

Ensirelvir for COVID-19: real-time meta analysis of 7 studies

@CovidAnalysis, July 2025, Version 13

<https://c19early.org/enmeta.html>

Abstract

Significantly lower risk is seen for hospitalization, recovery, and viral clearance. 7 studies from 6 independent teams (all from the same country) show significant benefit.

Meta analysis using the most serious outcome reported shows 14% [2-25%] lower risk. Results are similar for Randomized Controlled Trials and worse for peer-reviewed studies.

Currently there is limited data, with only 3 control events for the most serious outcome in trials to date.

Variants may be resistant to ensirelvir^{1,2}.

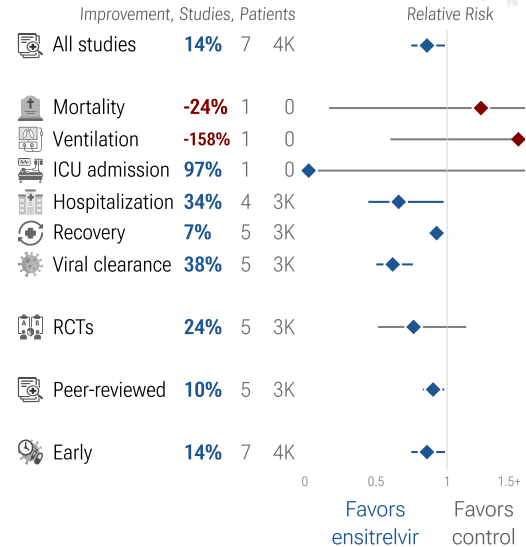
No treatment is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. Other treatments are more effective. All data and sources to reproduce this analysis are in the appendix.

Serious Outcome Risk



Ensirelvir for COVID-19

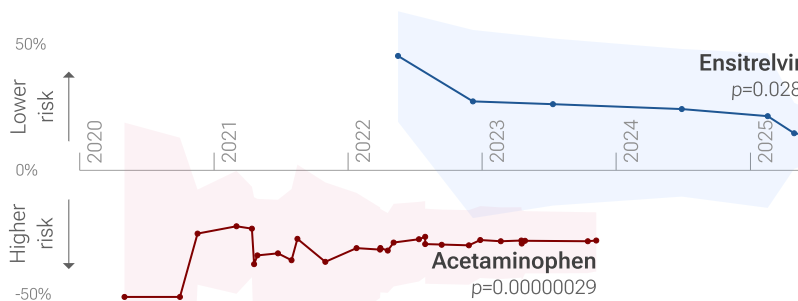
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Evolution of COVID-19 clinical evidence

Meta analysis results over time

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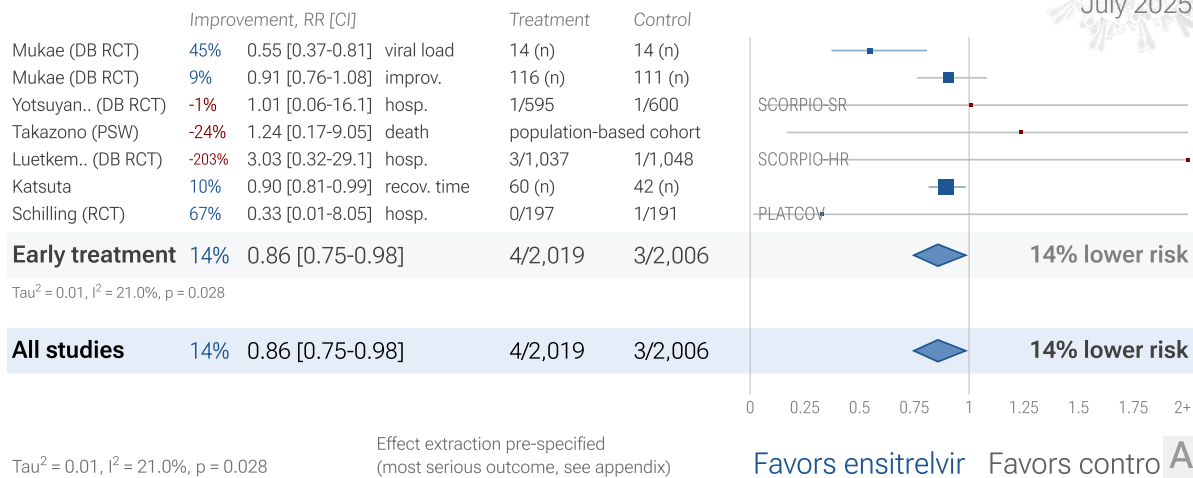
ENSIRELVR FOR COVID-19 — HIGHLIGHTS

Ensirelvir reduces risk with very high confidence for recovery and viral clearance, and high confidence for hospitalization and in pooled analysis, however increased risk is seen with very low confidence for mortality and ventilation.

48th treatment shown effective in July 2023, now with $p = 0.028$ from 7 studies.

Real-time updates and corrections with a consistent protocol for 172 treatments. Outcome specific analysis and combined evidence from all studies including treatment delay, a primary confounding factor.

7 ensitrelvir COVID-19 studies



Timeline of COVID-19 ensitrelvir studies (pooled effects)

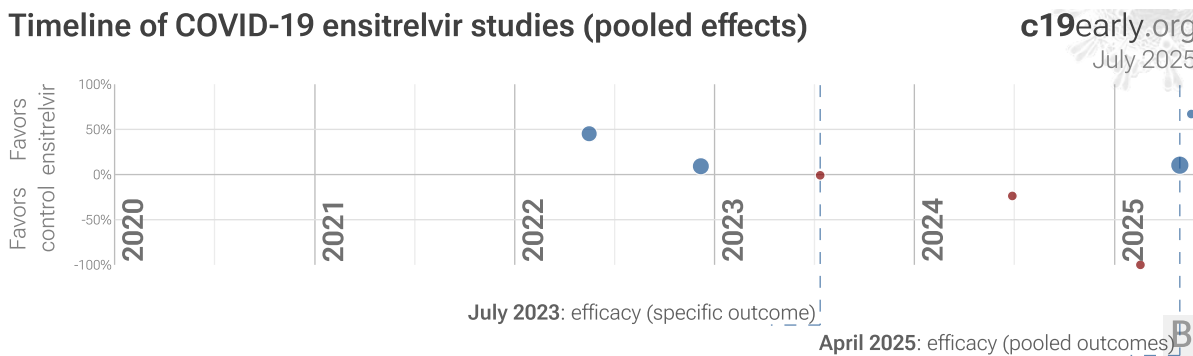


Figure 1. A. Random effects meta-analysis. This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the [appendix](#). **B. Timeline of results in ensitrelvir studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of $\geq 10\%$ from ≥ 3 studies for pooled outcomes and 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 injury⁴⁻¹⁶ and cognitive deficits^{7,12}, cardiovascular complications¹⁷⁻²¹, organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits²²—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. 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 100+ host and viral proteins and other factors^{A,23-30}, providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 9,000 compounds may reduce COVID-19 risk³¹, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

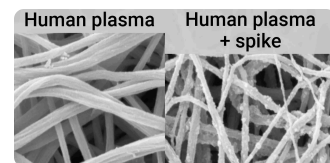


Figure 2. SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from³.

Supporting research

In Vitro studies demonstrate efficacy in VeroE6/TMPRSS2^{B,32}, HEK293T/ACE2-TMPRSS2^{C,32}, and MucilAir^{D,32} cells. Animal studies demonstrate efficacy in BALB/c mice^{E,32,33} and Syrian hamsters^{F,32}. Preclinical studies demonstrate efficacy for the ancestral^{G,32}, delta^{H,32}, and omicron^{I,32} 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 3 shows stages of possible treatment for COVID-19. Prophylaxis refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. Early Treatment refers to treatment immediately or soon after symptoms appear, while Late Treatment refers to more delayed treatment. Currently all ensitrelvir studies use early treatment.

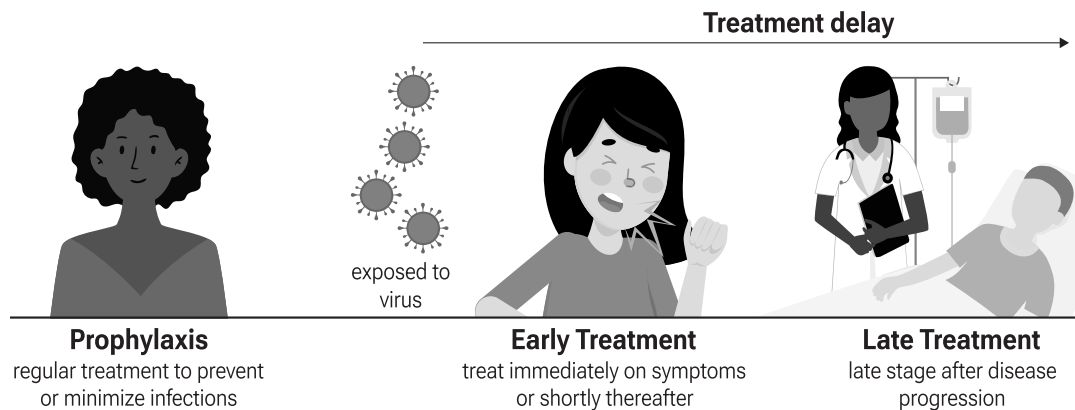


Figure 3. Treatment stages.

