Bemnifosbuvir for COVID-19: real-time meta analysis of 4 studies

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https://c19early.org/bfmeta.html

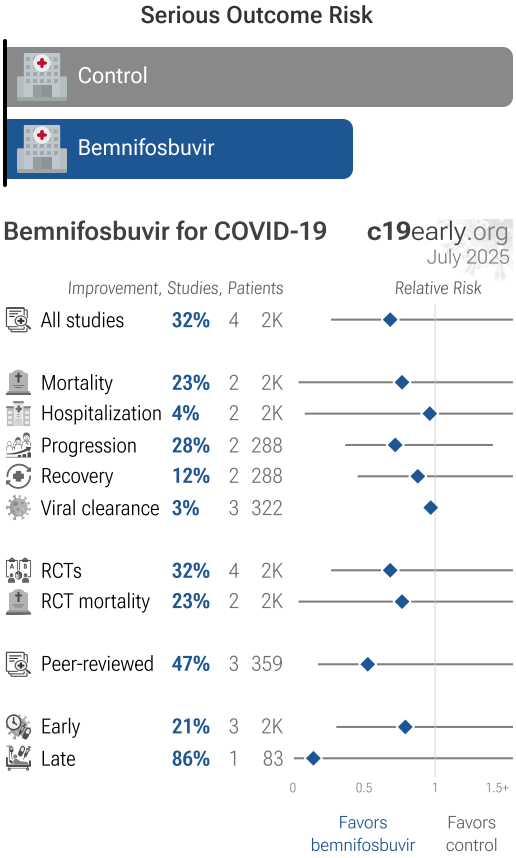
Abstract

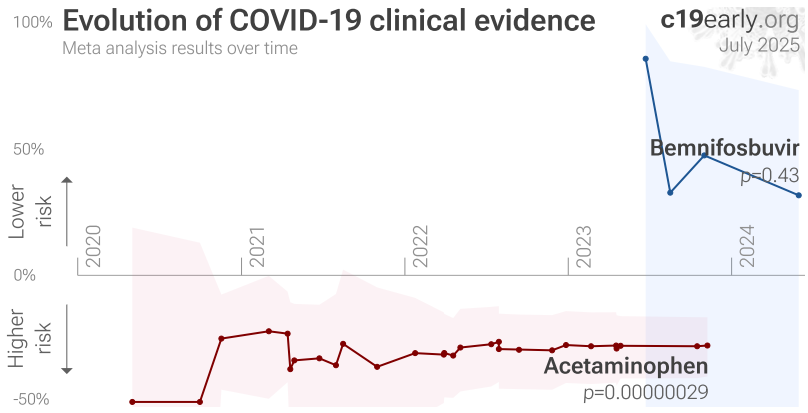
Meta analysis using the most serious outcome reported shows 32% [-74-73%] lower risk, without reaching statistical significance. Results are better for peer-reviewed studies. Currently all studies are RCTs.

2 studies (both from the same team/sponsor) show significant benefit.

Currently there is limited data, with only 11 control events for the most serious outcome in trials to date. All studies to date are from the same group.

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.

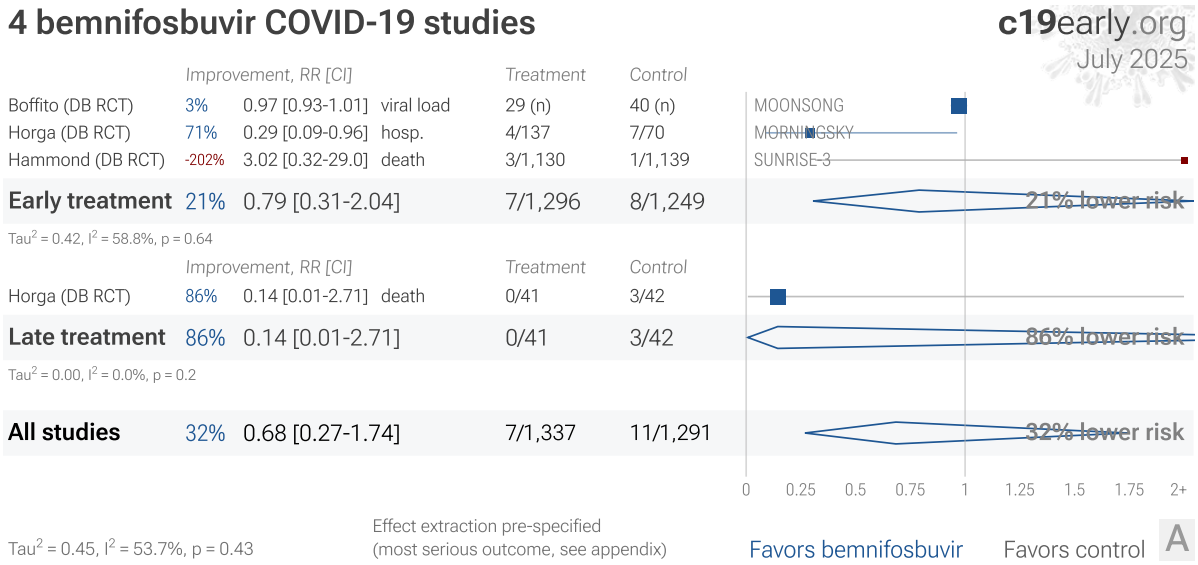




BEMNIFOSBUVIR FOR COVID-19 — HIGHLIGHTS

Meta analysis of studies to date shows no significant improvements with bemnifosbuvir.

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.



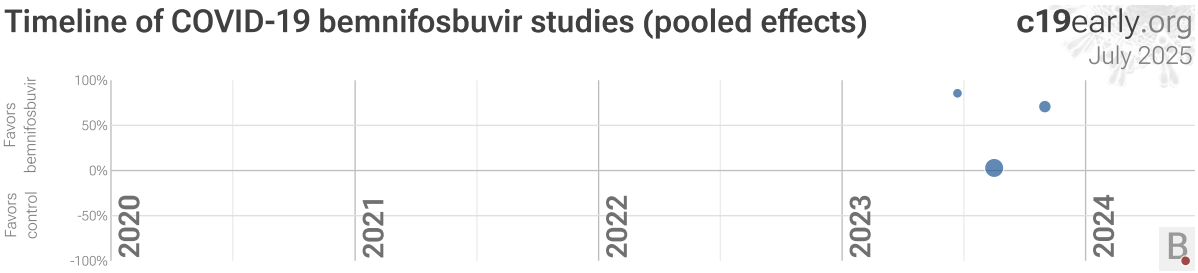


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in bemnifosbuvir studies.**

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 injury[2-14] and cognitive deficits[5,10], cardiovascular complications[15-19], organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits[20]—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Minimizing replication as early as possible is recommended.

