Fluvoxamine for COVID-19: real-time meta analysis of 21 studies

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https://c19early.org/fmeta.html

Abstract

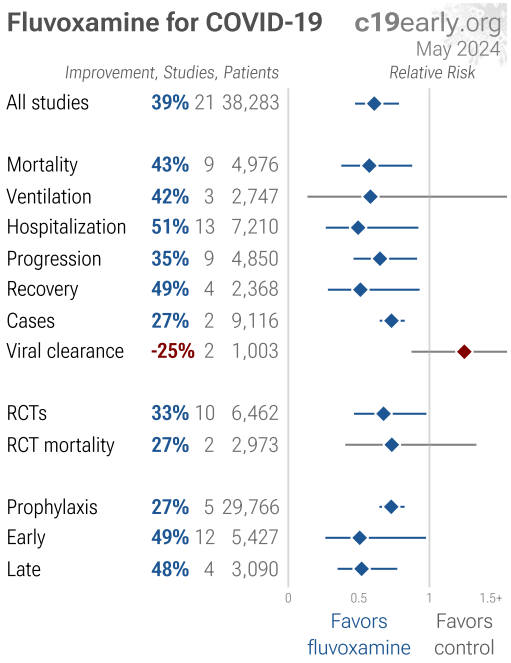
Statistically significant lower risk is seen for mortality, hospitalization, progression, recovery, and cases. 14 studies from 14 independent teams in 8 countries show statistically significant improvements.

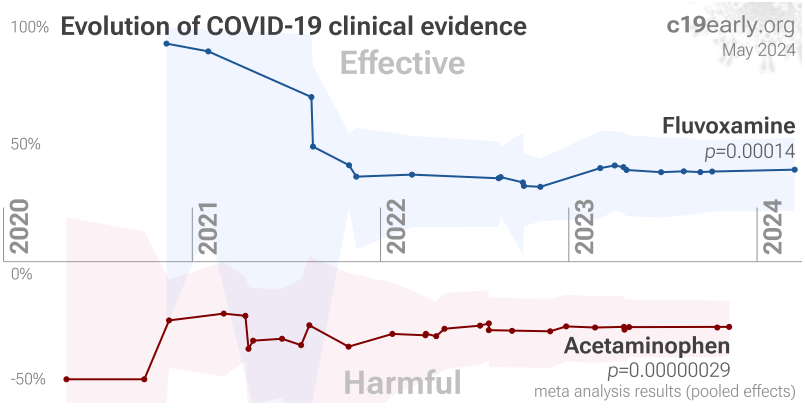
Meta analysis using the most serious outcome reported shows 39% [22-53%] lower risk. Results are similar for Randomized Controlled Trials.

Results are robust — in exclusion sensitivity analysis 12 of 21 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

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.

All data to reproduce this paper and sources are in the appendix. Other meta analyses show significant improvements with fluvoxamine for mortality [Deng], hospitalization [Deng, Deng (B), Lee, Lu, Marcec], and severity [Nakhaee].





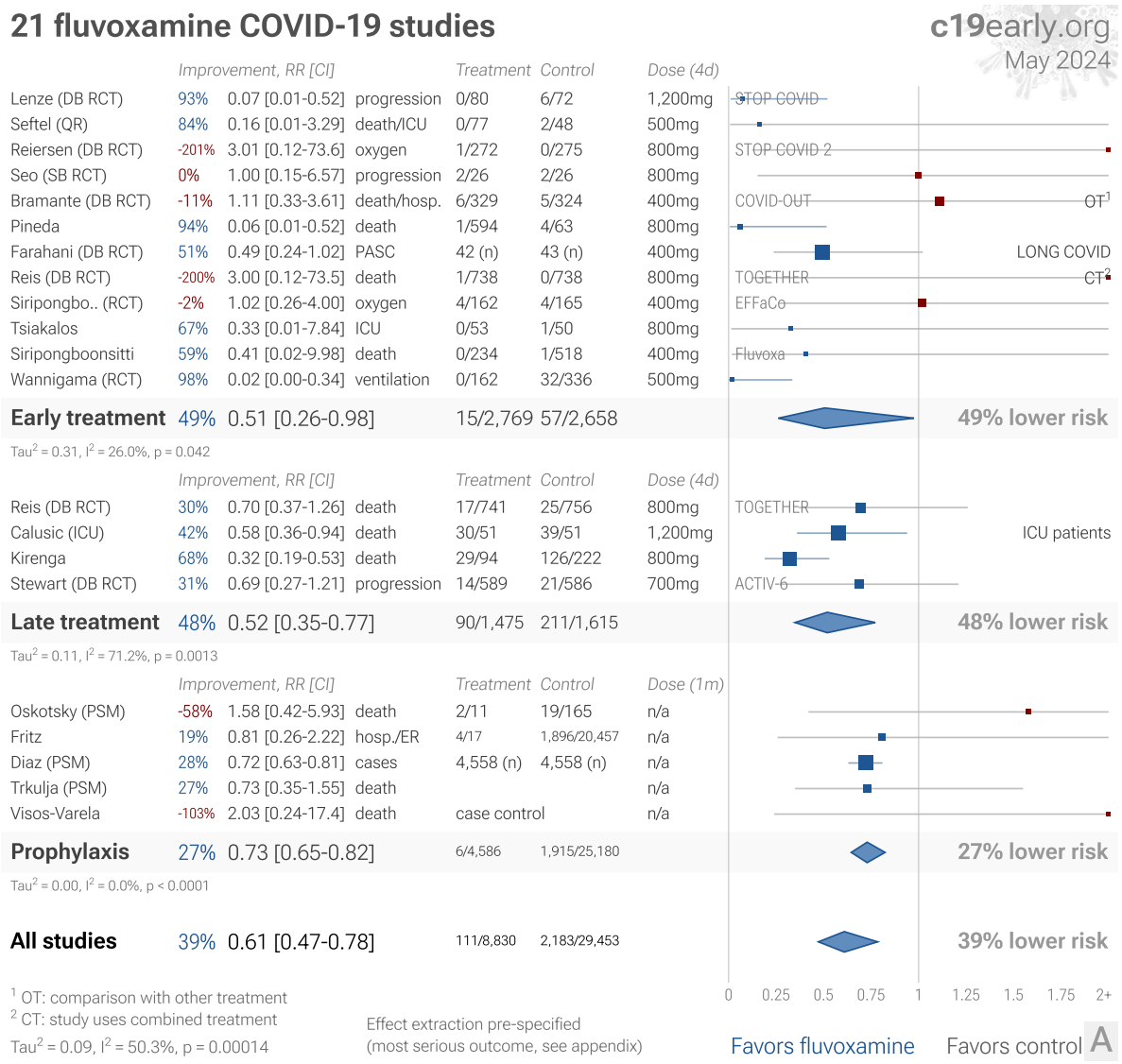
HIGHLIGHTS

Fluvoxamine reduces risk for COVID-19 with very high confidence for pooled analysis, high confidence for mortality, hospitalization, progression, and recovery, and low confidence for cases, however increased risk is seen with very low confidence for viral clearance.

26th treatment shown effective with ≥3 clinical studies in November 2021, now with p = 0.00014 from 21 studies, and recognized in 3 countries.

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

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 69 treatments.



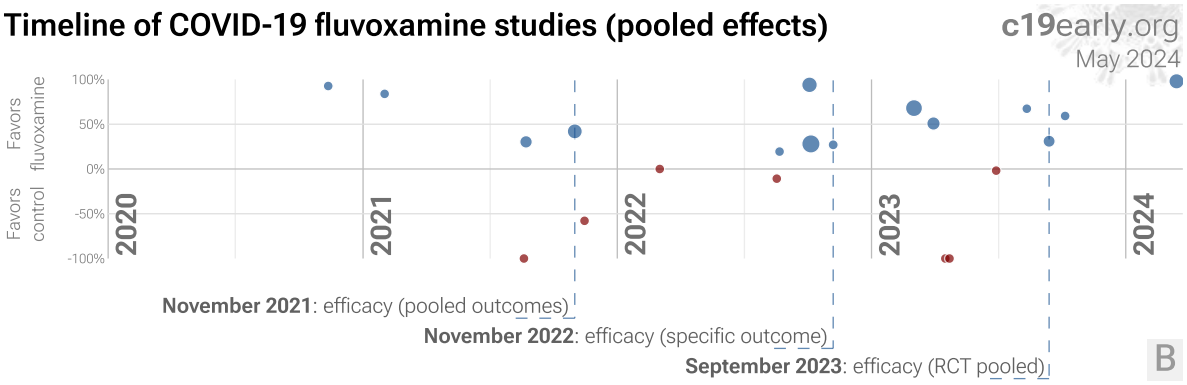


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in fluvoxamine 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 RCTs only was delayed by 22.4 months, compared to using all studies. Efficacy based on specific outcomes was delayed by 12.2 months, compared to using pooled outcomes.

Introduction

Immediate treatment recommended. SARS-CoV-2 infection primarily begins in the upper respiratory tract and may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems, which may lead to cytokine storm, pneumonia, ARDS, neurological issues [Duloquin, Hampshire, Scardua-Silva, Sodagar, Yang], cardiovascular complications [Eberhardt], organ failure, and death. Minimizing replication as early as possible is recommended.

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, Niarakis], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 7,000 compounds may reduce COVID-19 risk [c19early.org], 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 fluvoxamine 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, 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.

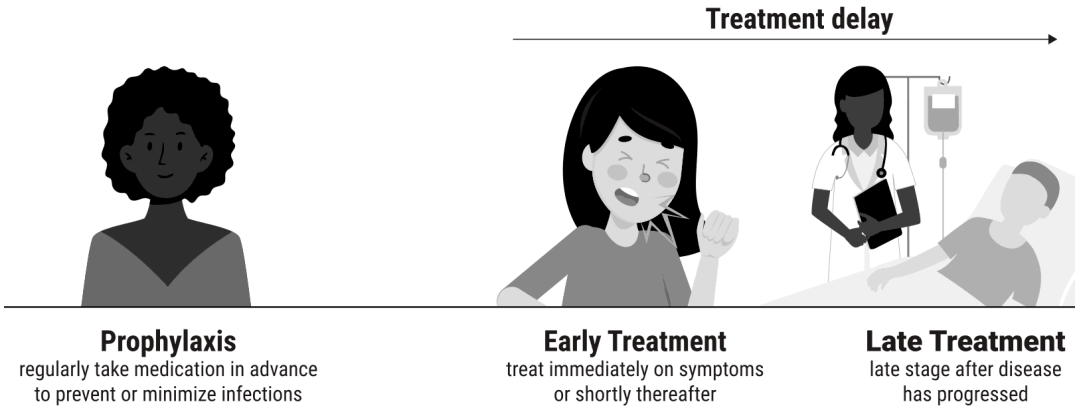


Figure 2. Treatment stages.

Mechanisms of Action

Table 1 shows potential mechanisms of action for the treatment of COVID-19 using fluvoxamine.

FIASMA	Fluvoxamine is a functional inhibitor of acid sphingomyelinase (FIASMA). SARS-CoV-2 activates the ASM/ceramide system which may facilitate viral entry. ASM inhibition may reduce the concentration of ceramides and inhibit viral entry [Carpinteiro, Carpinteiro (B), Hashimoto, Hoertel].
Sigma-1 activation	Fluvoxamine may reduce clinical deterioration via σ-1 (S1R) receptor activation, which regulates cytokine production [Hashimoto, Hashimoto (B), Sukhatme].
Platelet activation	Platelet activation may contribute to COVID-19 severity. Fluvoxamine inhibits platelet activation [Battinelli, Sukhatme].
Lysosomal trafficking	SARS-CoV-2 uses lysosomal trafficking to escape from infected cells. Fluvoxamine is lysosomotropic and interferes with endolysosomal viral trafficking [Hashimoto, Norinder, Sukhatme].
Heme oxygenase	COVID-19 risk may be related to low intracellular heme oxygenase (HO-1). Fluvoxamine increases HO-1 and HO-1 has cytoprotective and anti-inflammatory properties [Almási, Hooper, Hooper (B)].
Mast cell degranulation	Fluvoxamine may reduce cytokine storm due to decreased mast cell degranulation [Sukhatme].
Melatonin	Melatonin may be beneficial for COVID-19, and fluvoxamine may elevate melatonin levels via CYP1A2 and CYP2C19 inhibition [Anderson, Camp, Hashimoto, Ramos, Sukhatme].

Table 1. **Fluvoxamine mechanisms of action.**

Preclinical Research

2 *In Silico* studies support the efficacy of fluvoxamine [Abatematteo, Alkafaas].

An *In Vitro* study supports the efficacy of fluvoxamine [Abatematteo].

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 2 summarizes the results for all stages combined, for Randomized Controlled Trials, and for specific outcomes. Table 3 shows results by treatment stage. Figure 3 plots individual results by treatment stage. Figure 4, 5, 6, 7, 8, 9, 10, 11, and 12 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, recovery, cases, and viral clearance.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	39% [22-53%] ***	21	38,283	307
Randomized Controlled Trials	33% [2-53%] *	10	6,462	221
Mortality	43% [12-62%] *	9	4,976	134
Ventilation	42% [-151-86%]	3	2,747	60
ICU admission	-10% [-326-72%]	3	855	17
Hospitalization	51% [8-73%] *	13	7,210	245
Recovery	49% [7-72%] *	4	2,368	57
Cases	27% [18-35%] ****	2	9,116	10
Viral	-25% [-78-13%]	2	1,003	31
RCT mortality	27% [-33-60%]	2	2,973	62
RCT hospitalization	49% [-27-79%]	8	6,325	204

Table 2. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, and for specific outcomes.** Results show the percentage improvement with treatment and the 95% confidence interval. * p<0.05 ** p<0.01 **** p<0.0001.

	Early treatment	*Late treatment*	*Prophylaxis*
All studies	49% [2-74%] *	48% [23-65%] **	27% [18-35%] ****
Randomized Controlled Trials	33% [-37-67%]	31% [-9-56%]	
Mortality	67% [-236-97%]	51% [22-69%] **	5% [-76-49%]
Ventilation	77% [-1354-100%]	22% [-28-54%]	
ICU admission	37% [-160-85%]		-395% [-7042-66%]
Hospitalization	62% [5-85%] *	22% [-3-41%]	1% [-118-55%]
Recovery	88% [-446-100%]	45% [6-68%] *	
Cases			27% [18-35%] ****
Viral	-4% [-19-9%]	-49% [-138-6%]	
RCT mortality	-200% [-7253-88%]	30% [-26-63%]	
RCT hospitalization	53% [-69-87%]	22% [-3-41%]	

Table 3. **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<0.01 **** p<0.0001.

