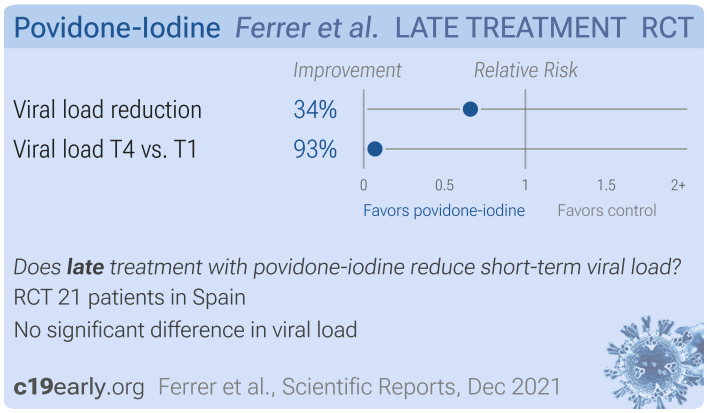
Elzein: Small RCT comparing mouthwashing with PVP-I, chlorhexidine, and water, showing significant efficacy for both PVP-I and chlorhexidine, with PVP-I increasing Ct by a mean of 4.45 ($p < 0.0001$) and chlorhexidine by a mean of 5.69 ($p < 0.0001$), compared to no significant difference for water.

Fantozzi



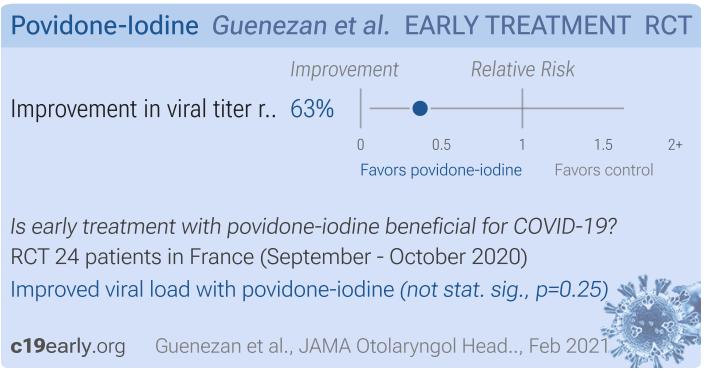
Fantozzi: Mouthrinse RCT in Italy comparing short-term viral load after a single 60 second treatment with povidone-iodine, hydrogen peroxide, chlorhexidine, and saline. The greatest efficacy was seen with povidone-iodine, especially for patients with low viral load at baseline.

Ferrer



Ferrer: Small very late (>50% 7+ days from symptom onset, 9 PVP-I patients) RCT testing mouthwashing with cetylpyridinium chloride, chlorhexidine, povidone-iodine, hydrogen peroxide, and distilled water, showing no significant differences. Over 30% of patients show >90% decrease in viral load @2 hrs with all 5. Authors note that a trend was observed for viral load decrease with PVP-I @2h for patients <6 days from onset (p=0.06, Wilcox test).

Guenezan

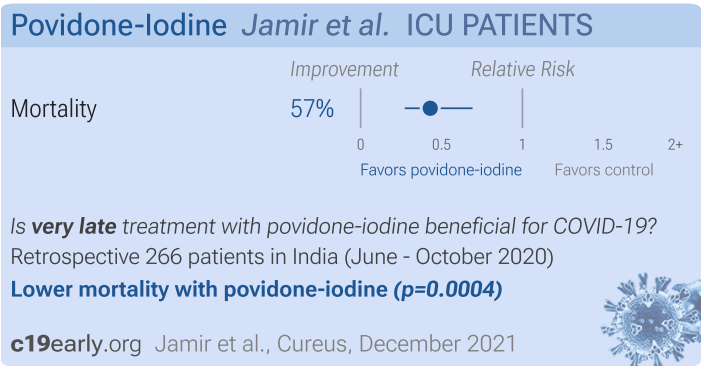


Guenezan: RCT of PCR+ patients with Ct<=20 with 12 treatment and 12 control patients, concluding that nasopharyngeal decolonization may reduce the carriage of infectious SARS-CoV-2 in adults with mild to moderate COVID-19. All patients but 1 had negative viral titer by day 3 (group not specified). There was no significant difference in viral RNA quantification over time. The mean relative difference in viral titers between baseline and day 1 was 75% [43%-95%] in the intervention group and 32% [10%-65%] in the control group. Thyroid dysfunction occurred in 42% of treated patients, with spontaneous resolution after the end of treatment. Patients in the treatment group were younger.