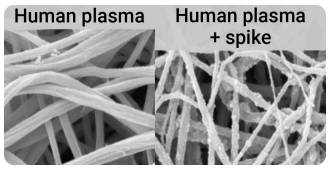


Figure 2. **SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from[1].**

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,21-28], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 9,000 compounds may reduce COVID-19 risk[29], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Bemnifosbuvir

Bemnifosbuvir (AT-527) is an orally bioavailable double prodrug of a guanosine nucleotide analogue that, once converted intracellularly to AT-9010, inhibits SARS-CoV-2 replication through a dual mechanism: it plugs the catalytic site of the viral RNA-dependent RNA polymerase and occupies the NiRAN domain that is essential for RNA capping,

thereby halting viral genome synthesis and maturation. *In Vitro* studies show sub-micromolar potency against multiple variants, and pharmacokinetic analysis shows that oral dosing achieves lung concentrations exceeding antiviral thresholds.

Analysis

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

Treatment timing

Figure 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.

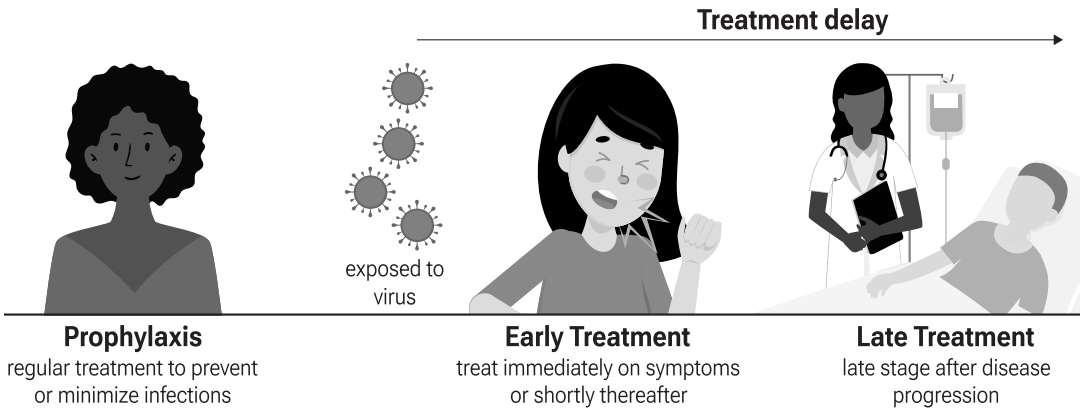


Figure 3. **Treatment stages.**

Results

Table 1 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, and for specific outcomes. Table 2 shows results by treatment stage. Figure 4 plots individual results by treatment stage. Figure 5, 6, 7, 8, 9, 10, and 11 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, hospitalization, progression, recovery, viral clearance, and peer reviewed studies.

	Relative Risk	Studies	Patients
All studies	0.68 [0.27-1.74]	4	2,628
Peer-reviewed	0.53 [0.18-1.57]	3	359
RCTs	0.68 [0.27-1.74]	4	2,628
Mortality	0.77 [0.04-14.90]	2	2,352
Hospitalization	0.96 [0.08-11.04]	2	2,332
Recovery	0.88 [0.45-1.69]	2	288
Viral	0.97 [0.93-1.01]	3	322
RCT mortality	0.77 [0.04-14.90]	2	2,352

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

	Early treatment	Late treatment
All studies	0.79 [0.31-2.04]	0.14 [0.01-2.71]
Peer-reviewed	0.62 [0.20-1.94]	0.14 [0.01-2.71]
RCTs	0.79 [0.31-2.04]	0.14 [0.01-2.71]
Mortality	3.02 [0.32-29.03]	0.14 [0.01-2.71]
Hospitalization	0.96 [0.08-11.04]	
Recovery	0.77 [0.28-2.07]	0.98 [0.41-2.35]
Viral	0.94 [0.81-1.09]	0.91 [0.54-1.51]
RCT mortality	3.02 [0.32-29.03]	0.14 [0.01-2.71]

Table 2. **Random effects meta-analysis results by treatment stage.** Results show the relative risk with treatment and the 95% confidence interval.

