Tixagevimab/cilgavimab reduced COVID-19 risk: real-time meta analysis of 19 studies

@CovidAnalysis, July 2025, Version 32
https://c19early.org/tcmeta.html

Abstract

Significantly lower risk is seen for mortality, hospitalization, and cases. 9 studies from 9 independent teams in 3 countries show significant benefit.

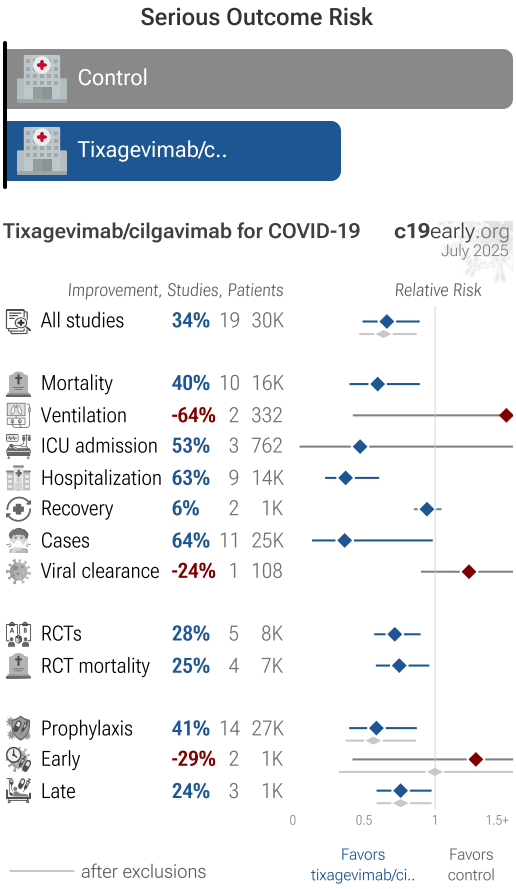
Meta analysis using the most serious outcome reported shows 34% [11-51%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies.

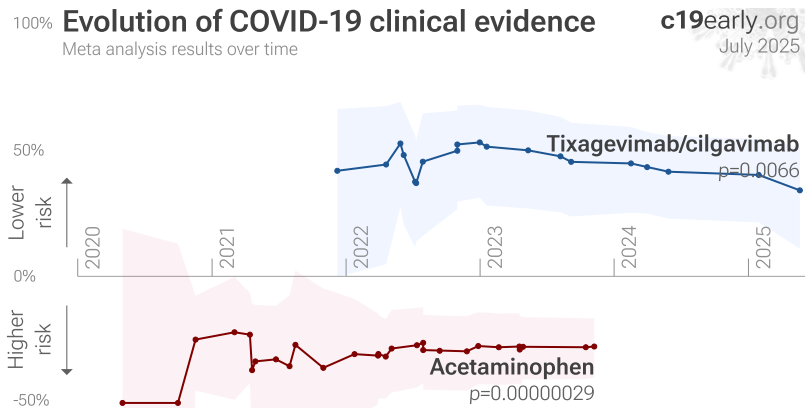
Results are robust — in exclusion sensitivity analysis 6 of 19 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

Efficacy is variant dependent. *In Vitro* research suggests a lack of efficacy for omicron BA.2.75.2, BA.4.6, and BQ.1.1[1], BA.5, BA.2.75, XBB[2,3], XBB.1.5[3], XBB.1.9.1[3], XBB.1.9.3, XBB.1.5.24, XBB.1.16, XBB.2.9, BQ.1.1.45, CL.1, and CH.1.1[4]. US EUA has been revoked. mAb use may create new variants that spread globally[5-7], and may be associated with prolonged viral loads, clinical deterioration, and immune escape[6,8-10].

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.

Soeroto et al. present another meta analysis for tixagevimab/cilgavimab, showing significant improvements for mortality, hospitalization, severity, and cases.





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TIXAGEVIMAB/CILGAVIMAB FOR COVID-19 — HIGHLIGHTS

Tixagevimab/cilgavimab reduces risk with very high confidence for hospitalization and in pooled analysis, and high confidence for mortality and cases, however increased risk is seen with very low confidence for ventilation and viral clearance.

Efficacy is variant dependent.

While effective during the pandemic, tixagevimab/cilgavimab may have reduced or no activity for recent variants.

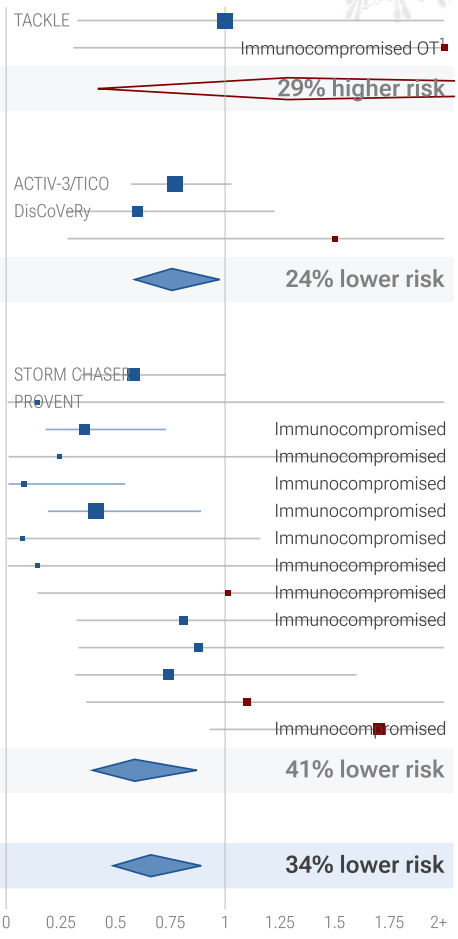
41st treatment shown effective in May 2022, now with $p = 0.0066$ from 19 studies, recognized in 33 countries.

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.

19 tixagevimab/cilgavimab COVID-19 studies

c19early.org
July 2025

	Improvement	RR [CI]		Treatment	Control
Montgom.. (DB RCT)	0%	1.00 [0.32-3.07]	death	6/452	6/451
Lombardi	-368%	4.68 [0.31-71.6]	death	1/19	1/89
Early treatment	-29%	1.29 [0.42-3.95]		7/471	7/540
$Tau^2 = 0.06$, $I^2 = 5.3\%$, p = 0.67					
	Improvement	RR [CI]		Treatment	Control
Holland (DB RCT)	23%	0.77 [0.57-1.03]	death	80/710	101/707
Hites (DB RCT)	40%	0.60 [0.28-1.23]	death	12/123	16/103
Chua (PSM)	-50%	1.50 [0.28-8.04]	ventilation	2/83	4/249
Late treatment	24%	0.76 [0.59-0.97]		94/916	121/1,059
$Tau^2 = 0.00$, $I^2 = 0.0\%$, p = 0.03					
	Improvement	RR [CI]		Treatment	Control
Levin (DB RCT)	42%	0.58 [0.34-1.00]	symp. case	27/749	23/372
Levin (DB RCT)	86%	0.14 [0.01-2.98]	death	0/3,441	2/1,731
Young-Xu (PSM)	64%	0.36 [0.18-0.73]	death	1,733 (n)	6,354 (n)
Ollila	76%	0.24 [0.01-5.61]	death	0/25	1/12
Kertes	92%	0.08 [0.01-0.54]	death/hosp.	1/825	63/4,299
Najjar-Debbiny	59%	0.41 [0.19-0.89]	hosp.	72/703	377/2,812
Kaminski	92%	0.08 [0.01-1.16]	death	1/333	2/97
Al Jurdi	86%	0.14 [0.01-2.75]	death	0/222	3/222
Sindu (PSM)	-1%	1.01 [0.14-7.21]	death	2/17	2/17
Din	19%	0.81 [0.32-2.04]	hosp.	5/23	11/41
Desai	12%	0.88 [0.33-2.35]	hosp.	391 (n)	391 (n)
Solera	26%	0.74 [0.32-1.60]	severe case	7/156	283/1,819
Bes-Berlandier	-10%	1.10 [0.37-3.31]	progression	3/14	15/77
Dluzynski	-70%	1.70 [0.93-3.12]	cases	70/471	11/126
Prophylaxis	41%	0.59 [0.40-0.87]		188/9,103	793/18,370
$Tau^2 = 0.24$, $I^2 = 60.1\%$, p = 0.0081					
All studies	34%	0.66 [0.49-0.89]		289/10,490	921/19,969



[1] OT: comparison with other treatment

$Tau^2 = 0.17$, $I^2 = 57.4\%$, p = 0.0066

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

Favors tixagevimab/ci.. Favors control A

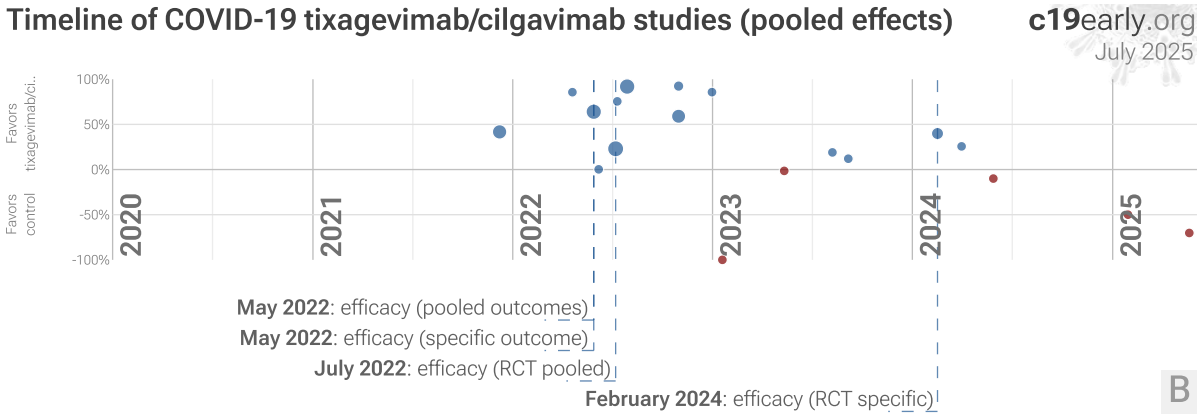


***Figure 1.* A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in tixagevimab/cilgavimab studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes, one or more specific outcome, pooled outcomes in RCTs, and one or more specific outcome in RCTs. Efficacy based on RCTs only was delayed by 1.3 months, compared to using all studies. Efficacy based on specific outcomes in RCTs was delayed by 19.3 months, compared to using pooled outcomes in RCTs.

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[13-25] and cognitive deficits[16,21], cardiovascular complications[26-30], organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits[31]—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Minimizing replication as early as possible is recommended.

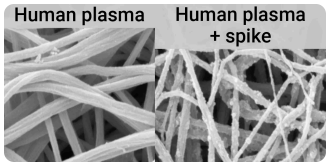


***Figure 2.* SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from[12].**

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,32-39], 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[40], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Monoclonal antibodies

Tixagevimab/cilgavimab is a combination of two monoclonal antibodies (mAbs). mAbs are laboratory-engineered proteins designed to mimic the immune system's ability to fight pathogens. In the context of COVID-19, mAbs typically target specific regions of the SARS-CoV-2 spike protein, inhibiting viral entry into human cells and neutralizing the virus. These antibodies are derived from the B cells of recovered patients or immunized animals and are produced in large quantities using recombinant DNA technology and cell culture methods.

Analysis

We analyze all significant controlled studies of tixagevimab/cilgavimab for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random effects meta-analysis results for all studies,

studies within each treatment stage, individual outcomes, peer-reviewed studies, Randomized Controlled Trials (RCTs), and higher quality studies.

Treatment timing

Figure 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.

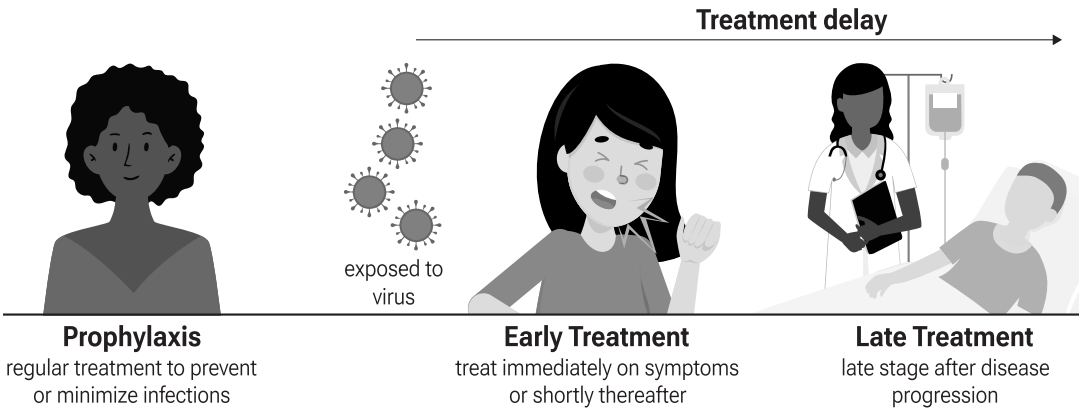


Figure 3. Treatment stages.

Variant Dependence

Extensive mutations in SARS-CoV-2 have resulted in variants that evade neutralizing antibodies from monoclonal antibody treatments[41,42], resulting in efficacy that is highly variant dependent. For example, *in vitro* research suggests that tixagevimab/cilgavimab is not effective for omicron BA.4.6 and BQ.1.1[1]. While the FDA has suspended the EUA for tixagevimab/cilgavimab due to a predicted lack of efficacy, it may retain efficacy for certain post-suspension variants[43]. Table 1 shows efficacy by variant for several monoclonal antibodies. This table covers earlier SARS-CoV-2 variants and has not been updated for more recent variants.

	Bamlanivimab/ etesevimab	*Casirivimab/ imdevimab*	*Sotrovimab*	*Bebtelovimab*	*Tixagevimab/ cilgavimab*
Alpha B.1.1.7					
Beta/Gamma BA1.351/P.1					
Delta B.1.617.2					
Omicron BA.1/BA.1.1					
Omicron BA.2					
Omicron BA.5					
Omicron BA.4.6					
Omicron BQ.1.1					

Table 1. Predicted efficacy by variant from *Davis et al.* (not updated for more recent variants). : likely effective : likely ineffective : unknown. Submit updates.

Results

Table 2 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes. Table 3 shows results by treatment stage. Figure 4 plots individual results by treatment stage. Figure 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, recovery, cases, viral clearance, and peer reviewed studies.