Preclinical Research

In Vitro studies demonstrate efficacy in VeroE6/TMPRSS2^{B,32}, HEK293T/ACE2-TMPRSS2^{C,32}, and MucilAir^{D,32} cells. Animal studies demonstrate efficacy in BALB/c mice^{E,32,33} and Syrian hamsters^{F,32}. Preclinical studies demonstrate efficacy for the ancestral^{G,32}, delta^{H,32}, and omicron^{I,32} variants.

2 *In Vitro* studies support the efficacy of ensitrelvir^{32,34}.

2 *In Vivo* animal studies support the efficacy of ensitrelvir^{32,33}.

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 4, 5, 6, 7, 8, 9, 10, and 11 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, recovery, viral clearance, and peer reviewed studies.

	Relative Risk	Studies	Patients
All studies	0.86 [0.75-0.98] *	7	4,025
Peer-reviewed	0.90 [0.83-0.98] *	5	3,609
RCTs	0.76 [0.51-1.13]	5	3,923
Hospitalization	0.66 [0.45-0.97] *	4	3,668
Recovery	0.93 [0.89-0.96] ****	5	3,754
Viral	0.62 [0.50-0.76] ****	5	3,572
RCT hospitalization	1.29 [0.28-6.01]	3	3,668

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

7 ensitrelvir COVID-19 studies

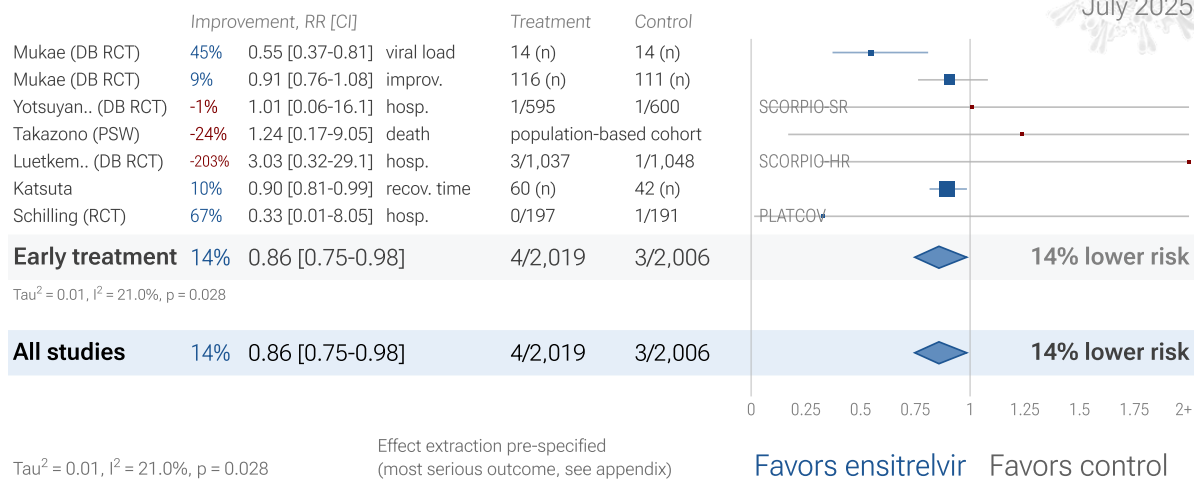


Figure 4. Random effects meta-analysis for all studies. This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details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

1 ensitrelvir COVID-19 mortality result

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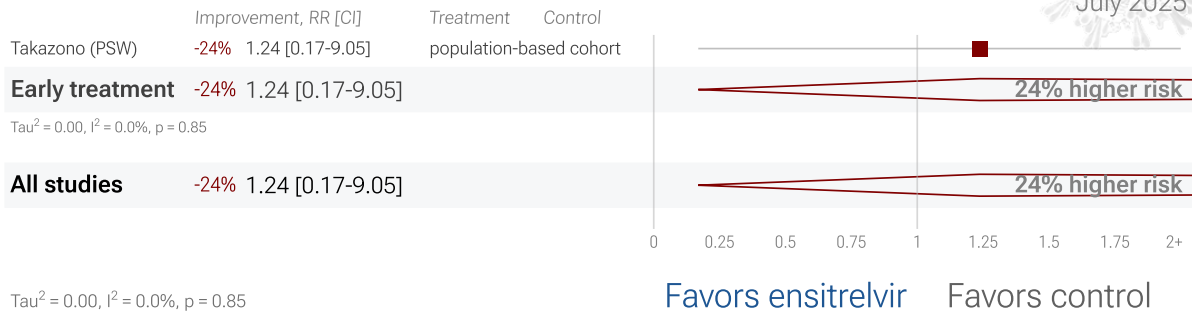


Figure 5. Random effects meta-analysis for mortality results.

1 ensitrelvir COVID-19 mechanical ventilation result

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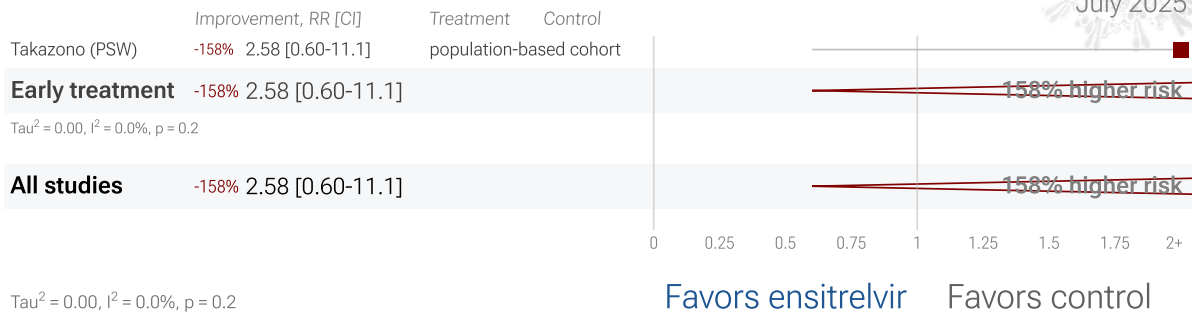


Figure 6. Random effects meta-analysis for ventilation.

1 ensitrelvir COVID-19 ICU result

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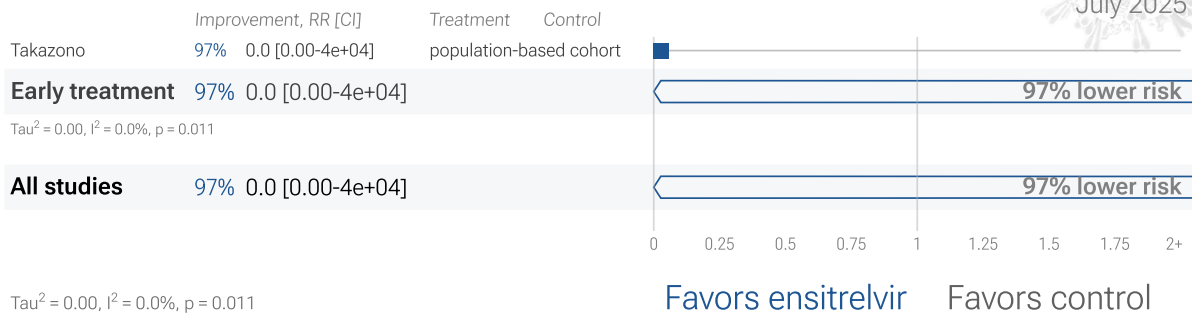


Figure 7. Random effects meta-analysis for ICU admission.

4 ensitrelvir COVID-19 hospitalization results

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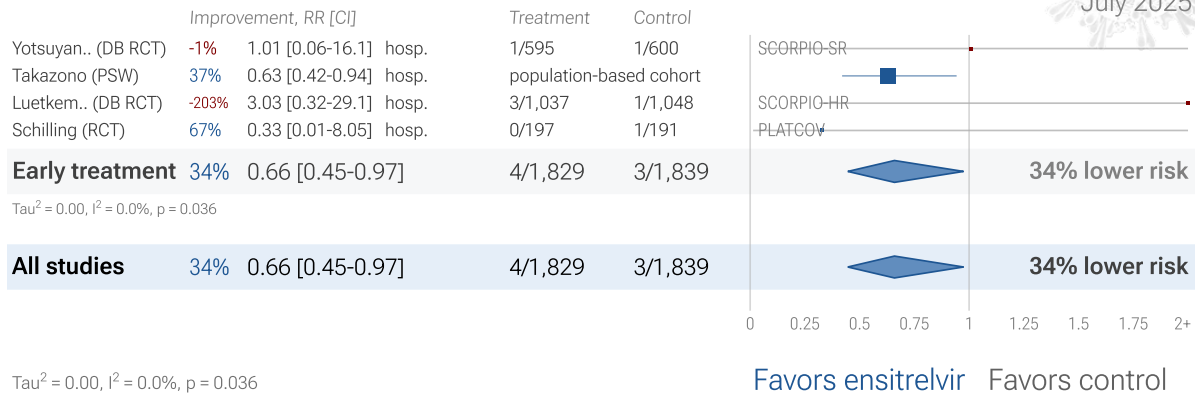


Figure 8. Random effects meta-analysis for hospitalization.