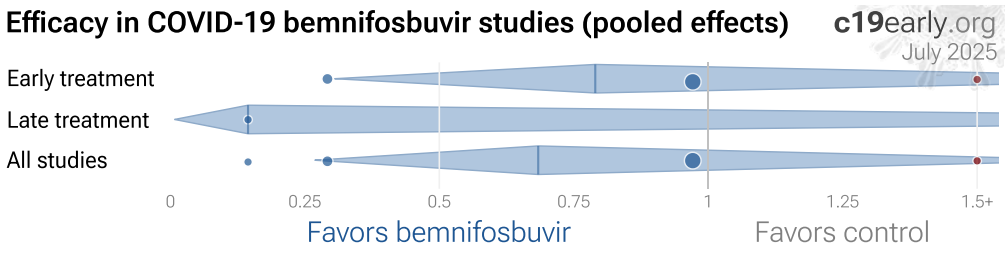


Figure 4. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

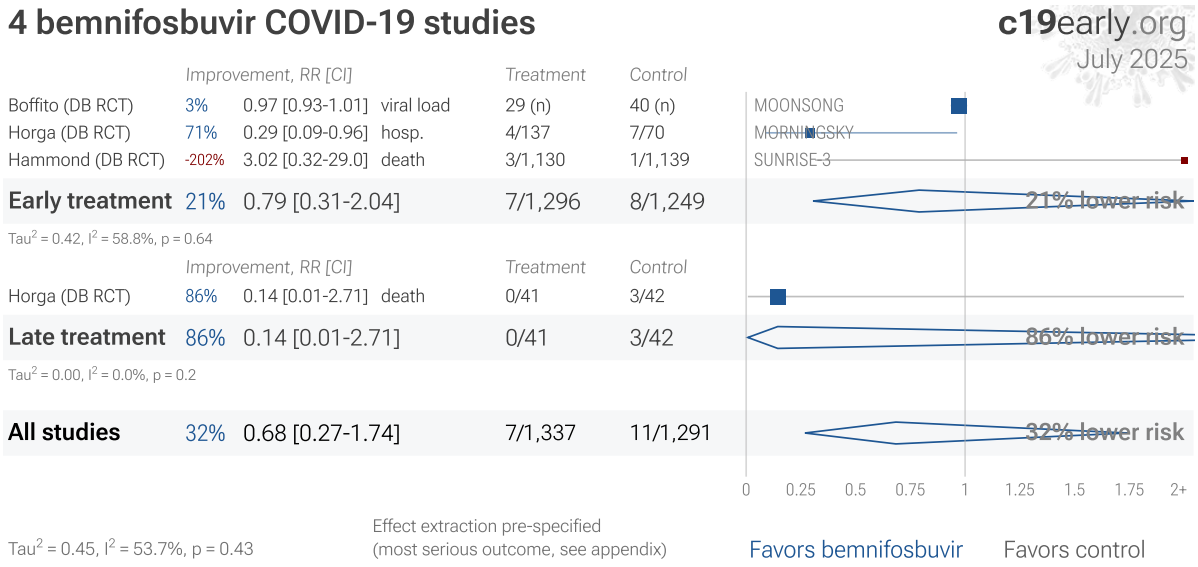


Figure 5. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

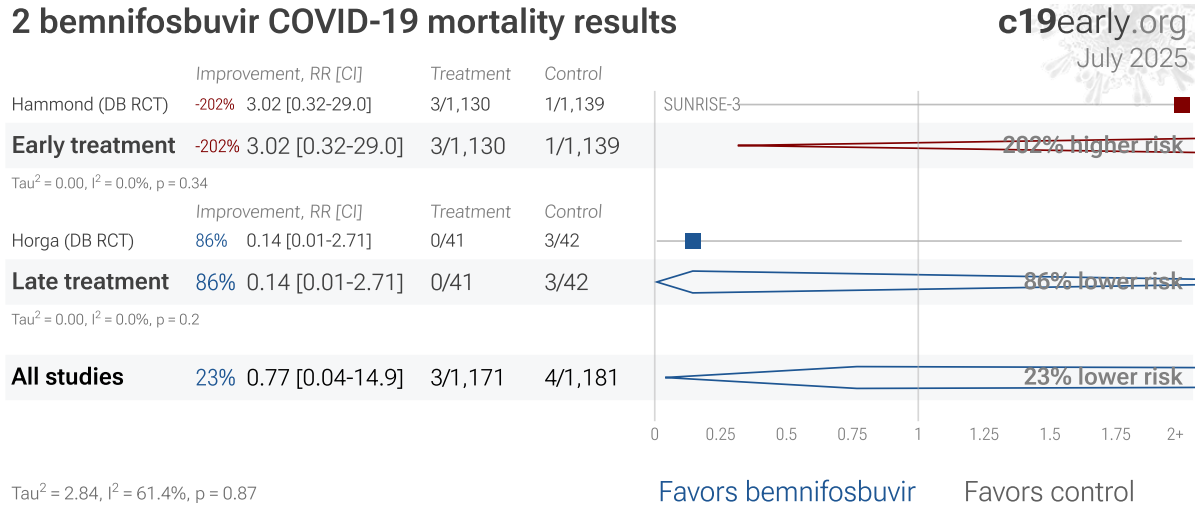


Figure 6. **Random effects meta-analysis for mortality results.**

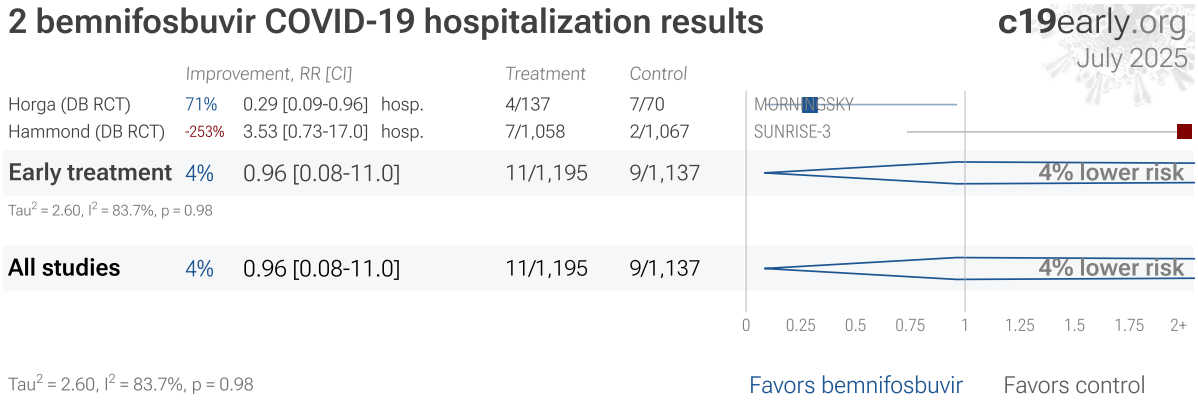


Figure 7. **Random effects meta-analysis for hospitalization.**

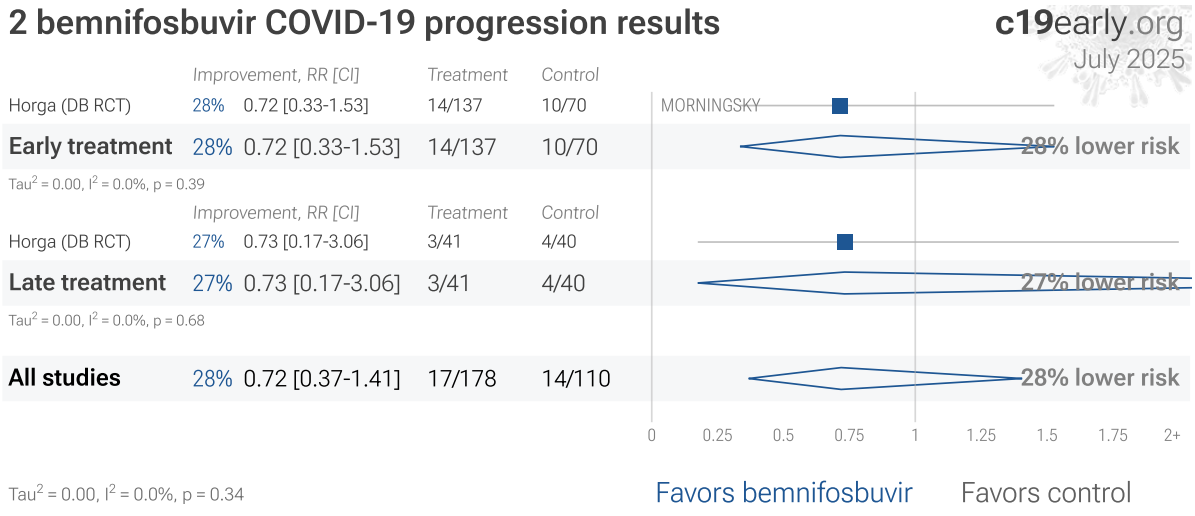


Figure 8. Random effects meta-analysis for progression.