	Relative Risk	Studies	Patients
All studies	0.66 [0.49-0.89] **	19	30K
After exclusions	0.64 [0.47-0.87] **	17	30K
Peer-reviewed	0.68 [0.50-0.93] *	17	20K
RCTs	0.72 [0.57-0.90] **	5	8,839
Mortality	0.60 [0.40-0.89] *	10	10K
Ventilation	1.64 [0.42-6.41]	2	332
ICU admission	0.47 [0.05-4.72]	3	762
Hospitalization	0.37 [0.23-0.61] ****	9	10K
Recovery	0.94 [0.85-1.04]	2	1,643
Cases	0.36 [0.13-0.98] *	11	20K
RCT mortality	0.75 [0.58-0.96] *	4	7,718

Table 2. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes.** Results show the relative risk with treatment and the 95% confidence interval. * $p<0.05$ ** $p<0.01$ *** $p<0.001$.

	Early treatment	Late treatment	Prophylaxis
All studies	1.29 [0.42-3.95]	0.76 [0.59-0.97] *	0.59 [0.40-0.87] **
After exclusions	1.00 [0.32-3.07]	0.76 [0.59-0.97] *	0.57 [0.37-0.86] **
Peer-reviewed	1.00 [0.32-3.07]	0.76 [0.59-0.97] *	0.62 [0.40-0.95] *
RCTs	1.00 [0.32-3.07]	0.75 [0.58-0.96] *	0.56 [0.33-0.95] *
Mortality	1.29 [0.42-3.95]	0.75 [0.58-0.96] *	0.33 [0.18-0.61] ***
Ventilation		1.50 [0.28-8.04]	1.96 [0.18-21.60]
ICU admission		0.92 [0.31-2.75]	0.35 [0.01-21.78]
Hospitalization	0.45 [0.26-0.76] **		0.33 [0.17-0.65] **
Recovery		0.94 [0.85-1.04]	
Cases			0.36 [0.13-0.98] *
RCT mortality	1.00 [0.32-3.07]	0.75 [0.58-0.96] *	0.14 [0.01-2.98]

Table 3. **Random effects meta-analysis results by treatment stage.** Results show the relative risk with treatment and the 95% confidence interval. * $p<0.05$ ** $p<0.01$ *** $p<0.001$.

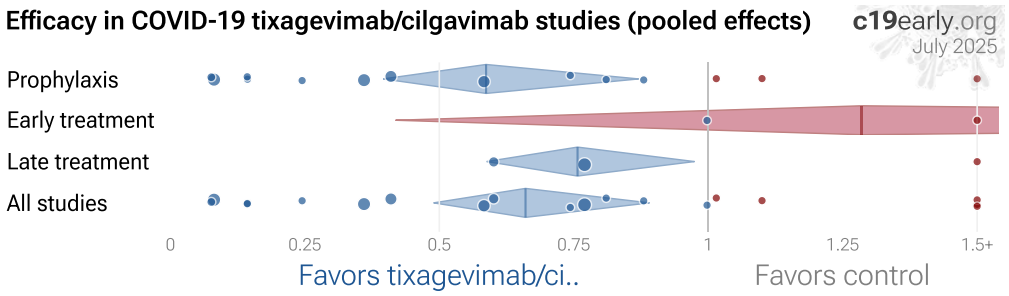


Figure 4. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

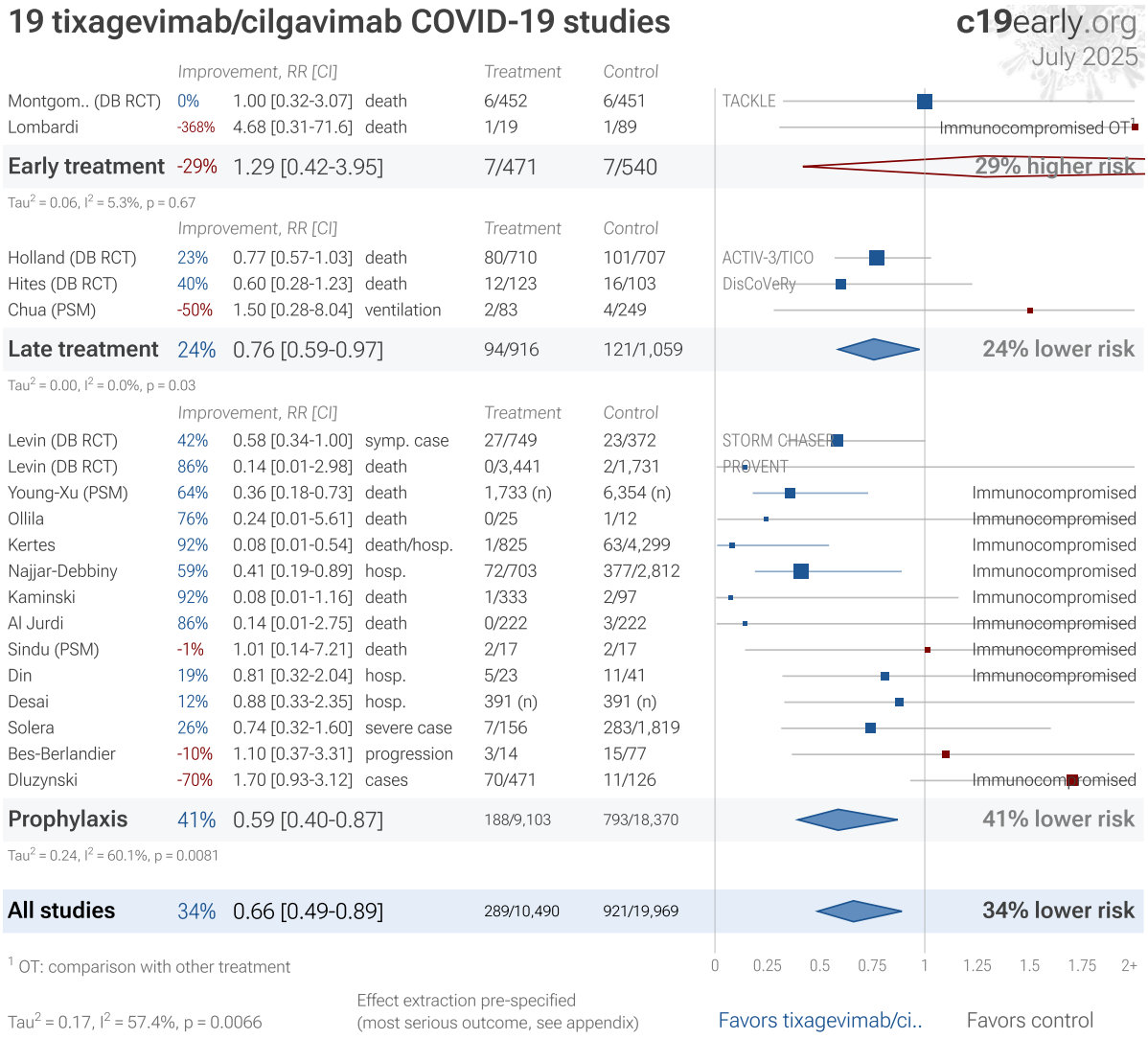


Figure 5. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For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

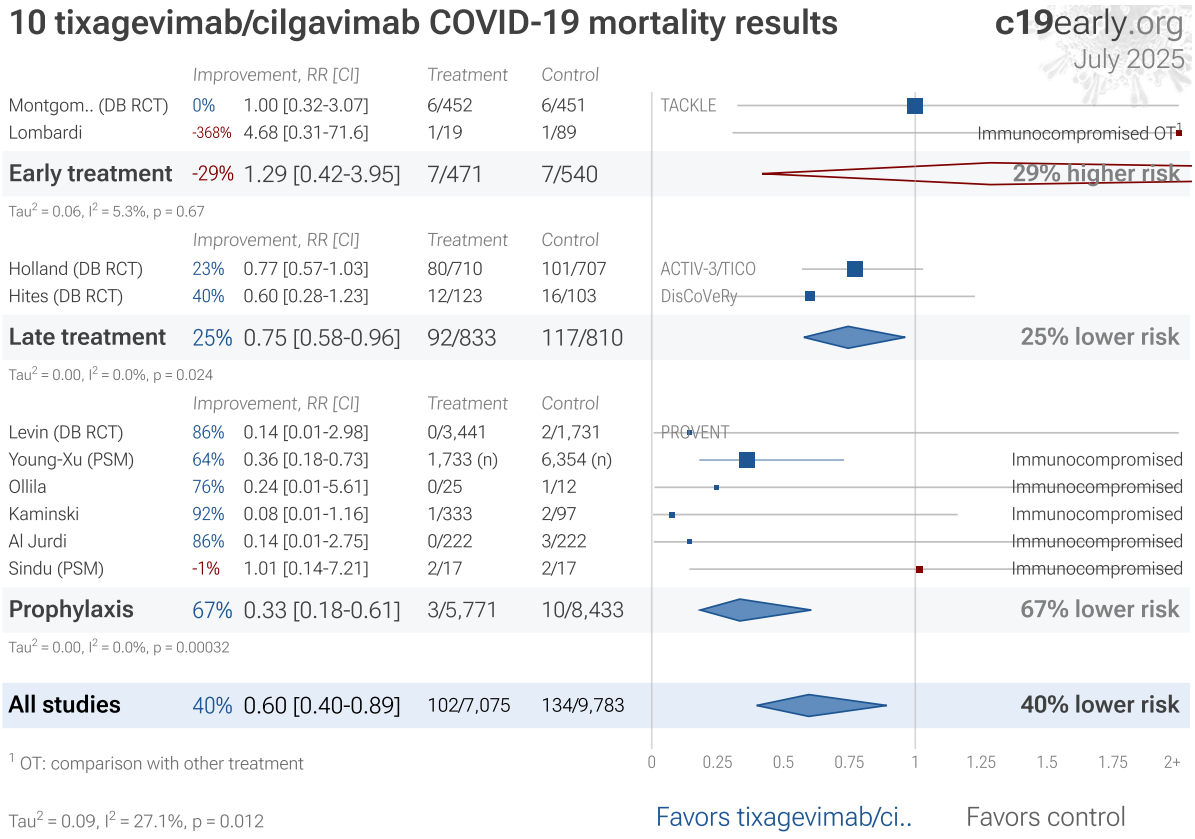


Figure 6. Random effects meta-analysis for mortality results.

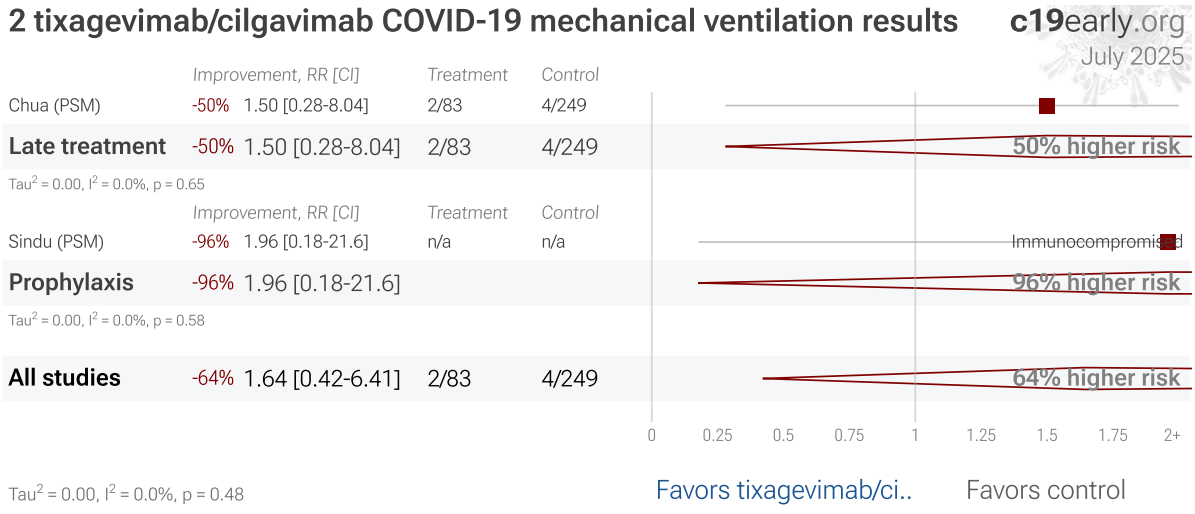


Figure 7. Random effects meta-analysis for ventilation.

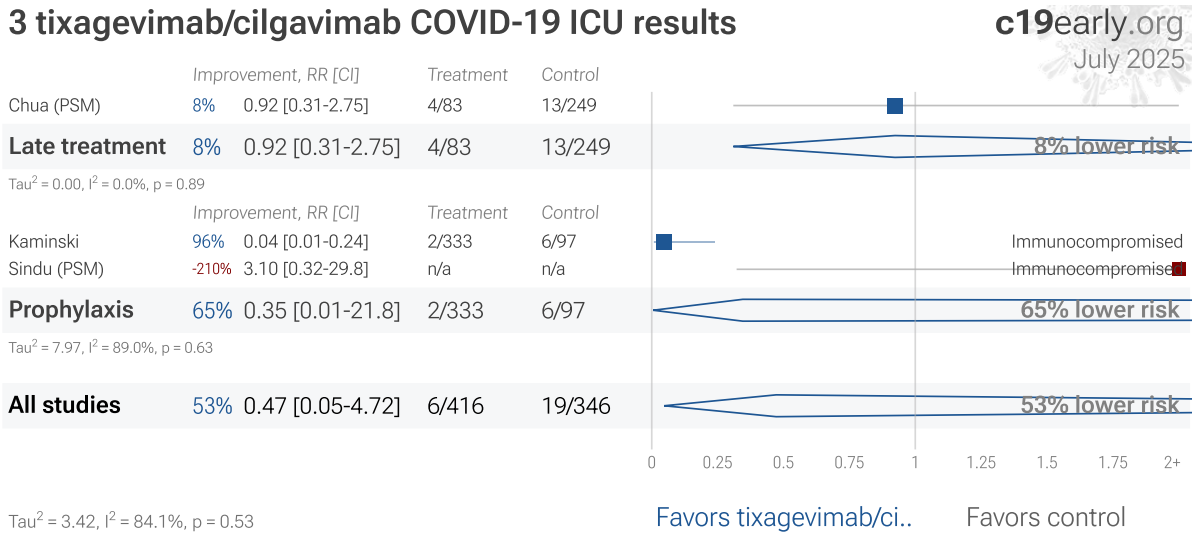


Figure 8. Random effects meta-analysis for ICU admission.