5 ensitrelvir COVID-19 recovery results

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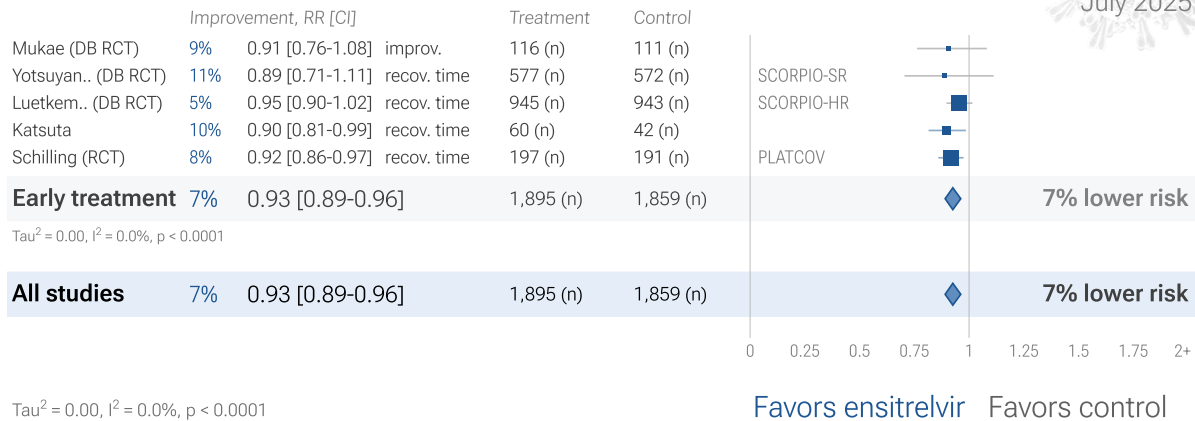


Figure 9. Random effects meta-analysis for recovery.

5 ensitrelvir COVID-19 viral clearance results

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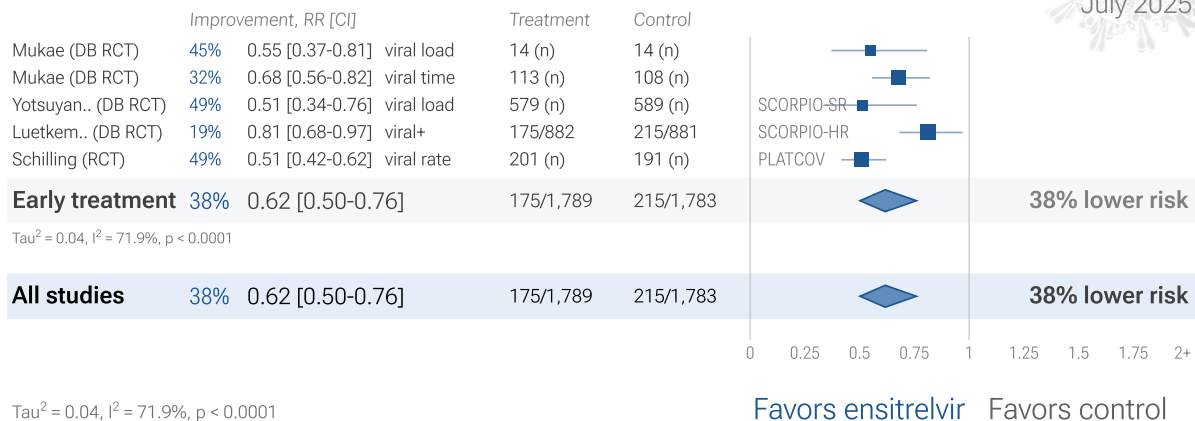


Figure 10. Random effects meta-analysis for viral clearance.

5 ensitrelvir COVID-19 peer reviewed studies

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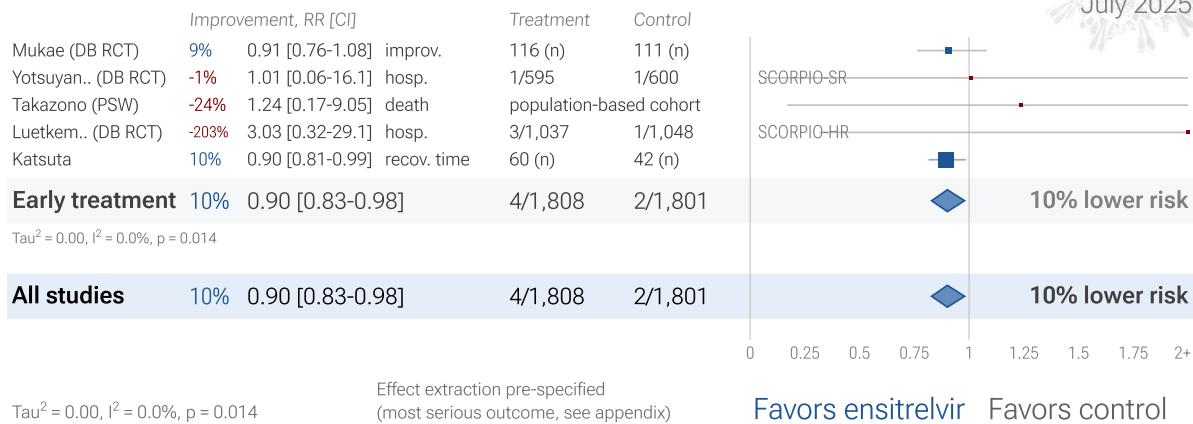


Figure 11. Random effects meta-analysis for peer reviewed studies. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. Zeraatkar *et al.* analyze 356 COVID-19 trials, finding no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

Davidson *et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

Randomized Controlled Trials (RCTs)

Figure 12 shows a comparison of results for RCTs and observational studies. Random effects meta analysis of RCTs shows 24% improvement, compared to 10% for other studies. Figure 13 and 14 show forest plots for random effects meta-analysis of all Randomized Controlled Trials and RCT hospitalization results. RCT results are included in Table 1.

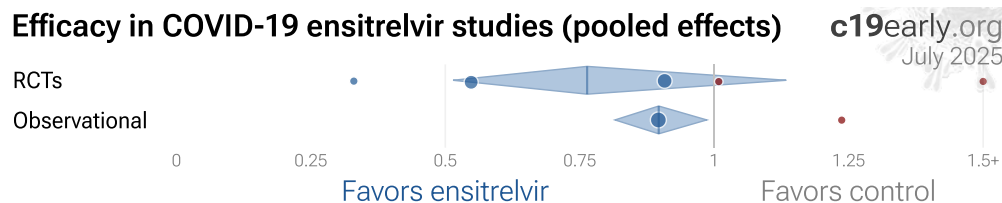


Figure 12. Results for RCTs and observational studies.

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 biases³⁷, and analysis of double-blind RCTs has identified extreme levels of bias³⁸. 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 172 treatments we have analyzed, 67% 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.

Observational studies have been shown to be reliable

Evidence shows that observational 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.* analyzed reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. We performed a similar analysis across

the 172 treatments we cover, showing no significant difference in the results of RCTs compared to observational studies, RR 0.98 [0.92-1.05]⁴³. Similar results are found for all low-cost treatments, RR 1.00 [0.91-1.09]. High-cost treatments show a non-significant trend towards RCTs showing greater efficacy, RR 0.92 [0.84-1.02]. Details can be found in the [supplementary data](#). *Lee et al.* showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or remote 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^{45,46}.

RCT vs. observational from 5,918 studies

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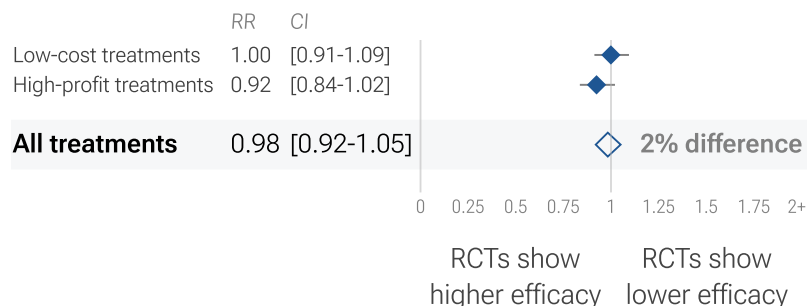


Figure 15. For COVID-19, observational study results do not systematically differ from RCTs, RR 0.98 [0.92-1.05] across 172 treatments⁴⁰.

