# Ensitrelvir for COVID-19: real-time meta analysis of 3 studies

@CovidAnalysis, March 2024, Version 9
https://c19early.org/enmeta.html

## Abstract

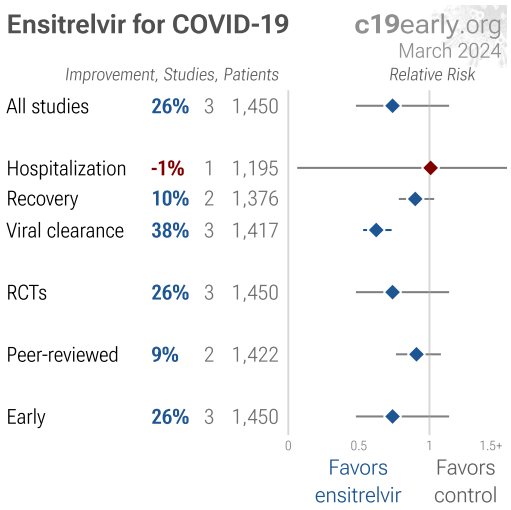
Statistically significant lower risk is seen for viral clearance. 3 studies from 2 independent teams (all from the same country) show statistically significant improvements.

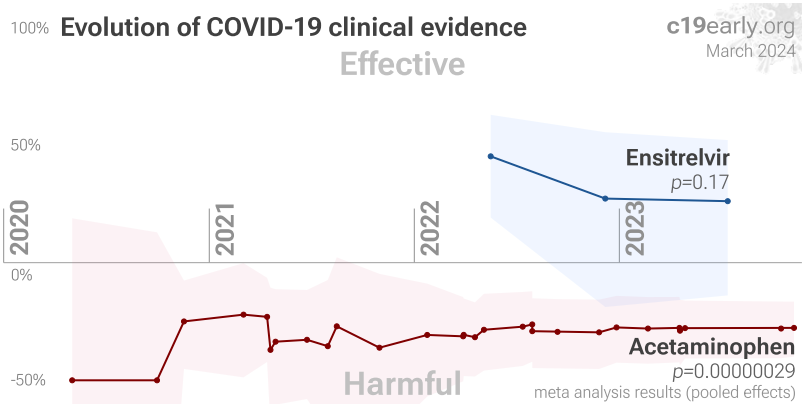
Meta analysis using the most serious outcome reported shows 26% [-14-52%] lower risk, without reaching statistical significance. Results are worse for peer-reviewed studies. Currently all studies are RCTs.

Currently there is limited data, with only 1 control event for the most serious outcome in trials to date. Studies to date are from only 2 different groups.

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 are more effective.

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




## HIGHLIGHTS

Ensitrelvir reduces risk for COVID-19 with very high confidence for viral clearance and very low confidence for recovery and in pooled analysis.

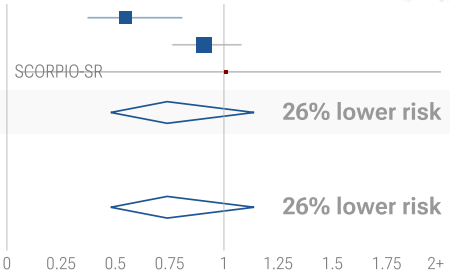
We show traditional outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor in COVID-19 studies.

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

## 3 ensitrelvir COVID-19 studies

c19early.org
March 2024

| | Improvement, RR [CI] | | | Treatment | Control |
|---|---|---|---|---|---|
| Mukae (DB RCT) | 45% | 0.55 [0.37-0.81] | viral load | 14 (n) | 14 (n) |
| Mukae (DB RCT) | 9% | 0.91 [0.76-1.08] | improv. | 116 (n) | 111 (n) |
| Yotsuyan.. (DB RCT) | -1% | 1.01 [0.06-16.1] | hosp. | 1/595 | 1/600 |
| **Early treatment** | 26% | 0.74 [0.48-1.14] | | 1/725 | 1/725 |
| Tau² = 0.08, I² = 63.0%, p = 0.17 | | | | | |
| **All studies** | 26% | 0.74 [0.48-1.14] | | 1/725 | 1/725 |




Tau² = 0.08, I² = 63.0%, p = 0.17

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

Favors ensitrelvir Favors control

A

## Efficacy in COVID-19 ensitrelvir studies (pooled effects)

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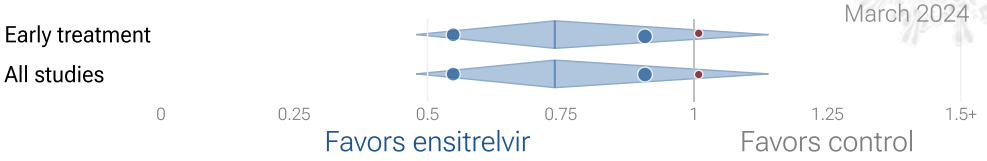