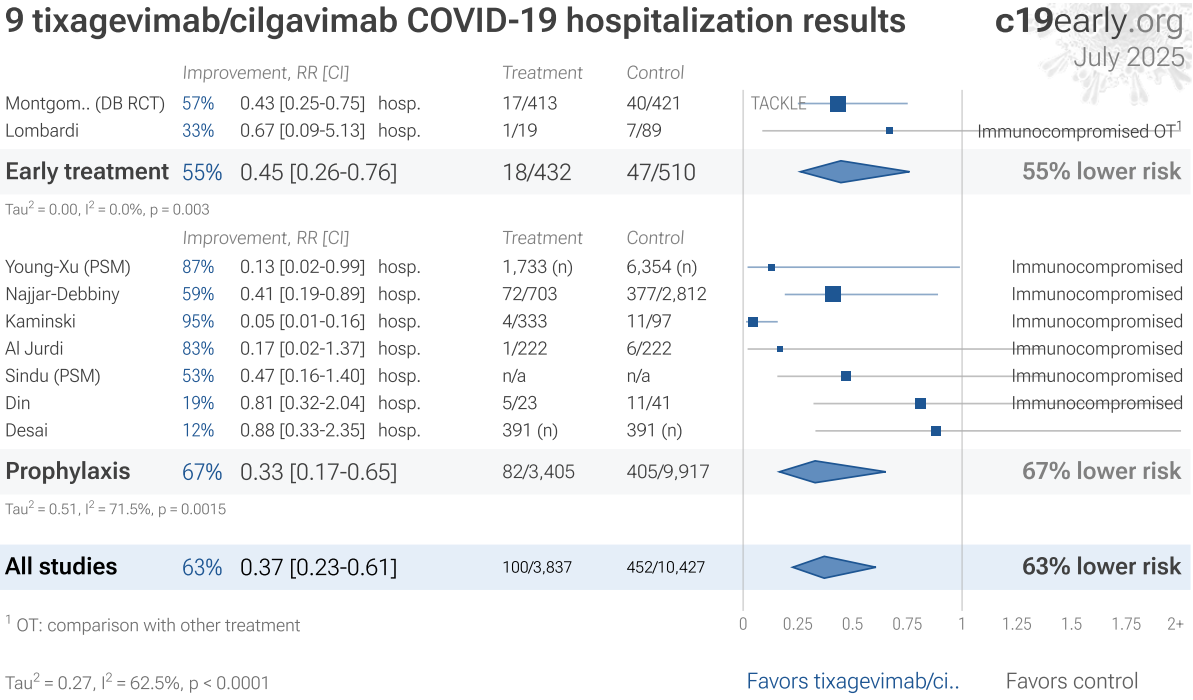


Figure 9. Random effects meta-analysis for hospitalization.

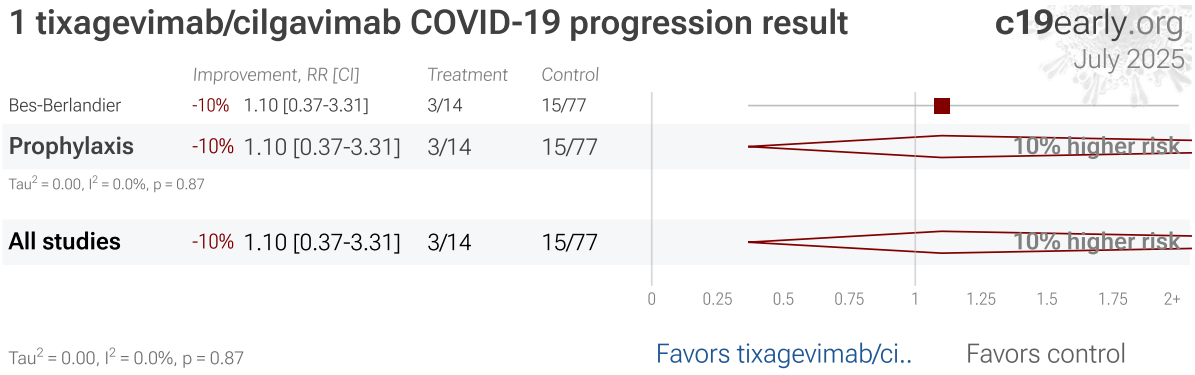


Figure 10. Random effects meta-analysis for progression.

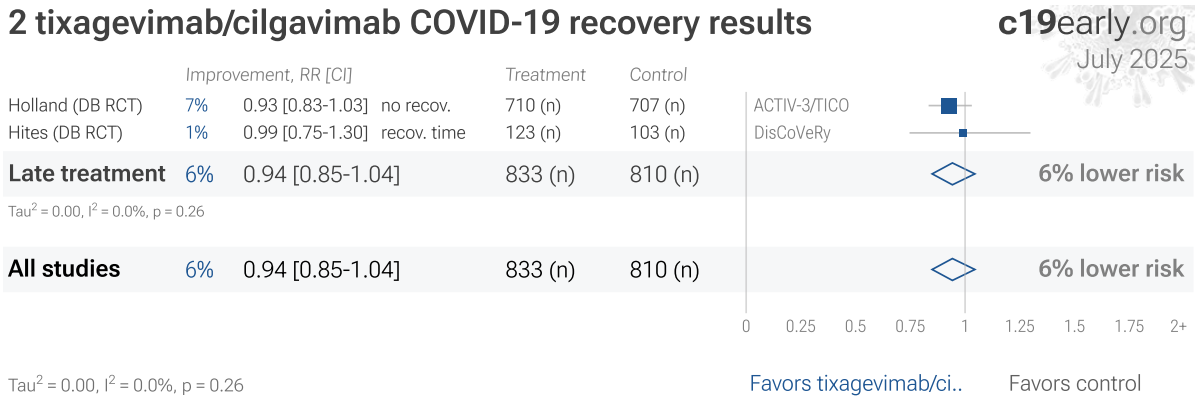


Figure 11. Random effects meta-analysis for recovery.

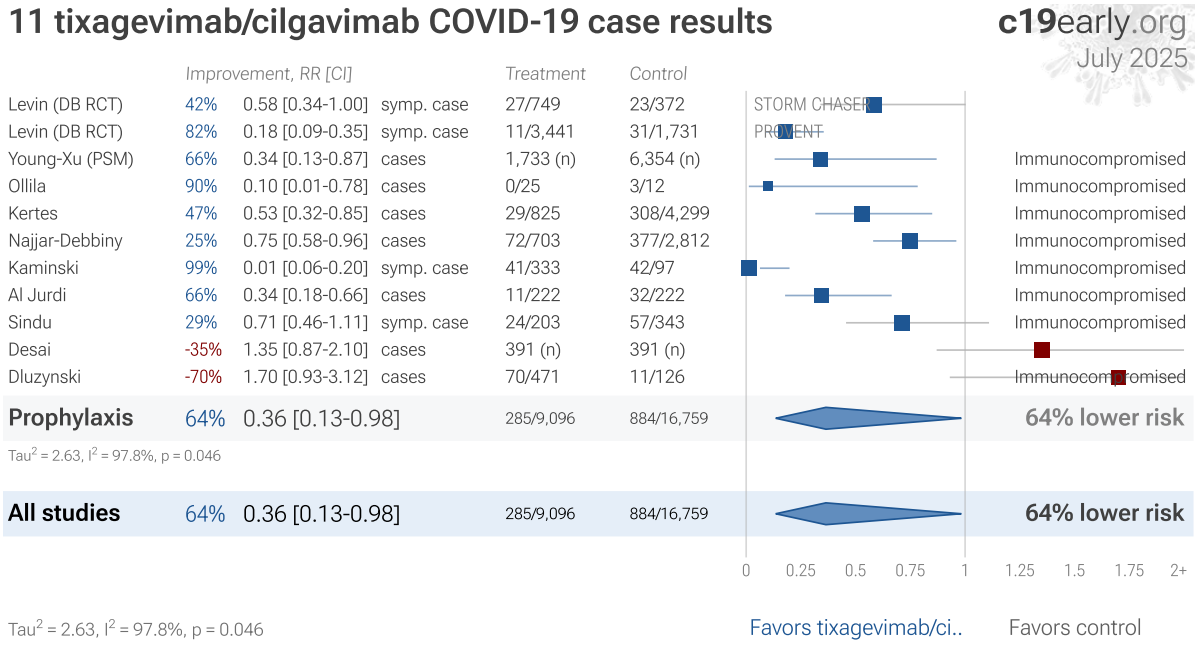


Figure 12. Random effects meta-analysis for cases.

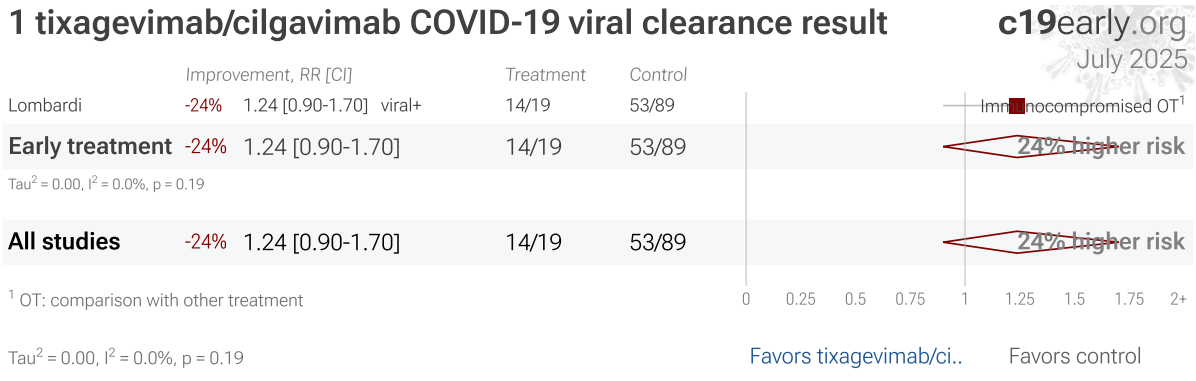


Figure 13. Random effects meta-analysis for viral clearance.

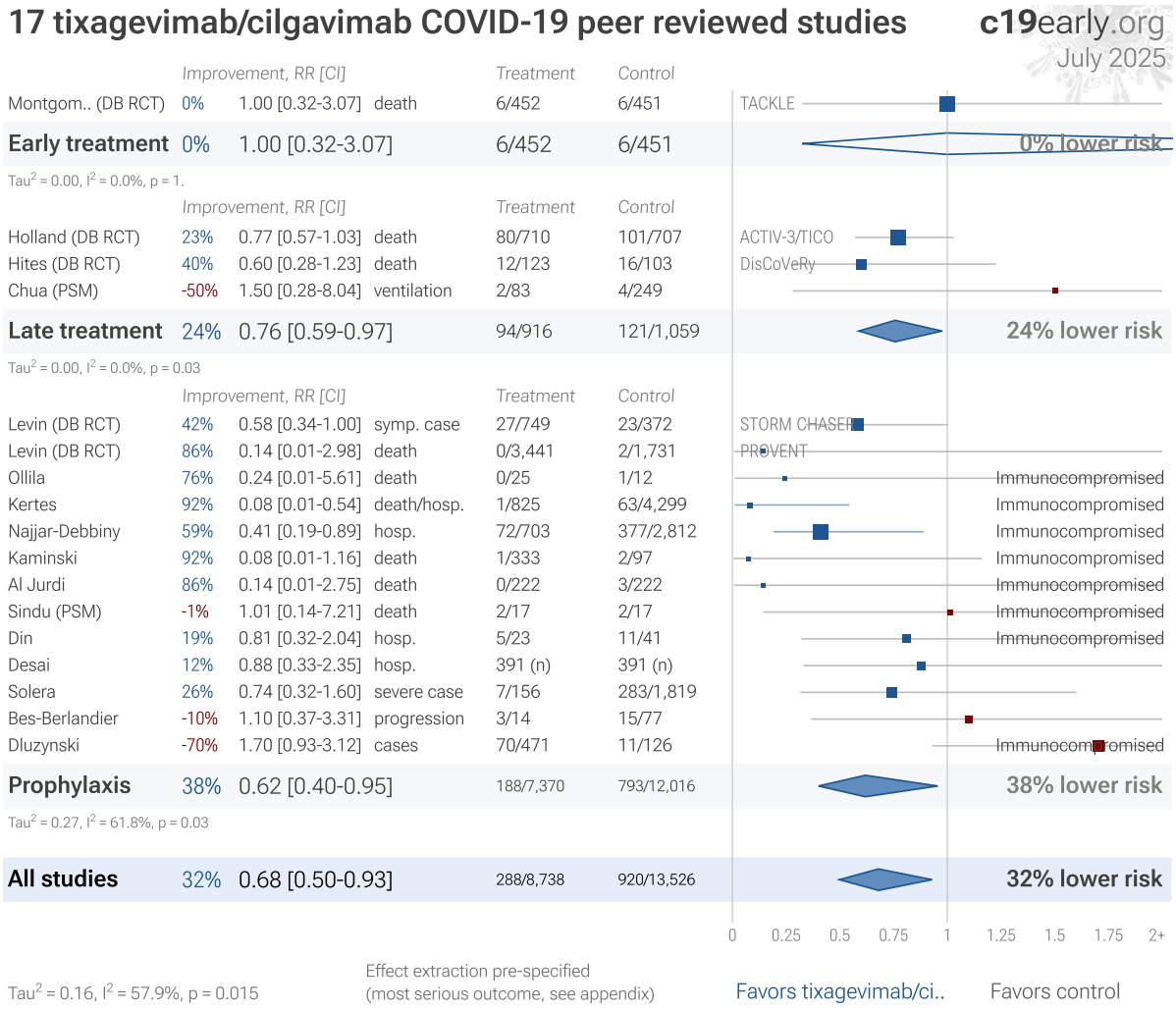


Figure 14. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding 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 15 shows a comparison of results for RCTs and observational studies. Figure 16 and 17 show forest plots for random effects meta-analysis of all Randomized Controlled Trials and RCT mortality results. RCT results are included in Table 2 and Table 3.

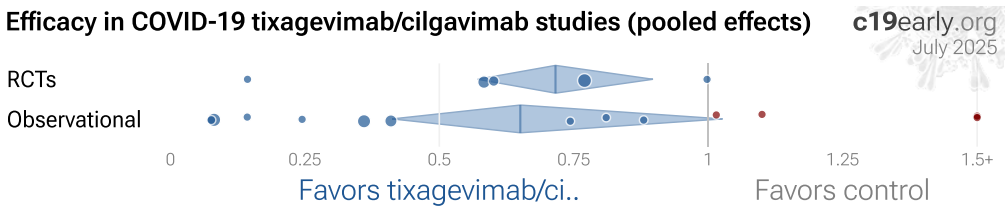


Figure 15. **Results for RCTs and observational studies.**

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 biases[47], and analysis of double-blind RCTs has identified extreme levels of bias[48]. 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][53]. 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.