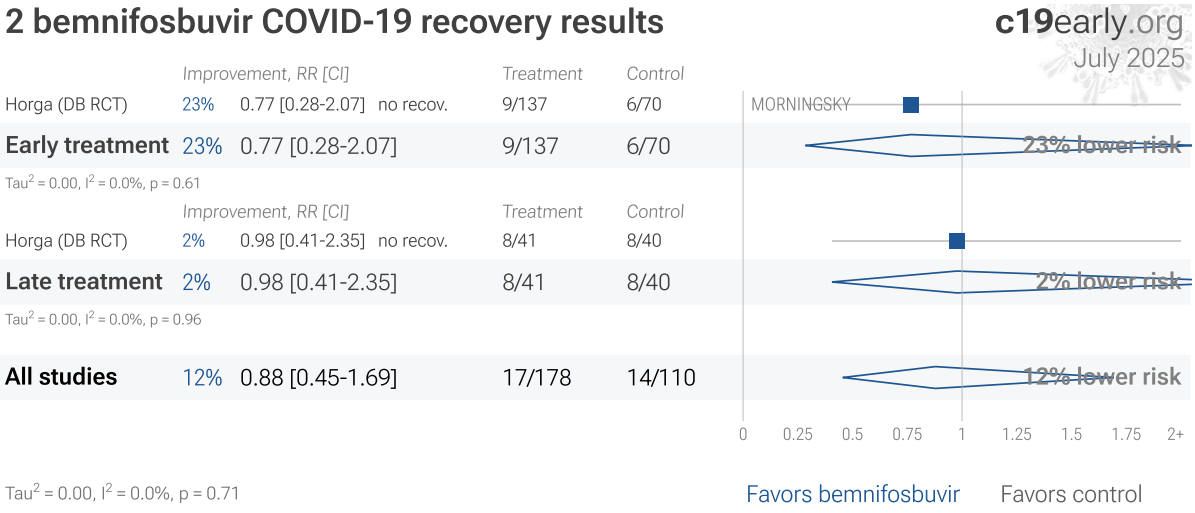


Figure 9. Random effects meta-analysis for recovery.

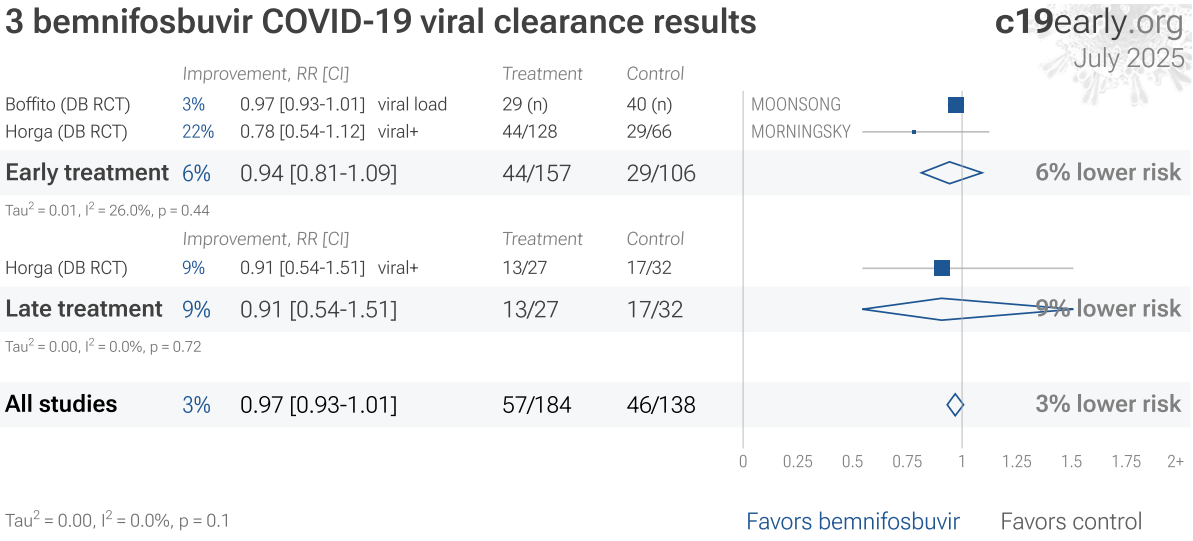


Figure 10. Random effects meta-analysis for viral clearance.

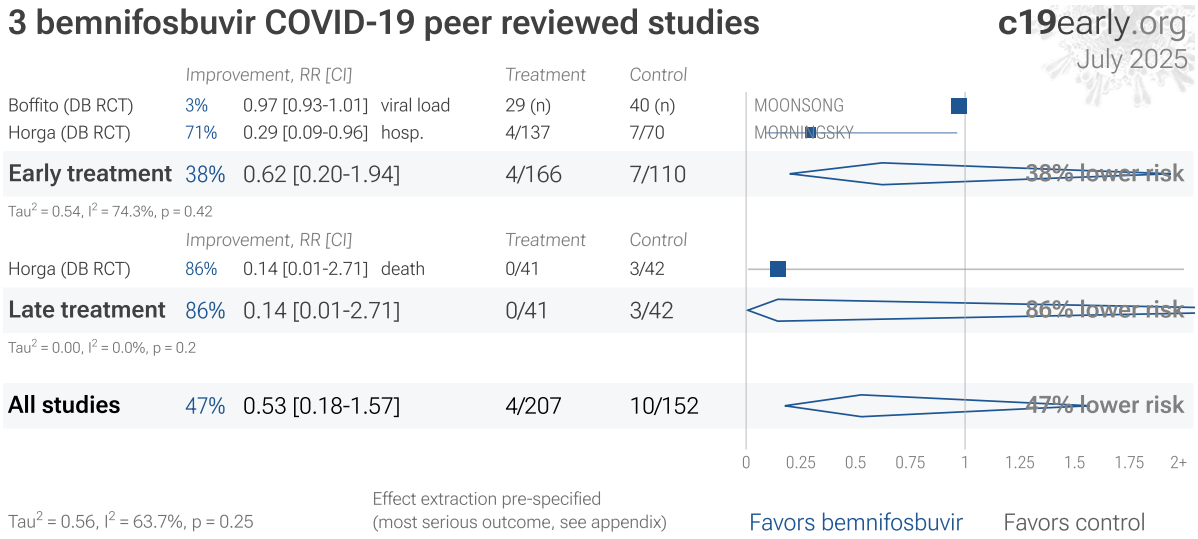


Figure 11. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding 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)

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[32,33]. 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 [34]
<24 hours	-33 hours symptoms [35]
24-48 hours	-13 hours symptoms [35]
Inpatients	-2.5 hours to improvement [36]

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

Figure 12 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.