Favors ensitrelvir Favors control

B

## Efficacy in COVID-19 studies (pooled effects)

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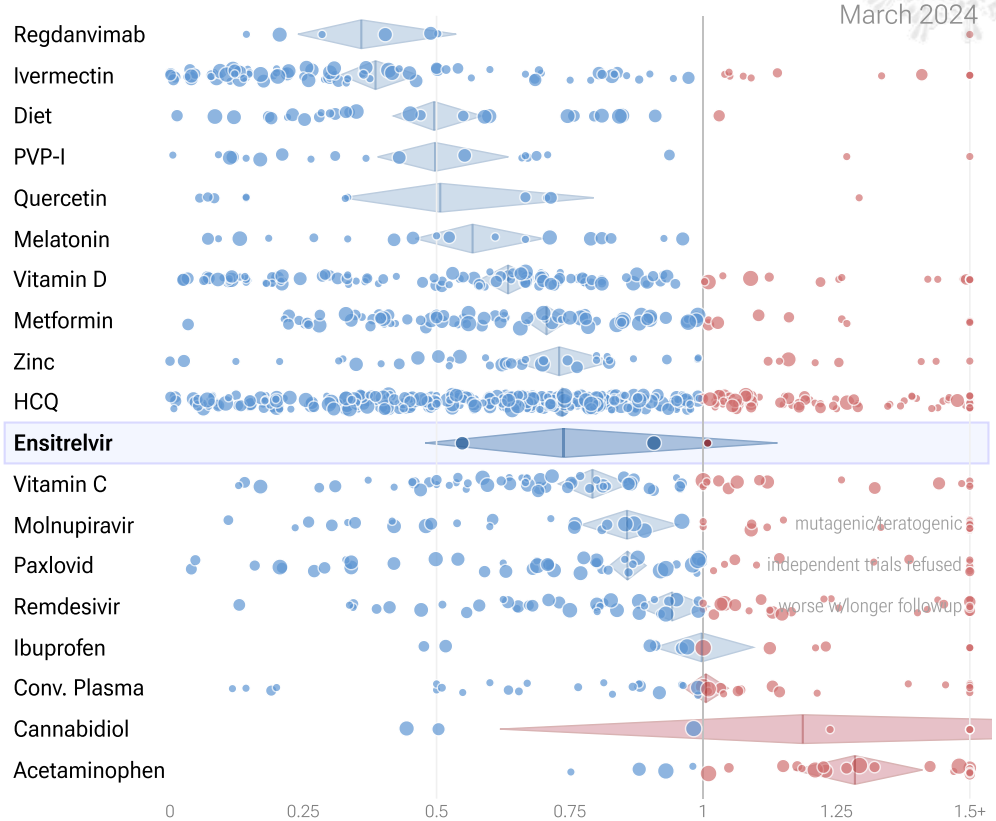



Lower risk Increased risk

C

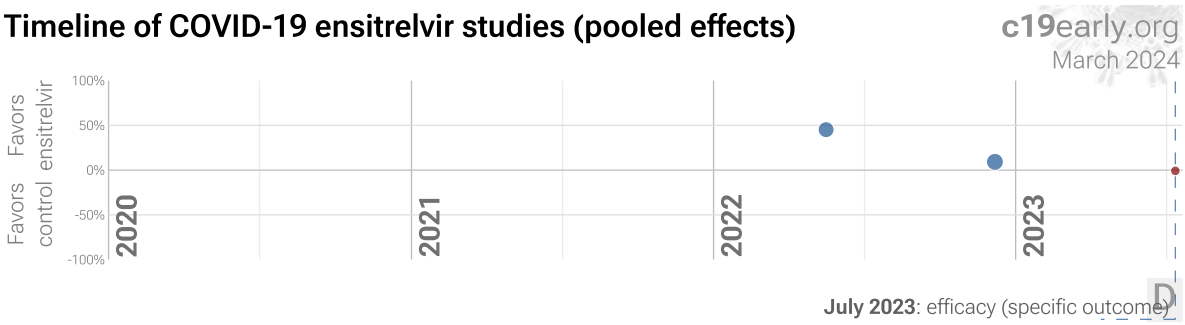



***Figure 1.*** **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see 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 ensitrelvir studies.** The marked date indicates the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for one or more specific outcome.

## 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 *Scardua-Silva, 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*, 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.

**Supporting research.** *In Vitro* studies demonstrate efficacy in VeroE6/TMPRSS2 *Note B, Kuroda*, HEK293T/ACE2-TMPRSS2 *Note C, Kuroda*, and MucilAir *Note D, Kuroda* cells. Animal studies demonstrate efficacy in BALB/c mice *Note E, Nobori, Kuroda* and Syrian hamsters *Note F, Kuroda*. Preclinical studies demonstrate efficacy for the ancestral *Note G, Kuroda*, delta *Note H, Kuroda*, and omicron *Note I, Kuroda* variants.

**Analysis.** We analyze all significant controlled studies of ensitrelvir for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random effects meta-analysis results for all studies, individual outcomes, peer-reviewed studies, and Randomized Controlled Trials (RCTs).

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

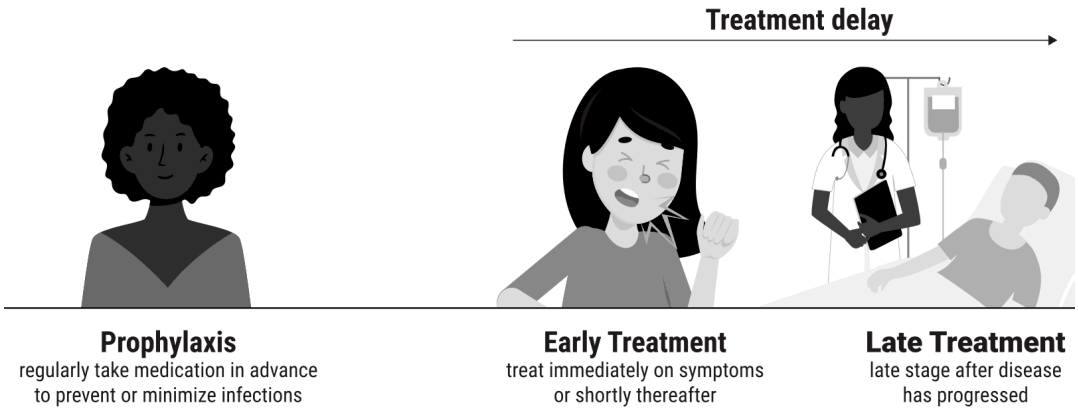



***Figure 2.*** Treatment stages.

## Preclinical Research

*In Vitro* studies demonstrate efficacy in VeroE6/TMPRSS2 *Note B, Kuroda*, HEK293T/ACE2-TMPRSS2 *Note C, Kuroda*, and MucilAir *Note D, Kuroda* cells. Animal studies demonstrate efficacy in BALB/c mice *Note E, Nobori, Kuroda* and Syrian hamsters *Note F, Kuroda*. Preclinical studies demonstrate efficacy for the ancestral *Note G, Kuroda*, delta *Note H, Kuroda*, and omicron *Note I, Kuroda* variants.