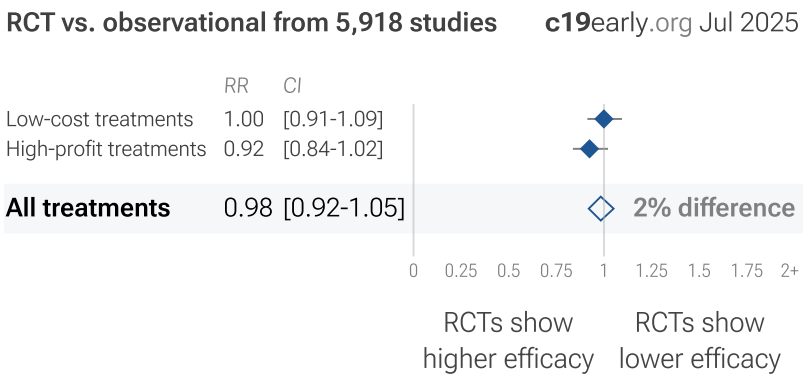


Figure 18. **For COVID-19, observational study results do not systematically differ from RCTs, RR 0.98 [0.92-1.05] across 172 treatments[50].**

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[55,56].

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 ≥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.

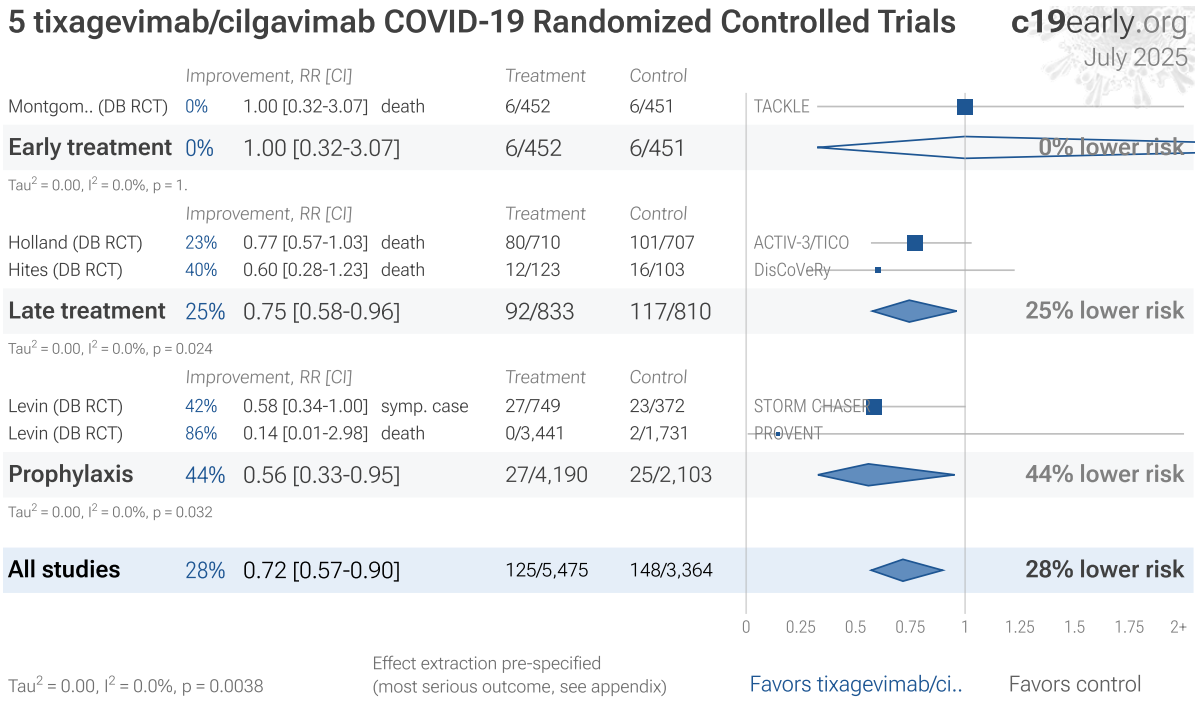


Figure 16. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

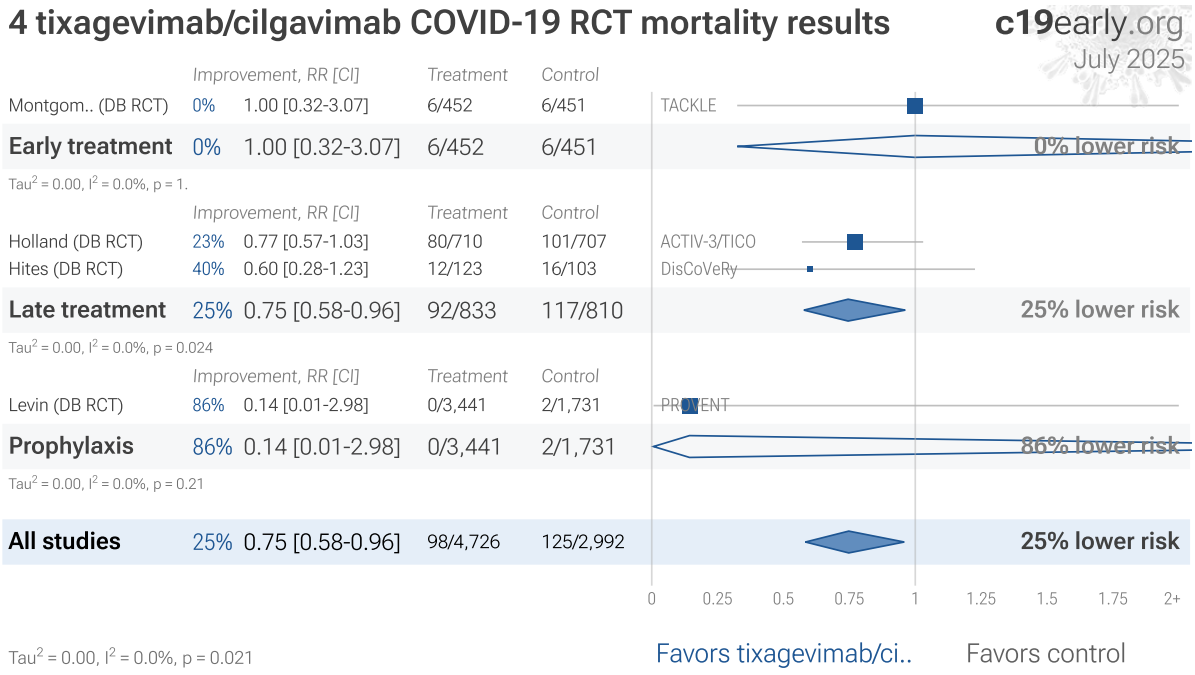


Figure 17. **Random effects meta-analysis for RCT mortality results.**

Exclusions

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

The studies excluded are as below. Figure 19 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Din, unadjusted results with no group details.

Lombardi, study compares against another treatment showing significant efficacy.

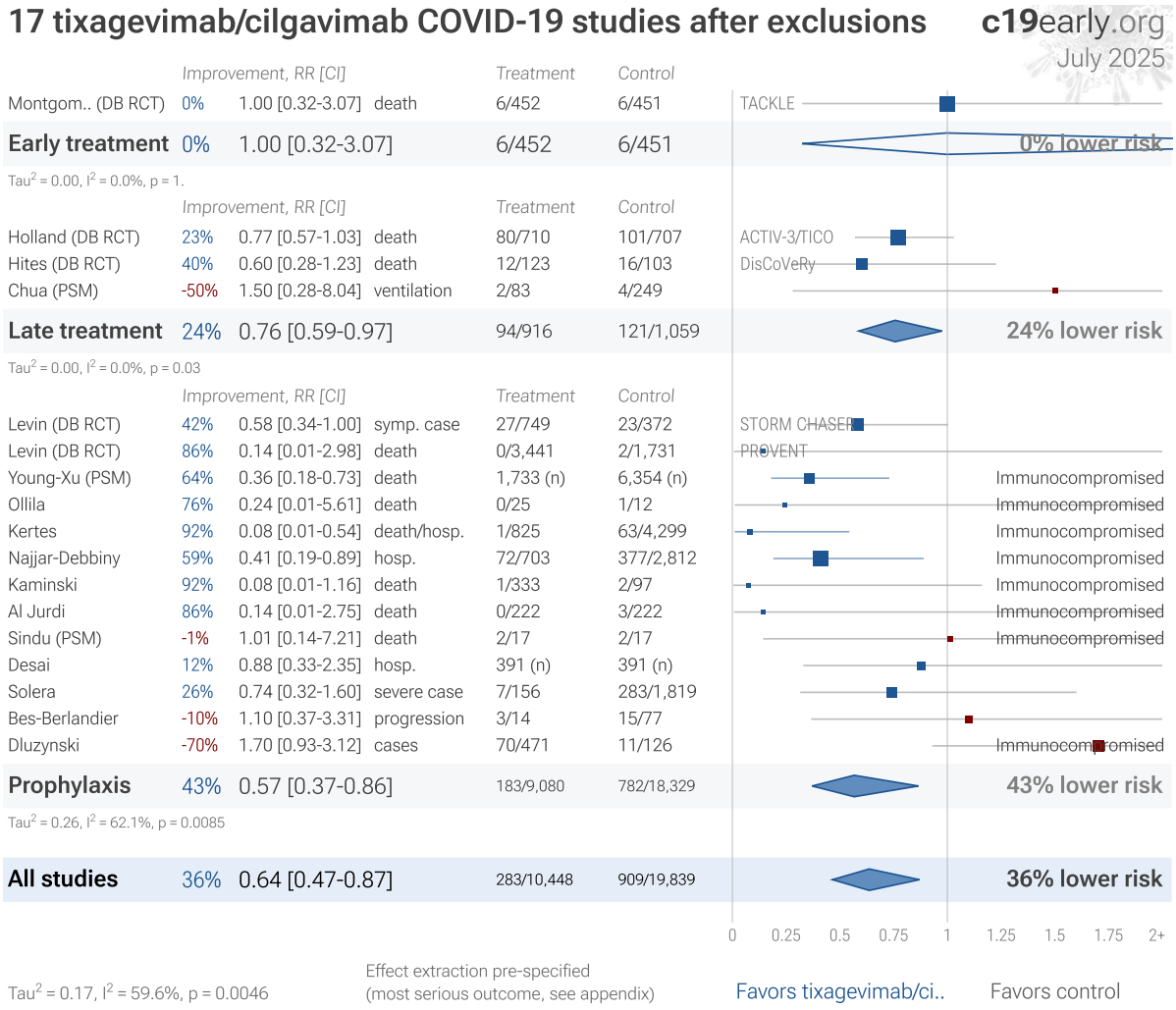


Figure 19. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome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

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[59,60]. 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[61]
<24 hours	-33 hours symptoms[62]
24-48 hours	-13 hours symptoms[62]
Inpatients	-2.5 hours to improvement[63]

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

Figure 20 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.

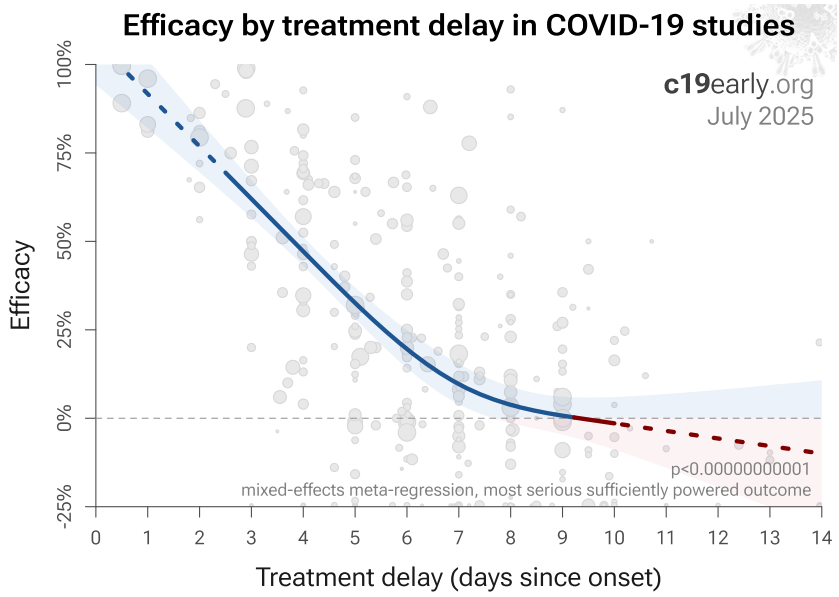


Figure 20. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 172 treatments.

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[65], for example the Gamma variant shows significantly different characteristics[66-69]. 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[70,71].

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 [74-90], 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 May 2022

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 tixagevimab/cilgavimab as of May 2022. Efficacy is now known based on specific outcomes for all studies and when restricted to RCTs. Efficacy based on specific outcomes in RCTs was delayed by 19.3 months compared to using pooled outcomes in RCTs.

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 21 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 22 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 23 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 $p = 0.0000000033$.