Jacox

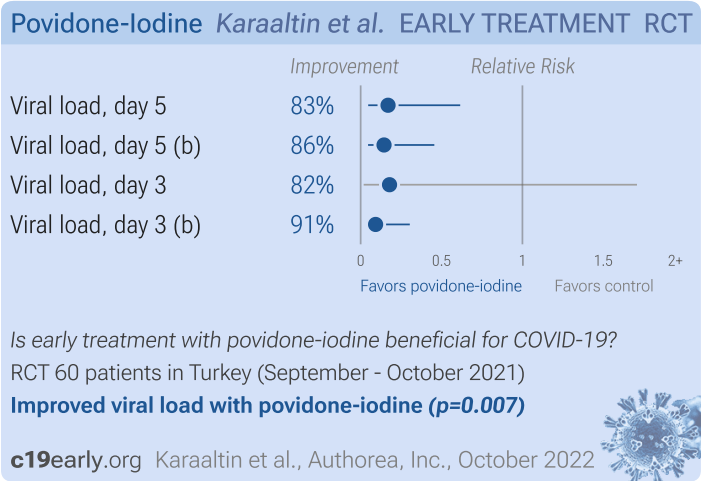
Jacox: 129 patient povidone-iodine early treatment RCT with results not reported over 2 years after completion.

Jamir



Jamir: Retrospective 266 COVID-19 ICU patients in India, showing significantly lower mortality with PVP-I oral gargling and topical nasal use, and non-statistically significant higher mortality with ivermectin and lower mortality with remdesivir.

Karaaltin



Karaaltin: RCT 120 outpatients in Turkey, showing improved reduction in viral load with PVP-I nasal irrigation.

PVP-I prepared with hypertonic alkaline solution had better results. *Kreutzberger* show that SARS-CoV-2 requires acidic pH to infect cells, therefore alkalinization may add additional benefits.

All patients received favipiravir. PVP-I 1% 4 times per day.

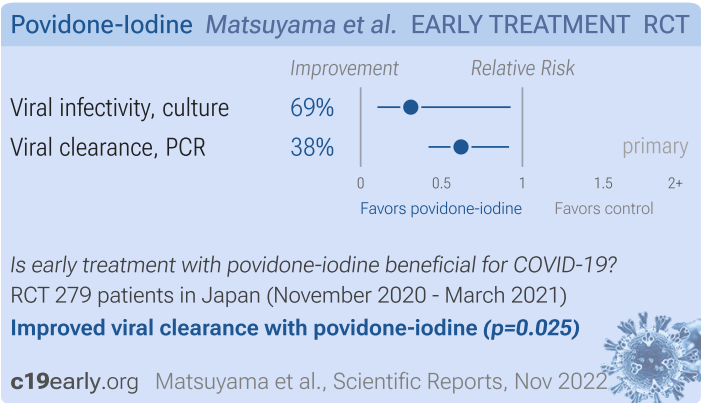
Keating

Keating: 245 participant povidone-iodine + chlorhexidine prophylaxis RCT with results not reported over 1.5 years after completion.

Khan

Khan: Estimated 50 patient povidone-iodine early treatment RCT with results not reported over 1.5 years after estimated completion.

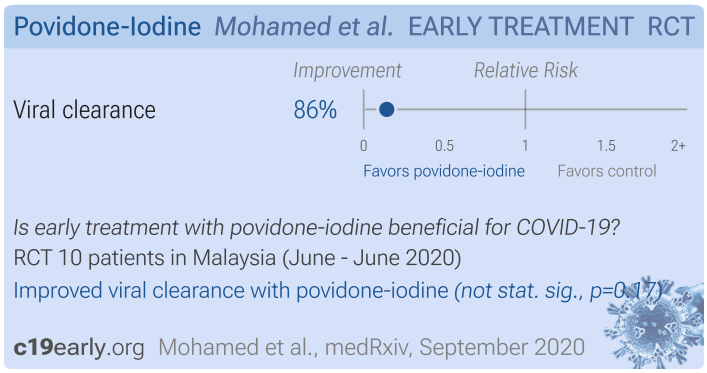
Matsuyama



Matsuyama: RCT 430 COVID+ patients in Japan, showing significantly lower viral infectivity from culture, and significantly faster PCR viral clearance with PVP-I.