An *In Vitro* study supports the efficacy of ensitrelvir *Kuroda*.

2 *In Vivo* animal studies support the efficacy of ensitrelvir *Kuroda, Nobori*.

Preclinical research is an important part of the development of treatments, however results may be very different in clinical trials. Preclinical results are not used in this paper.

## Results

Table 1 summarizes the results for all studies, for Randomized Controlled Trials, for peer-reviewed studies, and for specific outcomes. Figure 3, 4, 5, 6, and 7 show forest plots for random effects meta-analysis of all studies with pooled effects, hospitalization, recovery, viral clearance, and peer reviewed studies.

| | *Improvement* | *Studies* | *Patients* | *Authors* |
|---|---|---|---|---|
| All studies | 26% [-14-52%] | 3 | 1,450 | 37 |
| Peer-reviewed studies | **9%** [-8-24%] | 2 | 1,422 | 24 |
| Randomized Controlled Trials | 26% [-14-52%] | 3 | 1,450 | 37 |
| | | | | |
| Recovery | **10%** [-3-22%] | 2 | 1,376 | 24 |
| Viral | 38% [27-47%] **** | 3 | 1,417 | 37 |

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

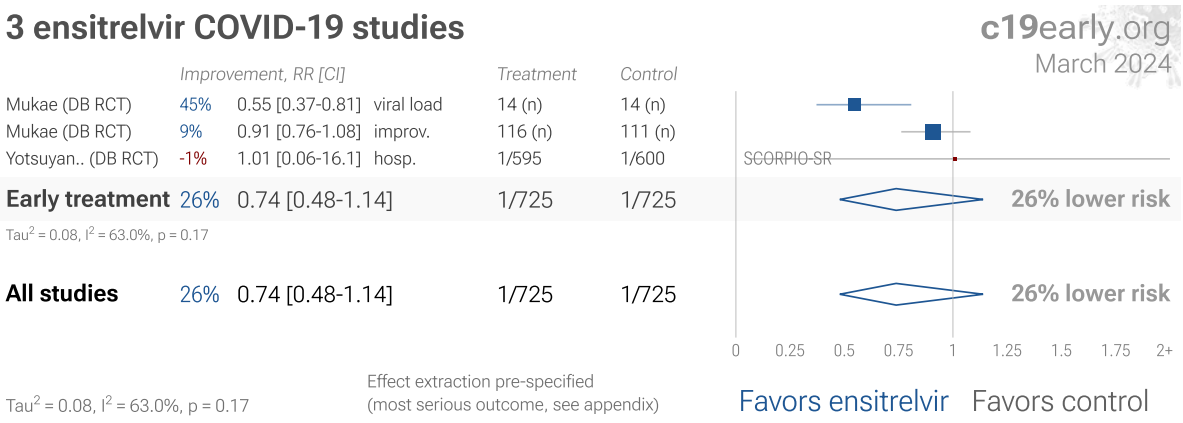



***Figure 3.*** **Random effects meta-analysis for all studies with pooled effects.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For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