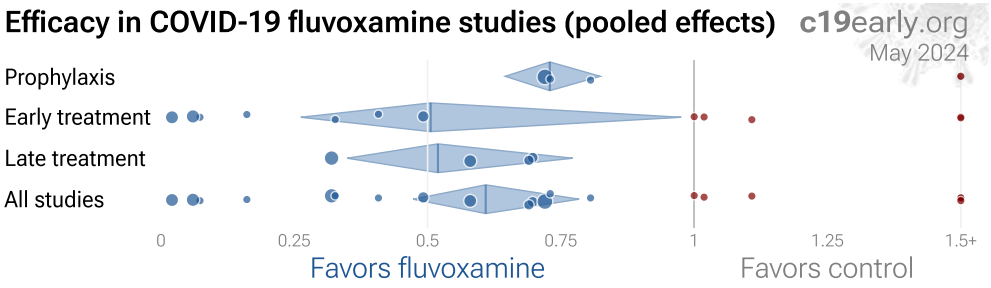


Figure 3. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

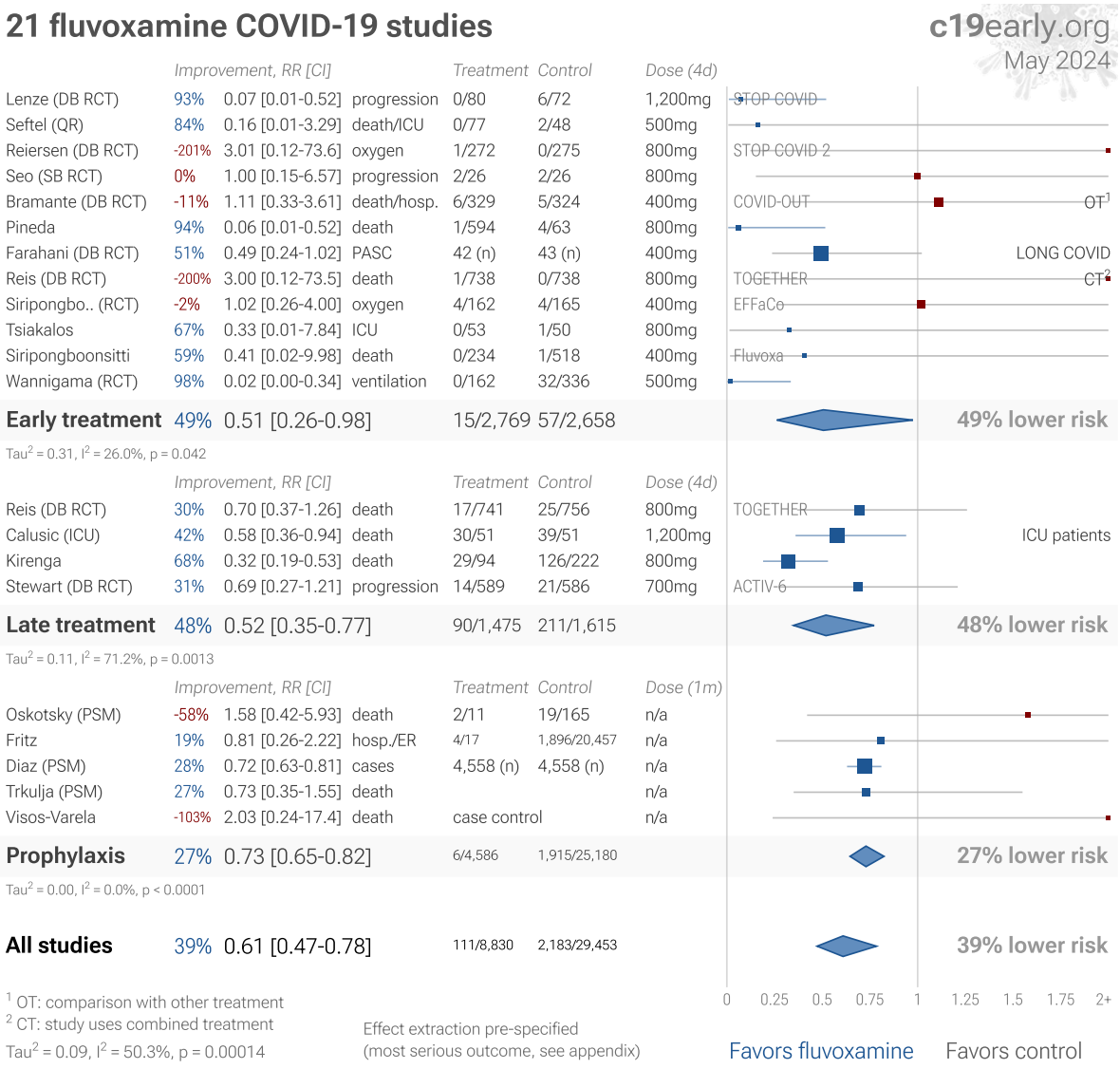


Figure 4. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

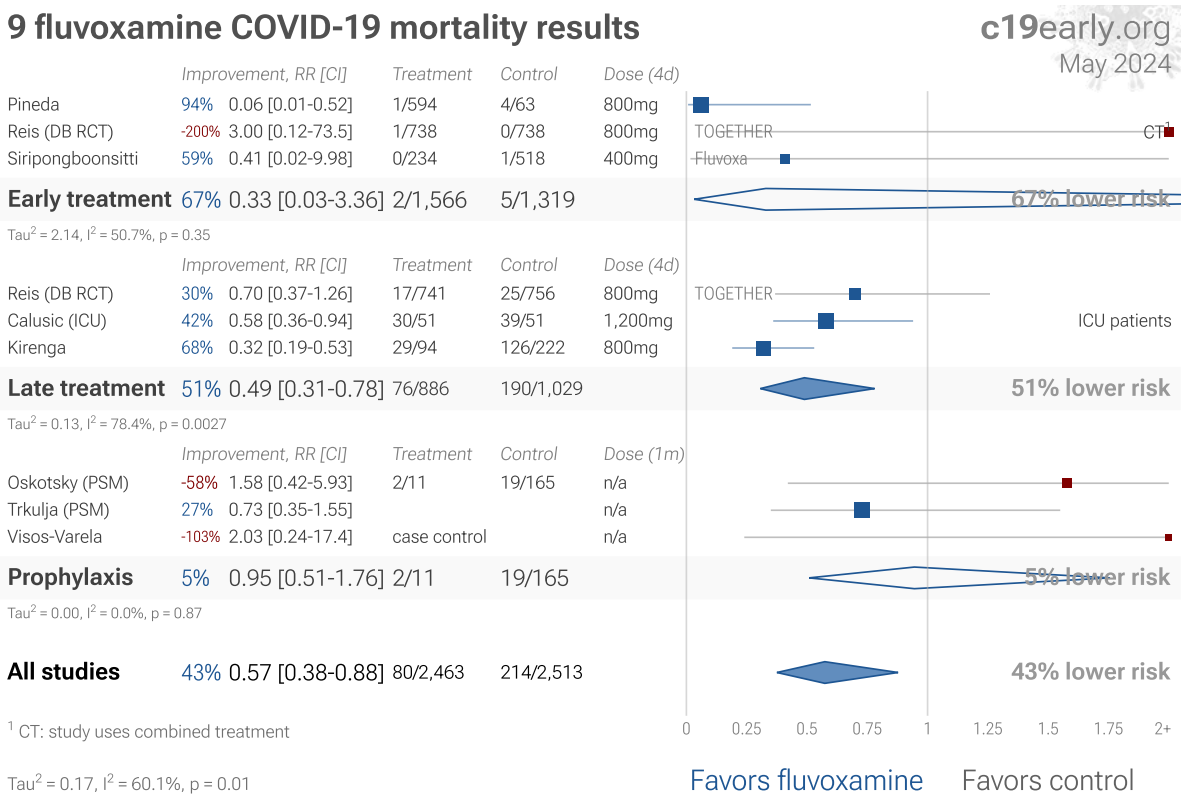


Figure 5. Random effects meta-analysis for mortality results.

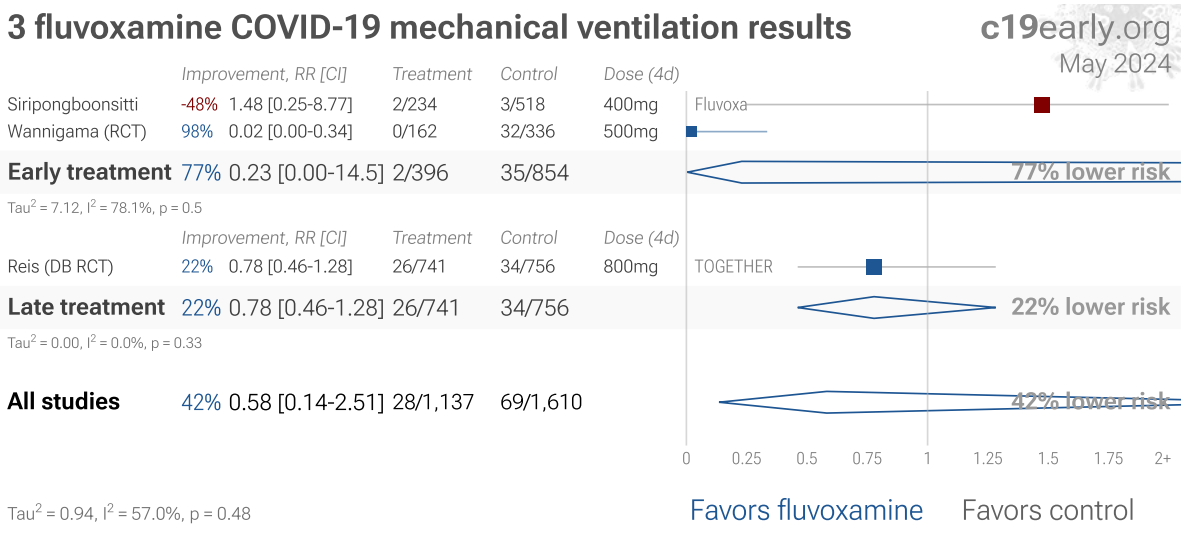


Figure 6. Random effects meta-analysis for ventilation.

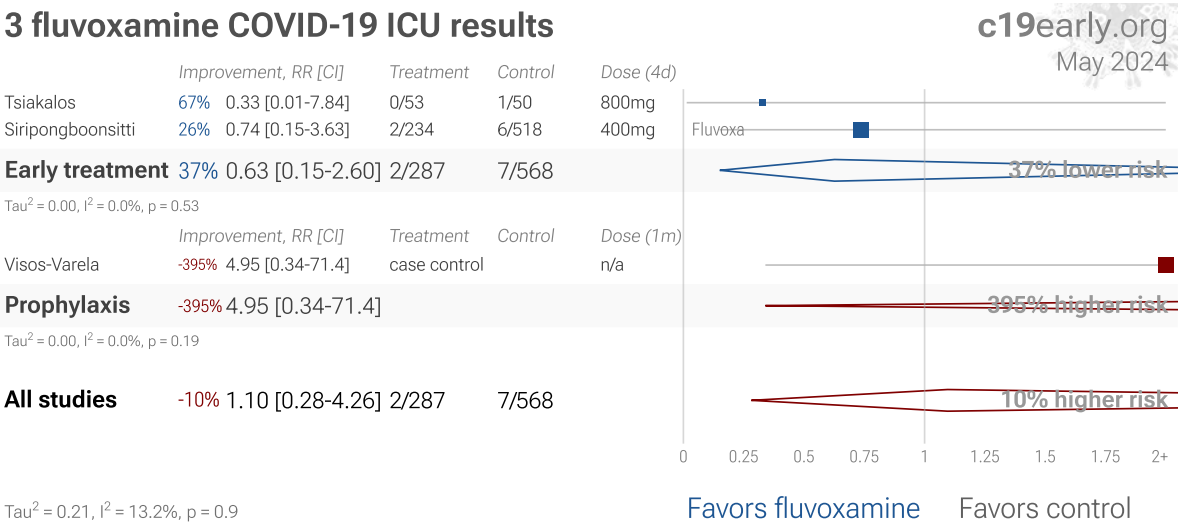


Figure 7. Random effects meta-analysis for ICU admission.

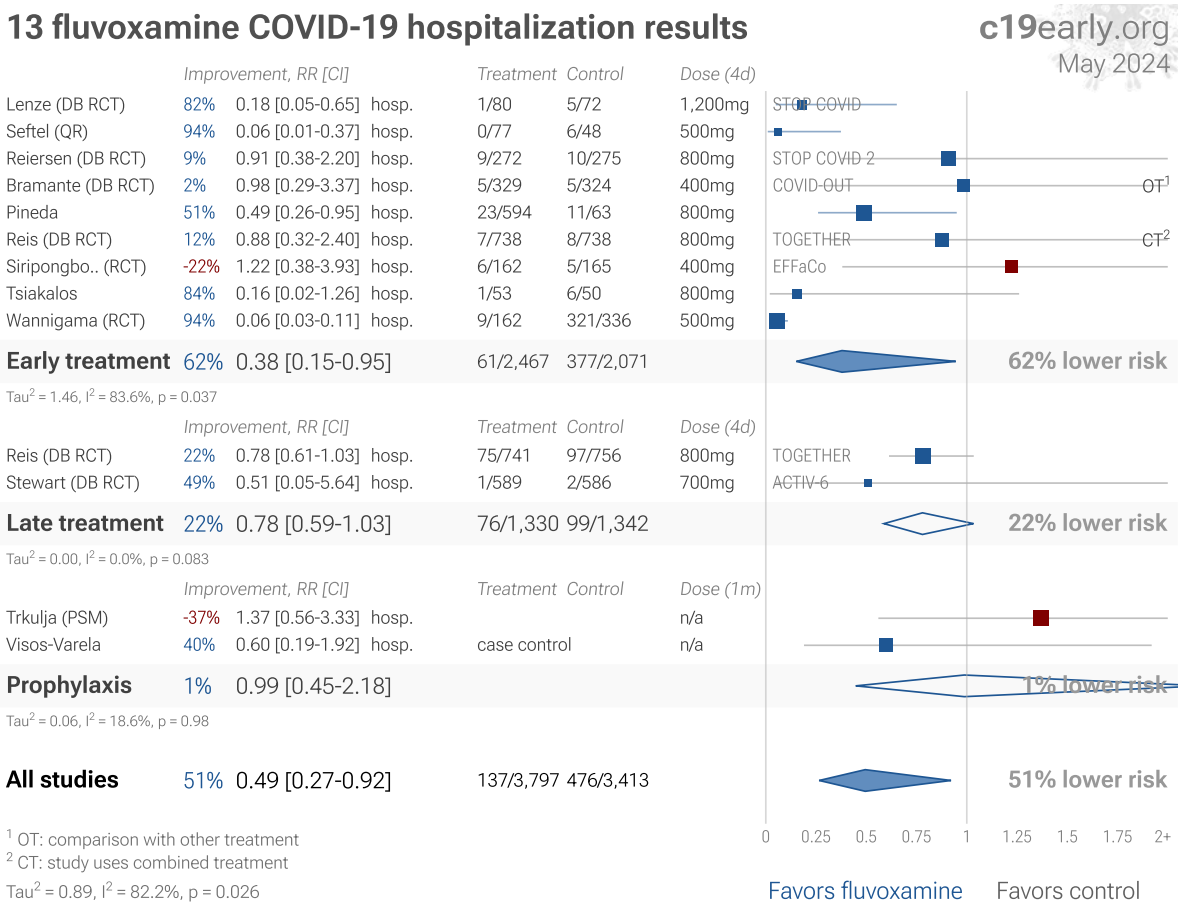


Figure 8. Random effects meta-analysis for hospitalization.

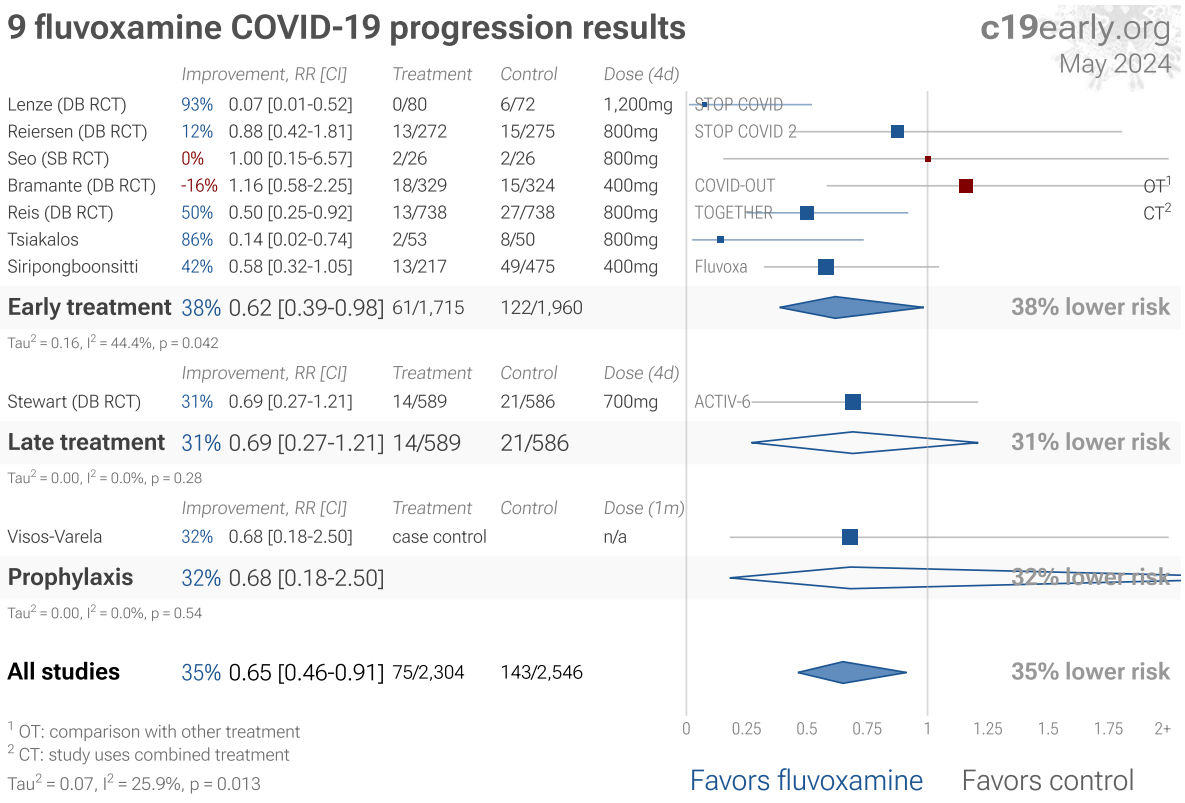


Figure 9. Random effects meta-analysis for progression.