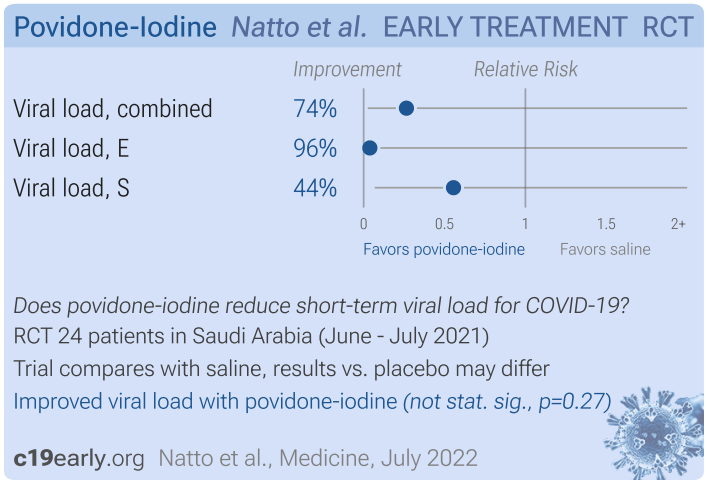
For days 2-4 the study compares treatment with PVP-I vs. water (on day 5 both groups received PVP-I). Most patients were asymptomatic. 4 times per day mouthwashing and gargling with 20mL of 15-fold diluted PVP–I 7% or water.

Mohamed



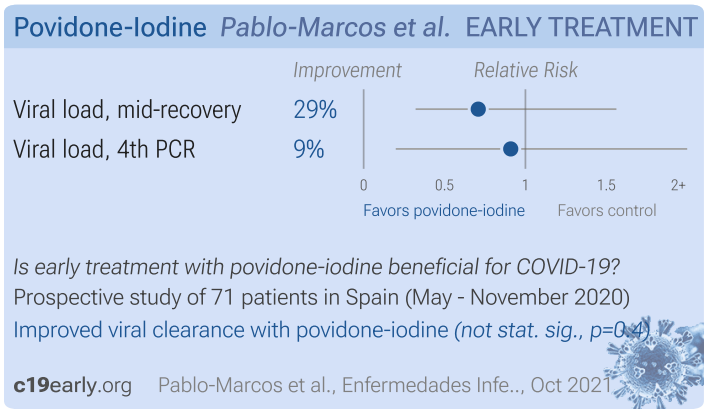
Mohamed: Tiny RCT with 5 PVP-I patients, gargling 30 seconds, 3x per day, and 5 control patients (essential oils and tap water were also tested), showing improved viral clearance with PVP-I.

Natto



Natto: 60 patient RCT comparing chlorhexidine, PVP-I, and saline in Saudi Arabia with a single mouth rinse treatment and PCR testing 5 minutes later, showing statistically significant improvement in Ct value for PVP-I. PVP-I showed greater improvement than saline, without statistical significance.

Pablo-Marcos

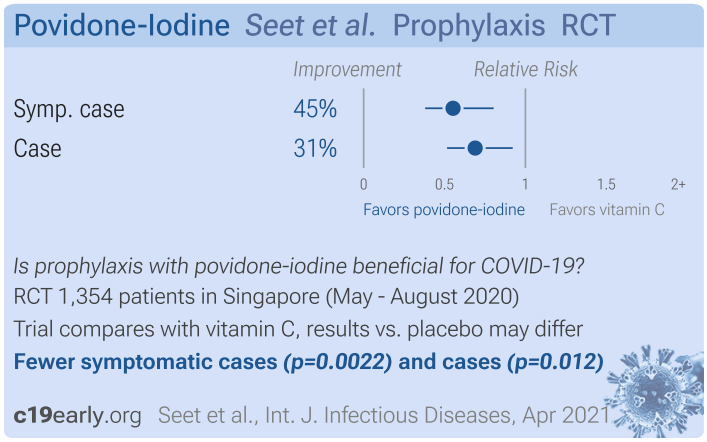


Pablo-Marcos: Small prospective study with 31 patients gargling povidone-iodine, 17 hydrogen peroxide, and 40 control patients, showing lower viral load mid-recovery with povidone-iodine, without reaching statistical significance. Oropharyngeal only, and only every 8 hours for two days. Results may be better with the addition of nasopharyngeal

use, more frequent use, and without the two day limit.

Authors report only one of the 7 previous trials for PVP-I and COVID-19. Non-randomized study with no adjustments or group details. Some results in Figure 1 appear to be switched compared to the text and the labels in the figure. The viral clearance figures do not match the group sizes - for example authors report 62% PCR- for PVP-I at the 3rd test, however there is no number of 31 patients that rounds to 62%.