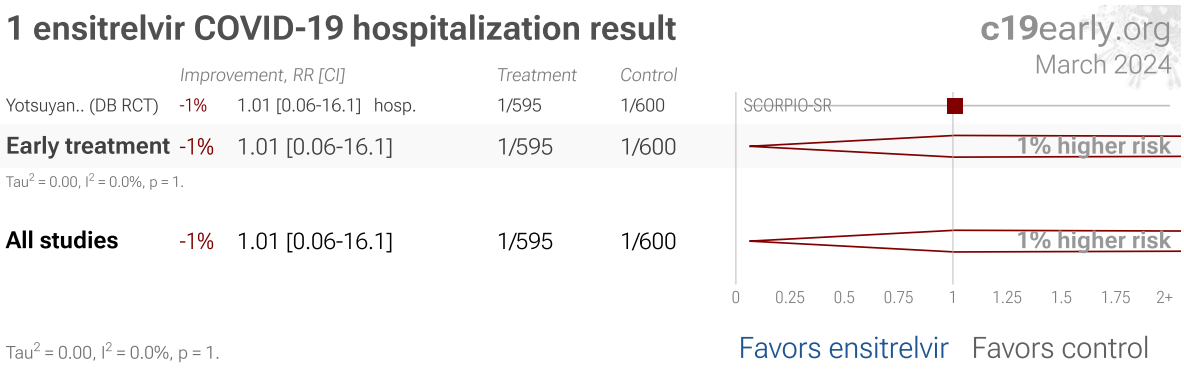



***Figure 4.*** **Random effects meta-analysis for hospitalization.**

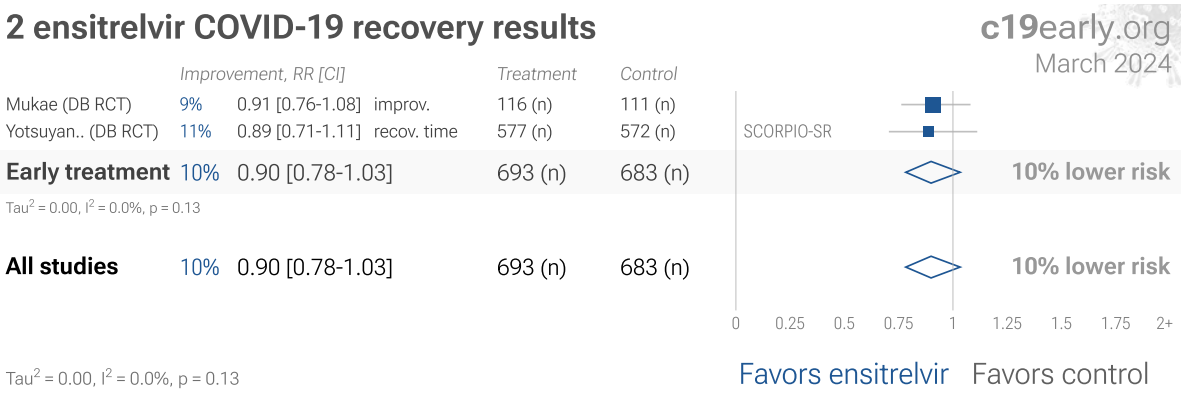



***Figure 5.*** **Random effects meta-analysis for recovery.**

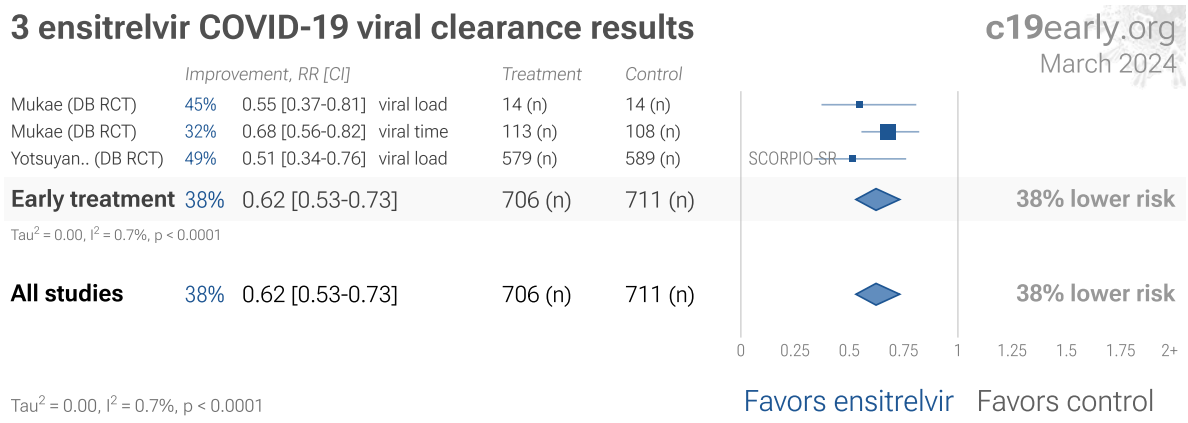



***Figure 6.*** **Random effects meta-analysis for viral clearance.**

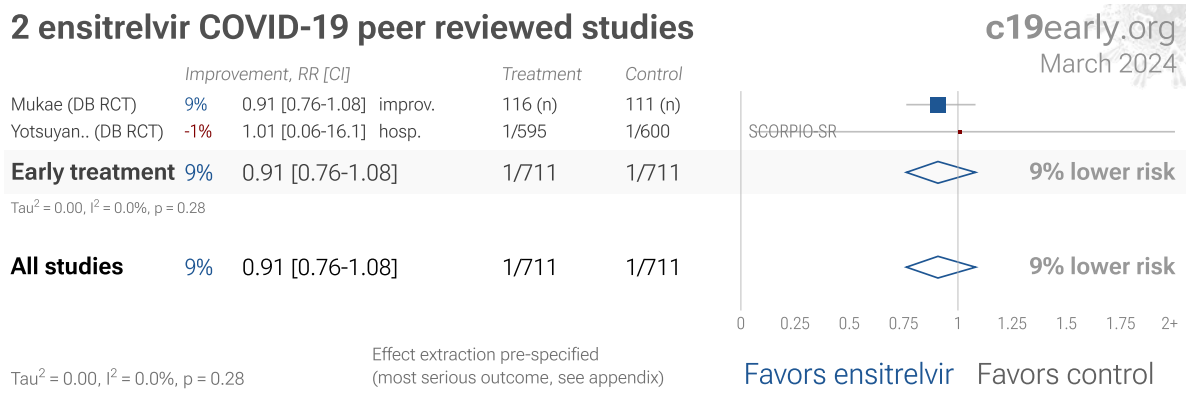



***Figure 7.*** **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent 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)

Currently all studies are RCTs.

## Heterogeneity

Heterogeneity in COVID-19 studies arises from many factors including:

**Treatment delay.** The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours [McLean, Treanor]. Baloxavir studies for influenza also show that treatment delay is critical — *Ikematsu* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and *Kumar* report only 2.5 hours improvement for inpatient treatment.

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

***Table 2.*** **Studies of baloxavir for influenza show that early treatment is more effective.**

Figure 8 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.

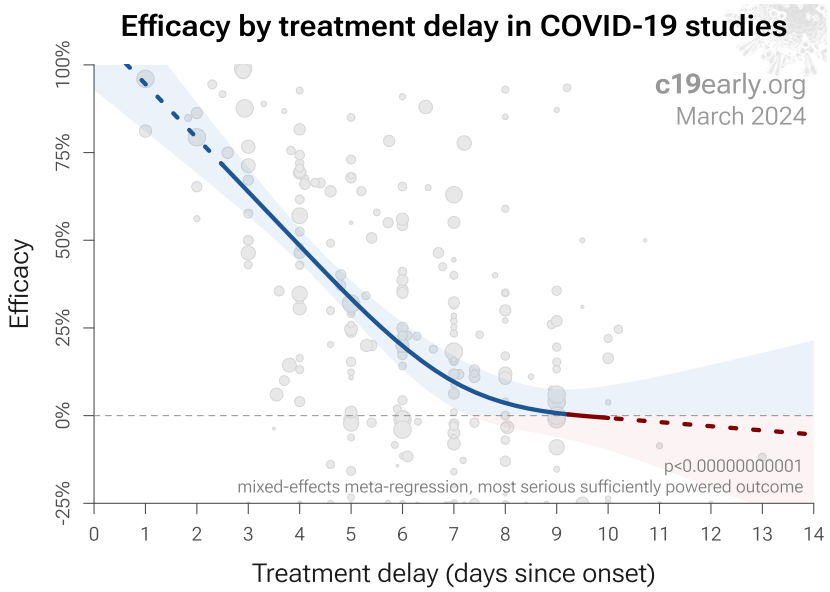



***Figure 8.*** **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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