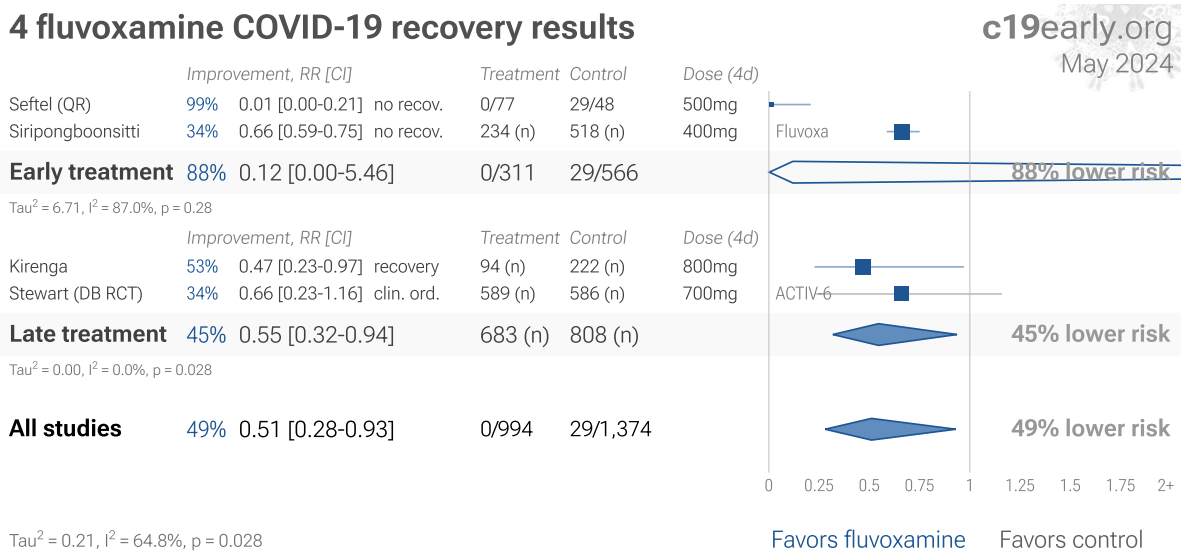


Figure 10. Random effects meta-analysis for recovery.

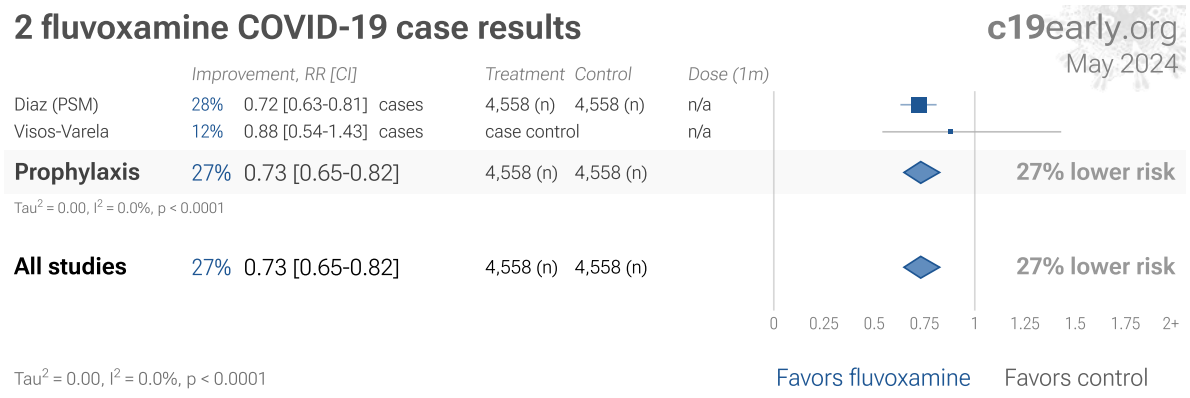


Figure 11. Random effects meta-analysis for cases.

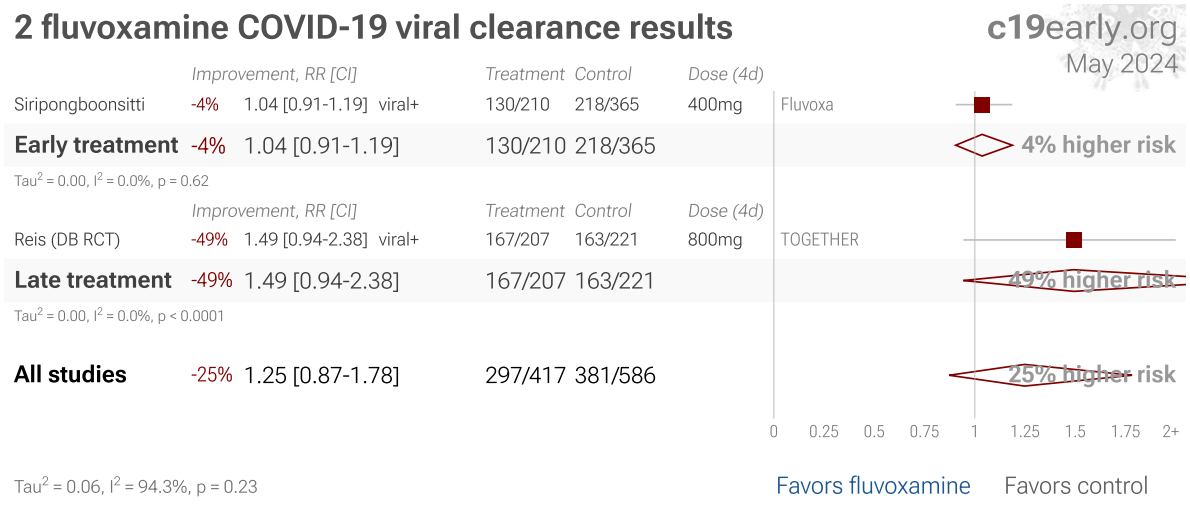


Figure 12. Random effects meta-analysis for viral clearance.

Randomized Controlled Trials (RCTs)

Figure 13 shows a comparison of results for RCTs and non-RCT studies. Figure 14, 15, and 16 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 2 and Table 3.

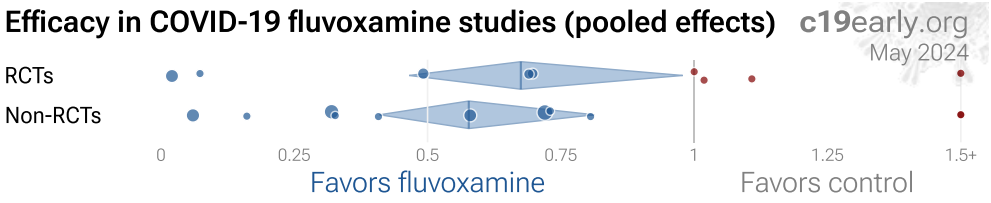


Figure 13. Results for RCTs and non-RCT studies.

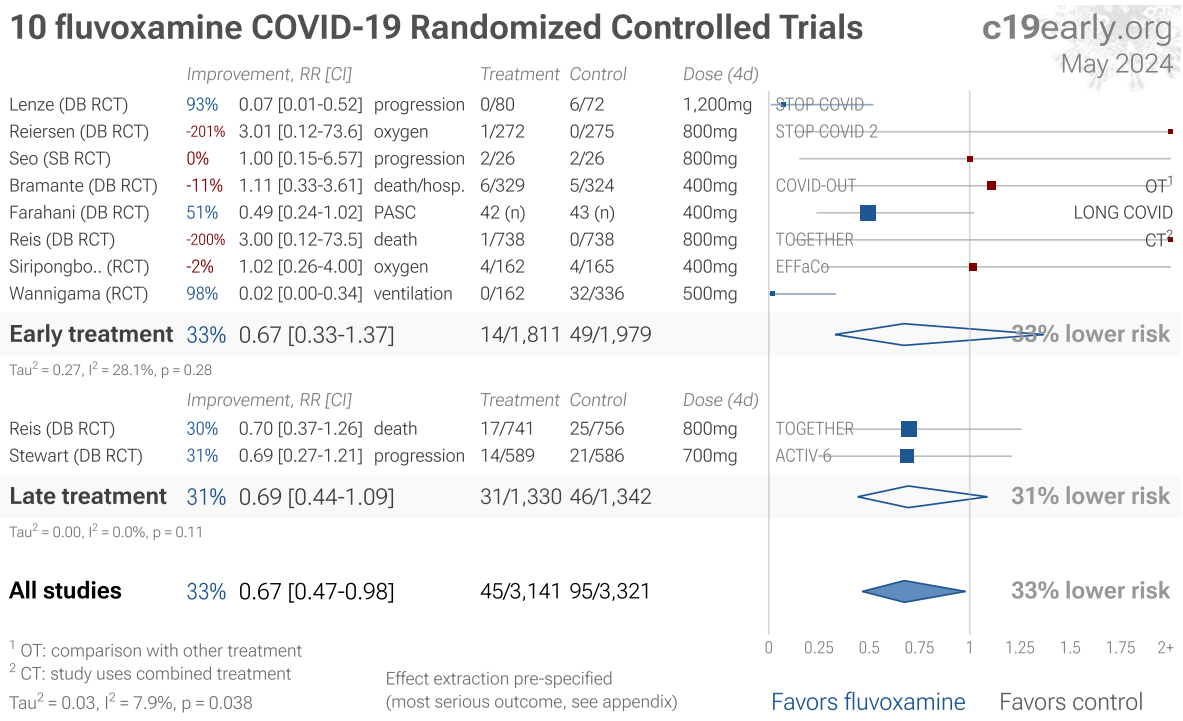


Figure 14. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

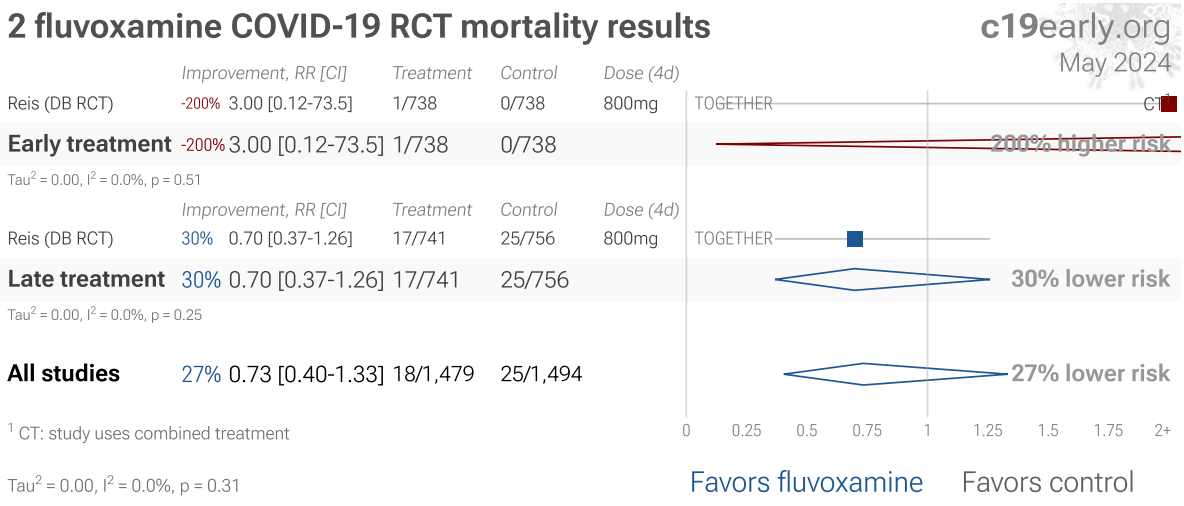


Figure 15. **Random effects meta-analysis for RCT mortality results.**

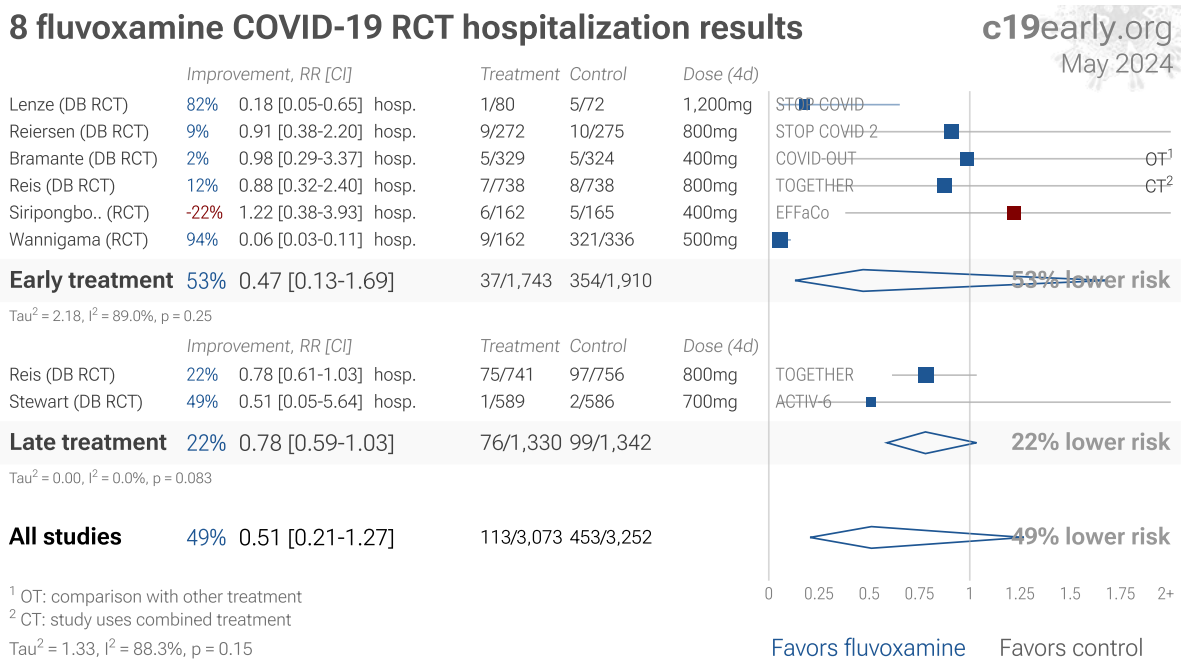


Figure 16. **Random effects meta-analysis for RCT hospitalization results.**

RCTs have many potential biases. 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, reporting, 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 69 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 fluvoxamine 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 studies 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 (B) 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 may 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 7+ months faster (8+ months for low-cost treatments). 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 these, 28 have been confirmed in RCTs, with a mean delay of 7.0 months. When considering only low cost treatments, 23 have been confirmed with a delay of 8.4 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.