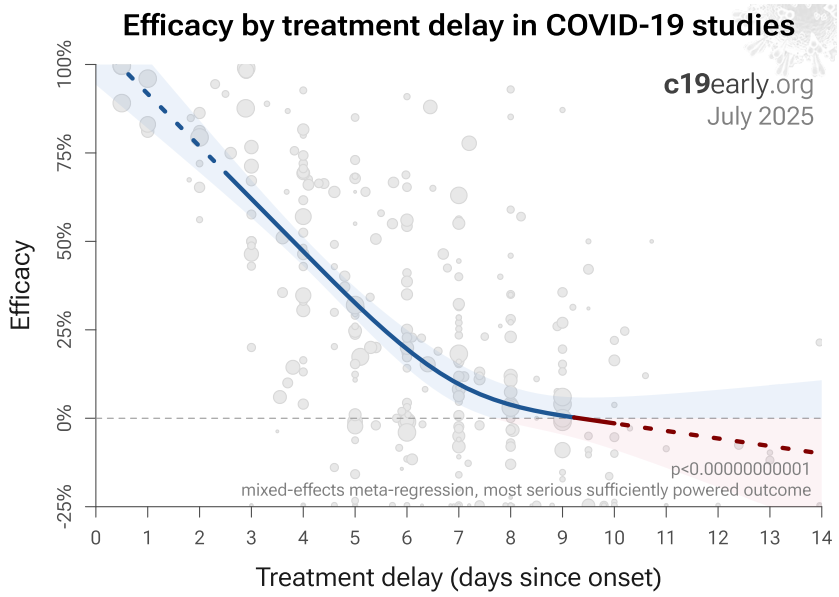


Figure 12. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 172 treatments.

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 variants [38], for example the Gamma variant shows significantly different characteristics [39-42]. 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 [43,44].

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 synergistic[47-63], 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

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 13 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 14 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 15 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 $p = 0.0000000033$.

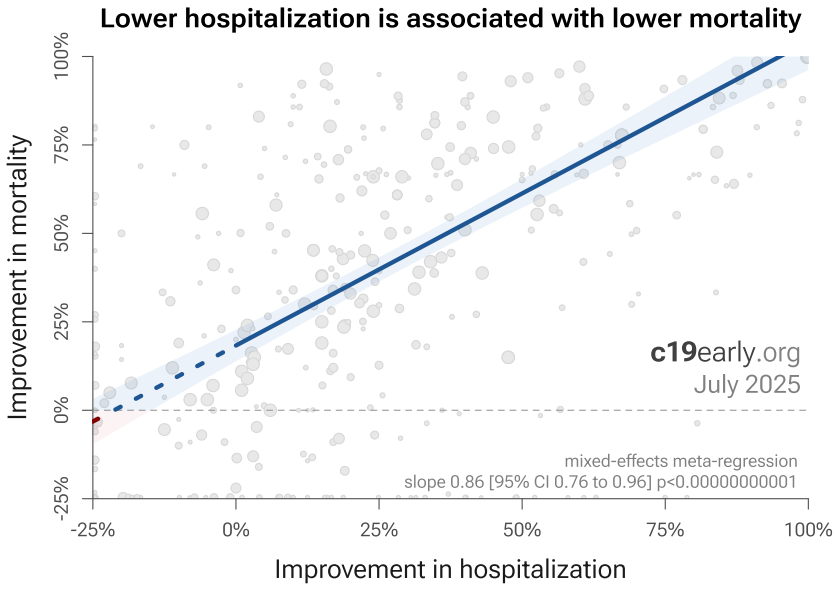


Figure 13. **Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.**

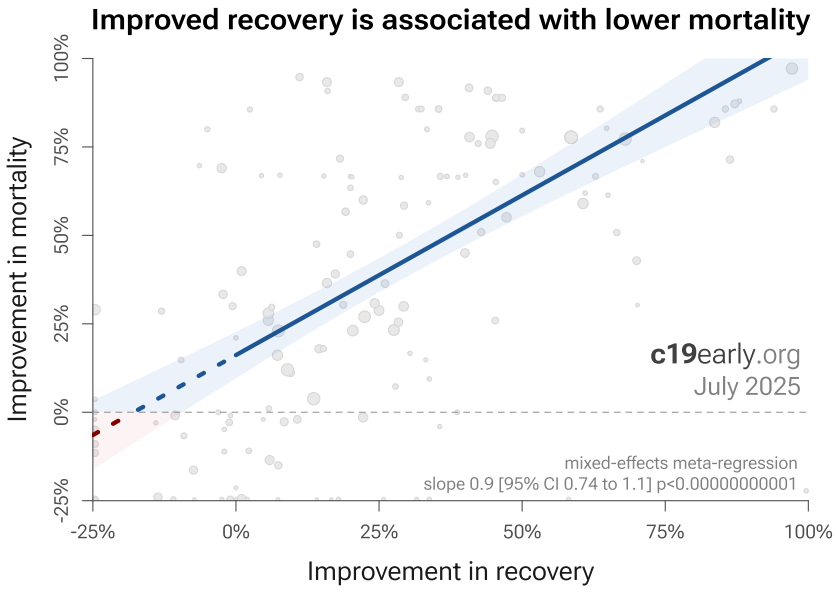


Figure 14. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

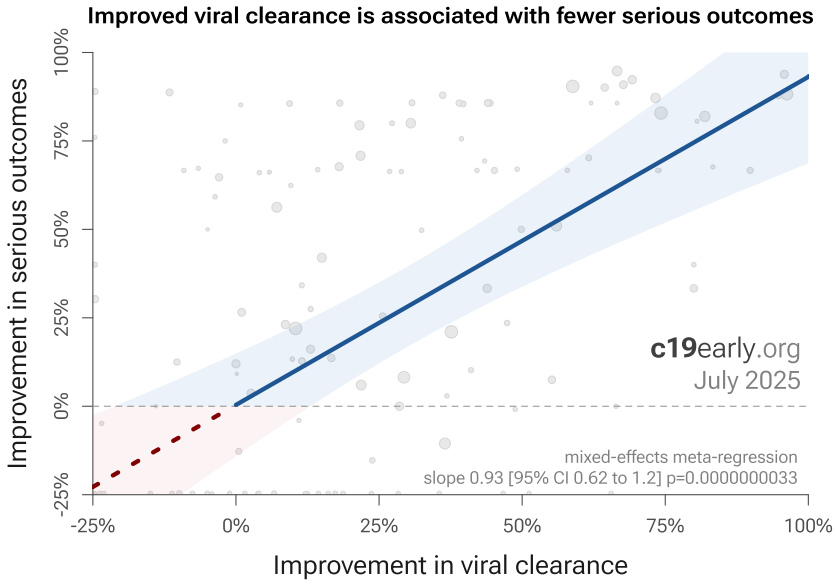


Figure 13. Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.