Using all studies identifies efficacy 8+ months faster (9+ months for low-cost treatments)

Currently, 55 of the treatments we analyze show statistically significant efficacy or harm, defined as $\geq 10\%$ decreased risk or $>0\%$ increased risk from ≥ 3 studies. Of these, 58% have been confirmed in RCTs, with a mean delay of 7.7 months (64% with 8.9 months delay for low-cost treatments). The remaining treatments either have no RCTs, or the point estimate is consistent.

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.

5 ensitrelvir COVID-19 Randomized Controlled Trials

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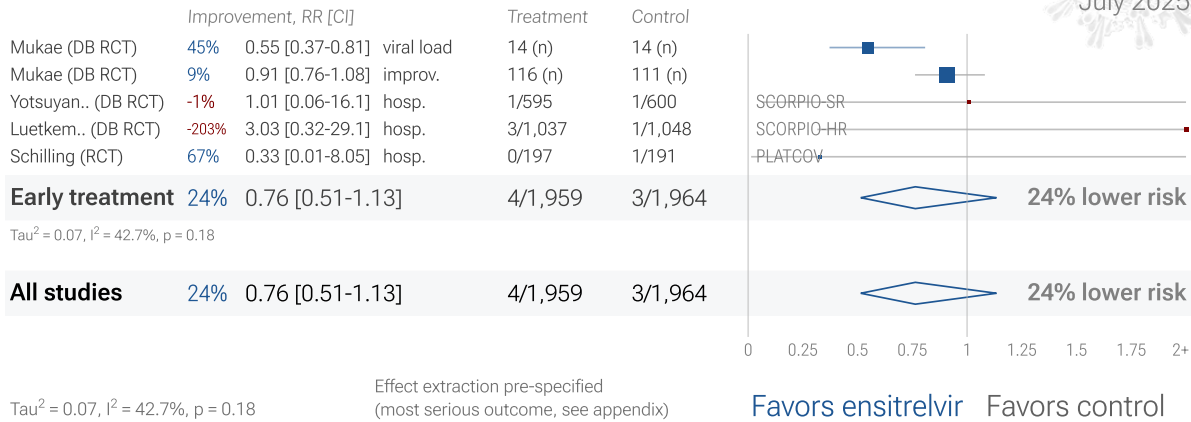


Figure 13. Random effects meta-analysis for all Randomized Controlled Trials. This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

3 ensitrelvir COVID-19 RCT hospitalization results

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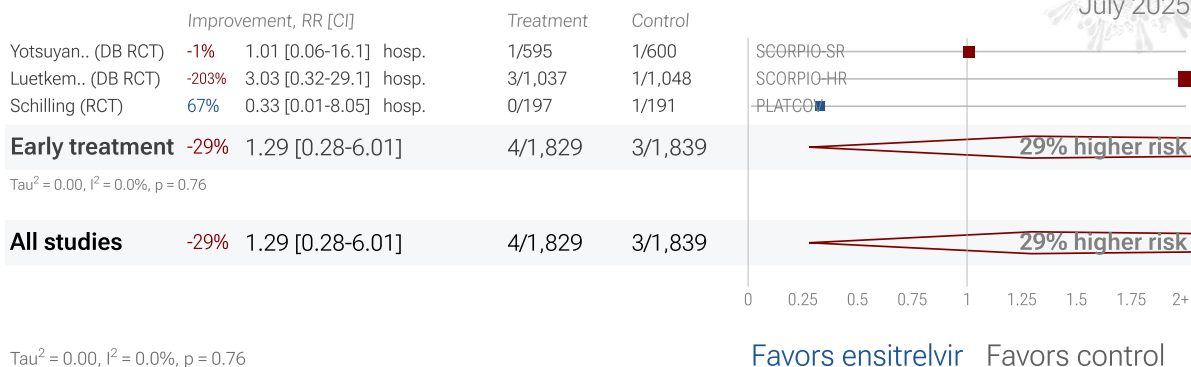


Figure 14. Random effects meta-analysis for RCT hospitalization results.

Heterogeneity

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

Treatment delay

The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours^{47,48}. Baloxavir marboxil studies for influenza also show that treatment delay is critical — Ikematsu *et al.* report an 86% reduction in cases for post-exposure prophylaxis, Hayden *et al.* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and Kumar *et al.* report only 2.5 hours improvement for inpatient treatment.

Treatment delay	Result
Post-exposure prophylaxis	86% fewer cases ⁴⁹
<24 hours	-33 hours symptoms ⁵⁰
24-48 hours	-13 hours symptoms ⁵⁰
Inpatients	-2.5 hours to improvement ⁵¹

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

Figure 16 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 172 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

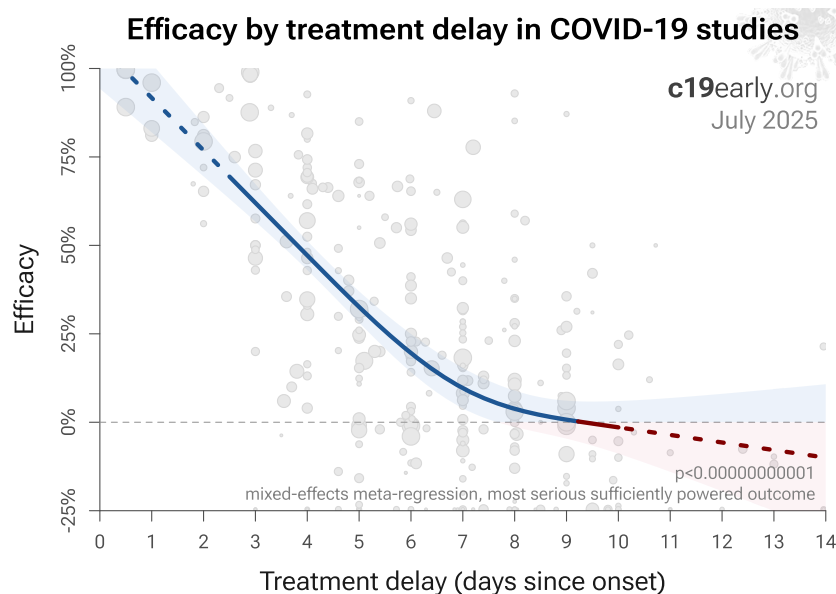


Figure 16. Early treatment is more effective. Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 172 treatments.

Patient demographics

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

SARS-CoV-2 variants

Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants⁵³, for example the Gamma variant shows significantly different characteristics⁵⁴⁻⁵⁷. 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^{58,59}.

Treatment regimen

Effectiveness may depend strongly on the dosage and treatment regimen.

Medication quality

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

Other treatments

The use of other treatments may significantly affect outcomes, including supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic⁶²⁻⁷⁸, therefore efficacy may depend strongly on combined treatments.

Effect measured

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

Meta analysis

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

Pooled Effects

Pooled effects are no longer required to show efficacy as of July 2023

This section validates the use of pooled effects for COVID-19, which enables earlier detection of efficacy, however pooled effects are no longer required for ensitrelvir as of July 2023. Efficacy is now known based on specific outcomes.

Combining studies is required

For COVID-19, delay in clinical results translates into additional death and morbidity, as well as additional economic and societal damage. Combining the results of studies reporting different outcomes is required. There may be no mortality in a trial with low-risk patients, however a reduction in severity or improved viral clearance may translate into lower mortality in a high-risk population. Different studies may report lower severity, improved recovery, and lower mortality, and the significance may be very high when combining the results. "*The studies reported different outcomes*" is not a good reason for disregarding results. Pooling the results of studies reporting different outcomes allows us to use more of the available information. Logically we should, and do, use additional information when evaluating treatments—for example dose-response and treatment delay-response relationships provide additional evidence of efficacy that is considered when reviewing the evidence for a treatment.

Specific outcome and pooled analyses

We present both specific outcome and pooled analyses. In order to combine the results of studies reporting different outcomes we use the most serious outcome reported in each study, based on the thesis that improvement in the most serious outcome provides comparable measures of efficacy for a treatment. A critical advantage of this

approach is simplicity and transparency. There are many other ways to combine evidence for different outcomes, along with additional evidence such as dose-response relationships, however these increase complexity.

Ethical and practical issues limit high-risk trials

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

Validating pooled outcome analysis for COVID-19

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

Analysis of the the association between different outcomes across studies from all 172 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 17 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 18 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 19 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to *Singh et al.*, with higher confidence due to the larger number of studies. As with *Singh et al.*, the confidence increases when excluding the outlier treatment, from $p = 0.000000082$ to $p = 0.0000000033$.