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 et al.* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden et al.* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and *Kumar et al.* report only 2.5 hours improvement for inpatient treatment.

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

Table 4. **Studies of baloxavir for influenza show that early treatment is more effective.**

Figure 17 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 69 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

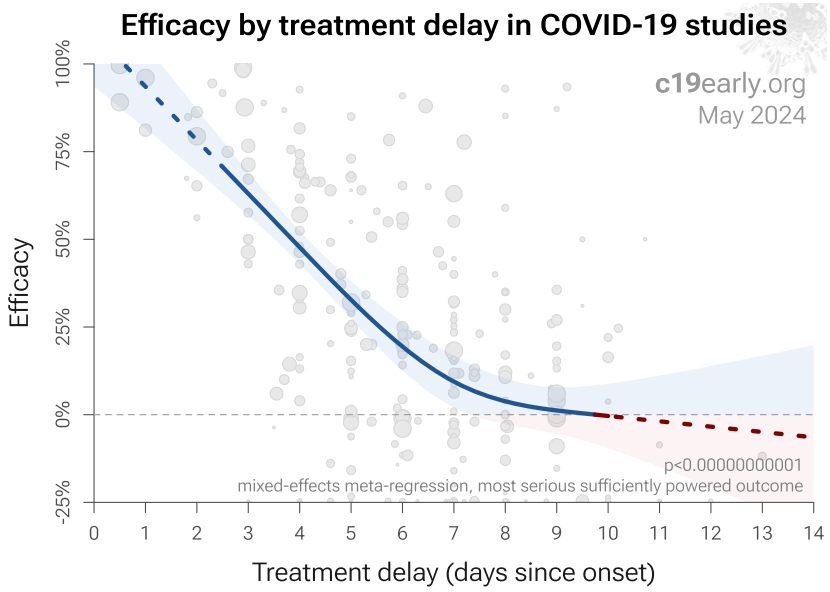


Figure 17. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 69 treatments.

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

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

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

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

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

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

Meta analysis. The distribution of studies will alter the outcome of a meta analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though early treatment is very effective. All meta analyses combine heterogeneous studies, varying in population, variants, and potentially all factors above, and therefore may obscure efficacy by including studies where treatment is less effective. Generally, we expect the estimated effect size from meta analysis to be less than that for the optimal case. Looking at all studies is valuable for providing an overview of all research, important to avoid cherry-picking, and informative when a positive result is found despite combining less-optimal situations. However, the resulting estimate does not apply to specific cases such as early treatment in high-risk populations. While we present results for all studies, we also present treatment time and individual outcome analyses, which may be more informative for specific use cases.

Pooled Effects

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

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

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

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

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

Validating pooled outcome analysis for COVID-19. Analysis of the the association between different outcomes across studies from all 69 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 18 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 19 shows that improved recovery is very strongly associated with lower mortality ($p < 0.000000000001$). Considering the extremes, *Singh et al.* show an association between viral clearance and hospitalization or death, with $p = 0.003$ after excluding one large outlier from a mutagenic treatment, and based on 44 RCTs including 52,384 patients. Figure 20 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to *Singh et al.*, with higher confidence due to the larger number of studies. As with *Singh et al.*, the confidence increases when excluding the outlier treatment, from $p = 0.0000031$ to $p = 0.0000000067$.

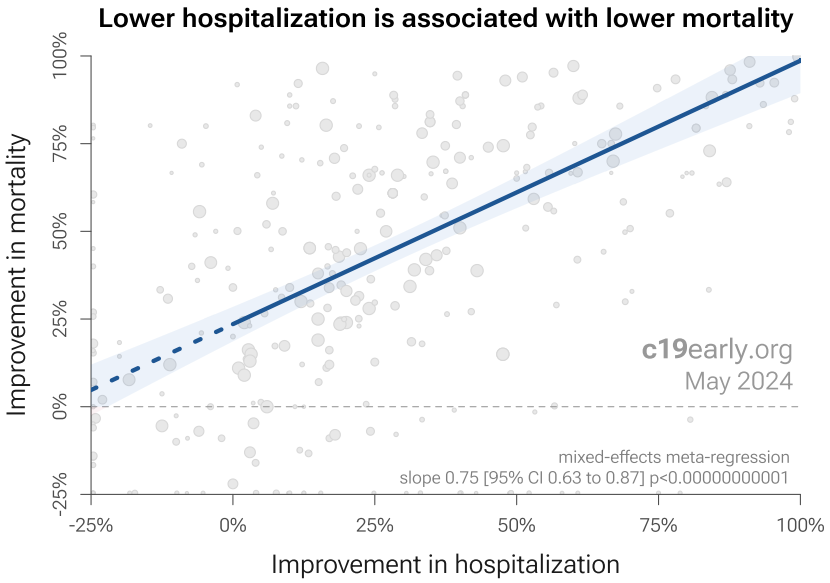


Figure 18. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

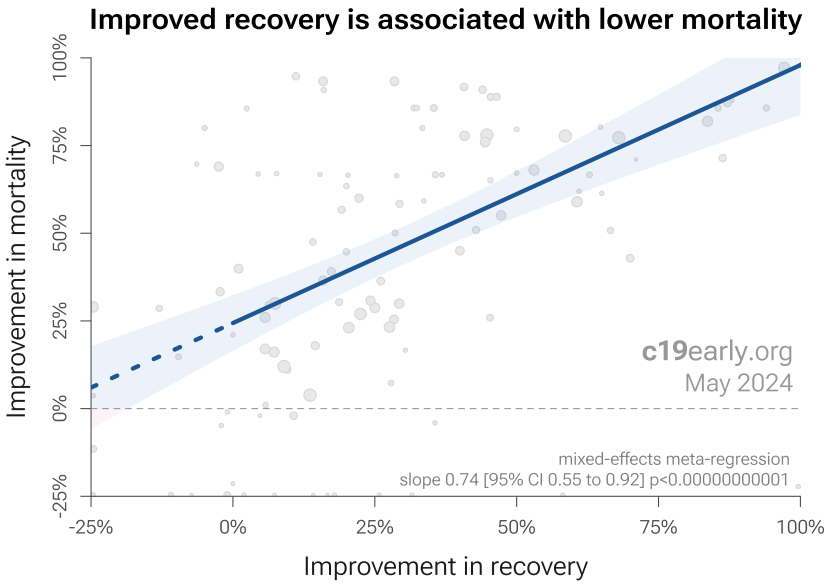


Figure 19. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

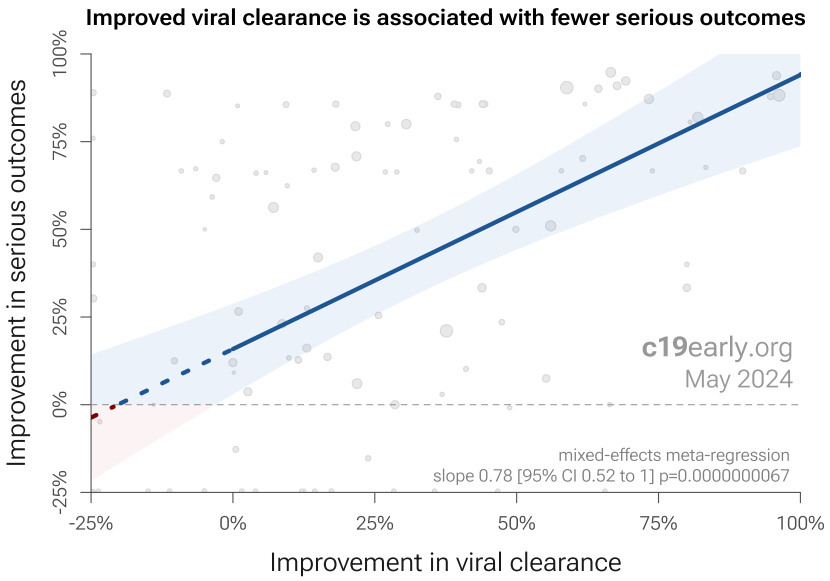


Figure 18. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

Pooled outcomes identify efficacy 5 months faster (6 months for RCTs). 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 these have been confirmed with one or more specific outcomes, with a mean delay of 4.7 months. When restricting to RCTs only, 54% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 5.5 months. Figure 21 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

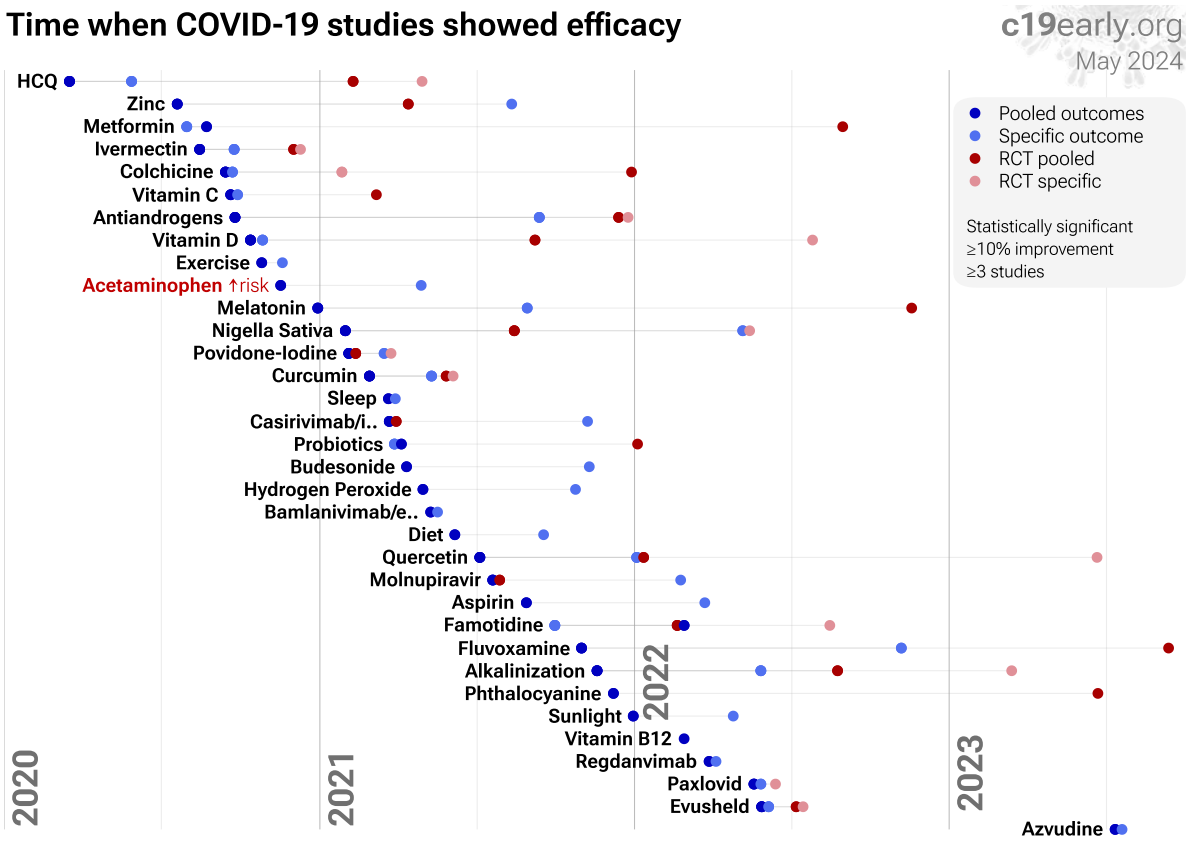


Figure 21. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

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

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

Discussion

Publication bias. Publishing is often biased towards positive results, however evidence suggests that there may be a negative bias for inexpensive treatments for COVID-19. Both negative and positive results are very important for COVID-19, media in many countries prioritizes negative results for inexpensive treatments (inverting the typical incentive for scientists that value media recognition), and there are many reports of difficulty publishing positive results *Boulware, Meeus, Meneguesso, twitter.com*. For fluvoxamine, 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 22 shows a scatter plot of results for prospective and retrospective studies. 71% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 64% of prospective studies, consistent with a bias toward publishing positive results. The median effect size for retrospective studies is 27% improvement, compared to 36% for prospective studies, suggesting a potential bias towards publishing results showing lower efficacy.

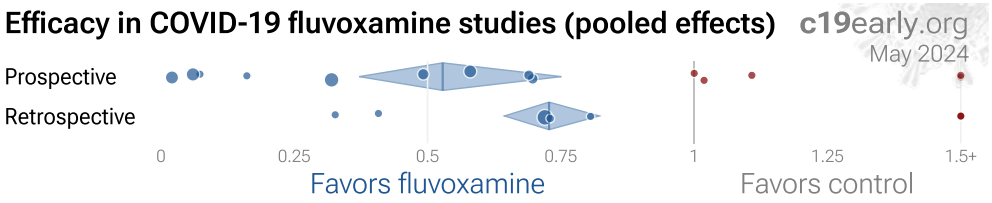


Figure 22. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

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 23 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.

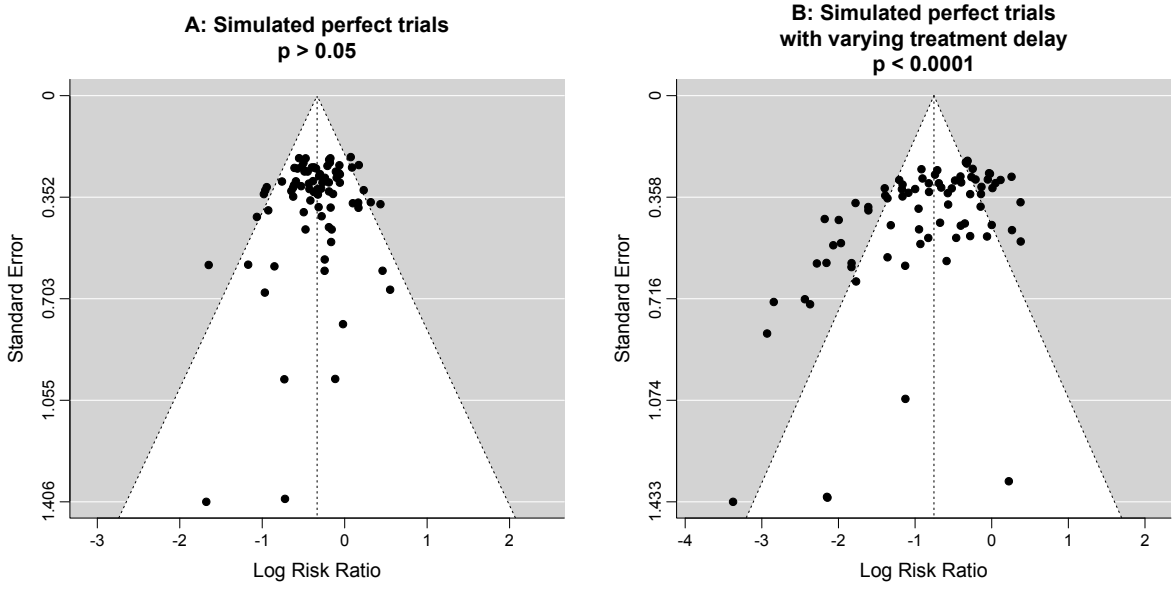


Figure 23. **Example funnel plot analysis for simulated perfect trials.**

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. Fluvoxamine for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 fluvoxamine 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 fluvoxamine trials represent the optimal conditions for efficacy.

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

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

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

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

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

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone *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 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 21 studies compare against other treatments, which may reduce the effect seen. 1 of 21 studies combine treatments. The results of fluvoxamine alone may differ. 1 of 10 RCTs use combined treatment. Currently all studies are peer-reviewed. Other meta analyses show significant improvements with fluvoxamine for mortality *Deng*, hospitalization *Deng, Deng (B), Lee, Lu, Marcec*, and severity *Nakhaee*.

Reviews. Many reviews cover fluvoxamine for COVID-19, presenting additional background on mechanisms and related results, including *Hashimoto, Hashimoto (B), Hashimoto (C), Hoertel (B), Kirsch, Scheim, Sukhatme*.