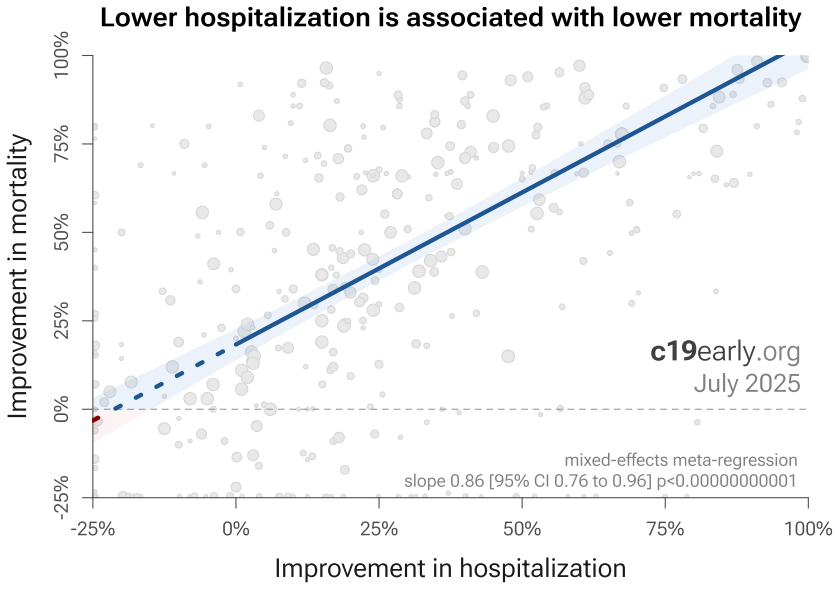


Figure 21. **Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.**

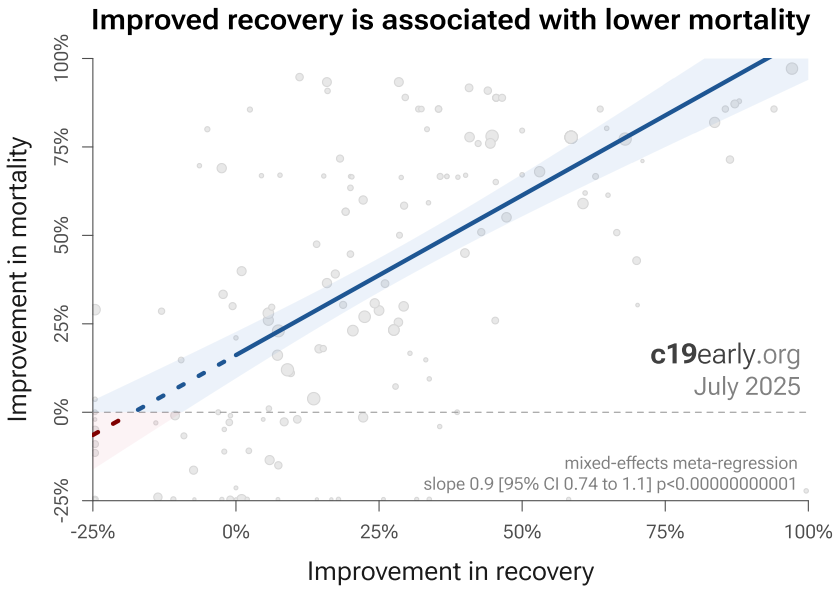


Figure 22. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

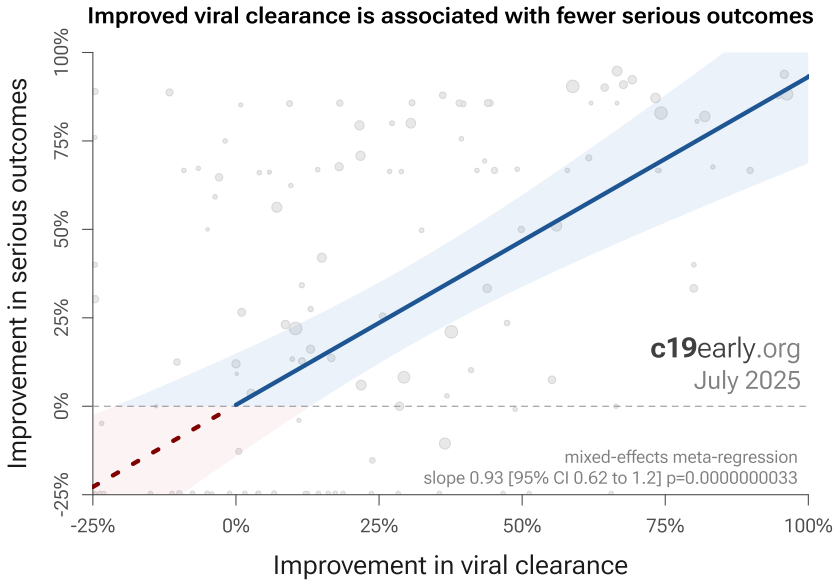


Figure 21. Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.

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

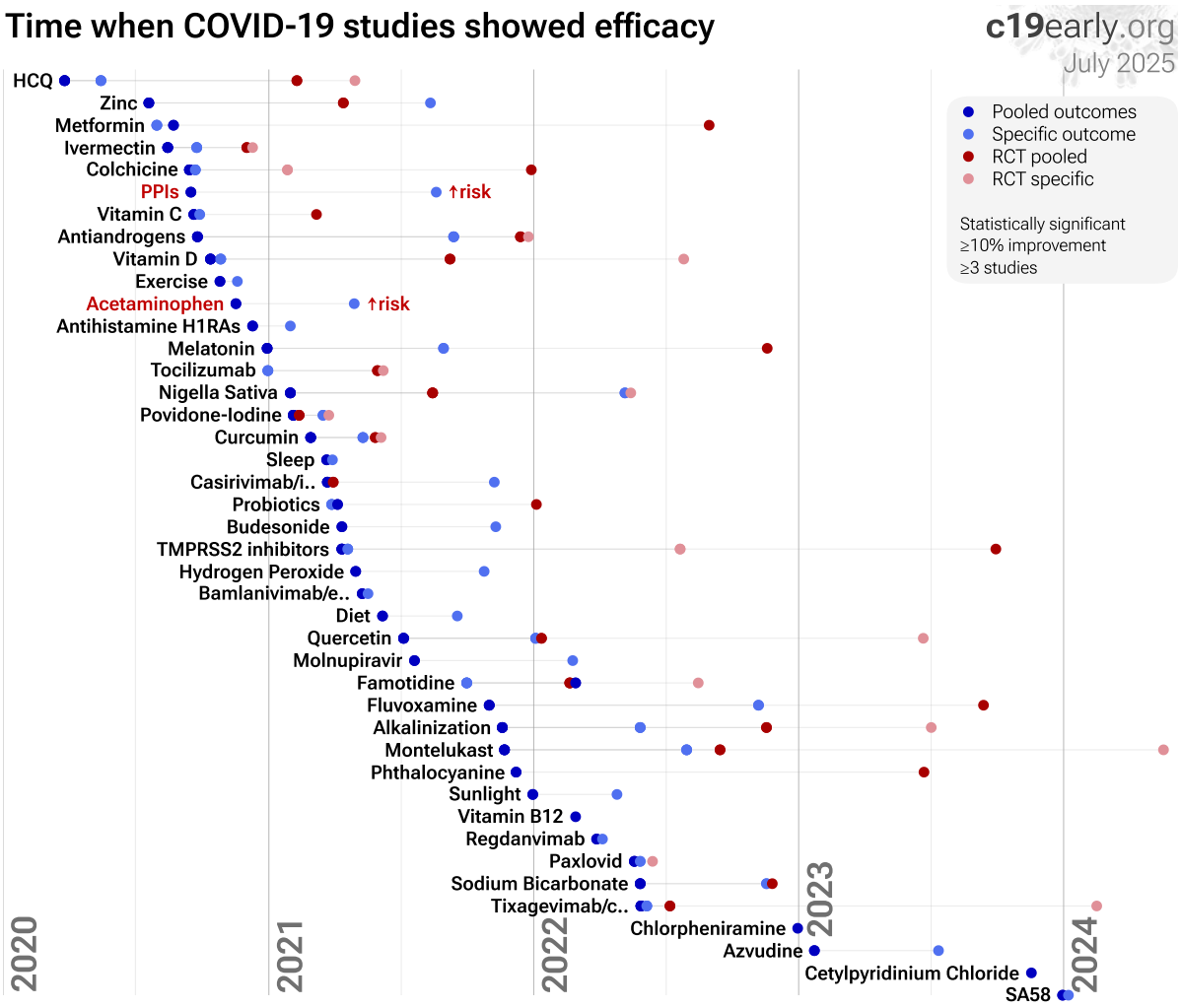


Figure 24. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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 tixagevimab/cilgavimab, 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 25 shows a scatter plot of results for prospective and retrospective studies. 43% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 60% of prospective studies, consistent with a bias toward publishing negative results. The median effect size for retrospective studies is 22% improvement, compared to 40% for prospective studies, suggesting a potential bias towards publishing results showing lower efficacy.

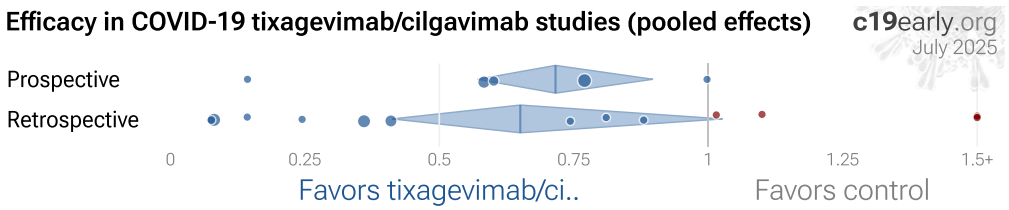


Figure 25. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

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 26 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 $p < 0.05$ [92-99]. 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.

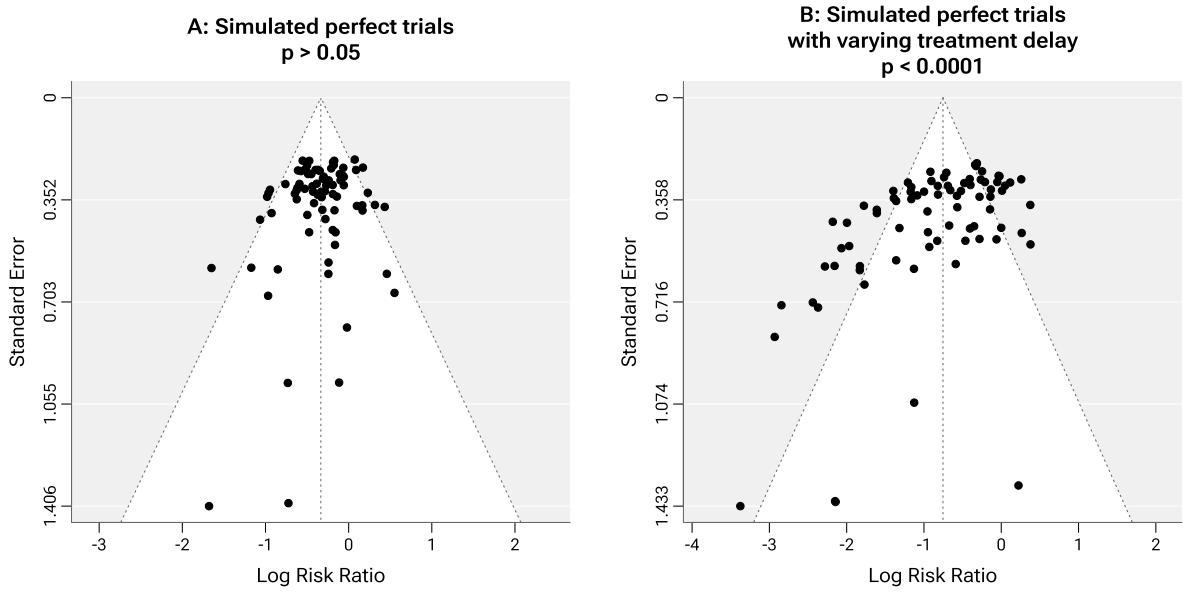


Figure 26. **Example funnel plot analysis for simulated perfect trials.**

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 alone [74-90]. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

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

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

Notes

1 of the 19 studies compare against other treatments, which may reduce the effect seen. *Soeroto et al.* present another meta analysis for tixagevimab/cilgavimab, showing significant improvements for mortality, hospitalization, severity, and cases.

Reviews

Multiple reviews cover tixagevimab/cilgavimab for COVID-19, presenting additional background on mechanisms and related results, including [5,42,100-102].

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 [32-39], providing many therapeutic targets. Over 9,000 compounds have been predicted to reduce COVID-19 risk [40], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 27 shows an overview of the results for tixagevimab/cilgavimab in the context of multiple COVID-19 treatments, and Figure 28 shows a plot of efficacy vs. cost for COVID-19 treatments.

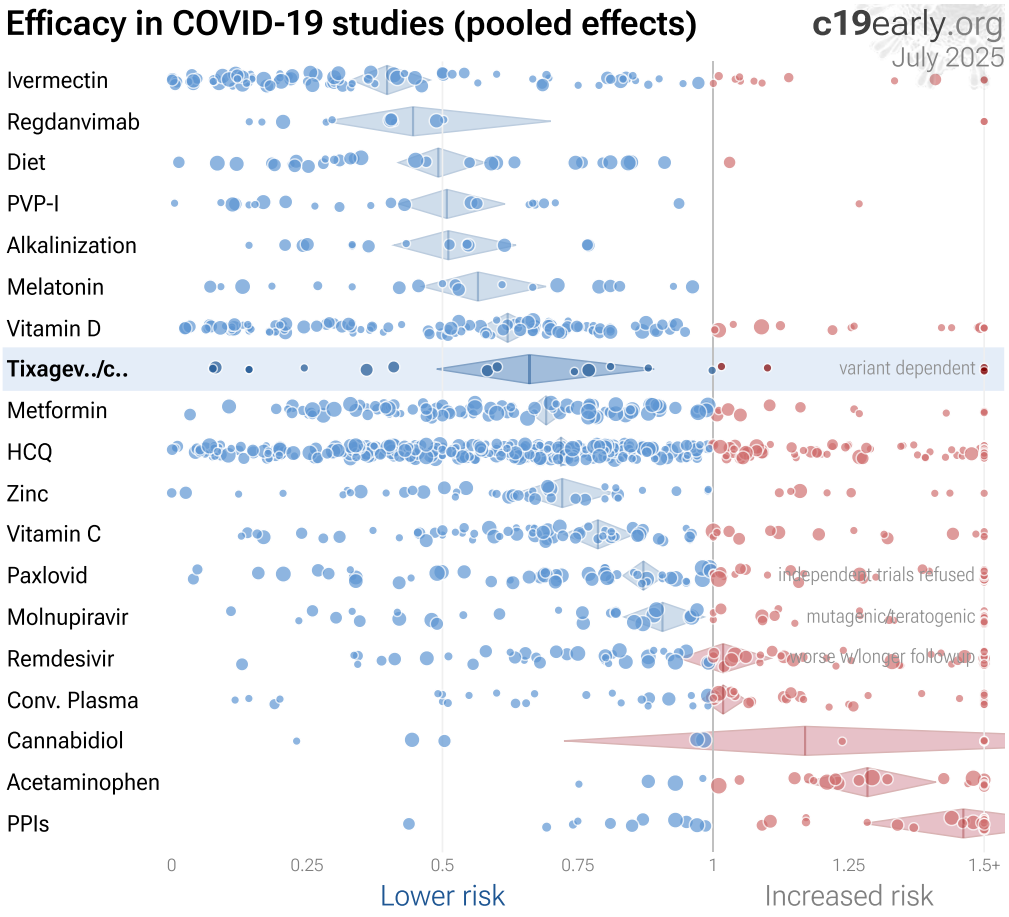


Figure 27. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy [103].