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

**Variants.** There are many different variants of SARS-CoV-2 and efficacy may depend critically on the distribution of variants encountered by the patients in a study. For example, the Gamma variant shows significantly different characteristics *Faria, Karita, Nonaka, Zavascki*. Different mechanisms of action may be more or less effective depending on variants, for example the viral entry process for the omicron variant has moved towards TMPRSS2-independent fusion, suggesting that TMPRSS2 inhibitors may be less effective *Peacock, Willett*.

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

**Other treatments.** The use of other treatments may significantly affect outcomes, including anything from supplements, other medications, or other kinds of treatment such as prone positioning.

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

**Pooled outcome analysis.** We present both pooled analyses and specific outcome analyses. Notably, pooled analysis often results in earlier detection of efficacy as shown in Figure 9. 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.

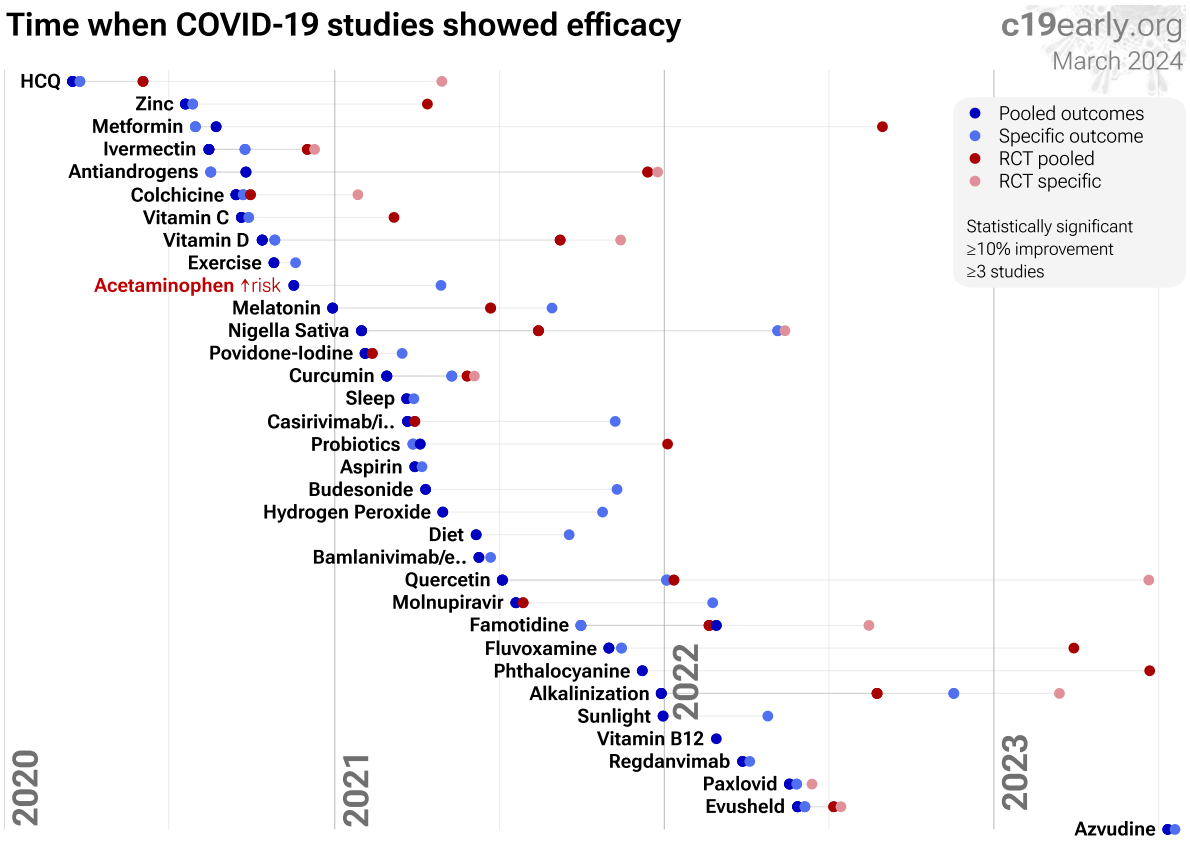



***Figure 9.*** **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when 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

**Publication bias.** Publishing is often biased towards positive results. Trials with patented drugs may have a financial conflict of interest that results in positive studies being more likely to be published, or bias towards more positive results. For example with molnupiravir, trials with negative results remain unpublished to date (CTRI/2021/05/033864 and CTRI/2021/08/0354242). For ensitrelvir, there is currently not enough data to evaluate publication bias with high confidence.

**Funnel plot analysis.** Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 10 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.