Perspective

Results compared with other treatments. SARS-CoV-2 infection and replication involves a complex interplay of 50+ host and viral proteins and other factors *Lui, Lv, Malone, Murigneux, Niarakis*, providing many therapeutic targets. Over 7,000 compounds have been predicted to reduce COVID-19 risk *c19early.org*, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 24 shows an overview of the results for fluvoxamine in the context of multiple COVID-19 treatments, and Figure 25 shows a plot of efficacy vs. cost for COVID-19 treatments.

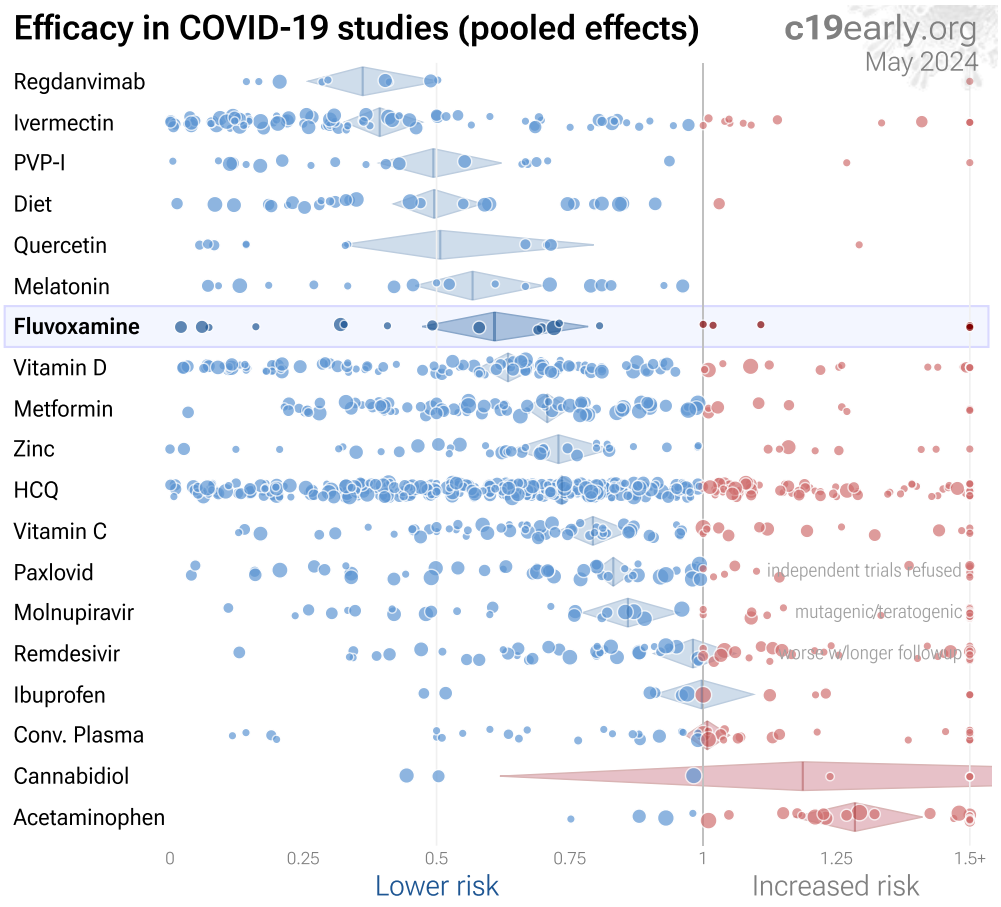


Figure 24. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 7,000+ proposed treatments show efficacy *c19early.org (B)*.

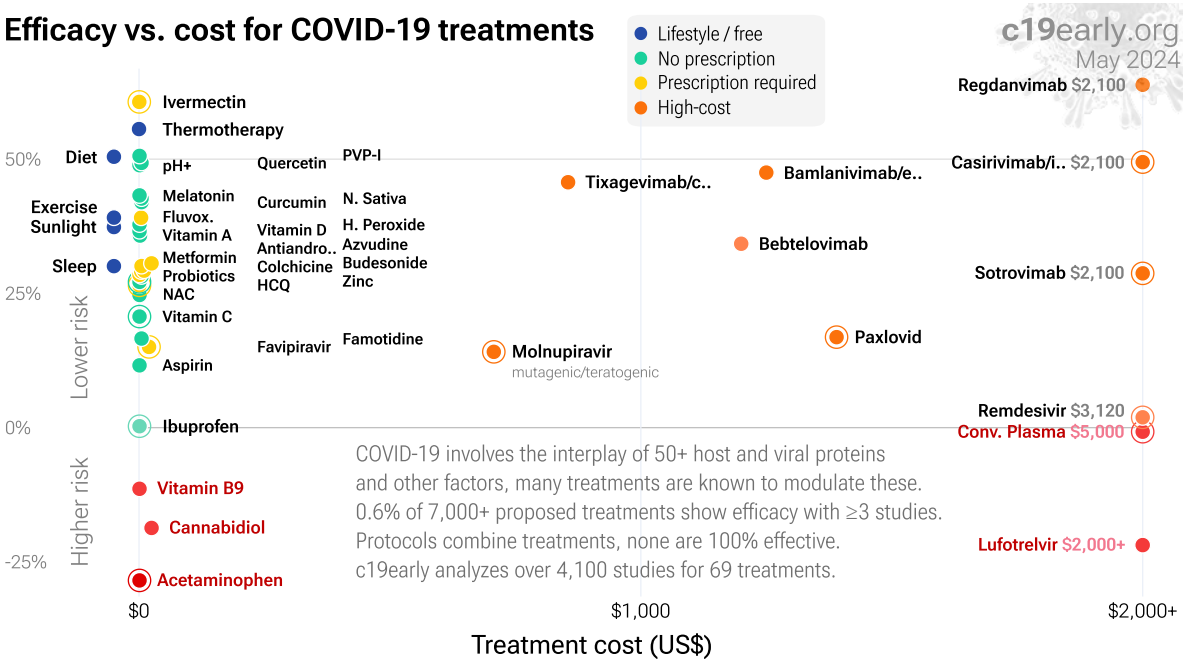


Figure 25. Efficacy vs. cost for COVID-19 treatments.

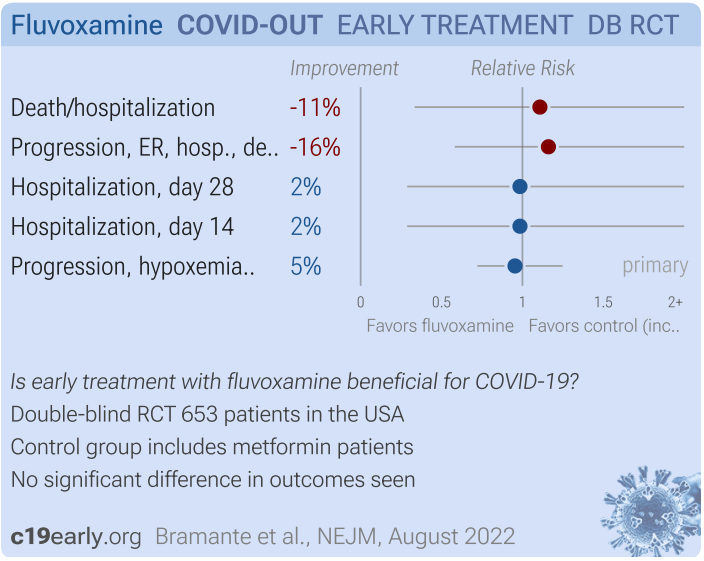
Conclusion

Fluvoxamine is an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality, hospitalization, progression, recovery, and cases. 14 studies from 14 independent teams in 8 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 39% [22-53%] lower risk. Results are similar for Randomized Controlled Trials. Results are robust — in exclusion sensitivity analysis 12 of 21 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

Other meta analyses show significant improvements with fluvoxamine for mortality *Deng*, hospitalization *Deng, Deng (B), Lee, Lu, Marcec*, and severity *Nakhaee*.

Study Notes

Bramante



COVID-OUT remotely operated RCT, showing no significant difference in outcomes. Results for other treatments are listed separately - metformin, ivermectin.

The "control" group includes patients receiving metformin, which is known to be beneficial for COVID-19 *c19early.org (C)*.

Authors note that the dosage used in the trial is lower than that of other trials *twitter.com (B)*.

Control arm results are very different between treatments, for example considering hospitalization/death, this was 1.0% for ivermectin vs. 2.7% for overall control, however it was 1.3% for the ivermectin-specific control. 394 control patients are shared. The rate for the non-shared 261 metformin control patients is 5%, compared to 1.3% for ivermectin control patients. The metformin arm started earlier, however it is unclear why the difference in outcomes is so large.

Results were delayed for 6 months with no explanation, with followup ending Feb 14, 2022.

Multiple outcomes are missing, for example time to recovery (where ACTIV-6 showed superiority of ivermectin).

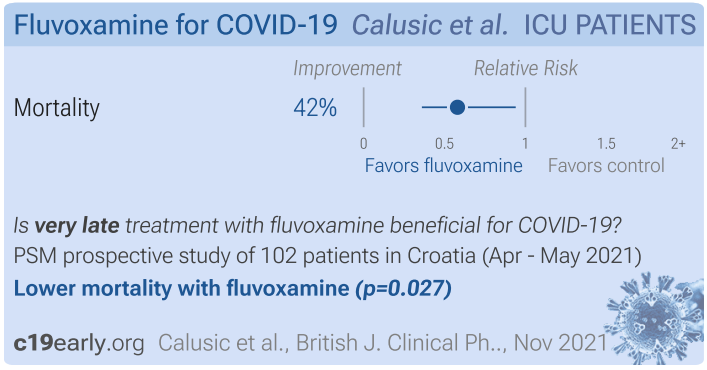
Adherence was very low, with 77% overall reporting 70+% adherence. Numbers for 100% adherence are not provided.

Treatment was 14 days for metformin and fluvoxamine, but only 3 days for ivermectin.

Trial outcomes were changed on January 20, 2022 *clinicaltrials.gov*, and again on March 2, 2022 *clinicaltrials.gov (B)*. COVIDOUT.

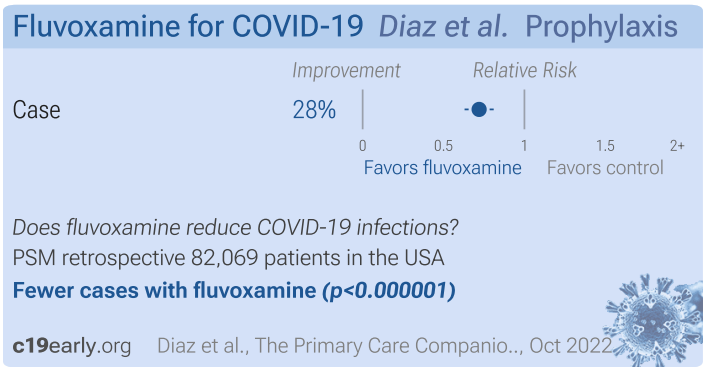
Medication delivery varied significantly over the trial. In this presentation *vimeo.com*, author indicates that delivery was initially local, later via FedEx, was much slower in August, there were delays due to team bandwidth issues, and they only realized they could use FedEx same day delivery in September.

Calusic



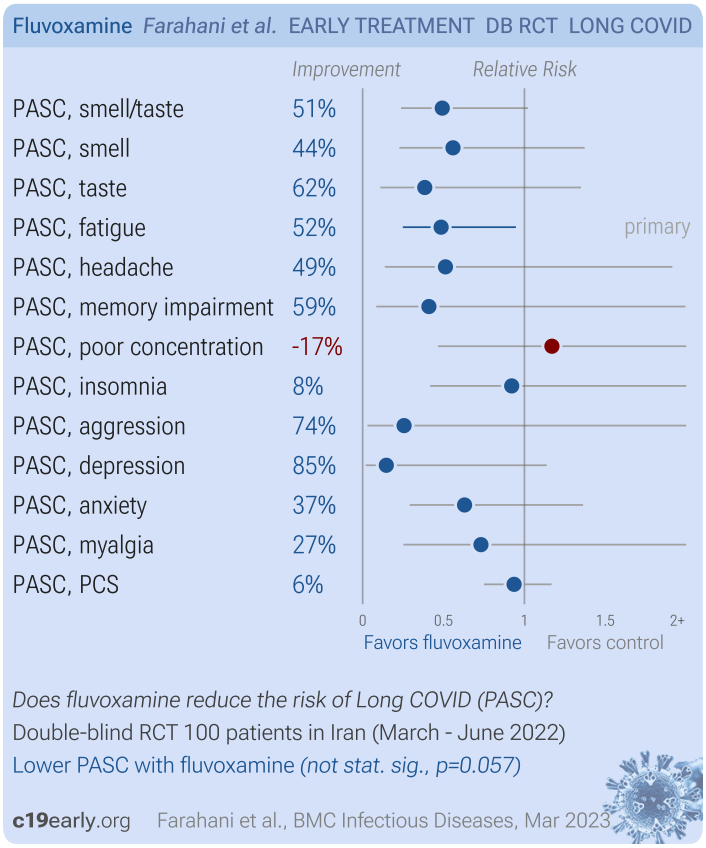
Calusic: Prospective PSM study of 51 COVID-19 ICU patients in Croatia and 51 matched controls, showing significantly lower mortality with treatment.

Diaz



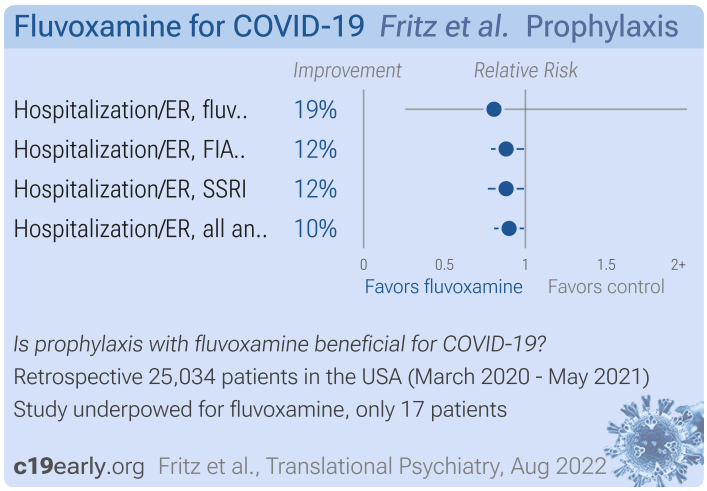
Diaz: TriNetX PSM retrospective 82,069 OCD patients, showing lower risk of COVID-19 with fluvoxamine use.

Farahani



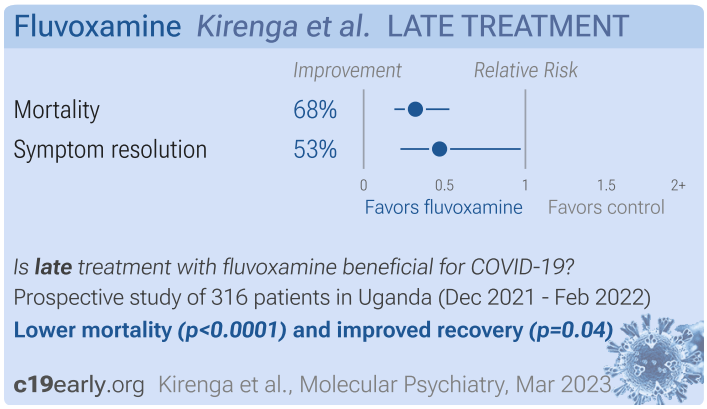
Farahani: RCT 100 mild/moderate COVID-19 outpatients in Iran, showing lower post COVID symptoms 12 weeks after infection, statistically significant only for fatigue with the small sample size. All symptoms may occur for non-COVID-19 reasons, smell/taste disorder may be the most likely to be related to COVID-19 infection. Fluvoxamine 100mg daily for 10 days.