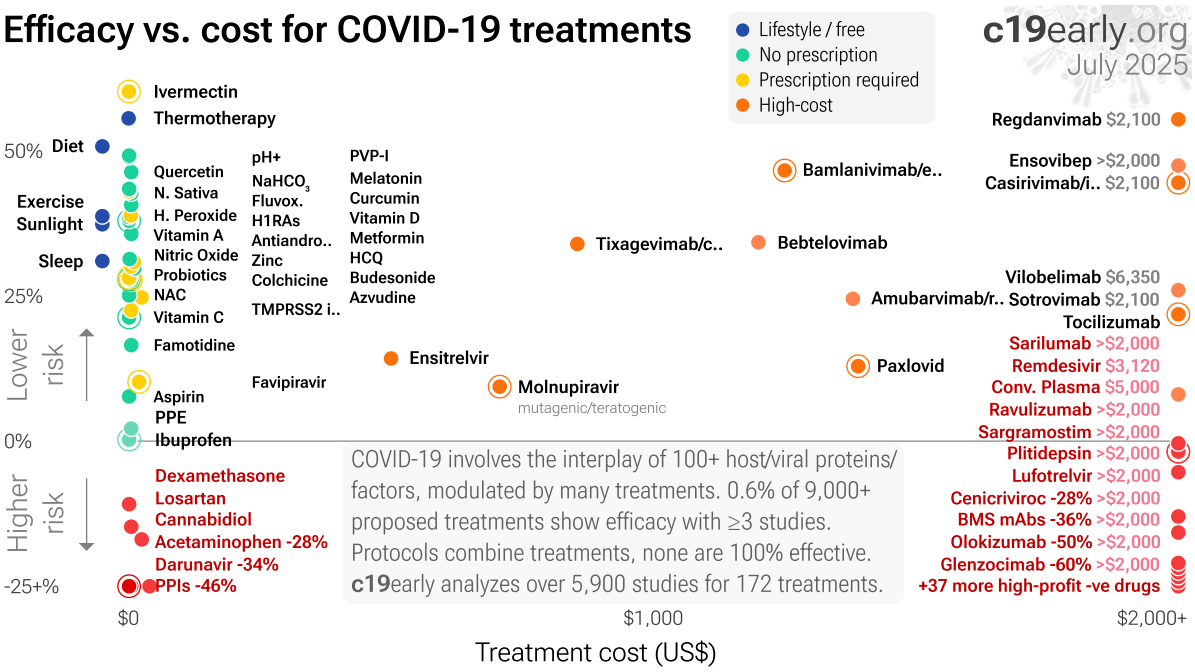


Figure 28. Efficacy vs. cost for COVID-19 treatments.

Conclusion

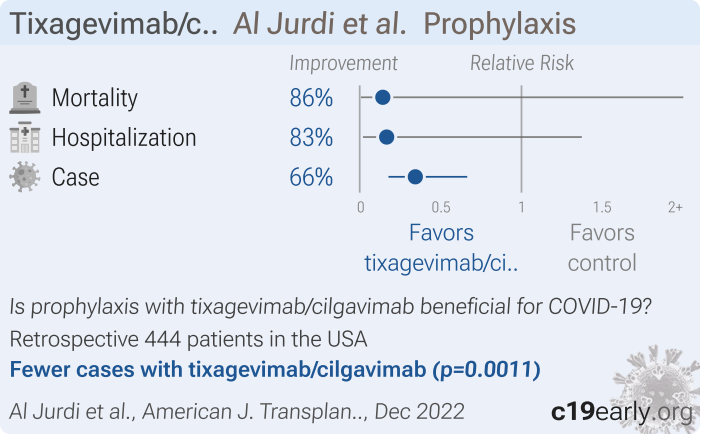
Tixagevimab/cilgavimab is an effective treatment for COVID-19. Significantly lower risk is seen for mortality, hospitalization, and cases. 9 studies from 9 independent teams in 3 countries show significant benefit. Meta analysis using the most serious outcome reported shows 34% [11-51%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies. Results are robust — in exclusion sensitivity analysis 6 of 19 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

Efficacy is variant dependent. *In Vitro* research suggests a lack of efficacy for omicron BA.2.75.2, BA.4.6, and BQ.1.1[1], BA.5, BA.2.75, XBB[2,3], XBB.1.5[3], XBB.1.9.1[3], XBB.1.9.3, XBB.1.5.24, XBB.1.16, XBB.2.9, BQ.1.1.45, CL.1, and CH.1.1[4]. US EUA has been revoked. mAb use may create new variants that spread globally[5-7], and may be associated with prolonged viral loads, clinical deterioration, and immune escape[6,8-10].

Soeroto et al. present another meta analysis for tixagevimab/cilgavimab, showing significant improvements for mortality, hospitalization, severity, and cases.

Study Notes

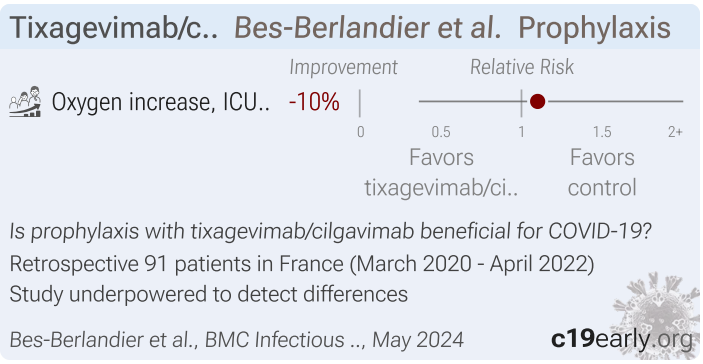
Al Jurdi



Retrospective cohort study of 444 solid organ transplant recipients showing significantly lower risk of SARS-CoV-2 breakthrough infections with tixagevimab/cilgavimab pre-exposure prophylaxis compared to controls during the omicron period.

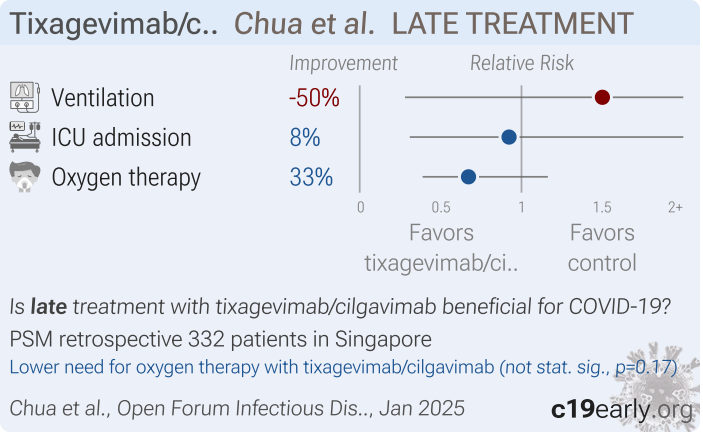
Confounding by treatment propensity. This study analyzes a population where only a fraction of eligible patients received the treatment. Patients receiving treatment may be more likely to follow other recommendations, more likely to receive additional care, and more likely to use additional treatments that are not tracked in the data (e.g., nasal/oral hygiene[104,105], vitamin D[106], etc.) — either because the physician recommending tixagevimab/cilgavimab also recommended them, or because the patient seeking out tixagevimab/cilgavimab is more likely to be familiar with the efficacy of additional treatments and more likely to take the time to use them. Therefore, these kind of studies may overestimate the efficacy of treatments.

Bes-Berlandier



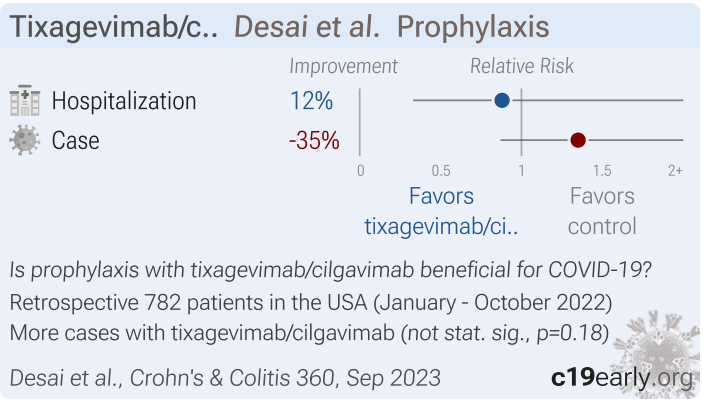
Retrospective 91 lung transplant recipients with COVID-19 showing no significant difference in poor outcomes with casirivimab/imdevimab or tixagevimab/cilgavimab prophylaxis in univariate analysis.

Chua



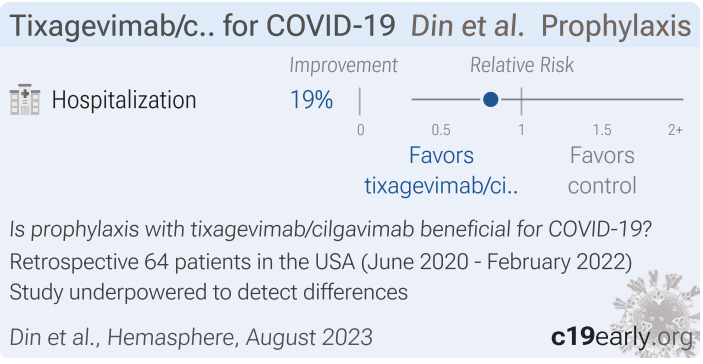
PSM retrospective 366 hospitalized COVID-19 patients in Singapore showing no statistically significant reduction in severe outcomes with monoclonal antibodies (mAbs), except for lower oxygen use in patients treated with sotrovimab during the Omicron wave. The 2021 numbers for sotrovimab do not appear to be reported correctly, for example showing >96% intubation and higher incidence of ICU admission than the composite outcome that includes ICU admission. Multiple numbers appear to have been transposed.

Desai



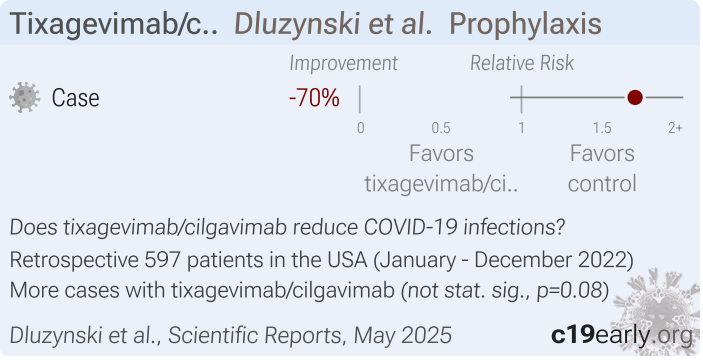
TriNetX PSM retrospective 408 IBD patients receiving tixagevimab/cilgavimab and matched controls, showing no significant difference in COVID-19 cases or hospitalization.

Din



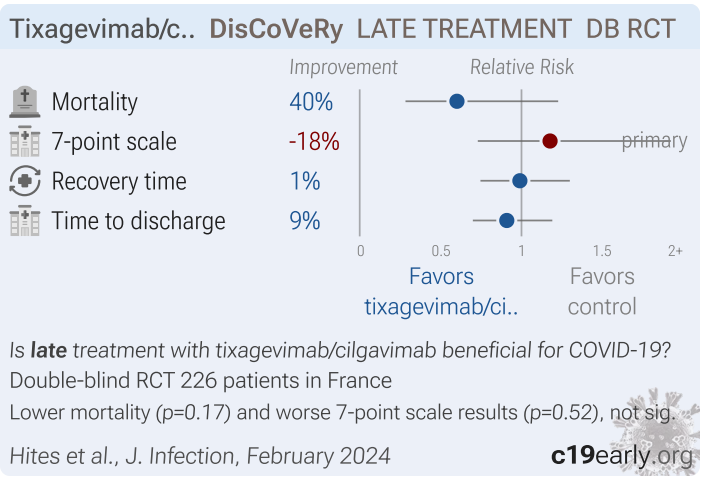
Retrospective 64 COVID+ CAR-T cell therapy recipients, showing lower hospitalization with tixagevimab/cilgavimab prophylaxis in unadjusted results, without statistical significance.

Dluzynski



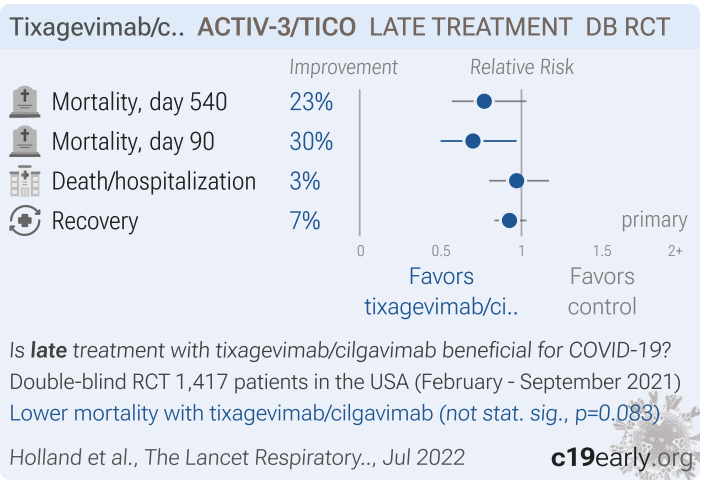
Retrospective 597 immunocompromised individuals showing no significant difference in infection rates over the entire study period. However, when truncating data to November 1, 2022 (before resistant variants dominated), effectiveness increased with higher cumulative doses.

Hites



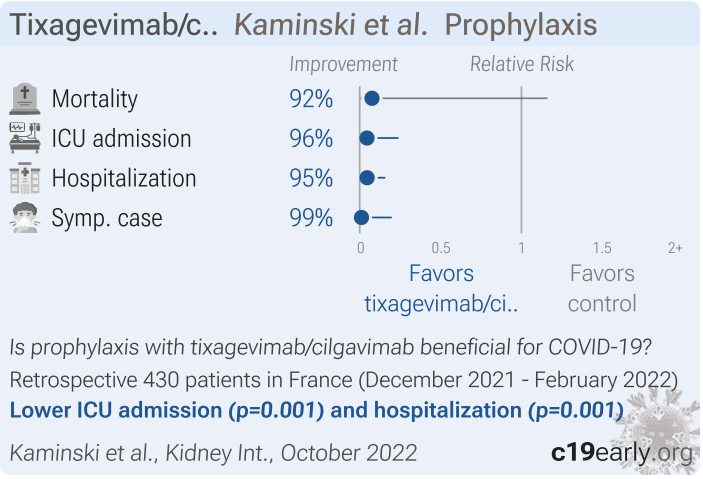
RCT 173 hospitalized COVID-19 patients showing no significant difference in clinical status, time to recovery, viral clearance, or mortality with tixagevimab/cilgavimab. Mortality was lower, without statistical significance. The trial was terminated early due to concerns about reduced efficacy against circulating variants.