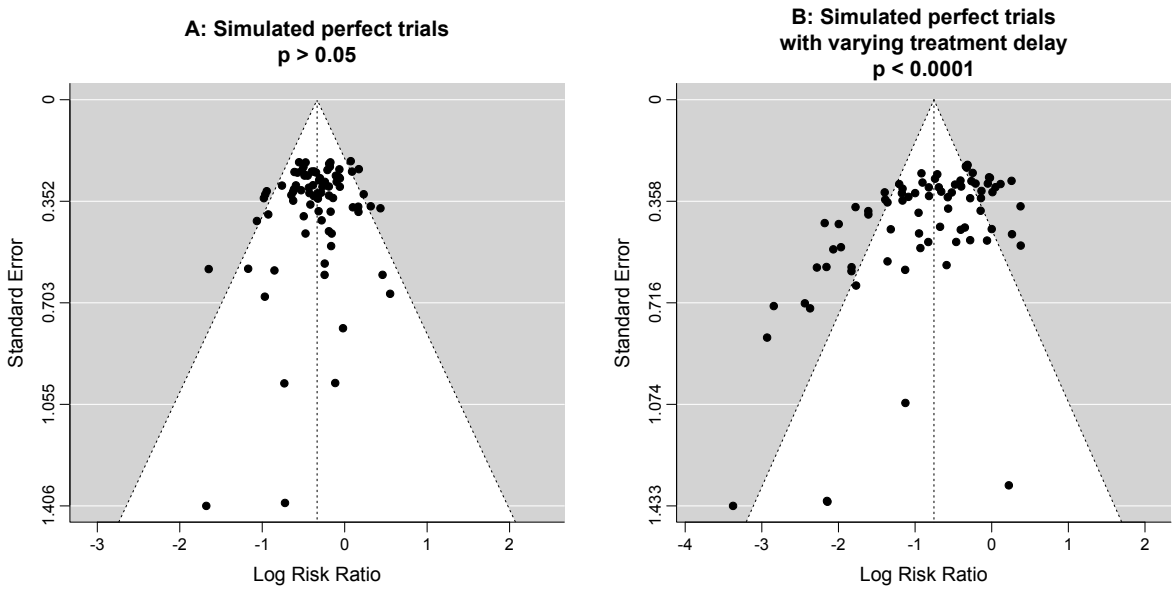



***Figure 10.*** **Example funnel plot analysis for simulated perfect trials.**

**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.

**Reviews.** *Bischof et al.* present a review covering ensitrelvir for COVID-19.

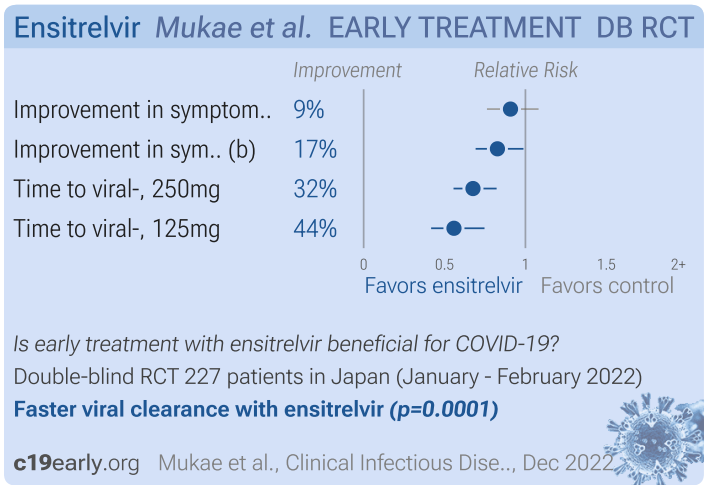
## Conclusion

Statistically significant lower risk is seen for viral clearance. 3 studies from 2 independent teams (all from the same country) show statistically significant improvements. Meta analysis using the most serious outcome reported shows 26% [-14-52%] lower risk, without reaching statistical significance. Results are worse for peer-reviewed studies. Currently all studies are RCTs.

Currently there is limited data, with only 1 control event for the most serious outcome in trials to date. Studies to date are from only 2 different groups.