Seet

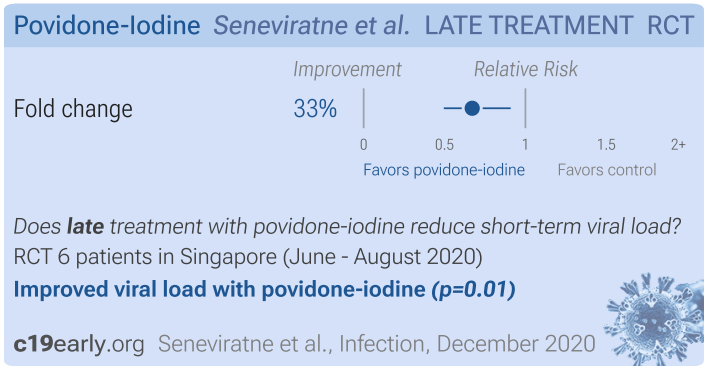


Seet: Prophylaxis RCT in Singapore with 3,037 low risk patients, showing lower serious cases, lower symptomatic cases, and lower confirmed cases of COVID-19 with all treatments (ivermectin, HCQ, PVP-I, and Zinc + vitamin C) compared to vitamin C.

Meta-analysis of vitamin C in 6 previous trials shows a benefit of 16%, so the actual benefit of ivermectin, HCQ, and PVP-I may be higher. Cluster RCT with 40 clusters.

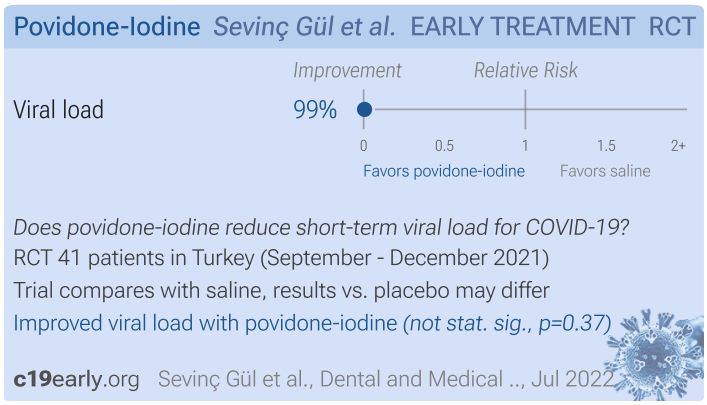
There were no hospitalizations and no deaths. NCT04446104.

Seneviratne



Seneviratne: Small mouthwash RCT with 4 PVP-I patients and 2 water patients concluding that PVP-I may have a sustained effect on reducing the salivary SARS-CoV-2 level in COVID-19 patients. ISRCTN95933274.

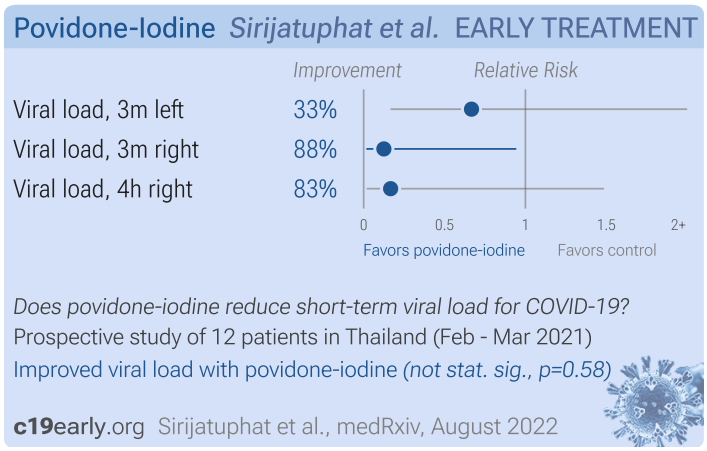
Sevinç Gül



Sevinç Gül: RCT with 21 PVP-I and 20 saline patients gargling for 30 seconds and testing PCR Ct after 30 minutes, showing greater improvement with PVP-I, without statistical significance.

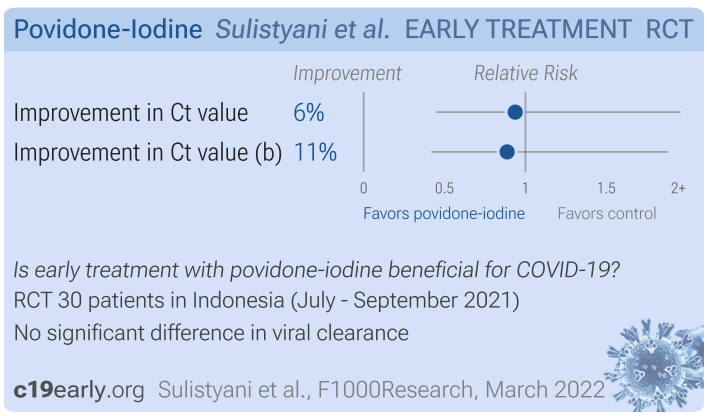
Ct values differ across testing platforms, however the reported Ct value difference can represent a large difference in viral load. For example, using the calibration included with the ct2vl converter, the reported difference in mean Ct values corresponds to a reduction in viral load of over 3x for PVP-I.