Holland



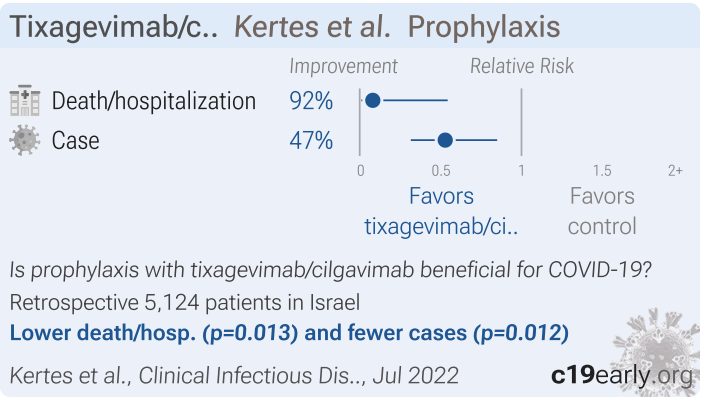
RCT with 710 hospitalized patients treated with tixagevimab/cilgavimab, and 707 placebo patients, showing lower mortality with treatment. Long-term results are reported in *Mourad et al.*

Kaminski



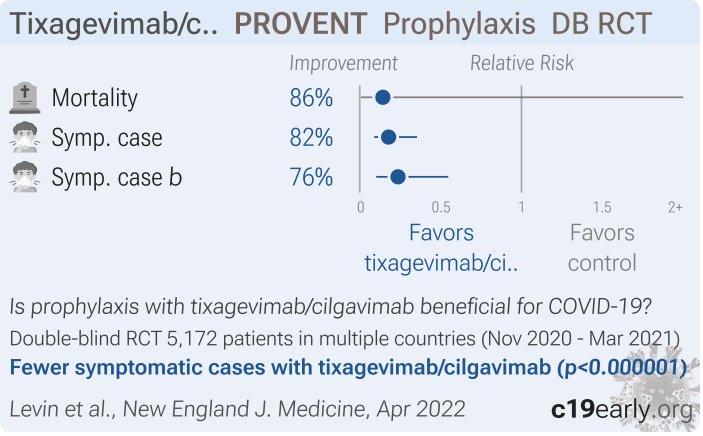
Retrospective 430 kidney transplant recipients showing significantly lower symptomatic COVID-19 and hospitalization with tixagevimab/cilgavimab preexposure prophylaxis compared to 97 patients who did not receive it, during an omicron wave.

Kertes



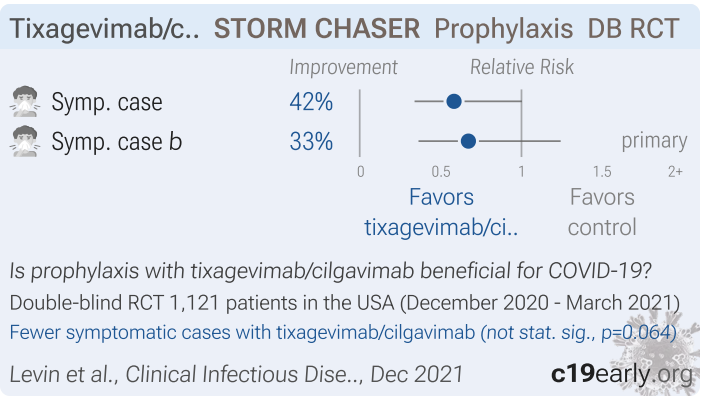
Retrospective 825 immunocompromised individuals treated with tixagevimab-cilgavimab and 4229 untreated in Israel, showing significantly lower infection and hospitalization/death with treatment. Omicron was the dominant variant.

Levin



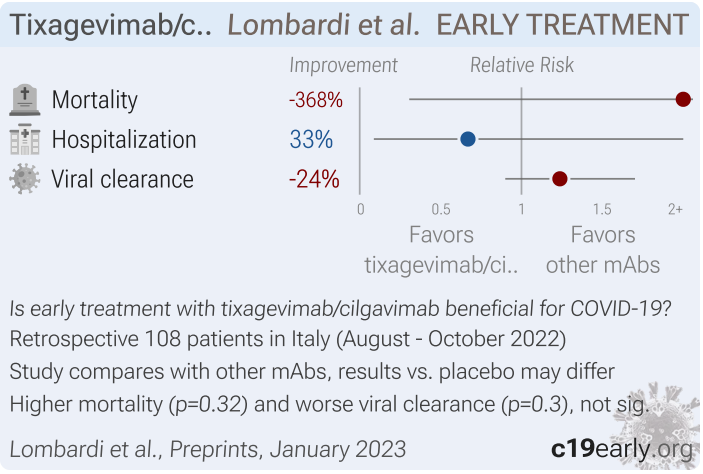
PrEP RCT with 3,441 tixagevimab/cilgavimab patients and 1,731 control patients, showing lower risk of symptomatic cases with treatment.

Levin



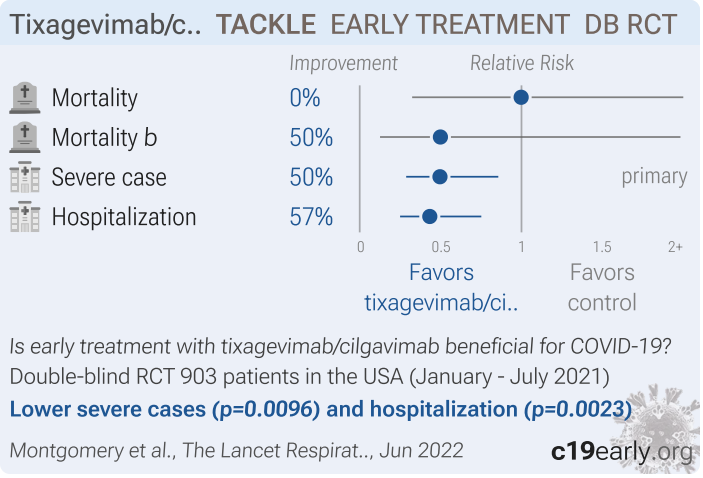
1,121 patient PEP RCT showing lower symptomatic cases with tixagevimab/cilgavimab, without statistical significance.

Lombardi



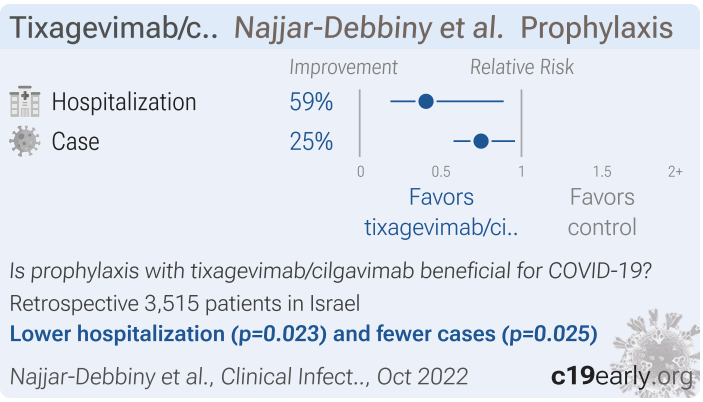
Retrospective immunocompromised patients, showing no significant difference between tixagevimab/cilgavimab and other mAbs.

Montgomery



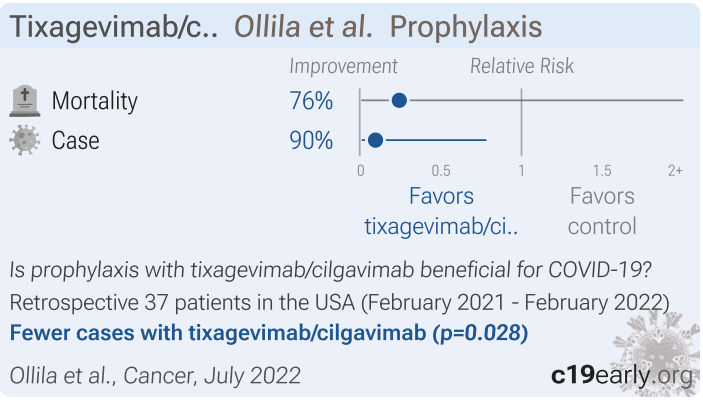
RCT 910 outpatients in the USA, 456 treated with tixagevimab/cilgavimab, showing significantly lower severe cases and hospitalization with treatment, but no difference in mortality.

Najjar-Debbiny



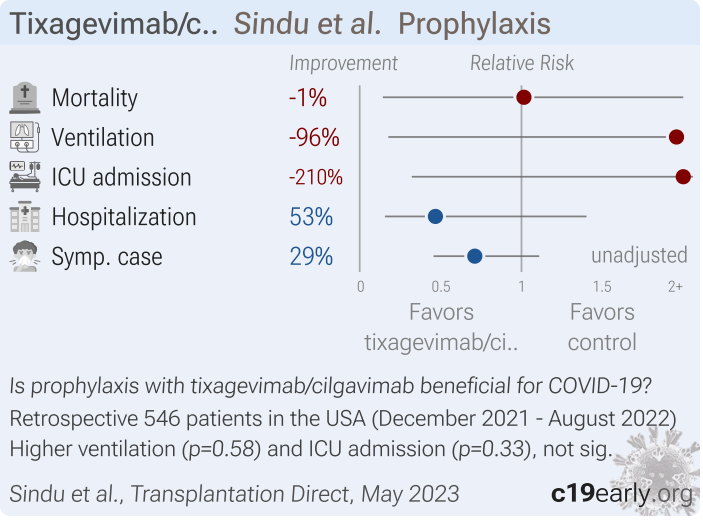
Retrospective 732 immunocompromised patients in Israel treated with tixagevimab/cilgavimab, and 2,812 matched controls, showing significantly lower cases and hospitalization with treatment.

Ollila



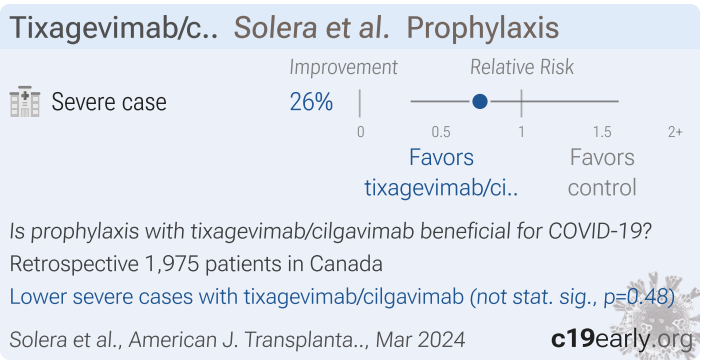
Retrospective 378 patients with hematologic malignancies analyzing seroconversion and outcomes post-vaccination. Among 25 seronegative patients after booster vaccination who received tixagevimab/cilgavimab prophylaxis, no COVID-19 infections occurred, whereas 3 infections and 1 death occurred among 12 comparable patients not receiving prophylaxis.

Sindu



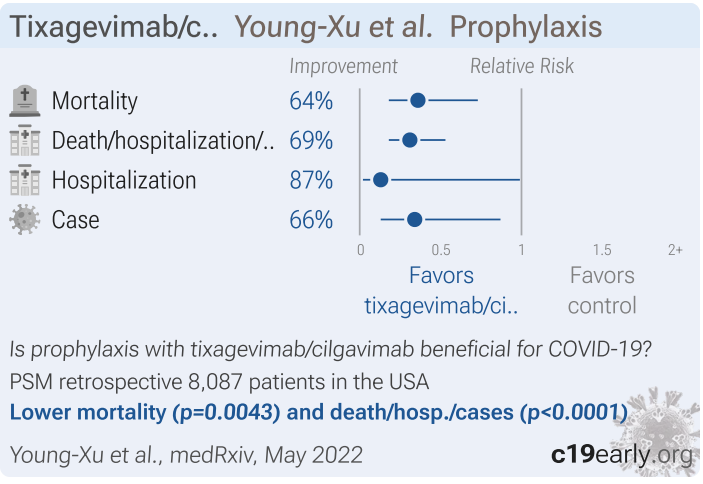
Retrospective 546 lung transplant recipients, 203 receiving tixagevimab/cilgavimab, and 343 out of state or declining treatment, showing a trend towards lower incidence of cases, but no significant difference in clinical outcomes.

Solera



Retrospective 1,975 solid organ transplant recipients with COVID-19 showing lower risk of severe cases with tixagevimab/cilgavimab prophylaxis, without statistical significance.

Young-Xu



PSM retrospective 1,848 immunocompromised patients given tixagevimab/cilgavimab prophylaxis, showing lower mortality, hospitalization, and cases.

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

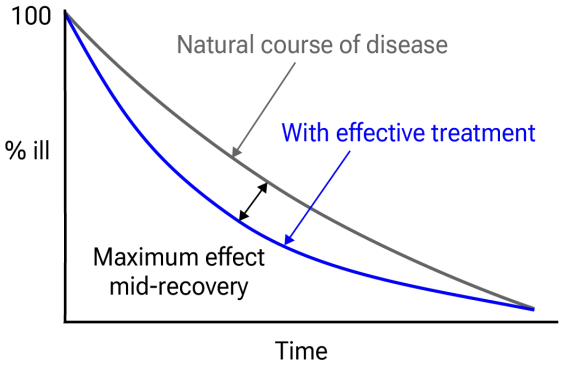


Figure 29. **Mid-recovery results can more accurately reflect efficacy when almost all patients recover.** *Mateja et al.* **confirm that intermediate viral load results more accurately reflect hospitalization/death.**

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 [108]. 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 (B) 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 [112]. 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 [113] 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 [59,60].

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/tcmeta.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.

Lombardi, 1/19/2023, retrospective, Italy, preprint, 21 authors, study period 28 August, 2022 - 15 October, 2022, this trial compares with another treatment - results may be better when compared to placebo, excluded in exclusion analyses: study compares against another treatment showing significant efficacy.	**risk of death, 368.4% higher, RR 4.68, *p* = 0.32**, treatment 1 of 19 (5.3%), control 1 of 89 (1.1%), day 14.
	risk of hospitalization, 33.1% lower, RR 0.67, *p* = 1.00, treatment 1 of 19 (5.3%), control 7 of 89 (7.9%), NNT 38, day 14.
	risk of no viral clearance, 23.7% higher, RR 1.24, *p* = 0.30, treatment 14 of 19 (73.7%), control 53 of 89 (59.6%), day 14.
Montgomery, 6/7/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, mean age 46.0, 20 authors, study period 28 January, 2021 - 22 July, 2021, trial NCT04723394 (history) (TACKLE).	**risk of death, 0.2% lower, RR 1.00, *p* = 1.00**, treatment 6 of 452 (1.3%), control 6 of 451 (1.3%), NNT 33975, all cause mortality.
	risk of death, 50.1% lower, RR 0.50, *p* = 0.34, treatment 3 of 452 (0.7%), control 6 of 451 (1.3%), NNT 150, COVID-19 mortality.
	risk of severe case, 50.4% lower, RR 0.50, *p* = 0.010, treatment 18 of 407 (4.4%), control 37 of 415 (8.9%), NNT 22, primary outcome.
	risk of hospitalization, 56.7% lower, RR 0.43, *p* = 0.002, treatment 17 of 413 (4.1%), control 40 of 421 (9.5%), NNT 19.