Fritz



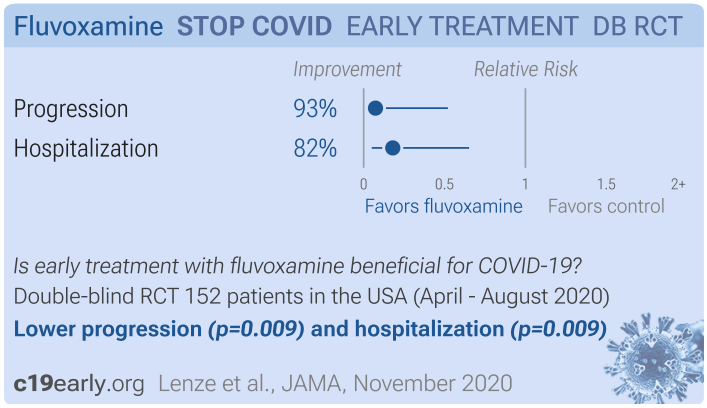
Fritz: Retrospective 25,034 COVID+ outpatients showing significantly lower ER/hospitalization with antidepressants and FIASMA antidepressants, and a dose-dependent response.

Kirenga



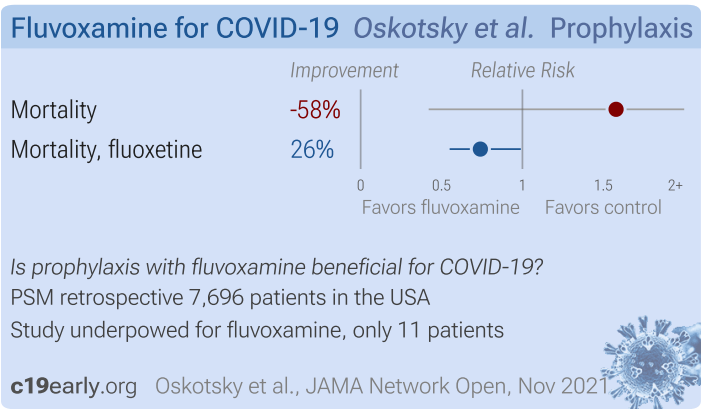
Kirenga: Prospective study of 316 hospitalized patients in Uganda, 94 receiving fluvoxamine, showing significantly lower mortality and improved recovery with treatment.

Lenze



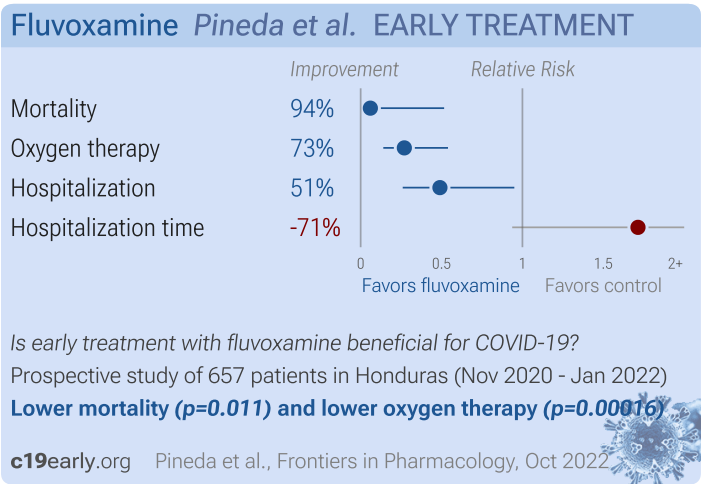
Lenze: RCT 152 outpatients, 80 treated with fluvoxamine showing lower progression with treatment (0 of 80 versus 6 of 72 control).

Oskotsky



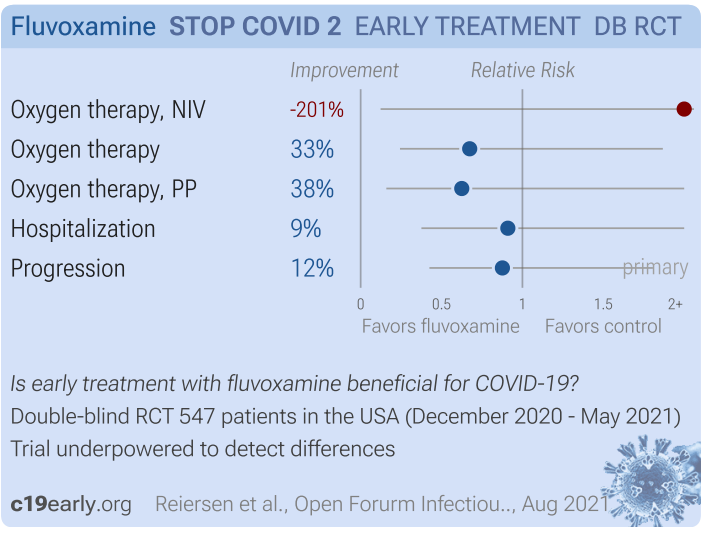
Oskotsky: Retrospective database analysis of 83,584 patients in the USA, showing lower mortality with existing fluoxetine use in PSM analysis. There were 11 fluvoxamine patients, showing non-statistically significant higher mortality.

Pineda



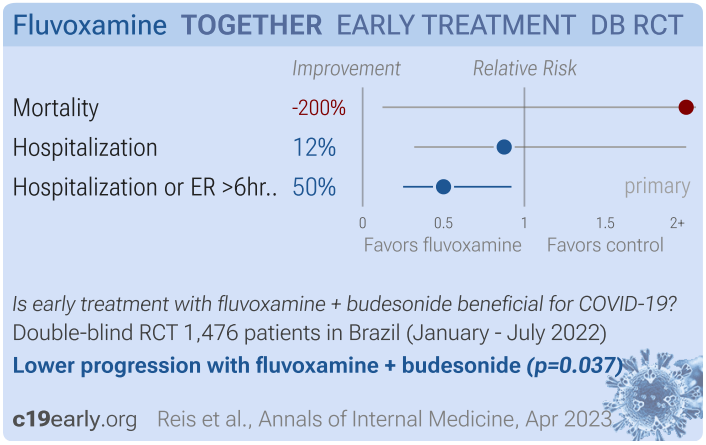
Pineda: Prospective study of 657 COVID+ outpatients in Honduras, 594 accepting fluvoxamine treatment, showing significantly lower mortality and hospitalization with treatment.

Reiersen



Reiersen: Remote RCT 547 outpatients a median of 5 days from onset, showing no significant differences with fluvoxamine. The trial was stopped early and underpowered due to low event rates. The trial does not report outcomes that may not be underpowered like time to recovery. Authors note that treatment may have been too late.

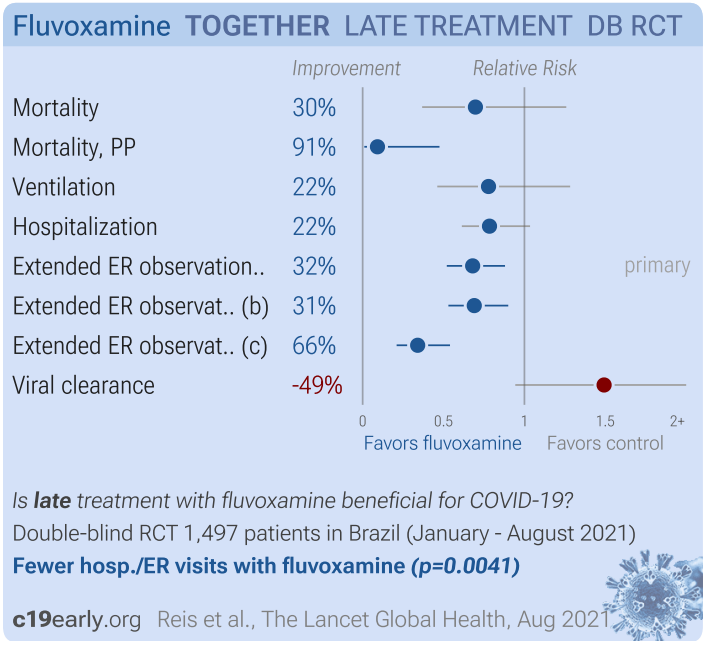
Reis



Reis: Low-risk (1% hospitalization) outpatient RCT with 738 fluvoxamine + budesonide patients and 738 placebo patients, showing significantly lower hospitalization/ER visits with treatment.

The TOGETHER trial has extreme COI, impossible data, blinding failure, randomization failure, uncorrected errors, and many protocol violations. Authors do not respond to these issues and they have refused to release the data as promised. Some issues may apply only to specific arms. For more details see *Reis (B), Reis (C), Reis (D), Reis (E), Reis (F)*.

Reis



Reis (B): Together Trial showing significantly lower hospitalization/extended ER visits with fluvoxamine treatment. Adherence was only 73.2%. Symptom onset was unspecified or >= 4 days for 57% of patients. The schedule of study activities specifies treatment administration only one day after randomization, adding an additional day delay. Overall mortality is high for the patient population. Results may be impacted by late treatment, poor SOC, and may be specific to local variants *science.sciencemag.org, thelancet.com*. Per-protocol analysis shows significantly improved results in this trial, however this may be subject to bias - the probability of adherence may be related to the probability of the outcome.

Regarding the combined hospitalization/extended ER observation outcome, authors have noted that at the study sites, extended medical observation was essentially equivalent to being hospitalized. “These were not standard emergency rooms but instead were COVID-19 emergency centers that were set up due to hospitals being overloaded,” Reiersen noted in an email to The Scientist. “A stay in these centers >6 hours was an indication that the patient was receiving care equivalent to hospitalization.”

Authors state "this study is only the second study to show an important treatment benefit for a repurposed drug in the early treatment population", however the actual number is at least 66 based on our database at the time of publication, using a conservative definition of at least 10% benefit (with statistical significance).

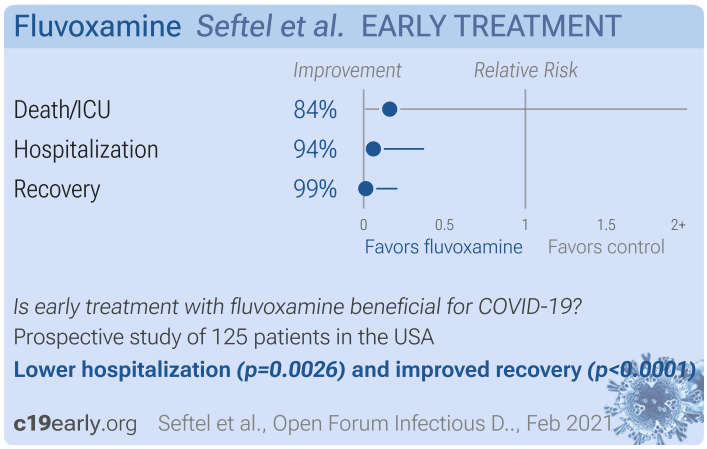
The total dose used is less than half of that in Lenze et al. There is an unusual amount of missing data - age is unknown for 6.5% of patients according to the sub-group analysis. Both age <=50 and >50 show better results on the primary outcome than the overall result. The number of placebo patients changed significantly between the preprint and journal version. The number of treatment patients with viral clearance results reduced significantly between the preprint and journal version. Also see *twitter.com (C)*. NCT04727424.

Authors do not specify if the placebo looks identical to the film-coated Luvox tablets. Reportedly there is no registration of manufacturing for matching tablets by Abbott in Brazil, and no import license for identical placebo tablets abroad. This would be an additional reason for blinding failure if the placebo tablets are not identical in appearance.

For other issues with this trial see: *twitter.com (D), twitter.com (E), twitter.com (F)*.

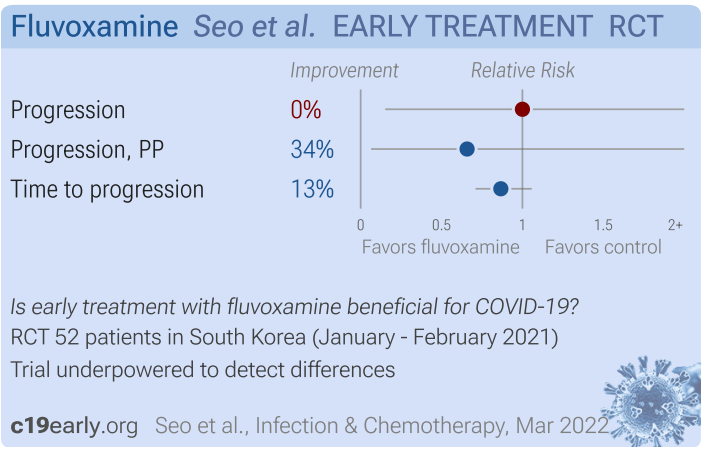
The TOGETHER trial has extreme COI, impossible data, blinding failure, randomization failure, uncorrected errors, and many protocol violations. Authors do not respond to these issues and they have refused to release the data as promised. Some issues may apply only to specific arms. For more details see *Reis, Reis (C), Reis (D), Reis (E), Reis (F)*.

Seftel



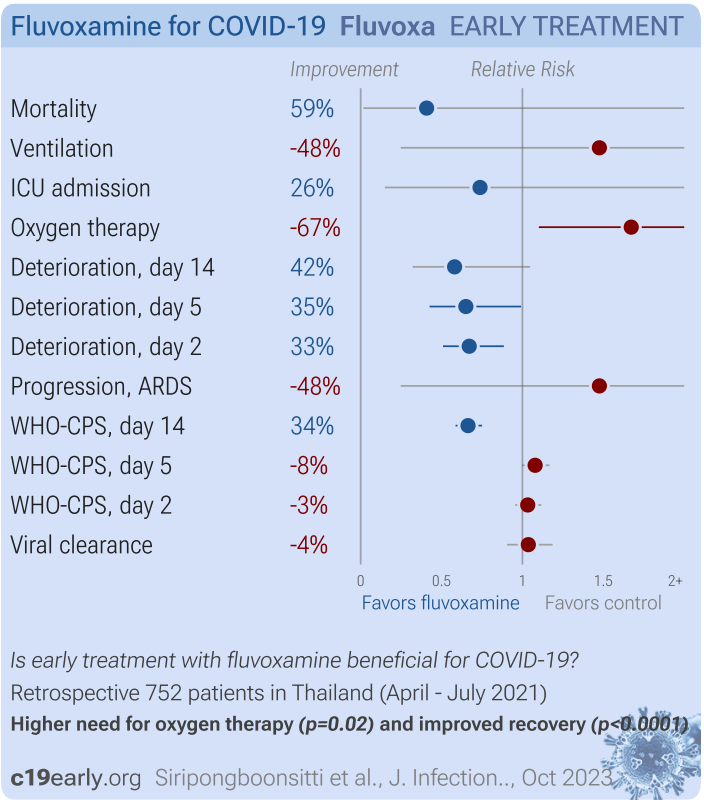
Seftel: Prospective quasi-randomized (patient choice) study with 125 outpatients, 77 treated with fluvoxamine, showing lower death/ICU admission (0 of 77 vs. 2 of 48), lower hospitalization (0 of 77 vs. 6 of 48), and faster recovery with treatment. Note that 12 treatment patients were added but are not reflected in the table in the paper (because the numbers had been previously published and the IRB did not allow updating the table).

Seo



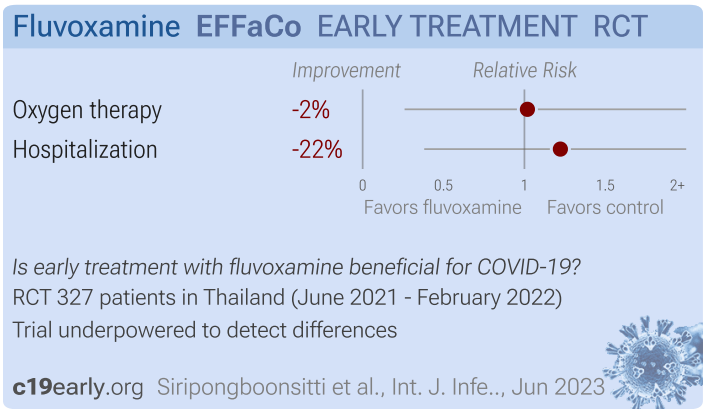
Seo: Early terminated RCT with 52 COVID+ patients in South Korea, showing no significant difference in progression with fluvoxamine treatment. There were only 2 events in each arm, and only one event for fluvoxamine in PP analysis. The trial was terminated early because the treatment center closed. 100mg fluvoxamine bid for 10 days.