Sirijatuphat



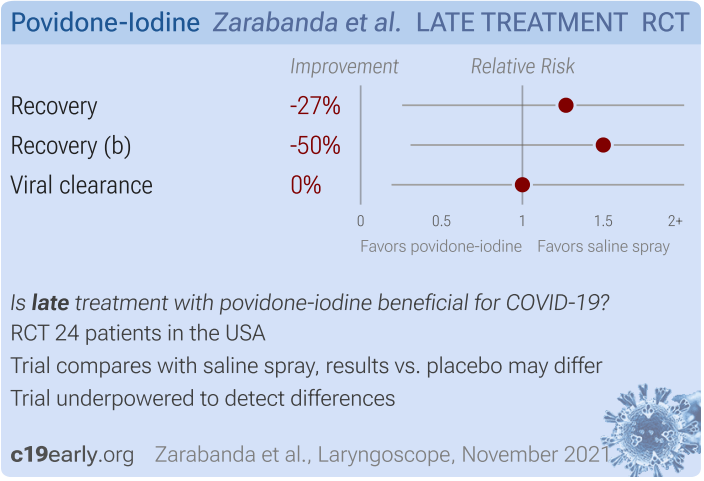
Sirijatuphat: Small single-arm trial testing short-term viral load change after a single administration of three puffs of 0.4% PVP-I, showing lower viral titer at 3 minutes and 4 hours, not reaching statistical significance. Authors note that one reason for the lower change compared to in vitro results is that the spray administration may be less effective.

Sulistyani



Sulistyani: Small mouth rinsing and gargling RCT with 15 1% PVP-I, 12 0.5% PVP-I, 15 3% hydrogen peroxide, 12 1.5% hydrogen peroxide, and 15 water patients, showing rapid improvement in Ct value in all groups, and no significant differences between groups.

Zarabanda



Zarabanda: Very late treatment (7 days from onset) RCT comparing 11 & 13 PVP-I (0.5% and 2%), and 11 saline spray patients in the USA, showing no significant differences. There was no control group (saline is likely not a placebo, showing efficacy in other trials). There are large unadjusted differences between groups, e.g. 7.1 days from onset for PVP-I versus 4.8 for saline. Baseline Ct was higher for PVP-I, providing less room for improvement. Authors note that they cannot determine if earlier use is more beneficial.

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 povidone-iodine 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 povidone-iodine for COVID-19 that report a comparison with a control group are included in the main analysis. Sensitivity analysis is performed, excluding studies with major issues, epidemiological studies, and studies with minimal available information. 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/pmeta.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.

Arefin, 5/18/2021, Randomized Controlled Trial, Bangladesh, peer-reviewed, 9 authors, study period 1 July, 2020 - 30 October, 2020, trial NCT04549376 (history), excluded in exclusion analyses: study only provides short-term viral load results.	risk of no viral clearance, 78.9% lower, RR 0.21, *p* = 0.02, treatment 4 of 27 (14.8%), control 19 of 27 (70.4%), NNT 1.8, 0.6% nasal irrigation.
	risk of no viral clearance, 89.5% lower, RR 0.11, *p* < 0.001, treatment 2 of 27 (7.4%), control 19 of 27 (70.4%), NNT 1.6, 0.5% nasal irrigation.
	risk of no viral clearance, 52.6% lower, RR 0.47, *p* = 0.006, treatment 9 of 27 (33.3%), control 19 of 27 (70.4%), NNT 2.7, 0.4% nasal irrigation.
	risk of no viral clearance, 80.0% lower, RR 0.20, *p* < 0.001, treatment 5 of 27 (18.5%), control 25 of 27 (92.6%), NNT 1.4, 0.6% nasal spray.
	risk of no viral clearance, 64.0% lower, RR 0.36, *p* < 0.001, treatment 9 of 27 (33.3%), control 25 of 27 (92.6%), NNT 1.7, 0.5% nasal spray.