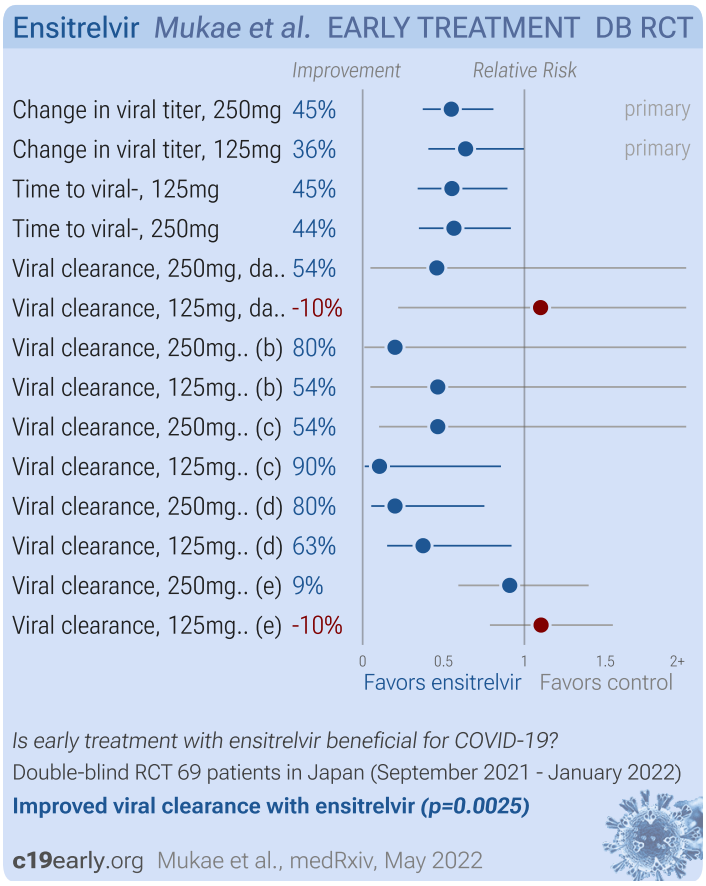
## Study Notes

### Mukae



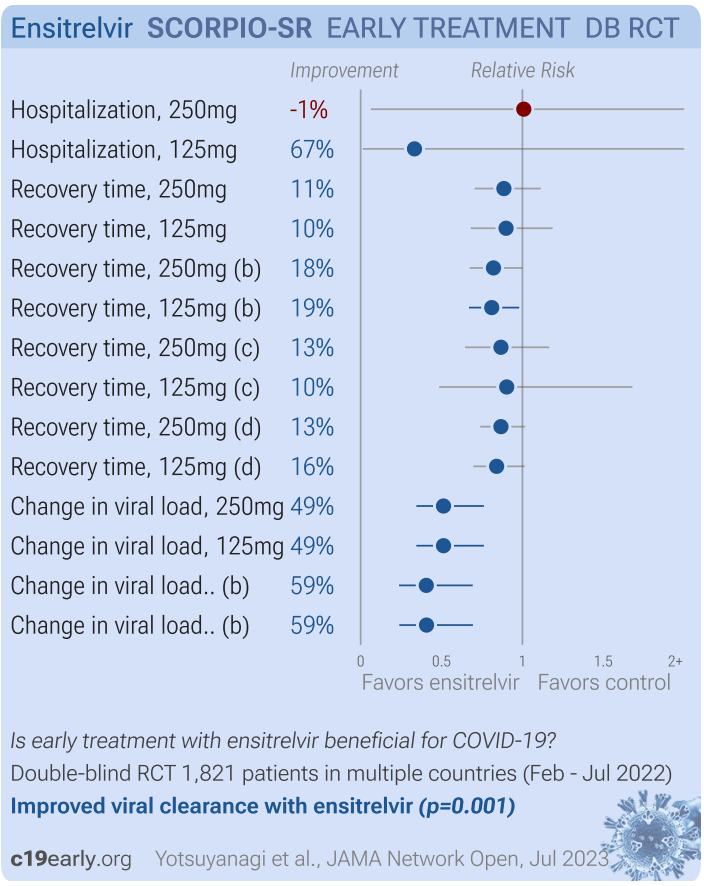

*Mukae*: RCT 428 COVID-19 patients in Japan showing faster viral clearance and improved recovery with ensitrelvir.

**Mukae**




*Mukae (B)*: RCT 69 patients in in Japan, showing faster viral clearance with ensitrelvir. 5-day ensitrelvir (375mg on day 1 followed by 125 mg daily or 750mg on day 1 followed by 250mg daily).

**Yotsuyanagi**




*Yotsuyanagi*: RCT 1,821 COVID-19 outpatients in Japan, Vietnam, and South Korea, showing improved viral clearance and improved recovery (significant for patients treated within 3 days of onset) with ensitrelvir. Only 2 hospitalizations were reported, with no deaths.

## 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 ensitrelvir 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 ensitrelvir for COVID-19 that report a comparison with a control group are included in the main analysis. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral test status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low $SpO_2$ is more important than cough. When results provide an odds ratio, we compute the

relative risk when possible, or convert to a relative risk according to *Zhang*. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 *Sweeting*. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.12.2) with scipy (1.12.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.1), and plotly (5.19.0).

Forest plots are computed using PythonMeta *Deng* with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the $I^2$ statistic. Mixed-effects meta-regression results are computed with R (4.1.2) using the metafor (3.0-2) and rms (6.2-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a p-value less than 0.05 was considered statistically significant. Grobid 0.8.0 is used to parse PDF documents.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment (for example based on oxygen status or lung involvement), and treatment started within 5 days of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of patients contributing most to the events (for example, consider a study where most patients are treated early but late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective *McLean, Treanor*.

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

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

| | |
|---|---|
| *Mukae*, 12/7/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Japan, peer-reviewed, 11 authors, study period 2 January, 2022 - 9 February, 2022, trial jRCT2031210350. | relative improvement in symptom score, 9.2% better, RR 0.91, *p* = 0.28, treatment mean 5.42 (±3.7) n=116, control mean 4.92 (±3.25) n=111, 250mg, Table 2. |
| | relative improvement in symptom score, 17.3% better, RR 0.83, *p* = 0.04, treatment mean 5.95 (±4.02) n=114, control mean 4.92 (±3.25) n=111, 125mg, Table 2. |
| | time to viral-, 32.4% lower, relative time 0.68, *p* < 0.001, treatment 113, control 108, relative time to first negative viral titer, 250mg, Figure 3. |
| | time to viral-, 44.2% lower, relative time 0.56, *p* < 0.001, treatment 113, control 108, relative time to first negative viral titer, 125mg, Figure 3. |