Siripongboonsitti



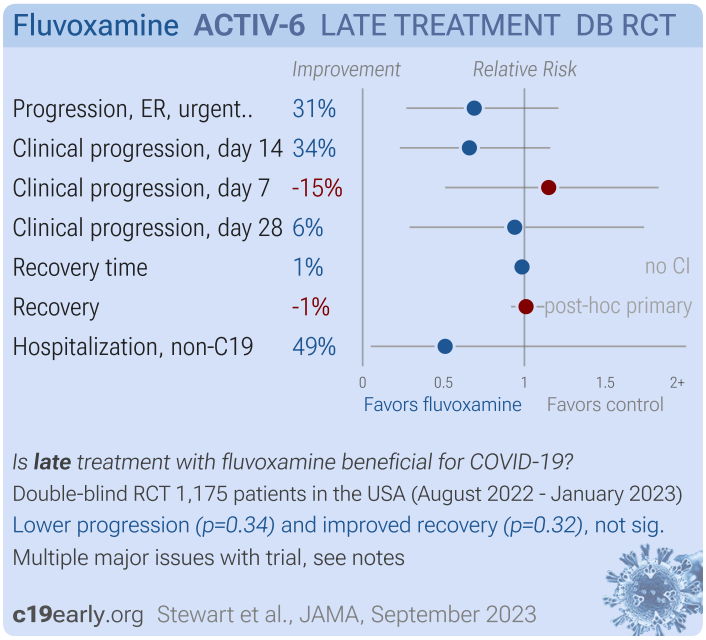
Siripongboonsitti: Retrospective 752 patients in Thailand showing mixed results with 50mg fluvoxamine bid. Authors note that trials showing benefit mostly used 100mg bid.

Siripongboonsitti



Siripongboonsitti (B): RCT 327 outpatients in Thailand, showing no significant difference with 50mg fluvoxamine bid added to favipiravir. Authors note that trials showing benefit mostly used 100mg bid.

Stewart



Stewart: Late treatment low risk population RCT showing lower progression to hospitalization or urgent care/ER visits with fluvoxamine, without statistical significance.

There was no mortality and only three hospitalizations. Authors provide no details on the cause of hospitalization, but they appear to be unrelated to COVID-19. eFigure 5 shows no COVID-19 clinical progression to hospitalization (note that a hospitalization can be seen in the equivalent plot for the low dose arm), and the text indicates that the *"COVID clinical progression scale simplified into a self-reported evaluation of home levels (limited vs not)"*.

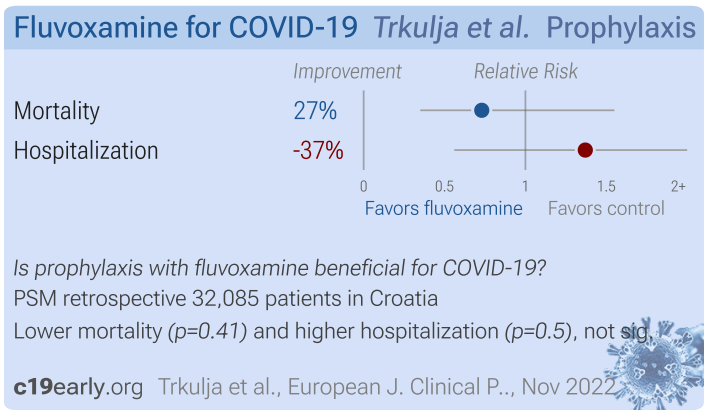
Note that the urgent care/ER visit outcome is also likely diluted due to inclusion of all-cause events, and could be statistically significant for only COVID-19 events.

The sustained recovery outcome, which shows no difference, was a post-hoc creation used to hide efficacy for ivermectin, and is not logical for evaluating efficacy in this trial. The definition includes any minor symptom within a three day period - e.g., any minor cough, headache, body ache, or fatigue that occurs in a three day period, regardless of cause, results in the treatment being considered a failure. For example, late treatment that is effective at minimizing progression, but has no improvement in resolution of cough, would not be detected. (Authors even use the end of the three day period to further minimize efficacy).

Late treatment - median 5 days, 75% 4+ days, 25% 7+ days, up to 12 days.

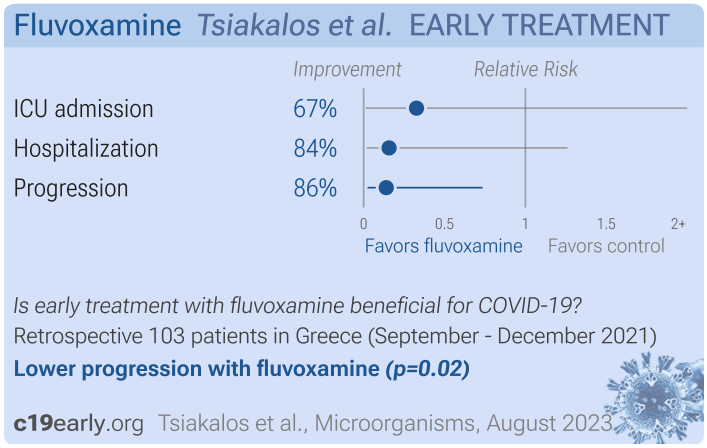
Also see *Naggie* for many issues with this trial, and *McCarthy* for the lower dose arm.

Trkulja



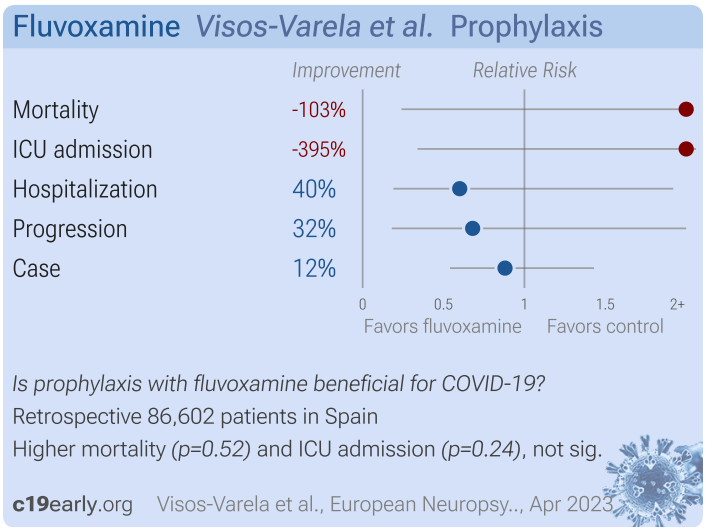
Trkulja: Retrospective COVID+ patients in Croatia, showing no significant difference in outcomes with fluvoxamine prophylaxis.

Tsiakalos



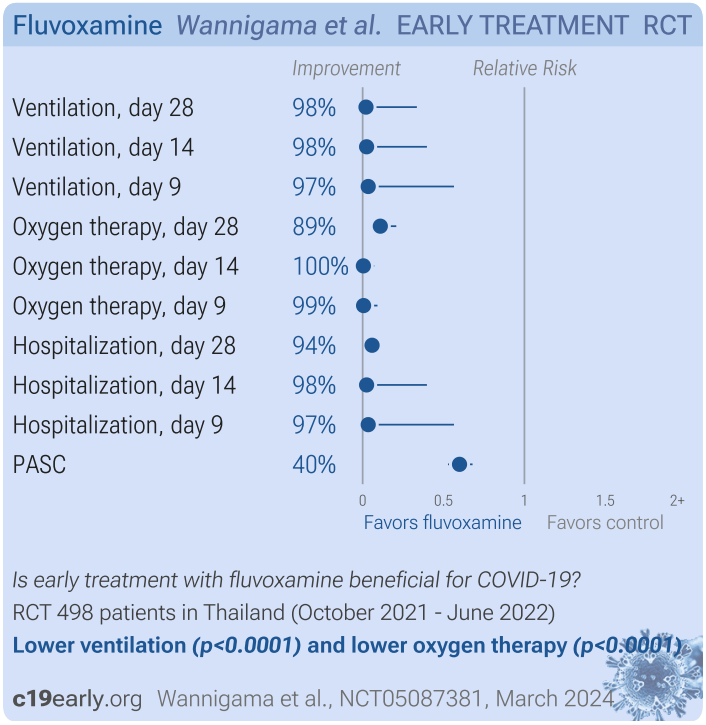
Tsiakalos: Retrospective 103 outpatients in Greece, showing lower risk of progression with fluvoxamine 100mg bid for 10 days. 2 patients (4%) in the fluvoxamine group had clinical deterioration compared to 8 patients (16%) in the standard care group (p<0.05). After adjusting for confounders, fluvoxamine was associated with a lower risk of clinical deterioration (adjusted OR 0.12, p=0.02). Fluvoxamine was also associated with improved lymphocyte count. Control patients were during Sep-Nov 2021, and treatment patients Nov-Dec 2021, introducing potential confounding by time due to changes in variants, although the change in risk during this period is expected to be relatively low.

Visos-Varela



Visos-Varela: Retrospective 86,602 patients in Spain, showing lower COVID-19 risk SSRIs citalopram and paroxetine. There were no significant difference for fluvoxamine, which few patients were taking.

Wannigama



Wannigama: RCT 995 outpatients showing significantly lower progression with early treatment within 48 hours using fluvoxamine, fluvoxamine+bromhexine, fluvoxamine+cyproheptadine, and niclosamide+bromhexine.

70% of patients received treatment within 12 hours of symptom onset.

Treatments groups showed significantly lower long COVID (PASC). The combined treatment groups showed significantly lower viral load as early as day 3. The 3 combination arms were superior to fluvoxamine alone.

The study was open-label. 593 out of 1,900 randomized participants did not receive the treatment, mostly due to inability to confirm eligibility, however baseline characteristics were similar for these patients.

There was a very high hospitalization rate in the control arm. Authors note that the majority of cases were mild - the threshold for hospitalization may have been very low (in some places/times all cases were hospitalized). Authors also note that the patients requiring high flow oxygen all had the delta/alpha variants, and that the population has many health disparities.

Publication was over 500 days after the 90 day followup.

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 fluvoxamine 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 fluvoxamine 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 (3.12.3) with scipy (1.13.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.2), and plotly (5.21.0).

Forest plots are computed using PythonMeta *Deng (C)* 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/fmeta.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.

Bramante, 8/18/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 37 authors, average treatment delay 5.0 days, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04510194 (history) (COVID-OUT).	risk of death/hospitalization, 10.8% higher, RR 1.11, $p = 0.88$, treatment 6 of 329 (1.8%), control 5 of 324 (1.5%), odds ratio converted to relative risk.
	risk of progression, 16.1% higher, RR 1.16, $p = 0.68$, treatment 18 of 329 (5.5%), control 15 of 324 (4.6%), odds ratio converted to relative risk, combined ER, hospitalization, death.
	risk of hospitalization, 1.5% lower, RR 0.98, $p = 1.00$, treatment 5 of 329 (1.5%), control 5 of 324 (1.5%), NNT 4264, Figure S8, day 28.
	risk of hospitalization, 1.5% lower, RR 0.98, $p = 1.00$, treatment 5 of 329 (1.5%), control 5 of 324 (1.5%), NNT 4264, Figure S7, day 14.
	risk of progression, 4.6% lower, RR 0.95, $p = 0.75$, treatment 79 of 329 (24.0%), control 80 of 321 (24.9%), NNT 110, odds ratio converted to relative risk, combined hypoxemia, ER, hospitalization, death, primary outcome.
Farahani, 3/31/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, peer-reviewed, mean age 38.5, 3 authors, study period March 2022 - June 2022.	risk of PASC, 50.8% lower, RR 0.49, $p = 0.06$, treatment 42, control 43, smell and taste disturbance combined.
	risk of PASC, 44.2% lower, RR 0.56, $p = 0.28$, treatment 6 of 42 (14.3%), control 11 of 43 (25.6%), NNT 8.9, smell.
	risk of PASC, 61.6% lower, RR 0.38, $p = 0.20$, treatment 3 of 42 (7.1%), control 8 of 43 (18.6%), NNT 8.7, taste.
	risk of PASC, 51.5% lower, RR 0.48, $p = 0.04$, treatment 9 of 42 (21.4%), control 19 of 43 (44.2%), NNT 4.4, fatigue, primary outcome.
	risk of PASC, 48.8% lower, RR 0.51, $p = 0.48$, treatment 3 of 42 (7.1%), control 6 of 43 (14.0%), NNT 15, headache.
	risk of PASC, 59.0% lower, RR 0.41, $p = 0.43$, treatment 2 of 42 (4.8%), control 5 of 43 (11.6%), NNT 15, memory impairment.

	risk of PASC, 17.0% higher, RR 1.17, *p* = 0.78, treatment 8 of 42 (19.0%), control 7 of 43 (16.3%), poor concentration.
	risk of PASC, 7.9% lower, RR 0.92, *p* = 1.00, treatment 9 of 42 (21.4%), control 10 of 43 (23.3%), NNT 55, insomnia.
	risk of PASC, 74.4% lower, RR 0.26, *p* = 0.36, treatment 1 of 42 (2.4%), control 4 of 43 (9.3%), NNT 14, aggression.
	risk of PASC, 85.4% lower, RR 0.15, *p* = 0.06, treatment 1 of 42 (2.4%), control 7 of 43 (16.3%), NNT 7.2, depression.
	risk of PASC, 37.0% lower, RR 0.63, *p* = 0.32, treatment 8 of 42 (19.0%), control 13 of 43 (30.2%), NNT 8.9, anxiety.
	risk of PASC, 26.9% lower, RR 0.73, *p* = 0.76, treatment 5 of 42 (11.9%), control 7 of 43 (16.3%), NNT 23, myalgia.
	risk of PASC, 6.4% lower, RR 0.94, *p* = 0.60, treatment 32 of 42 (76.2%), control 35 of 43 (81.4%), NNT 19, PCS.
Lenze, 11/12/2020, Double Blind Randomized Controlled Trial, USA, peer-reviewed, 11 authors, study period 10 April, 2020 - 5 August, 2020, average treatment delay 4.0 days, trial NCT04342663 (history) (STOP COVID).	**risk of progression, 92.7% lower, RR 0.07, *p* = 0.009**, treatment 0 of 80 (0.0%), control 6 of 72 (8.3%), NNT 12, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), clinical deterioration over 15 days.
	risk of hospitalization, 82.0% lower, RR 0.18, *p* = 0.009, treatment 1 of 80 (1.2%), control 5 of 72 (6.9%), NNT 18, COVID-19 hospitalization within 15 days, see supplemental appendix for details.
Pineda, 10/4/2022, prospective, Honduras, peer-reviewed, mean age 48.1, 24 authors, study period November 2020 - January 2022.	**risk of death, 94.0% lower, RR 0.06, *p* = 0.01**, treatment 1 of 594 (0.2%), control 4 of 63 (6.3%), NNT 16, adjusted per study.
	risk of oxygen therapy, 73.0% lower, RR 0.27, *p* < 0.001, treatment 15 of 594 (2.5%), control 13 of 63 (20.6%), NNT 5.5, adjusted per study.
	risk of hospitalization, 51.0% lower, RR 0.49, *p* = 0.04, treatment 23 of 594 (3.9%), control 11 of 63 (17.5%), NNT 7.4, adjusted per study.
	hospitalization time, 71.4% higher, relative time 1.71, *p* = 0.08, treatment 23, control 11.
Reiersen, 8/20/2021, Double Blind Randomized Controlled Trial, USA, peer-reviewed, median age 47.0 (treatment) 48.0 (control), 24 authors, study period 22 December, 2020 - 21 May, 2021, average treatment delay 5.0 days, trial NCT04668950 (history) (STOP COVID 2).	**risk of oxygen therapy, 201.1% higher, RR 3.01, *p* = 0.50**, treatment 1 of 272 (0.4%), control 0 of 275 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), non-invasive ventilation.
	risk of oxygen therapy, 32.6% lower, RR 0.67, *p* = 0.60, treatment 6 of 272 (2.2%), control 9 of 275 (3.3%), NNT 94.
	risk of oxygen therapy, 37.5% lower, RR 0.62, *p* = 0.74, treatment 3 of 164 (1.8%), control 6 of 205 (2.9%), NNT 91, per-