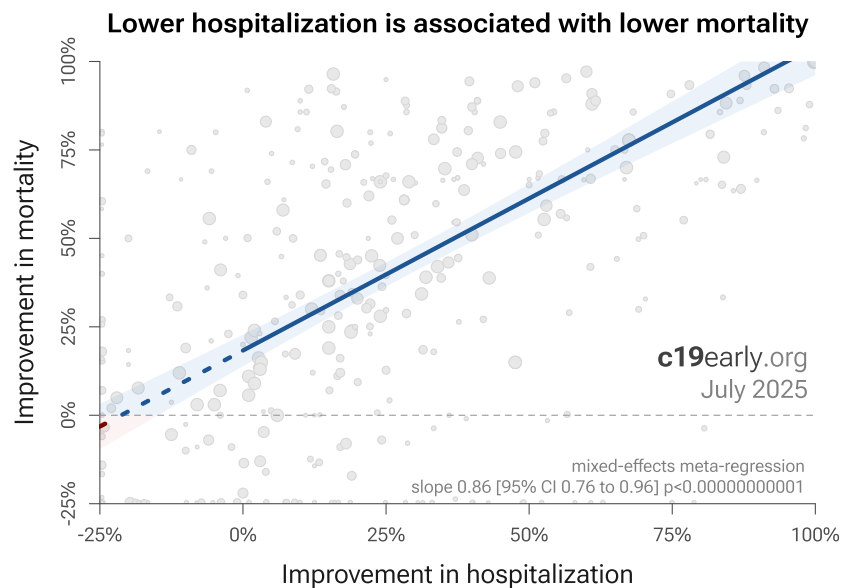


Figure 17. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

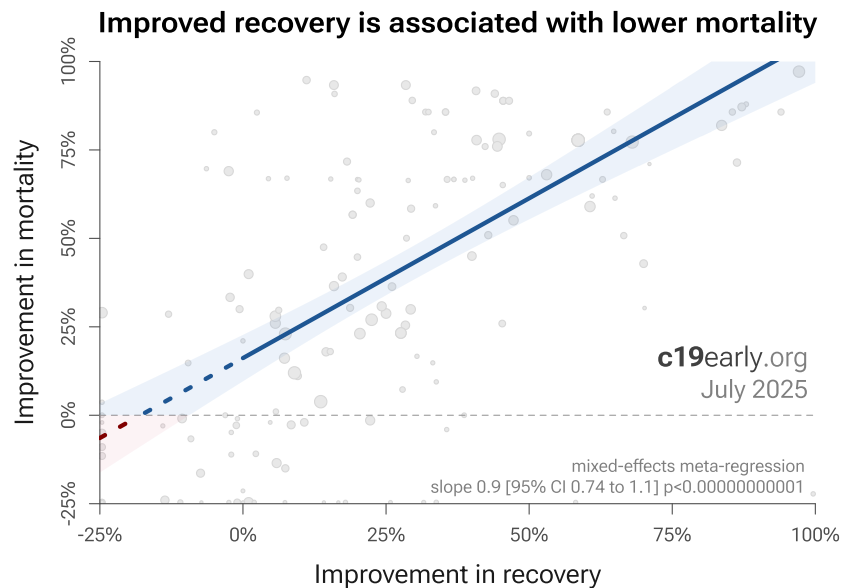


Figure 18. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

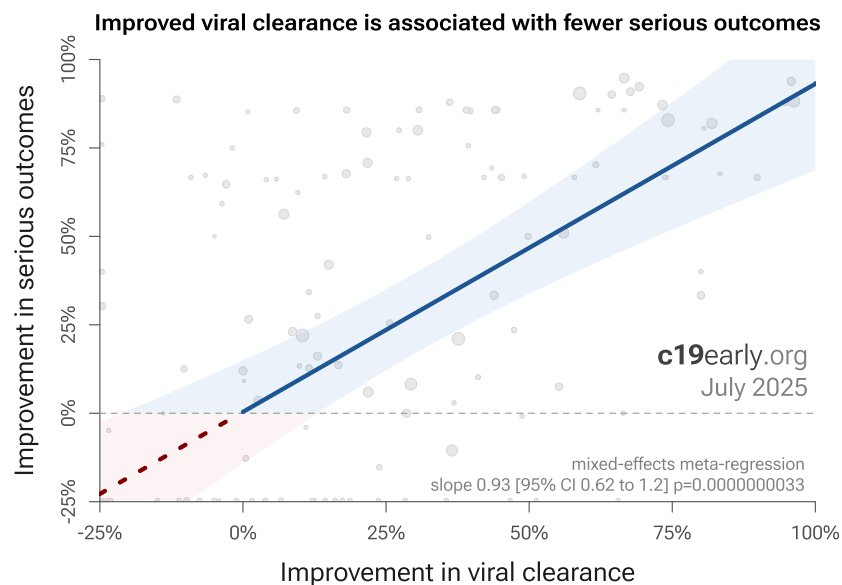


Figure 17. Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.

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

Currently, 55 of the treatments we analyze show statistically significant efficacy or harm, defined as $\geq 10\%$ 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 4.9 months. When restricting to RCTs only, 57% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 7.3 months. Figure 20 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

Time when COVID-19 studies showed efficacy

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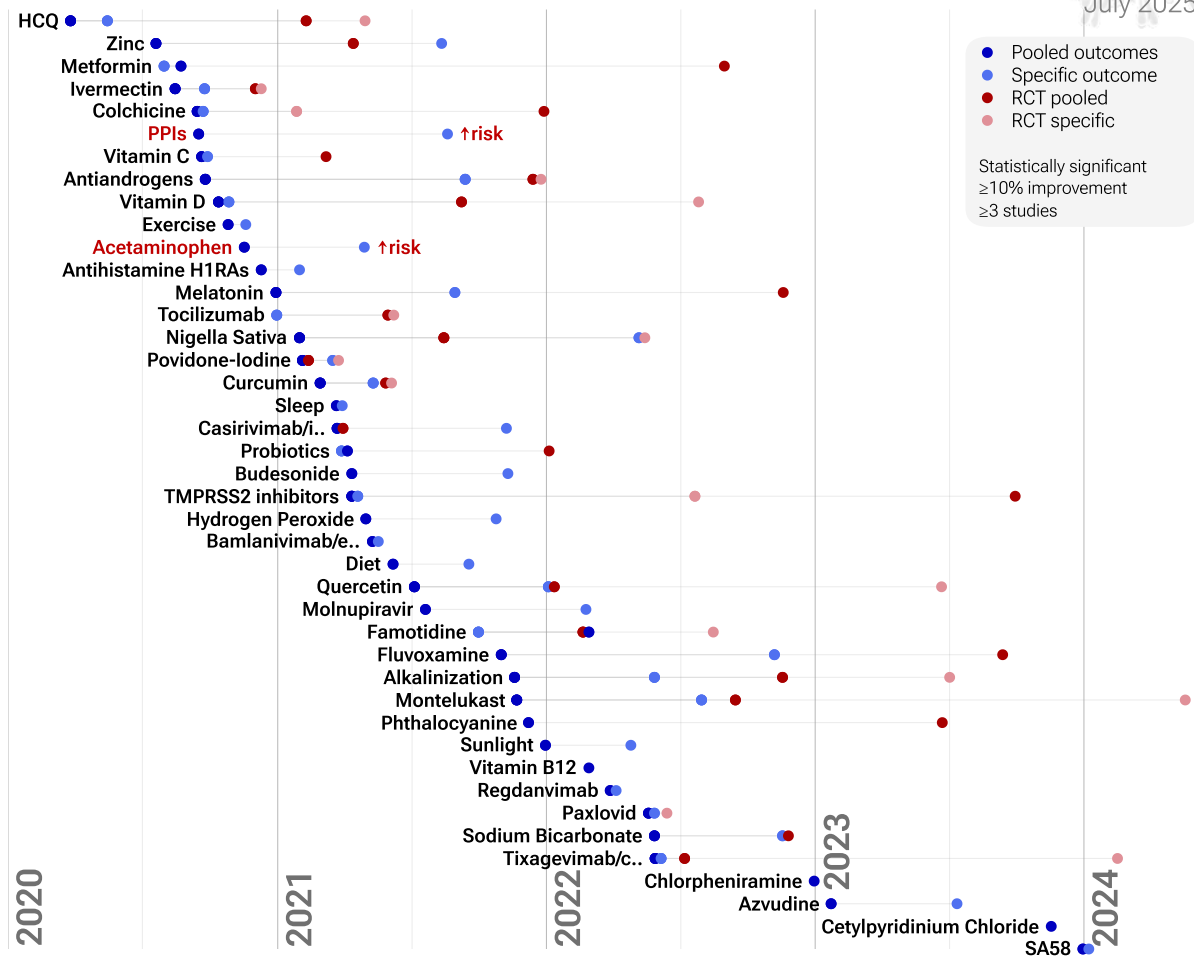


Figure 20. The time when studies showed that treatments were effective, defined as statistically significant improvement of $\geq 10\%$ from ≥ 3 studies. Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when 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. 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.

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 21 shows a scatter plot of results for prospective and retrospective studies. 100% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 100% of prospective studies, showing no difference.