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 ≥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 16 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

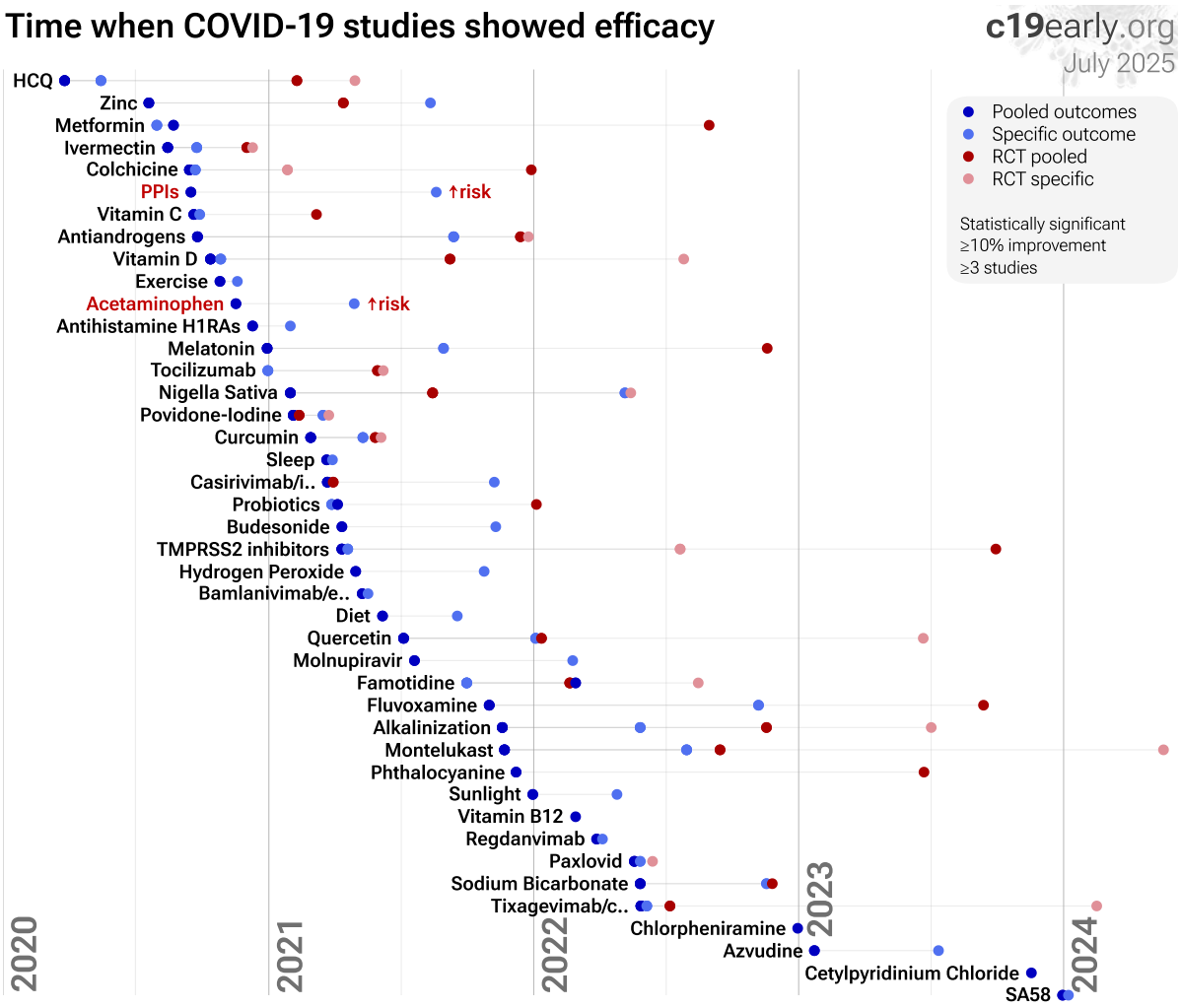


Figure 16. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

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 bemnifosbuvir, there is currently not enough data to evaluate publication bias with high confidence.

Limitations

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

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

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

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

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

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone[47-63]. 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.

Other studies

Lan et al. also suggests potential benefits of bemnifosbuvir for COVID-19. We have not reviewed this paper 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[21-28], providing many therapeutic targets. Over 9,000 compounds have been predicted to reduce COVID-19 risk[29], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 17 shows an overview of the results for bemnifosbuvir in the context of multiple COVID-19 treatments, and Figure 18 shows a plot of efficacy vs. cost for COVID-19 treatments.

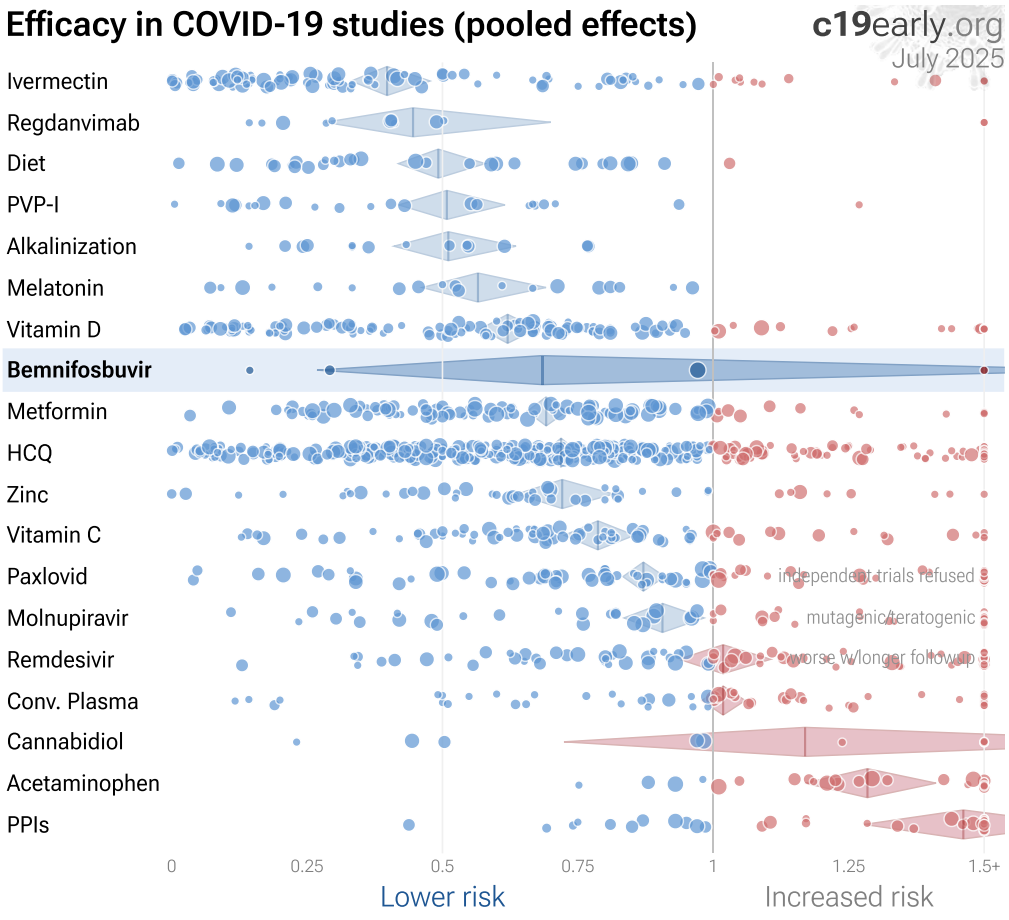


Figure 17. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy[70].