	risk of no viral clearance, 73.6% lower, RR 0.26, $p < 0.001$, treatment 29 of 135 (21.5%), control 44 of 54 (81.5%), NNT 1.7, all treatment vs. all control.
Baxter, 8/25/2022, Randomized Controlled Trial, USA, peer-reviewed, 12 authors, study period 24 September, 2020 - 21 December, 2020, average treatment delay 4.0 days, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04559035 (history).	risk of hospitalization, 213.5% higher, RR 3.14, $p = 0.47$, treatment 1 of 37 (2.7%), control 0 of 42 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), preprint result reversed.
	risk of no recovery, 56.8% lower, RR 0.43, $p = 0.03$, treatment 6 of 27 (22.2%), control 18 of 35 (51.4%), NNT 3.4, preprint V2.
	risk of transmission, 13.6% lower, RR 0.86, $p = 1.00$, treatment 4 of 27 (14.8%), control 6 of 35 (17.1%), NNT 43, preprint V2.
Choudhury, 12/3/2020, Randomized Controlled Trial, Bangladesh, peer-reviewed, 6 authors, study period 1 February, 2020 - 30 August, 2020.	risk of death, 88.2% lower, RR 0.12, $p < 0.001$, treatment 2 of 303 (0.7%), control 17 of 303 (5.6%), NNT 20.
	risk of hospitalization, 84.4% lower, RR 0.16, $p < 0.001$, treatment 12 of 303 (4.0%), control 77 of 303 (25.4%), NNT 4.7.
	risk of no viral clearance, 96.2% lower, RR 0.04, $p < 0.001$, treatment 8 of 303 (2.6%), control 213 of 303 (70.3%), NNT 1.5, day 7.
Elsersy, 4/19/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Egypt, peer-reviewed, 8 authors, study period March 2021 - July 2021, this trial uses multiple treatments in the treatment arm (combined with glycyrrhizic acid) - results of individual treatments may vary, trial PACTR202101875903773.	risk of hospitalization, 90.9% lower, RR 0.09, $p = 0.06$, treatment 0 of 100 (0.0%), control 5 of 100 (5.0%), NNT 20, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	recovery time, 14.6% lower, relative time 0.85, $p = 0.008$, treatment mean 7.6 (±2.0) n=100, control mean 8.9 (±2.0) n=100.
	recovery time, 49.1% lower, relative time 0.51, $p < 0.001$, treatment mean 5.6 (±1.3) n=100, control mean 11.0 (±3.4) n=100, smell.
	recovery time, 48.2% lower, relative time 0.52, $p < 0.001$, treatment mean 5.7 (±1.0) n=100, control mean 11.0 (±4.0) n=100, taste.
	risk of no viral clearance, 67.7% lower, RR 0.32, $p < 0.001$, treatment 21 of 100 (21.0%), control 65 of 100 (65.0%), NNT 2.3, mid-recovery, day 7.
	risk of no viral clearance, 90.0% lower, RR 0.10, $p = 0.010$, treatment 1 of 100 (1.0%), control 10 of 100 (10.0%), NNT 11, day 10.
	risk of no viral clearance, 29.3% lower, RR 0.71, $p < 0.001$, treatment 70 of 100 (70.0%), control 99 of 100 (99.0%), NNT 3.4, day 4.
	risk of transmission, 91.9% lower, RR 0.08, $p < 0.001$, treatment 12 of 194 (6.2%), control 173 of 227 (76.2%), NNT 1.4,

	symptomatic.
	risk of transmission, 94.0% lower, RR 0.06, $p < 0.001$, treatment 8 of 194 (4.1%), control 157 of 227 (69.2%), NNT 1.5, PCR+.
Elzein, 3/17/2021, Double Blind Randomized Controlled Trial, Lebanon, peer-reviewed, 7 authors, study period June 2020 - September 2020, excluded in exclusion analyses: study only provides short-term viral load results.	relative improvement in Ct value, 88.8% better, RR 0.11, $p < 0.05$, treatment 25, control 9.
Guenezan, 2/4/2021, Randomized Controlled Trial, France, peer-reviewed, 7 authors, study period 1 September, 2020 - 23 October, 2020, trial NCT04371965 (history).	relative improvement in viral titer reduction between baseline and day 1, 63.2% better, RR 0.37, $p = 0.25$, treatment 12, control 12.
Jacox, 10/20/2021, Double Blind Randomized Controlled Trial, USA, trial NCT04584684 (history) (MOR).	129 patient RCT with results unknown and over 2 years late.
Karaaltin, 10/26/2022, Randomized Controlled Trial, Turkey, preprint, 16 authors, study period September 2021 - October 2021.	viral load, 83.1% lower, relative load 0.17, $p = 0.007$, treatment 30, control 30, relative change in viral load, PVP-I vs. control, day 5.
	viral load, 85.5% lower, relative load 0.14, $p = 0.001$, treatment 30, control 30, relative change in viral load, PVP-I + HANI vs. control, day 5.
	viral load, 82.1% lower, relative load 0.18, $p = 0.14$, treatment 30, control 30, relative change in viral load, PVP-I vs. control, day 3.
	viral load, 90.8% lower, relative load 0.09, $p < 0.001$, treatment 30, control 30, relative change in viral load, PVP-I + HANI vs. control, day 3.
Khan, 7/31/2022, Double Blind Randomized Controlled Trial, Pakistan, trial NCT04341688 (history) (GARGLES).	Estimated 50 patient RCT with results unknown and over 1.5 years late.
Matsuyama, 11/28/2022, Randomized Controlled Trial, Japan, peer-reviewed, mean age 45.1, 4 authors, study period 30 November, 2020 - 17 March, 2021, trial jRCT1051200078.	viral infectivity, 69.0% lower, RR 0.31, $p = 0.03$, treatment 4 of 139 (2.9%), control 13 of 140 (9.3%), NNT 16, viral infectivity from culture, day 5.
	risk of no viral clearance, 38.0% lower, HR 0.62, $p = 0.01$, treatment 139, control 140, inverted to make HR<1 favor treatment, day 5, primary outcome.
Mohamed, 9/9/2020, Randomized Controlled Trial, Malaysia, preprint, 16 authors, study period 22 June, 2020 - 29 June, 2020, trial NCT04410159 (history).	risk of no viral clearance, 85.7% lower, RR 0.14, $p = 0.17$, treatment 0 of 5 (0.0%), control 3 of 5 (60.0%), NNT 1.7, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 12.
Natto, 7/29/2022, Randomized Controlled Trial, Saudi Arabia, peer-reviewed, 7 authors, study period June 2021 - July 2021, this trial compares with another treatment - results may be better when	risk of viral load, 73.6% lower, RR 0.26, $p = 0.27$, treatment 12, control 12, relative improvement in Ct value, both genes combined.