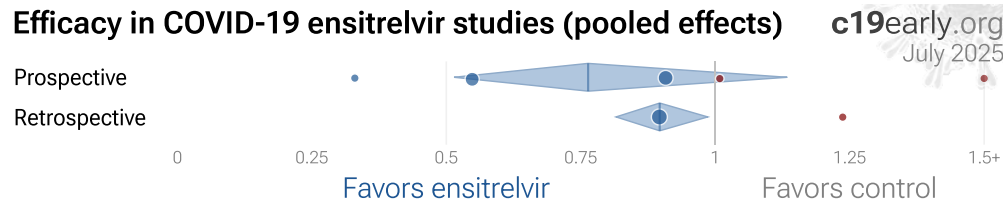


Figure 21. Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.

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 22 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 $p < 0.05$ ⁸⁰⁻⁸⁷. 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.

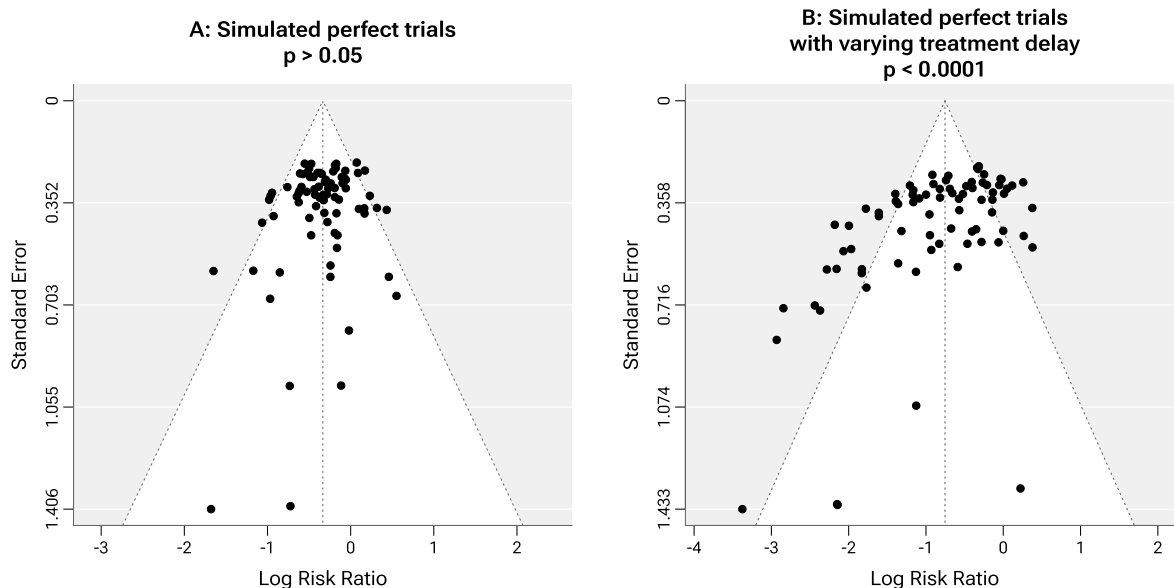


Figure 22. Example funnel plot analysis for simulated perfect trials.

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 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 alone⁶²⁻⁷⁸. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

This real-time analysis is constantly updated based on submissions. Accuracy benefits from widespread review and submission of updates and corrections from reviewers. Less popular treatments may receive fewer reviews.

No treatment or intervention is 100% available and effective for all current and future variants. Efficacy may vary significantly with different variants and within different populations. All treatments have potential side effects. Propensity to experience side effects may be predicted in advance by qualified physicians. We do not provide medical advice. Before taking any medication, consult a qualified physician who can compare all options, provide personalized advice, and provide details of risks and benefits based on individual medical history and situations.

Reviews

Multiple reviews cover ensitrelvir for COVID-19, presenting additional background on mechanisms and related results, including ^{1,88}.

Other studies

Additional preclinical or review papers suggesting potential benefits of ensitrelvir for COVID-19 include ⁹⁶⁻¹¹⁴. We have not reviewed these studies in detail.

Perspective

Results compared with other treatments

SARS-CoV-2 infection and replication involves a complex interplay of 100+ host and viral proteins and other factors ²³⁻³⁰, providing many therapeutic targets. Over 9,000 compounds have been predicted to reduce COVID-19 risk ³¹, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 23 shows an overview of the results for ensitrelvir in the context of multiple COVID-19 treatments, and Figure 24 shows a plot of efficacy vs. cost for COVID-19 treatments.

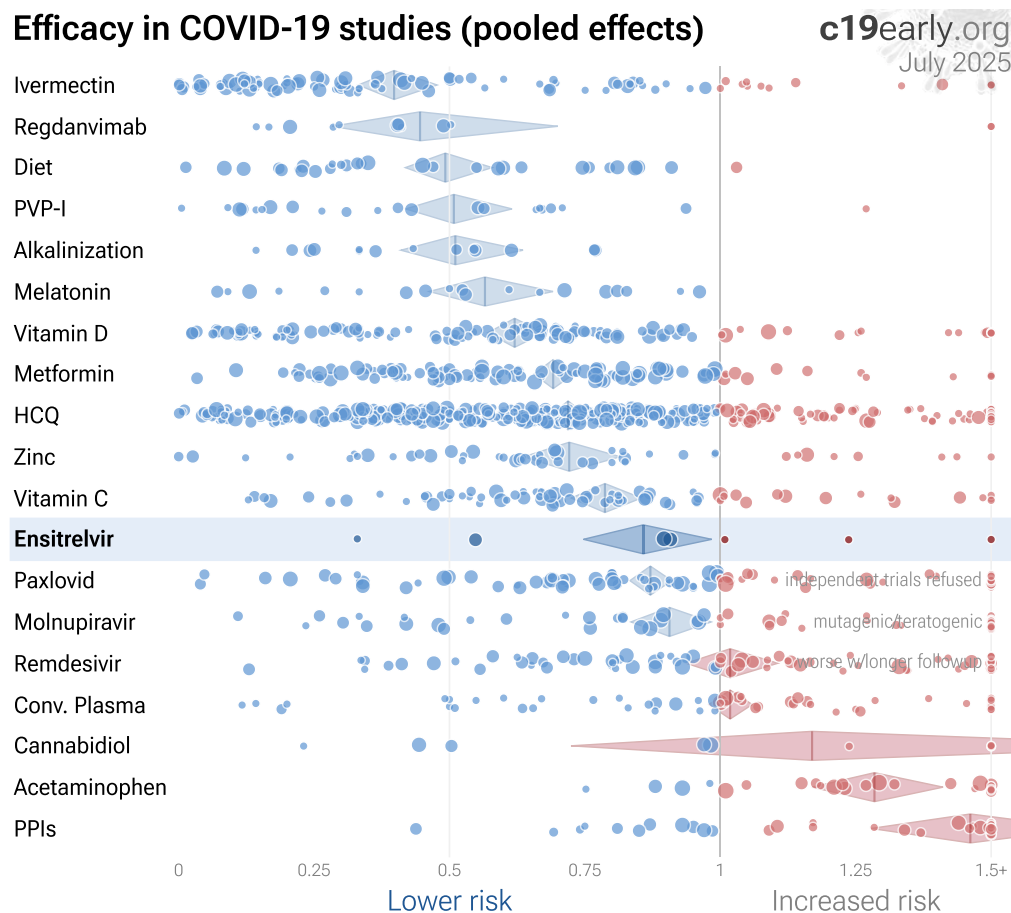


Figure 23. Scatter plot showing results within the context of multiple COVID-19 treatments. Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy ¹¹⁵.

Efficacy vs. cost for COVID-19 treatments

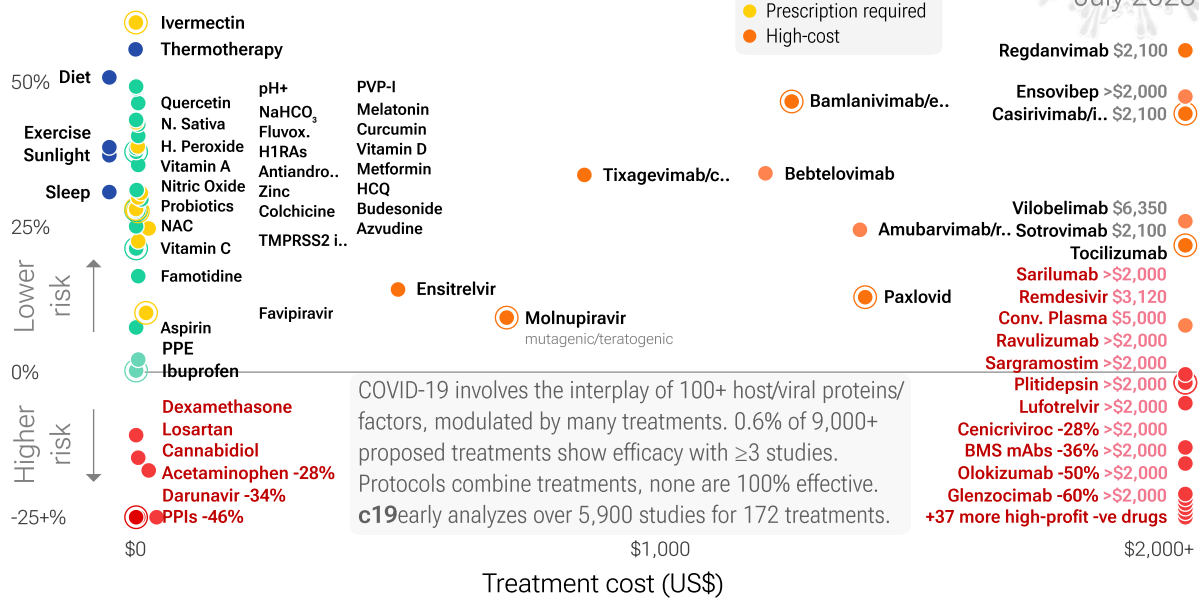


Figure 24. Efficacy vs. cost for COVID-19 treatments.