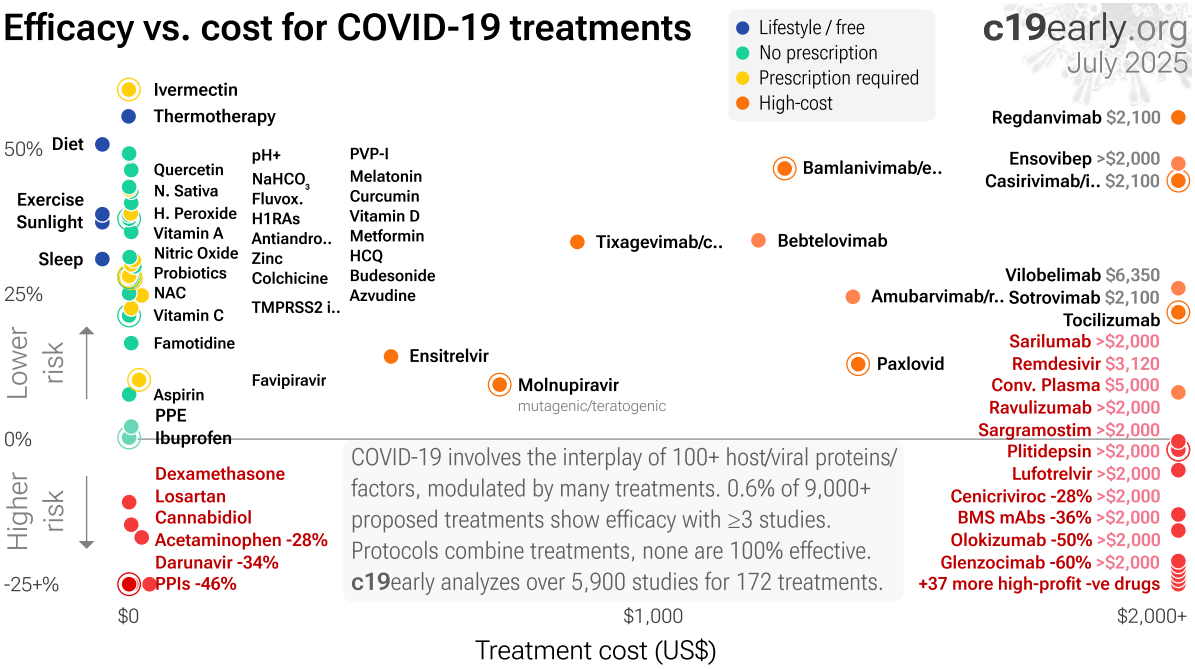


Figure 18. **Efficacy vs. cost for COVID-19 treatments.**

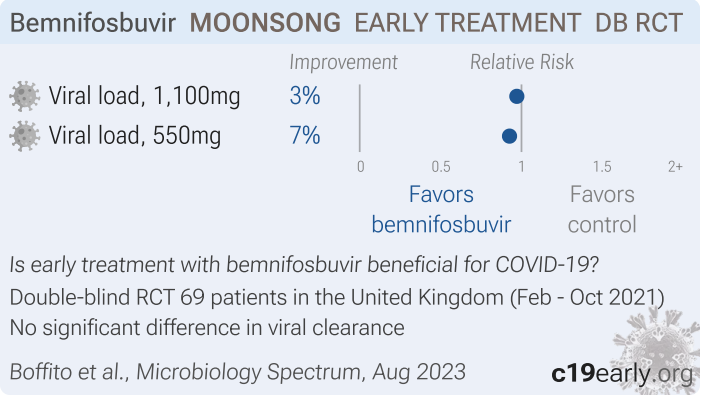
Conclusion

Meta analysis using the most serious outcome reported shows 32% [-74-73%] lower risk, without reaching statistical significance. Results are better for peer-reviewed studies. Currently all studies are RCTs. 2 studies (both from the same team/sponsor) show significant benefit.

Currently there is limited data, with only 11 control events for the most serious outcome in trials to date. All studies to date are from the same group.

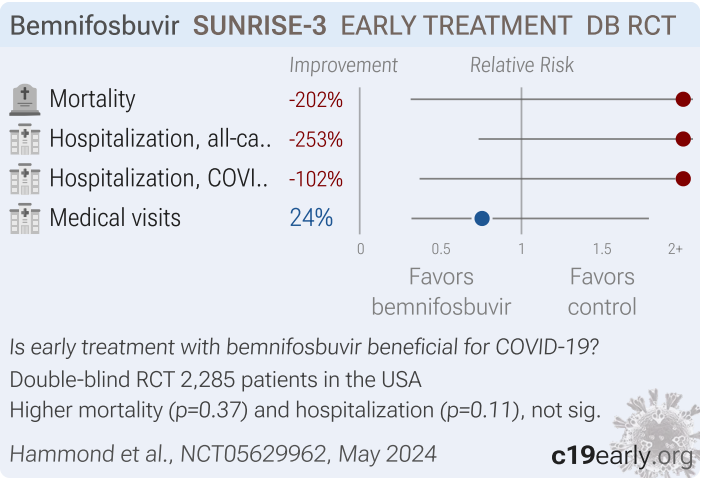
Study Notes

Boffito



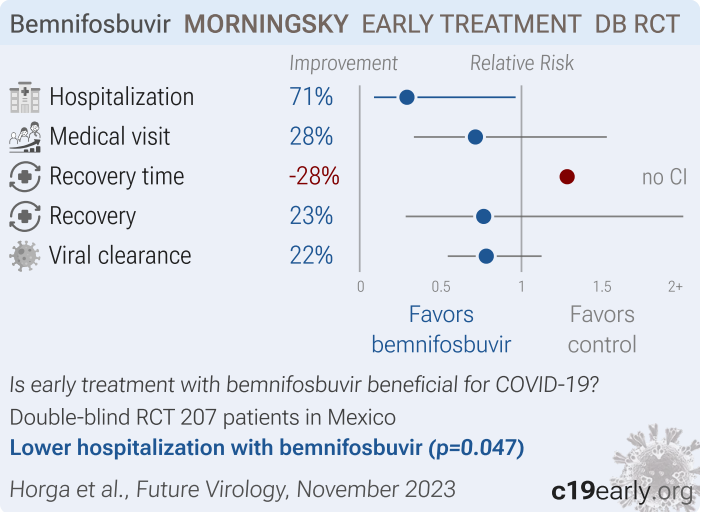
RCT 100 mild/moderate COVID-19 patients showing no significant difference in nasopharyngeal viral load reduction between bemnifosbuvir (550mg or 1100mg twice daily for 5 days) and placebo groups.