compared to placebo, trial NCT04941131 (history), excluded in exclusion analyses: study only provides short-term viral load results.	risk of viral load, 96.2% lower, RR 0.04, *p* = 0.12, treatment mean 4.43 (±4.78) n=12, control mean 0.17 (±7.67) n=12, relative improvement in Ct value, E gene.
	risk of viral load, 44.4% lower, RR 0.56, *p* = 0.60, treatment mean 3.33 (±5.6) n=12, control mean 1.85 (±7.68) n=12, relative improvement in Ct value, S gene.
Pablo-Marcos, 10/25/2021, prospective, Spain, peer-reviewed, mean age 43.0, 6 authors, study period May 2020 - November 2020, excluded in exclusion analyses: unadjusted results with no group details.	relative viral load, 29.2% better, RR 0.71, *p* = 0.40, treatment 31, control 40, 3rd PCR (mid-recovery).
	relative viral load, 9.1% better, RR 0.91, *p* = 0.91, treatment 31, control 40, 4th PCR (most patients recovered).
Sevinç Gül, 7/29/2022, Randomized Controlled Trial, Turkey, peer-reviewed, 4 authors, study period 1 September, 2021 - 1 December, 2021, this trial compares with another treatment - results may be better when compared to placebo, trial NCT05214196 (history), excluded in exclusion analyses: study only provides short-term viral load results.	risk of viral load, 99.5% lower, RR 0.005, *p* = 0.37, treatment mean 1.85 (±7.06) n=21, control mean 0.01 (±5.89) n=20, relative improvement in Ct value.
Sirijatuphat, 8/22/2022, prospective, Thailand, preprint, median age 34.0, 4 authors, study period 15 February, 2021 - 15 March, 2021, trial TCTR20210125002, excluded in exclusion analyses: study only provides short-term viral load results.	viral load, 33.3% lower, relative load 0.67, *p* = 0.58, after median 2560.0 IQR 17790.0 n=12, before median 3840.0 IQR 9600.0 n=12, *before values 640.0 640.0 40960.0 2560.0 10240.0 10240.0 640.0 2560.0 10240.0 5120.0 40960.0 640.0*, *after values 10.0 40.0 2560.0 40960.0 5120.0 1280.0 160.0 2560.0 40960.0 40960.0 10240.0 40.0*, relative median viral titer, 3 min, left vs. baseline, Mann-Whitney, Table 3.
	viral load, 87.5% lower, relative load 0.12, *p* = 0.04, after median 480.0 IQR 4340.0 n=12, before median 3840.0 IQR 9600.0 n=12, *before values 640.0 640.0 40960.0 2560.0 10240.0 10240.0 640.0 2560.0 10240.0 5120.0 40960.0 640.0*, *after values 80.0 160.0 10240.0 320.0 320.0 10240.0 40.0 640.0 640.0 40960.0 2560.0 0.0*, relative median viral titer, 3 min, right vs. baseline, Mann-Whitney, Table 3.
	viral load, 83.3% lower, relative load 0.17, *p* = 0.11, after median 640.0 IQR 6240.0 n=12, before median 3840.0 IQR 9600.0 n=12, *before values 640.0 640.0 40960.0 2560.0 10240.0 10240.0 640.0 2560.0 10240.0 5120.0 40960.0 640.0*, *after values 160.0 10.0 10240.0 640.0 160.0 1280.0 320.0 640.0 5120.0 40960.0 20480.0 0.0*, relative median viral titer, 4 hours, right vs. baseline, Mann-Whitney, Table 3.
Sulistyani, 3/15/2022, Single Blind Randomized Controlled Trial, Indonesia, peer-reviewed, 9 authors, study period July 2021 - September 2021.	relative improvement in Ct value, 6.3% better, RR 0.94, *p* = 0.74, treatment mean 12.905 (±5.96) n=15, control mean 12.088 (±7.38) n=15, 1% PVP-I vs. water, day 5.
	relative improvement in Ct value, 11.3% better, RR 0.89, *p* = 0.54, treatment mean 13.628 (±6.28) n=15, control mean 12.088 (±7.38) n=15, 0.5% PVP-I vs. water, day 5.