Conclusion

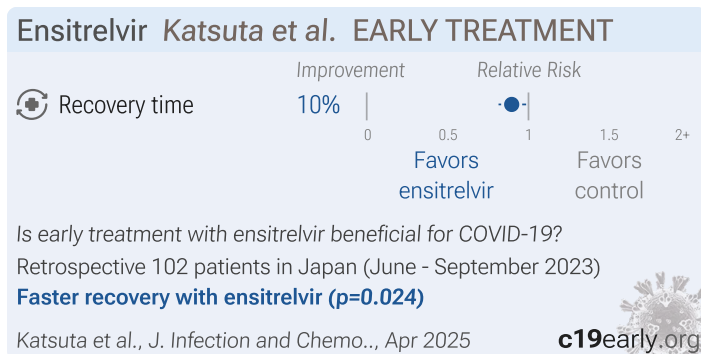
Significantly lower risk is seen for hospitalization, recovery, and viral clearance. 7 studies from 6 independent teams (all from the same country) show significant benefit. Meta analysis using the most serious outcome reported shows 14% [2-25%] lower risk. Results are similar for Randomized Controlled Trials and worse for peer-reviewed studies.

Currently there is limited data, with only 3 control events for the most serious outcome in trials to date.

Variants may be resistant to ensitrelvir^{1,2}.

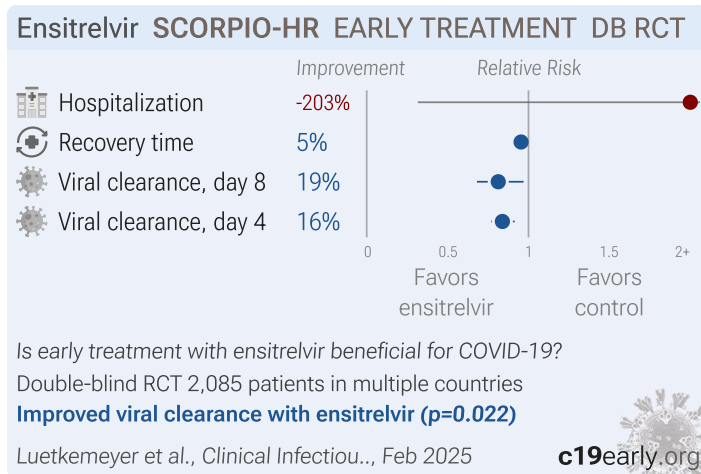
Study Notes

Katsuta



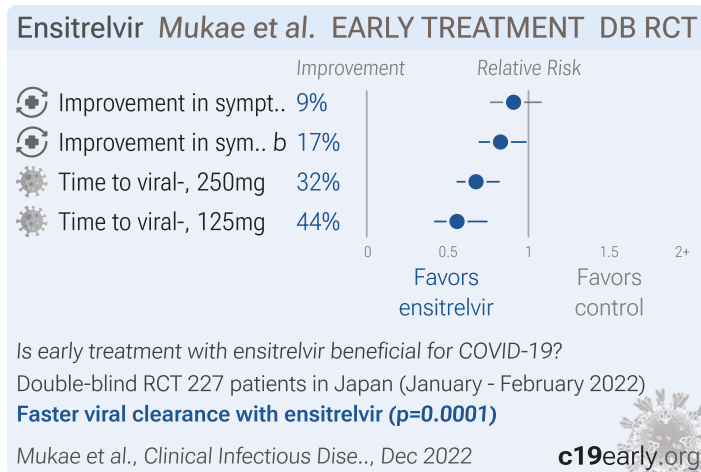
Retrospective 102 healthcare workers in Japan showing shorter time to return-to-work with ensitrelvir treatment for COVID-19.

Luetkemeyer



RCT 2,093 outpatients with mild-to-moderate COVID-19 showing improved viral clearance but no significant difference in time to symptom resolution with ensirelvir. Participants were randomized to receive ensirelvir or placebo within five days of symptom onset, with the primary analysis focusing on those treated within three days. A mid-trial protocol change excluded participants treated more than three days post-symptom onset from the primary analysis.

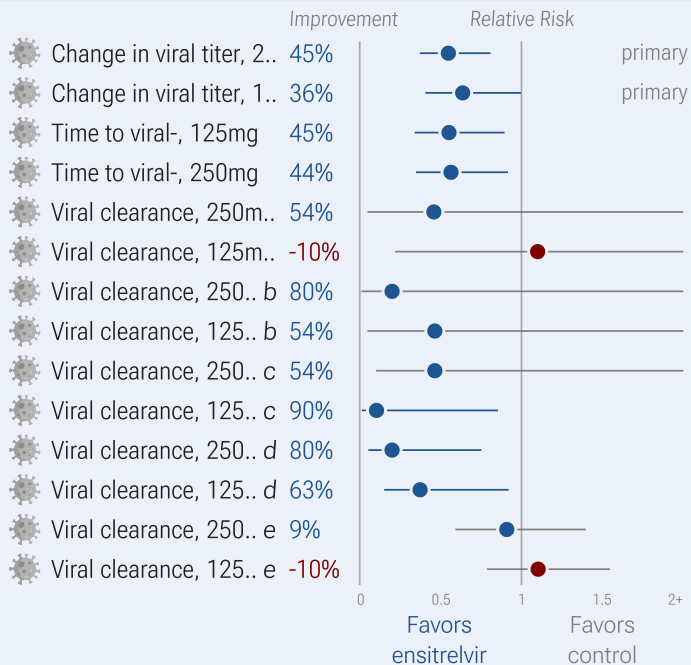
Mukae



RCT 428 COVID-19 patients in Japan showing faster viral clearance and improved recovery with ensirelvir.

Mukae

Ensirelvir Mukae et al. EARLY TREATMENT DB RCT



Is early treatment with ensirelvir beneficial for COVID-19?

Double-blind RCT 69 patients in Japan (September 2021 - January 2022)

Improved viral clearance with ensirelvir ($p=0.0025$)

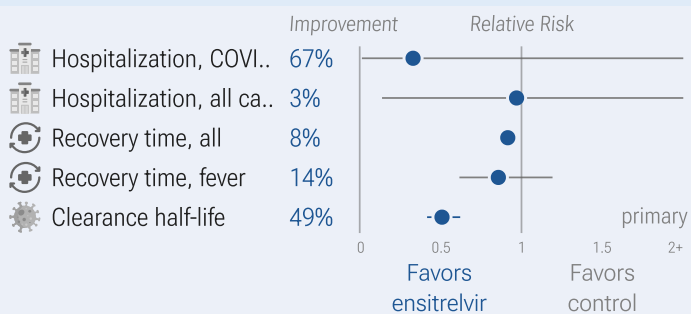
Mukae et al., medRxiv, May 2022

c19early.org

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

Schilling

Ensirelvir PLATCOV EARLY TREATMENT RCT



Is early treatment with ensirelvir beneficial for COVID-19?

RCT 392 patients in multiple countries (March 2023 - April 2024)

Faster recovery ($p=0.0058$) and improved viral clearance ($p<0.0001$)

Schilling et al., medRxiv, May 2025

c19early.org

RCT 604 low-risk adults with early COVID-19 symptoms showing significantly improved SARS-CoV-2 viral clearance with both ensirelvir and paxlovid.

Inclusion criteria selected for low-risk patients with high viral loads which may not generalize to high-risk patients or patients treated prior to having high viral load.

Authors indicate that "between March 2023 and April 2024 the three study arms randomised 604 patients", however

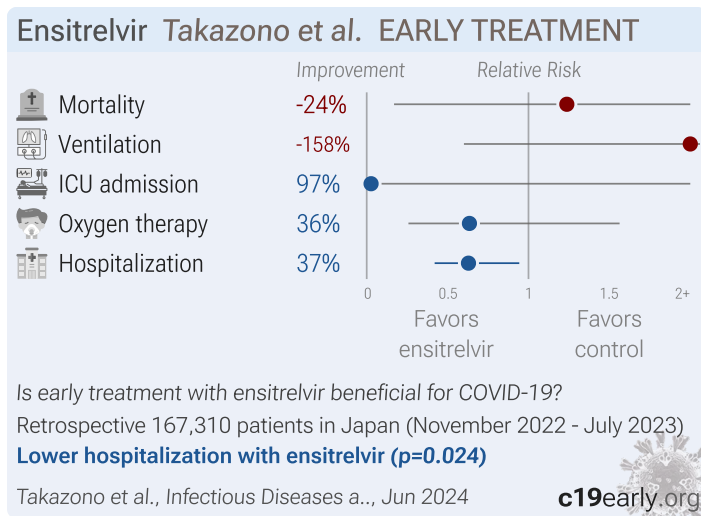
figure S7 shows paxlovid patients starting before July 2022.