Hammond



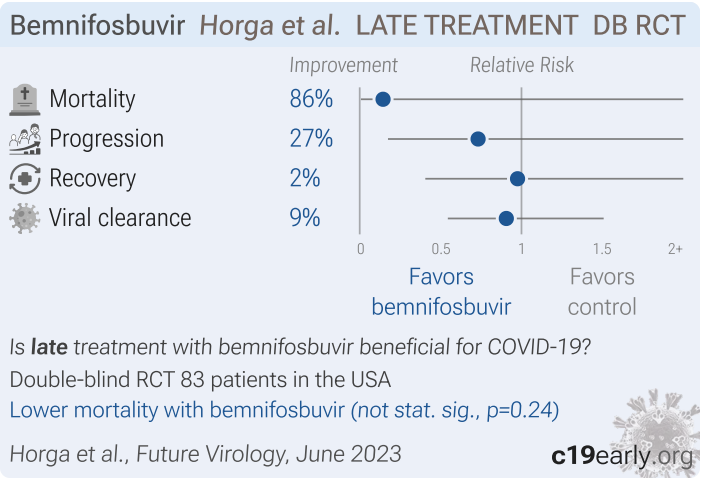
RCT 2,285 high-risk outpatients showing no significant difference in outcomes with bemnifosbuvir treatment.

Horga



MORNINGSKY RCT which was terminated early after enrolling only 216 of 1,386 planned participants. The trial did not meet its primary endpoint, with the bemnifosbuvir group having longer time to symptom improvement than placebo. However, compared to placebo, bemnifosbuvir was associated with a 71% relative risk reduction in COVID-19 hospitalizations and fewer COVID-19 complications and medically attended visits, despite no significant improvement in viral load.

Horga



Phase 2 RCT investigating bemnifosbuvir for the treatment of 81 high-risk COVID-19 patients hospitalized with moderate disease. The trial was terminated early due to difficulties with enrollment. There was no significant difference between bemnifosbuvir and placebo for the primary outcome of disease progression or most secondary outcomes. However, viral load declined faster in the bemnifosbuvir group between days 2 and 8. All 3 deaths occurred in the placebo group. The safety profile was similar between groups. While results are very limited by small sample size and early termination, they suggest bemnifosbuvir may accelerate viral clearance and could play a role in preventing progression.

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 bemnifosbuvir 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 bemnifosbuvir 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.

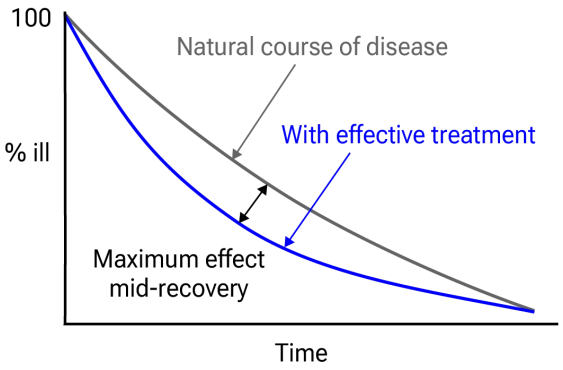


Figure 19. **Mid-recovery results can more accurately reflect efficacy when almost all patients recover.** *Mateja et al.* **confirm that intermediate viral load results more accurately reflect hospitalization/death.**

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 reduction [71]. 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 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 1 [75]. 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).

Forest plots are computed using PythonMeta [76] 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[32,33].

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/bfmeta.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.

Boffito, 8/17/2023, Double Blind Randomized Controlled Trial, placebo-controlled, United Kingdom, peer-reviewed, 11 authors, study period February 2021 - October 2021, trial NCT04709835 (history) (MOONSONG).	**viral load, 2.9% lower, relative load 0.97, $p = 0.14$**, treatment mean 2.78 (±0.24) n=29, control mean 2.7 (±0.21) n=40, 1,100mg, day 7.
	viral load, 7.4% lower, relative load 0.93, $p < 0.001$, treatment mean 3.38 (±0.22) n=29, control mean 3.13 (±0.22) n=29, 550mg, day 7.
Hammond, 5/30/2024, Double Blind Randomized Controlled Trial, placebo-controlled, USA, preprint, 1 author, trial NCT05629962 (history) (SUNRISE-3).	**risk of death, 202.4% higher, RR 3.02, $p = 0.37$**, treatment 3 of 1,130 (0.3%), control 1 of 1,139 (0.1%).
	risk of hospitalization, 253.0% higher, RR 3.53, $p = 0.11$, treatment 7 of 1,058 (0.7%), control 2 of 1,067 (0.2%), all-cause hospitalization or mortality.
	risk of hospitalization, 101.7% higher, RR 2.02, $p = 0.45$, treatment 4 of 1,058 (0.4%), control 2 of 1,067 (0.2%), COVID-19 hospitalization or all-cause mortality.
	medical visits, 24.4% lower, RR 0.76, $p = 0.66$, treatment 9 of 1,058 (0.9%), control 12 of 1,067 (1.1%), NNT 365, medical visits or mortality.
Horga, 11/1/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Mexico, peer-reviewed, 16 authors, trial NCT04889040 (history) (MORNINGSKY).	**risk of hospitalization, 70.8% lower, RR 0.29, $p = 0.047$**, treatment 4 of 137 (2.9%), control 7 of 70 (10.0%), NNT 14.
	medical visit, 28.5% lower, RR 0.72, $p = 0.49$, treatment 14 of 137 (10.2%), control 10 of 70 (14.3%), NNT 25.
	risk of no recovery, 23.4% lower, RR 0.77, $p = 0.58$, treatment 9 of 137 (6.6%), control 6 of 70 (8.6%), NNT 50.
	risk of no viral clearance, 21.8% lower, RR 0.78, $p = 0.21$, treatment 44 of 128 (34.4%), control 29 of 66 (43.9%), NNT 10, day 14.

Late treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Horga (B), 6/23/2023, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 8 authors, trial NCT04396106 (history).	risk of death, 85.6% lower, RR 0.14, $p = 0.24$, treatment 0 of 41 (0.0%), control 3 of 42 (7.1%), NNT 14, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of progression, 26.8% lower, RR 0.73, $p = 0.71$, treatment 3 of 41 (7.3%), control 4 of 40 (10.0%), NNT 37, PRI.
	risk of no recovery, 2.4% lower, RR 0.98, $p = 1.00$, treatment 8 of 41 (19.5%), control 8 of 40 (20.0%), NNT 205, clinical recovery.
	risk of no viral clearance, 9.4% lower, RR 0.91, $p = 0.80$, treatment 13 of 27 (48.1%), control 17 of 32 (53.1%), NNT 20, day 14.

Supplementary Data

Supplementary Data

Footnotes

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

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