	protocol.
	risk of hospitalization, 9.0% lower, RR 0.91, p = 1.00, treatment 9 of 272 (3.3%), control 10 of 275 (3.6%), NNT 305.
	risk of progression, 12.4% lower, RR 0.88, p = 0.85, treatment 13 of 272 (4.8%), control 15 of 275 (5.5%), NNT 148, primary outcome.
Reis, 4/17/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Brazil, peer-reviewed, 35 authors, study period 15 January, 2022 - 6 July, 2022, average treatment delay 3.0 days, this trial uses multiple treatments in the treatment arm (combined with budesonide) - results of individual treatments may vary, trial NCT04727424 (history) (TOGETHER).	risk of death, 200.0% higher, RR 3.00, p = 1.00, treatment 1 of 738 (0.1%), control 0 of 738 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of hospitalization, 12.5% lower, RR 0.88, p = 1.00, treatment 7 of 738 (0.9%), control 8 of 738 (1.1%), NNT 738.
	hospitalization or ER >6hrs, 50.0% lower, RR 0.50, p = 0.04, treatment 13 of 738 (1.8%), control 27 of 738 (3.7%), NNT 53, adjusted per study, day 28, primary outcome.
Seftel, 2/1/2021, prospective quasi-randomized (patient choice), USA, peer-reviewed, 2 authors.	risk of death/ICU, 83.9% lower, RR 0.16, p = 0.15, treatment 0 of 77 (0.0%), control 2 of 48 (4.2%), NNT 24, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 94.0% lower, RR 0.06, p = 0.003, treatment 0 of 77 (0.0%), control 6 of 48 (12.5%), NNT 8.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of no recovery, 98.7% lower, RR 0.01, p < 0.001, treatment 0 of 77 (0.0%), control 29 of 48 (60.4%), NNT 1.7, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
Seo, 3/3/2022, Single Blind Randomized Controlled Trial, placebo-controlled, South Korea, peer-reviewed, median age 53.5, 14 authors, study period 15 January, 2021 - 19 February, 2021.	risk of progression, no change, RR 1.00, p = 1.00, treatment 2 of 26 (7.7%), control 2 of 26 (7.7%).
	risk of progression, 34.2% lower, RR 0.66, p = 1.00, treatment 1 of 19 (5.3%), control 2 of 25 (8.0%), NNT 37, PP.
	time to progression, 13.3% lower, relative time 0.87, p = 0.16, treatment mean 6.5 (±0.7) n=26, control mean 7.5 (±3.5) n=26.
Siripongboonsitti, 10/6/2023, retrospective, Thailand, peer-reviewed, 4 authors, study period 16 April, 2021 - 24 July, 2021, trial TCTR20230401001 (Fluvoxa).	risk of death, 59.2% lower, RR 0.41, p = 1.00, treatment 0 of 234 (0.0%), control 1 of 518 (0.2%), NNT 518, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 28.
	risk of mechanical ventilation, 47.6% higher, RR 1.48, p = 0.65, treatment 2 of 234 (0.9%), control 3 of 518 (0.6%).
	risk of ICU admission, 26.2% lower, RR 0.74, p = 1.00, treatment 2 of 234 (0.9%), control 6 of 518 (1.2%), NNT 329.
	risk of oxygen therapy, 67.3% higher, RR 1.67, p = 0.02, treatment 34 of 234 (14.5%), control 45 of 518 (8.7%).

	risk of deterioration, 41.9% lower, RR 0.58, *p* = 0.08, treatment 13 of 217 (6.0%), control 49 of 475 (10.3%), NNT 23, day 14.
	risk of deterioration, 35.0% lower, RR 0.65, *p* = 0.047, treatment 23 of 166 (13.9%), control 88 of 413 (21.3%), NNT 13, day 5.
	risk of deterioration, 32.9% lower, RR 0.67, *p* = 0.004, treatment 51 of 217 (23.5%), control 132 of 377 (35.0%), NNT 8.7, day 2.
	risk of progression, 47.6% higher, RR 1.48, *p* = 0.65, treatment 2 of 234 (0.9%), control 3 of 518 (0.6%), ARDS.
	WHO-CPS, 33.6% lower, RR 0.66, *p* < 0.001, treatment mean 0.73 (±0.67) n=234, control mean 1.1 (±0.75) n=518, WHO-CPS score, day 14.
	WHO-CPS, 7.9% higher, RR 1.08, *p* = 0.06, treatment mean 2.06 (±1.07) n=234, control mean 1.91 (±0.98) n=518, WHO-CPS score, day 5.
	WHO-CPS, 3.3% higher, RR 1.03, *p* = 0.43, treatment mean 2.21 (±1.25) n=234, control mean 2.14 (±1.06) n=518, WHO-CPS score, day 2.
	risk of no viral clearance, 3.6% higher, RR 1.04, *p* = 0.66, treatment 130 of 210 (61.9%), control 218 of 365 (59.7%), day 14.
Siripongboonsitti (B), 6/29/2023, Randomized Controlled Trial, Thailand, peer-reviewed, 9 authors, study period 26 June, 2021 - 22 February, 2022, trial TCTR20210615002 (EFFaCo).	risk of oxygen therapy, 1.9% higher, RR 1.02, *p* = 1.00, treatment 4 of 162 (2.5%), control 4 of 165 (2.4%).
	risk of hospitalization, 22.2% higher, RR 1.22, *p* = 0.77, treatment 6 of 162 (3.7%), control 5 of 165 (3.0%), day 28.
Tsiakalos, 8/12/2023, retrospective, Greece, peer-reviewed, 5 authors, study period 1 September, 2021 - 31 December, 2021.	risk of ICU admission, 67.3% lower, RR 0.33, *p* = 0.49, treatment 0 of 53 (0.0%), control 1 of 50 (2.0%), NNT 50, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 84.3% lower, RR 0.16, *p* = 0.06, treatment 1 of 53 (1.9%), control 6 of 50 (12.0%), NNT 9.9.
	risk of progression, 86.0% lower, RR 0.14, *p* = 0.02, treatment 2 of 53 (3.8%), control 8 of 50 (16.0%), NNT 8.2, adjusted per study, odds ratio converted to relative risk, multivariable.
Wannigama, 3/14/2024, Randomized Controlled Trial, Thailand, peer-reviewed, 29 authors, study period 1 October, 2021 - 21 June, 2022, average treatment delay 0.5 days, trial NCT05087381 (history).	risk of mechanical ventilation, 97.9% lower, RR 0.02, *p* < 0.001, treatment 0 of 162 (0.0%), control 32 of 336 (9.5%), NNT 10, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 28.
	risk of mechanical ventilation, 97.6% lower, RR 0.02, *p* < 0.001, treatment 0 of 162 (0.0%), control 27 of 336 (8.0%), NNT 12, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 14.

	risk of mechanical ventilation, 96.6% lower, RR 0.03, $p < 0.001$, treatment 0 of 162 (0.0%), control 19 of 336 (5.7%), NNT 18, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 9.
	risk of oxygen therapy, 89.1% lower, RR 0.11, $p < 0.001$, treatment 9 of 162 (5.6%), control 171 of 336 (50.9%), NNT 2.2, day 28.
	risk of oxygen therapy, 99.6% lower, RR 0.004, $p < 0.001$, treatment 0 of 162 (0.0%), control 150 of 336 (44.6%), NNT 2.2, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 14.
	risk of oxygen therapy, 99.4% lower, RR 0.006, $p < 0.001$, treatment 0 of 162 (0.0%), control 117 of 336 (34.8%), NNT 2.9, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 9.
	risk of hospitalization, 94.2% lower, RR 0.06, $p < 0.001$, treatment 9 of 162 (5.6%), control 321 of 336 (95.5%), NNT 1.1, day 28.
	risk of hospitalization, 97.6% lower, RR 0.02, $p < 0.001$, treatment 0 of 162 (0.0%), control 27 of 336 (8.0%), NNT 12, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 14.
	risk of hospitalization, 96.6% lower, RR 0.03, $p < 0.001$, treatment 0 of 162 (0.0%), control 19 of 336 (5.7%), NNT 18, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 9.
	risk of PASC, 40.1% lower, RR 0.60, $p < 0.001$, treatment 97 of 162 (59.9%), control 336 of 336 (100.0%), NNT 2.5, day 90.

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.

Calusic, 11/1/2021, prospective, propensity score matching, Croatia, peer-reviewed, 7 authors, study period 1 April, 2021 - 31 May, 2021.	risk of death, 42.0% lower, HR 0.58, $p = 0.03$, treatment 30 of 51 (58.8%), control 39 of 51 (76.5%), NNT 5.7, adjusted per study, propensity score matching.
Kirenga, 3/3/2023, prospective, Uganda, peer-reviewed, 19 authors, study period December 2021 - February 2022.	risk of death, 68.0% lower, HR 0.32, $p < 0.001$, treatment 29 of 94 (30.9%), control 126 of 222 (56.8%), NNT 3.9, adjusted for unbalanced covariates, propensity score weighting, Cox proportional hazards.
	symptom resolution, 53.1% lower, HR 0.47, $p = 0.04$, treatment 94, control 222, inverted to make HR<1 favor treatment, propensity score weighting, Cox proportional hazards, RR approximated with OR.

Reis (B), 8/23/2021, Double Blind Randomized Controlled Trial, Brazil, peer-reviewed, 27 authors, study period 20 January, 2021 - 5 August, 2021, trial NCT04727424 (history) (TOGETHER).	risk of death, 30.3% lower, RR 0.70, $p = 0.24$, treatment 17 of 741 (2.3%), control 25 of 756 (3.3%), NNT 99, odds ratio converted to relative risk, ITT.
	risk of death, 90.8% lower, RR 0.09, $p = 0.02$, treatment 1 of 548 (0.2%), control 12 of 618 (1.9%), NNT 57, odds ratio converted to relative risk, per protocol.
	risk of mechanical ventilation, 22.2% lower, RR 0.78, $p = 0.33$, treatment 26 of 741 (3.5%), control 34 of 756 (4.5%), NNT 101, odds ratio converted to relative risk, ITT.
	risk of hospitalization, 21.6% lower, RR 0.78, $p = 0.10$, treatment 75 of 741 (10.1%), control 97 of 756 (12.8%), NNT 37, odds ratio converted to relative risk, ITT.
	extended ER observation or hospitalization, 32.0% lower, RR 0.68, $p = 0.004$, treatment 79 of 741 (10.7%), control 119 of 756 (15.7%), NNT 20, ITT, primary outcome.
	extended ER observation or hospitalization, 31.0% lower, RR 0.69, $p = 0.006$, treatment 78 of 740 (10.5%), control 115 of 752 (15.3%), NNT 21, mITT.
	extended ER observation or hospitalization, 66.0% lower, RR 0.34, $p < 0.001$, treatment 541, control 609, per protocol.
	risk of no viral clearance, 49.3% higher, RR 1.49, $p = 0.09$, treatment 167 of 207 (80.7%), control 163 of 221 (73.8%), adjusted per study, inverted to make RR<1 favor treatment.
Stewart, 9/13/2023, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 32 authors, study period 5 August, 2022 - 20 January, 2023, average treatment delay 5.0 days, trial NCT04885530 (history) (ACTIV-6).	risk of progression, 31.0% lower, RR 0.69, $p = 0.34$, treatment 14 of 589 (2.4%), control 21 of 586 (3.6%), NNT 83, adjusted per study, urgent or emergency care visits, hospitalizations, or death.
	clinical progression, 34.0% lower, OR 0.66, $p = 0.32$, treatment 589, control 586, mid-recovery, day 14, RR approximated with OR.
	clinical progression, 15.0% higher, OR 1.15, $p = 0.68$, treatment 589, control 586, day 7, RR approximated with OR.
	clinical progression, 6.0% lower, OR 0.94, $p = 0.90$, treatment 589, control 586, day 28, RR approximated with OR.
	risk of no recovery, 1.0% higher, HR 1.01, $p = 0.86$, treatment 589, control 586, inverted to make HR<1 favor treatment, post-hoc primary outcome.
	risk of hospitalization, 49.0% lower, RR 0.51, $p = 0.59$, treatment 1 of 589 (0.2%), control 2 of 586 (0.3%), NNT 583, non-COVID-19 hospitalization, day 28.

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.

Diaz, 10/6/2022, retrospective, USA, peer-reviewed, 2 authors.	**risk of case, 28.0% lower, OR 0.72, $p < 0.001$**, treatment 4,558, control 4,558, propensity score matching, RR approximated with OR.
Fritz, 8/22/2022, retrospective, USA, peer-reviewed, 5 authors, study period 1 March, 2020 - 16 May, 2021.	**risk of hospitalization/ER, 19.4% lower, RR 0.81, $p = 0.69$**, treatment 4 of 17 (23.5%), control 1,896 of 20,457 (9.3%), adjusted per study, odds ratio converted to relative risk, fluvoxamine, multivariable.
	risk of hospitalization/ER, 11.9% lower, RR 0.88, $p = 0.03$, treatment 707 of 3,414 (20.7%), control 1,896 of 20,457 (9.3%), adjusted per study, odds ratio converted to relative risk, FIASMA, multivariable.
	risk of hospitalization/ER, 11.9% lower, RR 0.88, $p = 0.04$, treatment 559 of 2,744 (20.4%), control 1,896 of 20,457 (9.3%), adjusted per study, odds ratio converted to relative risk, SSRI, multivariable.
	risk of hospitalization/ER, 10.1% lower, RR 0.90, $p = 0.04$, treatment 971 of 4,577 (21.2%), control 1,896 of 20,457 (9.3%), adjusted per study, odds ratio converted to relative risk, all antidepressants, multivariable.
Oskotsky, 11/15/2021, retrospective, propensity score matching, USA, peer-reviewed, 8 authors.	**risk of death, 57.9% higher, RR 1.58, $p = 0.62$**, treatment 2 of 11 (18.2%), control 19 of 165 (11.5%), fluvoxamine.
	risk of death, 26.0% lower, RR 0.74, $p = 0.04$, treatment 48 of 481 (10.0%), control 956 of 7,215 (13.3%), NNT 31, fluoxetine.
Trkulja, 11/7/2022, retrospective, Croatia, peer-reviewed, 2 authors.	**risk of death, 27.0% lower, RR 0.73, $p = 0.41$**, treatment 749, control 31,336, cohort A vs. B, propensity score matching.
	risk of hospitalization, 37.0% higher, RR 1.37, $p = 0.50$, treatment 749, control 31,336, cohort A vs. B, COVID-related, propensity score matching.
Visos-Varela, 4/23/2023, retrospective, Spain, peer-reviewed, 8 authors.	**risk of death, 103.0% higher, OR 2.03, $p = 0.52$**, treatment 1 of 413 (0.2%) cases, 7 of 7,408 (0.1%) controls, adjusted per study, case control OR.
	risk of ICU admission, 395.0% higher, OR 4.95, $p = 0.24$, treatment 1 of 228 (0.4%) cases, 2 of 4,398 (0.0%) controls, adjusted per study, case control OR.
	risk of hospitalization, 40.0% lower, OR 0.60, $p = 0.39$, treatment 3 of 3,060 (0.1%) cases, 69 of 56,785 (0.1%) controls, adjusted per study, case control OR.

	risk of progression, 32.0% lower, OR 0.68, p = 0.56, treatment 3 of 3,060 (0.1%) cases, 25 of 26,757 (0.1%) controls, adjusted per study, case control OR.
	risk of case, 12.0% lower, OR 0.88, p = 0.60, treatment 28 of 29,817 (0.1%) cases, 69 of 56,785 (0.1%) controls, adjusted per study, case control OR.

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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