120 day long COVID results in the protocol are not reported.

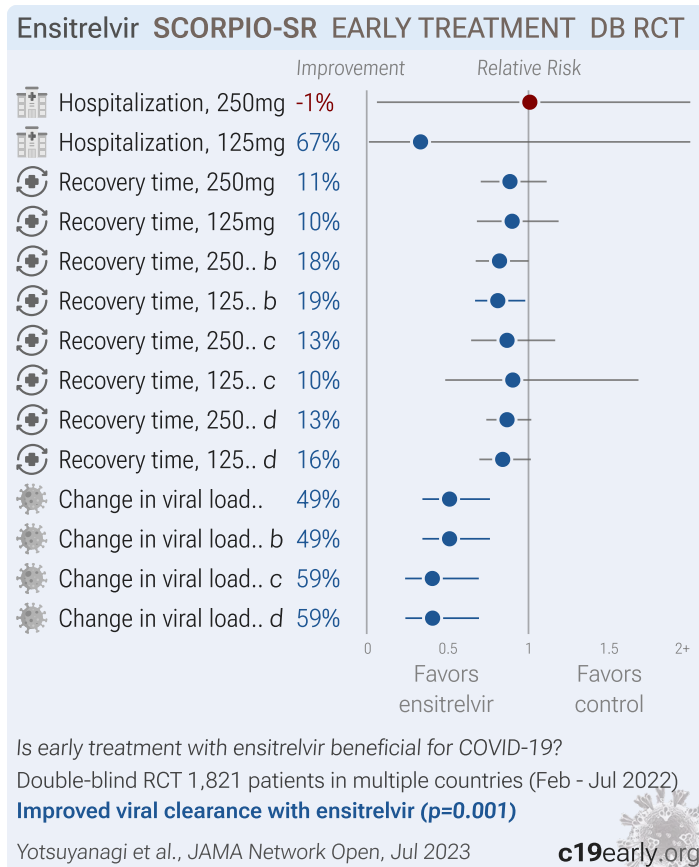
The protocol was modified mid-trial in October 2024: the number of patients was increased, the swabbing schedule was changed, and patient self-swabbing was added. Results appear to have improved in the post-change period.

The swabbing schedule in the paper conflicts with the October 2024 change reported in the protocol ("now swabbing day 0 to day 5 once or twice per day to characterise viral clearance").

Takazono



Retrospective 167,310 high-risk COVID-19 outpatients in Japan showing significantly lower hospitalization with ensirelvir treatment.



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 ensirelvir. 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 ensirelvir 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 ensirelvir for COVID-19 that report a comparison with a control group are included in the main analysis. Studies with major unexplained data issues, for example major outcome data that is impossible to be correct with no response from the authors, are excluded. 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 reported then they are both used in specific outcome analyses, while mortality is used for pooled analysis. If symptomatic results are reported at multiple times, we use the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral outcomes. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. An IPD meta-analysis confirms that intermediate viral load reduction is more closely associated with hospitalization/death than later viral load reduction¹¹⁶. If only individual symptom data is

available, the most serious symptom has priority, for example difficulty breathing or low SpO₂ 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 et al.* Reported confidence intervals and *p*-values are used when available, and adjusted values are used when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1¹²⁰. 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 (3.13.5) with scipy (1.16.0), pythonmeta (1.26), numpy (2.3.1), statsmodels (0.14.4), and plotly (6.2.0).

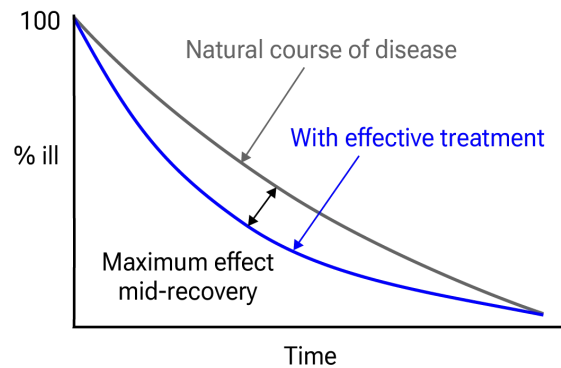


Figure 25. Mid-recovery results can more accurately reflect efficacy when almost all patients recover. *Mateja et al.* confirm that intermediate viral load results more accurately reflect hospitalization/death.

Forest plots are computed using PythonMeta¹²¹ 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 (4.4.0) using the metafor (4.6-0) and rms (6.8-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a *p*-value less than 0.05 was considered statistically significant. Grobid 0.8.2 is used to parse PDF documents.

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^{47,48}.

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.

<i>Katsuta</i> , 4/30/2025, retrospective, Japan, peer-reviewed, 8 authors, study period 1 June, 2023 - 30 September, 2023.	recovery time, 10.4% lower, relative time 0.90, <i>p</i> = 0.02, treatment mean 6.9 (±1.6) <i>n</i> =60, control mean 7.7 (±1.9) <i>n</i> =42.
<i>Luetkemeyer</i> , 2/17/2025, Double Blind Randomized Controlled Trial, placebo-controlled, multiple countries, peer-reviewed, 22 authors, SCORPIO-HR trial.	risk of hospitalization, 203.2% higher, RR 3.03, <i>p</i> = 0.37, treatment 3 of 1,037 (0.3%), control 1 of 1,048 (0.1%).

	recovery time, 4.6% lower, relative time 0.95, $p = 0.14$, treatment 945, control 943.
	risk of no viral clearance, 18.7% lower, RR 0.81, $p = 0.02$, treatment 175 of 882 (19.8%), control 215 of 881 (24.4%), NNT 22, day 8.
	risk of no viral clearance, 16.1% lower, RR 0.84, $p < 0.001$, treatment 420 of 835 (50.3%), control 517 of 862 (60.0%), NNT 10, day 4.
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.

	<p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>
<i>Schilling</i> , 5/21/2025, Randomized Controlled Trial, multiple countries, preprint, 37 authors, study period March 2023 - April 2024, trial NCT05041907 (history) (PLATCOV).	<p>risk of hospitalization, 67.0% lower, RR 0.33, $p = 0.49$, treatment 0 of 197 (0.0%), control 1 of 191 (0.5%), NNT 191, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), COVID-19 related.</p> <p>risk of hospitalization, 3.0% lower, RR 0.97, $p = 1.00$, treatment 2 of 197 (1.0%), control 2 of 191 (1.0%), NNT 3136, all cause.</p> <p>recovery time, 8.5% lower, relative time 0.92, $p = 0.006$, treatment mean 5.4 (± 1.79) $n=197$, control mean 5.9 (± 1.76) $n=191$, all.</p> <p>recovery time, 14.3% lower, relative time 0.86, $p = 0.37$, treatment mean 1.2 (± 2.51) $n=197$, control mean 1.4 (± 1.76) $n=191$, fever.</p> <p>relative clearance half-life, 49.1% better, RR 0.51, $p < 0.001$, treatment median 5.9 IQR 4.6 $n=201$, control median 11.6 IQR 6.4 $n=191$, primary outcome.</p>
<i>Takazono</i> , 6/28/2024, retrospective, Japan, peer-reviewed, 13 authors, study period November 2022 - July 2023.	<p>risk of death, 23.7% higher, RR 1.24, $p = 0.84$, treatment 5,177, control 162,133, propensity score weighting.</p> <p>risk of mechanical ventilation, 158.5% higher, RR 2.58, $p = 0.20$, treatment 5,177, control 162,133, propensity score weighting.</p> <p>risk of ICU admission, 97.3% lower, RR 0.03, $p = 0.63$, treatment 0 of 5,177 (0.0%), control 35 of 162,133 (0.0%), NNT 4632, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).</p> <p>risk of oxygen therapy, 36.5% lower, RR 0.64, $p = 0.33$, treatment 5,177, control 162,133, propensity score weighting.</p> <p>risk of hospitalization, 37.1% lower, RR 0.63, $p = 0.02$, treatment 5,177, control 162,133, propensity score weighting.</p>
<i>Yotsuyanagi</i> , 7/13/2023, Double Blind Randomized Controlled Trial, placebo-controlled, multiple countries, peer-reviewed, mean age 35.7, 13	<p>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.</p>

authors, study period 10 February, 2022 - 10 July, 2022, trial jRCT2031210350 (SCORPIO-SR).

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 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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