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.

Fantozzi, 7/28/2022, Randomized Controlled Trial, Italy, peer-reviewed, 14 authors, study period December 2020 - May 2021, this trial compares with another treatment - results may be better when compared to placebo, excluded in exclusion analyses: study only provides short-term viral load results.	risk of no viral clearance, 31.2% lower, RR 0.69, $p = 0.26$, treatment 5 of 8 (62.5%), control 10 of 11 (90.9%), NNT 3.5, T2.
	risk of no viral clearance, 58.7% lower, RR 0.41, $p = 0.04$, treatment 3 of 8 (37.5%), control 10 of 11 (90.9%), NNT 1.9, T1.
Ferrer, 12/22/2021, Randomized Controlled Trial, Spain, peer-reviewed, 19 authors, excluded in exclusion analyses: study only provides short-term viral load results.	relative viral load reduction, 34.0% better, RR 0.66, $p = 0.82$, treatment 9, control 12, PVP-I vs. water, data from Table S1.
	relative viral load T4 vs. T1, 93.0% better, RR 0.07, $p = 0.35$, treatment 9, control 9, data from Table S1.
Jamir, 12/13/2021, retrospective, India, peer-reviewed, 6 authors, study period June 2020 - October 2020.	risk of death, 57.0% lower, HR 0.43, $p < 0.001$, treatment 39 of 163 (23.9%), control 62 of 103 (60.2%), NNT 2.8, adjusted per study, multivariable, Cox proportional hazards.
Seneviratne, 12/14/2020, Randomized Controlled Trial, Singapore, peer-reviewed, 12 authors, study period June 2020 - August 2020, excluded in exclusion analyses: study only provides short-term viral load results.	relative fold change, 32.9% better, RR 0.67, $p < 0.01$, treatment 4, control 2, PVP-I vs. water, 6 hours.
Zarabanda, 11/1/2021, Randomized Controlled Trial, USA, peer-reviewed, 13 authors, average treatment delay 7.0 days, this trial compares with another treatment - results may be better when compared to placebo.	risk of no recovery, 26.9% higher, RR 1.27, $p = 1.00$, treatment 3 of 13 (23.1%), control 2 of 11 (18.2%), 2%.
	risk of no recovery, 50.0% higher, RR 1.50, $p = 1.00$, treatment 3 of 11 (27.3%), control 2 of 11 (18.2%), 0.5%.
	risk of no viral clearance, no change, RR 1.00, $p = 1.00$, treatment 2 of 7 (28.6%), control 2 of 7 (28.6%), day 5, minus strand PCR.

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.

Keating, 6/30/2022, Randomized Controlled Trial, USA, this trial uses multiple treatments in the treatment arm (combined with chlorhexidine) - results of individual treatments may vary, trial NCT04478019 (history) (SHIELD).	245 patient RCT with results unknown and over 1.5 years late.
Seet, 4/14/2021, Cluster Randomized Controlled Trial, Singapore, peer-reviewed, 15 authors, study period 13 May, 2020 - 31 August, 2020, this trial	risk of symptomatic case, 44.7% lower, RR 0.55, $p = 0.002$, treatment 42 of 735 (5.7%), control 64 of 619 (10.3%), NNT 22.

compares with another treatment - results may be better when compared to placebo, trial NCT04446104 (history).	risk of case, 31.1% lower, RR 0.69, p = 0.01, treatment 338 of 735 (46.0%), control 433 of 619 (70.0%), NNT 4.2, adjusted per study, odds ratio converted to relative risk, model 6.

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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