| | |
|---|---|
| *Mukae (B)*, 5/17/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Japan, preprint, 13 authors, study period 28 September, 2021 - 1 January, 2022, trial jRCT2031210350. | relative change in viral titer, 45.2% better, RR 0.55, *p* = 0.002, treatment mean 2.81 (±1.21) n=14, control mean 1.54 (±0.74) n=14, day 4, 250mg, primary outcome. |
| | relative change in viral titer, 36.4% better, RR 0.64, *p* = 0.048, treatment mean 2.42 (±1.42) n=15, control mean 1.54 (±0.74) n=14, day 4, 125mg, primary outcome. |
| | time to viral-, 44.8% lower, relative time 0.55, *p* = 0.02, treatment 15, control 14, 125mg. |
| | time to viral-, 43.6% lower, relative time 0.56, *p* = 0.02, treatment 13, control 14, 250mg. |
| | risk of no viral clearance, 54.2% lower, RR 0.46, *p* = 0.59, treatment 1 of 12 (8.3%), control 2 of 11 (18.2%), NNT 10, day 14, 250mg, Figure S1. |
| | risk of no viral clearance, 10.0% higher, RR 1.10, *p* = 1.00, treatment 3 of 15 (20.0%), control 2 of 11 (18.2%), day 14, 125mg, Figure S1. |
| | risk of no viral clearance, 80.0% lower, RR 0.20, *p* = 0.48, treatment 0 of 13 (0.0%), control 2 of 13 (15.4%), NNT 6.5, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 9, 250mg, Figure S1. |
| | risk of no viral clearance, 53.6% lower, RR 0.46, *p* = 0.60, treatment 1 of 14 (7.1%), control 2 of 13 (15.4%), NNT 12, day 9, 125mg, Figure S1. |
| | risk of no viral clearance, 53.6% lower, RR 0.46, *p* = 0.38, treatment 2 of 14 (14.3%), control 4 of 13 (30.8%), NNT 6.1, day 6, 250mg, Figure S1. |
| | risk of no viral clearance, 89.6% lower, RR 0.10, *p* = 0.03, treatment 0 of 15 (0.0%), control 4 of 13 (30.8%), NNT 3.2, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 6, 125mg, Figure S1. |
| | risk of no viral clearance, 80.0% lower, RR 0.20, *p* = 0.006, treatment 2 of 14 (14.3%), control 10 of 14 (71.4%), NNT 1.8, day 4, 250mg, Figure S1. |
| | risk of no viral clearance, 62.7% lower, RR 0.37, *p* = 0.03, treatment 4 of 15 (26.7%), control 10 of 14 (71.4%), NNT 2.2, day 4, 125mg, Figure S1. |
| | risk of no viral clearance, 9.1% lower, RR 0.91, *p* = 1.00, treatment 10 of 14 (71.4%), control 11 of 14 (78.6%), NNT 14, day 2, 250mg, Figure S1. |
| | risk of no viral clearance, 10.3% higher, RR 1.10, *p* = 0.65, treatment 13 of 15 (86.7%), control 11 of 14 (78.6%), day 2, |

| | |
|---|---|
| | 125mg, Figure S1. |
| *Yotsuyanagi*, 7/13/2023, Double Blind Randomized Controlled Trial, placebo-controlled, multiple countries, peer-reviewed, mean age 35.7, 13 authors, study period 10 February, 2022 - 10 July, 2022, trial jRCT2031210350 (SCORPIO-SR). | risk of hospitalization, 0.8% higher, RR 1.01, $p = 1.00$, treatment 1 of 595 (0.2%), control 1 of 600 (0.2%), 250mg. |
| | risk of hospitalization, 66.7% lower, RR 0.33, $p = 0.50$, treatment 0 of 603 (0.0%), control 1 of 600 (0.2%), NNT 600, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), 125mg. |
| | recovery time, 11.4% lower, relative time 0.89, $p = 0.30$, treatment 577, control 572, 14 symptoms, randomized within 120 hours, 250mg. |
| | recovery time, 10.1% lower, relative time 0.90, $p = 0.46$, treatment 582, control 572, 14 symptoms, randomized within 120 hours, 125mg. |
| | recovery time, 17.9% lower, relative time 0.82, $p = 0.05$, treatment 330, control 321, 14 symptoms, randomized within 72 hours, 250mg. |
| | recovery time, 19.0% lower, relative time 0.81, $p = 0.03$, treatment 336, control 321, 14 symptoms, randomized within 72 hours, 125mg. |
| | recovery time, 13.3% lower, relative time 0.87, $p = 0.35$, treatment 577, control 572, 12 symptoms, randomized within 120 hours, 250mg. |
| | recovery time, 9.7% lower, relative time 0.90, $p = 0.76$, treatment 582, control 572, 12 symptoms, randomized within 120 hours, 125mg. |
| | recovery time, 13.3% lower, relative time 0.87, $p = 0.08$, treatment 330, control 321, 12 symptoms, randomized within 72 hours, 250mg. |
| | recovery time, 15.9% lower, relative time 0.84, $p = 0.07$, treatment 336, control 321, 12 symptoms, randomized within 72 hours, 125mg. |
| | relative change in viral load, 48.8% better, RR 0.51, $p < 0.001$, treatment 579, control 589, randomized within 120 hours, 250mg. |
| | relative change in viral load, 48.8% better, RR 0.51, $p < 0.001$, treatment 592, control 589, randomized within 120 hours, 125mg. |
| | relative change in viral load, 59.4% better, RR 0.41, $p < 0.001$, treatment 330, control 321, randomized within 72 hours, 250mg. |
| | relative change in viral load, 59.3% better, RR 0.41, $p < 0.001$, treatment 336, control 321, randomized within 72 hours, 125mg. |

## Supplementary Data

Supplementary Data

## Footnotes

a. Viral infection and replication involves attachment, entry, uncoating and release, genome replication and transcription, translation and protein processing, assembly and budding, and release. Each step can be disrupted by therapeutics.

b. VeroE6/TMPRSS2 is a Vero E6 cell line engineered to express the human serine protease TMPRSS2, enabling SARS-CoV-2 S protein priming and entry.

c. HEK293T/ACE2-TMPRSS2 is a human embryonic kidney cell line engineered to express human ACE2 and TMPRSS2, making it highly susceptible to SARS-CoV-2 infection.

d. MucilAir cells are primary human nasal epithelial cells that mimic the structure and physiology of the human airway epithelium.

e. A mouse model commonly used in infectious disease and cancer research due to higher immune response and susceptibility to infection.

f. A small rodent model used in SARS-CoV-2 research that replicates key aspects of human infection including efficient replication in the upper and lower respiratory tract.

g. The original SARS-CoV-2 strain that emerged in Wuhan, China in late 2019. Also referred to as wild-type.

h. A variant of concern first identified in India in late 2020, delta (B.1.617.2) transmitted more efficiently than previous variants. It contains spike mutations including L452R which increases binding to the ACE2 receptor.

i. A highly transmissible variant of concern first detected in South Africa in late 2021. Omicron possesses many spike mutations which confer partial immune evasion, including deletions near the furin cleavage site.

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