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.

Chua, 1/29/2025, retrospective, Singapore, peer-reviewed, 9 authors.	**risk of mechanical ventilation, 50.0% higher, RR 1.50, *p* = 0.64**, treatment 2 of 83 (2.4%), control 4 of 249 (1.6%), propensity score matching.
	risk of ICU admission, 7.7% lower, RR 0.92, *p* = 1.00, treatment 4 of 83 (4.8%), control 13 of 249 (5.2%), NNT 249, propensity score matching.

	risk of oxygen therapy, 32.8% lower, RR 0.67, p = 0.17, treatment 13 of 83 (15.7%), control 58 of 249 (23.3%), NNT 13, propensity score matching.
Hites, 2/16/2024, Double Blind Randomized Controlled Trial, placebo-controlled, France, peer-reviewed, 86 authors, trial NCT04315948 (history) (DisCoVeRy).	**risk of death, 39.9% lower, RR 0.60, p = 0.17**, treatment 12 of 123 (9.8%), control 16 of 103 (15.5%), NNT 17, odds ratio converted to relative risk, day 90.
	risk of 7-point scale, 17.6% higher, OR 1.18, p = 0.52, treatment 123, control 103, inverted to make OR<1 favor treatment, day 15, primary outcome, RR approximated with OR.
	recovery time, 1.0% lower, relative time 0.99, p = 0.93, treatment 123, control 103, inverted to make RR<1 favor treatment.
	time to discharge, 9.1% lower, relative time 0.91, p = 0.49, treatment 123, control 103, inverted to make RR<1 favor treatment.
Holland, 7/8/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 103 authors, study period 10 February, 2021 - 30 September, 2021, average treatment delay 8.0 days, trial NCT04501978 (history) (ACTIV-3/TICO).	**risk of death, 23.0% lower, HR 0.77, p = 0.08**, treatment 80 of 710 (11.3%), control 101 of 707 (14.3%), NNT 33, Cox proportional hazards, day 540.
	risk of death, 30.0% lower, RR 0.70, p = 0.03, treatment 61 of 710 (8.6%), control 86 of 707 (12.2%), NNT 28, day 90.
	risk of death/hospitalization, 3.0% lower, HR 0.97, p = 0.77, treatment 212 of 710 (29.9%), control 213 of 707 (30.1%), NNT 373, Cox proportional hazards, day 540.
	risk of no recovery, 7.4% lower, RR 0.93, p = 0.21, treatment 710, control 707, inverted to make RR<1 favor treatment, sustained recovery, day 90, primary outcome.

Prophylaxis

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

Al Jurdi, 12/31/2022, retrospective, USA, peer-reviewed, 6 authors.	**risk of death, 85.7% lower, RR 0.14, p = 0.25**, treatment 0 of 222 (0.0%), control 3 of 222 (1.4%), NNT 74, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 83.3% lower, RR 0.17, p = 0.12, treatment 1 of 222 (0.5%), control 6 of 222 (2.7%), NNT 44.
	risk of case, 65.6% lower, RR 0.34, p = 0.001, treatment 11 of 222 (5.0%), control 32 of 222 (14.4%), NNT 11.
Bes-Berlandier, 5/28/2024, retrospective, France, peer-reviewed, median age 51.0, 10 authors, study period March 2020 - April 2022.	**oxygen increase, ICU, or mortality, 10.0% higher, RR 1.10, p = 1.00**, treatment 3 of 14 (21.4%), control 15 of 77 (19.5%).
Desai, 9/6/2023, retrospective, USA, peer-reviewed, 4 authors, study period 1 January, 2022 - 28 October, 2022.	**risk of hospitalization, 12.0% lower, OR 0.88, p = 0.81**, treatment 391, control 391, RR approximated with OR.
	risk of case, 35.0% higher, OR 1.35, p = 0.18, treatment 391, control 391, RR approximated with OR.

Din, 8/8/2023, retrospective, USA, peer-reviewed, 24 authors, study period June 2020 - February 2022, excluded in exclusion analyses: unadjusted results with no group details.	risk of hospitalization, 19.0% lower, RR 0.81, $p = 0.77$, treatment 5 of 23 (21.7%), control 11 of 41 (26.8%), NNT 20.
Dluzynski, 5/21/2025, retrospective, USA, peer-reviewed, mean age 61.0, 9 authors, study period 5 January, 2022 - 14 December, 2022.	risk of case, 70.2% higher, RR 1.70, $p = 0.08$, treatment 70 of 471 (14.9%), control 11 of 126 (8.7%).
Kaminski, 10/31/2022, retrospective, France, peer-reviewed, 21 authors, study period 28 December, 2021 - 28 February, 2022.	risk of death, 92.4% lower, HR 0.08, $p = 0.07$, treatment 1 of 333 (0.3%), control 2 of 97 (2.1%), NNT 57, Cox proportional hazards.
	risk of ICU admission, 95.5% lower, HR 0.04, $p = 0.001$, treatment 2 of 333 (0.6%), control 6 of 97 (6.2%), NNT 18, Cox proportional hazards.
	risk of hospitalization, 95.4% lower, HR 0.05, $p = 0.001$, treatment 4 of 333 (1.2%), control 11 of 97 (11.3%), NNT 9.9, Cox proportional hazards.
	risk of symptomatic case, 98.9% lower, HR 0.01, $p = 0.001$, treatment 41 of 333 (12.3%), control 42 of 97 (43.3%), NNT 3.2, Cox proportional hazards.
Kertes, 7/29/2022, retrospective, Israel, peer-reviewed, 10 authors.	risk of death/hospitalization, 91.9% lower, RR 0.08, $p = 0.01$, treatment 1 of 825 (0.1%), control 63 of 4,299 (1.5%), NNT 74, adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of case, 47.1% lower, RR 0.53, $p = 0.01$, treatment 29 of 825 (3.5%), control 308 of 4,299 (7.2%), NNT 27, adjusted per study, odds ratio converted to relative risk, multivariable.
Levin, 4/20/2022, Double Blind Randomized Controlled Trial, placebo-controlled, multiple countries, peer-reviewed, 24 authors, study period 21 November, 2020 - 22 March, 2021, trial NCT04625725 (history) (PROVENT).	risk of death, 85.7% lower, RR 0.14, $p = 0.11$, treatment 0 of 3,441 (0.0%), control 2 of 1,731 (0.1%), NNT 866, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of symptomatic case, 82.1% lower, RR 0.18, $p < 0.001$, treatment 11 of 3,441 (0.3%), control 31 of 1,731 (1.8%), NNT 68, 6 months.
	risk of symptomatic case, 76.3% lower, RR 0.24, $p < 0.001$, treatment 8 of 3,441 (0.2%), control 17 of 1,731 (1.0%), NNT 133, median 83 days followup.
Levin (B), 12/8/2021, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, mean age 46.0, 21 authors, study period 2 December, 2020 - 19 March, 2021, trial NCT04625972 (history) (STORM CHASER).	risk of symptomatic case, 41.7% lower, RR 0.58, $p = 0.06$, treatment 27 of 749 (3.6%), control 23 of 372 (6.2%), NNT 39, extended data cutoff.
	risk of symptomatic case, 32.8% lower, RR 0.67, $p = 0.23$, treatment 23 of 749 (3.1%), control 17 of 372 (4.6%), NNT 67, primary outcome.
Najjar-Debbiny, 10/31/2022, retrospective, Israel, peer-reviewed, 5 authors.	risk of hospitalization, 59.0% lower, HR 0.41, $p = 0.02$, treatment 72 of 703 (10.2%), control 377 of 2,812 (13.4%), Cox proportional hazards.
	risk of case, 25.0% lower, HR 0.75, $p = 0.03$, treatment 72 of 703 (10.2%), control 377 of 2,812 (13.4%), NNT 32, Cox proportional hazards.

Ollila, 7/11/2022, retrospective, USA, peer-reviewed, 13 authors, study period February 2021 - February 2022.	risk of death, 75.5% lower, RR 0.24, $p = 0.32$, treatment 0 of 25 (0.0%), control 1 of 12 (8.3%), NNT 12, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of case, 90.2% lower, RR 0.10, $p = 0.03$, treatment 0 of 25 (0.0%), control 3 of 12 (25.0%), NNT 4.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
Sindu, 5/12/2023, retrospective, USA, peer-reviewed, median age 67.4, 7 authors, study period December 2021 - August 2022.	risk of death, 1.5% higher, HR 1.01, $p = 0.99$, treatment 2 of 17 (11.8%), control 2 of 17 (11.8%), propensity score matching, Cox proportional hazards.
	risk of mechanical ventilation, 95.8% higher, HR 1.96, $p = 0.58$, propensity score matching, Cox proportional hazards.
	risk of ICU admission, 209.6% higher, HR 3.10, $p = 0.33$, propensity score matching, Cox proportional hazards.
	risk of hospitalization, 53.2% lower, HR 0.47, $p = 0.17$, propensity score matching, Cox proportional hazards.
	risk of symptomatic case, 28.9% lower, RR 0.71, $p = 0.14$, treatment 24 of 203 (11.8%), control 57 of 343 (16.6%), NNT 21, unadjusted.
Solera, 3/31/2024, retrospective, Canada, peer-reviewed, median age 57.5, 12 authors.	risk of severe case, 25.6% lower, RR 0.74, $p = 0.48$, treatment 7 of 156 (4.5%), control 283 of 1,819 (15.6%), NNT 9.0, adjusted per study, odds ratio converted to relative risk, multivariable.
Young-Xu, 5/29/2022, retrospective, propensity score matching, USA, preprint, 10 authors.	risk of death, 64.0% lower, HR 0.36, $p = 0.004$, treatment 1,733, control 6,354.
	risk of death/hospitalization/cases, 69.0% lower, HR 0.31, $p < 0.001$, treatment 17 of 1,733 (1.0%), control 206 of 6,354 (3.2%), NNT 44.
	risk of hospitalization, 87.0% lower, HR 0.13, $p = 0.04$, treatment 1,733, control 6,354.
	risk of case, 66.0% lower, HR 0.34, $p = 0.03$, treatment 1,733, control 6,354.

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.

References

1. **Planas** et al., *Resistance of Omicron subvariants BA.2.75.2, BA.4.6 and BQ.1.1 to neutralizing antibodies*, bioRxiv, doi:10.1101/2022.11.17.516888.
2. **Haars** et al., *Prevalence of SARS-CoV-2 Omicron Sublineages and Spike Protein Mutations Conferring Resistance against Monoclonal Antibodies in a Swedish Cohort during 2022–2023*, Microorganisms, doi:10.3390/microorganisms11102417.
3. **Uraki** et al., *Antiviral efficacy against and replicative fitness of an XBB.1.9.1 clinical isolate*, iScience, doi:10.1016/j.isci.2023.108147.
4. **Pochtovyi** et al., *In Vitro Efficacy of Antivirals and Monoclonal Antibodies against SARS-CoV-2 Omicron Lineages XBB.1.9.1, XBB.1.9.3, XBB.1.5, XBB.1.16, XBB.2.4, BQ.1.1.45, CH.1.1, and CL.1*, Vaccines, doi:10.3390/vaccines11101533.
5. **Focosi** et al., *Analysis of SARS-CoV-2 mutations associated with resistance to therapeutic monoclonal antibodies that emerge after treatment*, Drug Resistance Updates, doi:10.1016/j.drup.2023.100991.
6. **Leducq** et al., *Spike protein genetic evolution in patients at high-risk of severe COVID-19 treated by monoclonal antibodies*, The Journal of Infectious Diseases, doi:10.1093/infdis/jiad523.
7. **Bruhn** et al., *Somatic hypermutation shapes the viral escape profile of SARS-CoV-2 neutralising antibodies*, eBioMedicine, doi:10.1016/j.ebiom.2025.105770.
8. **Choudhary** et al., *Emergence of SARS-CoV-2 Resistance with Monoclonal Antibody Therapy*, medRxiv, doi:10.1101/2021.09.03.21263105.
9. **Günther** et al., *Variant-specific humoral immune response to SARS-CoV-2 escape mutants arising in clinically severe, prolonged infection*, medRxiv, doi:10.1101/2024.01.06.24300890.
10. **Casadevall** et al., *Single monoclonal antibodies should not be used for COVID-19 therapy: a call for antiviral stewardship*, Clinical Infectious Diseases, doi:10.1093/cid/ciae408.
11. **Soeroto** et al., *Efficacy and safety of tixagevimab-cilgavimab as pre-exposure prophylaxis for COVID-19: A systematic review and meta-analysis*, Reviews in Medical Virology, doi:10.1002/rmv.2420.
12. **Ryu** et al., *Fibrin drives thromboinflammation and neuropathology in COVID-19*, Nature, doi:10.1038/s41586-024-07873-4.
13. **Rong** et al., *Persistence of spike protein at the skull-meninges-brain axis may contribute to the neurological sequelae of COVID-19*, Cell Host & Microbe, doi:10.1016/j.chom.2024.11.007.
14. **Yang** et al., *SARS-CoV-2 infection causes dopaminergic neuron senescence*, Cell Stem Cell, doi:10.1016/j.stem.2023.12.012.
15. **Scardua-Silva** et al., *Microstructural brain abnormalities, fatigue, and cognitive dysfunction after mild COVID-19*, Scientific Reports, doi:10.1038/s41598-024-52005-7.
16. **Hampshire** et al., *Cognition and Memory after Covid-19 in a Large Community Sample*, New England Journal of Medicine, doi:10.1056/NEJMoa2311330.
17. **Duloquin** et al., *Is COVID-19 Infection a Multiorganic Disease? Focus on Extrapulmonary Involvement of SARS-CoV-2*, Journal of Clinical Medicine, doi:10.3390/jcm13051397.
18. **Sodagar** et al., *Pathological Features and Neuroinflammatory Mechanisms of SARS-CoV-2 in the Brain and Potential Therapeutic Approaches*, Biomolecules, doi:10.3390/biom12070971.
19. **Sagar** et al., *COVID-19-associated cerebral microbleeds in the general population*, Brain Communications, doi:10.1093/braincomms/fcae127.
20. **Verma** et al., *Persistent Neurological Deficits in Mouse PASC Reveal Antiviral Drug Limitations*, bioRxiv, doi:10.1101/2024.06.02.596989.
21. **Panagea** et al., *Neurocognitive Impairment in Long COVID: A Systematic Review*, Archives of Clinical Neuropsychology, doi:10.1093/arclin/acae042.
22. **Ariza** et al., *COVID-19: Unveiling the Neuropsychiatric Maze—From Acute to Long-Term Manifestations*, Biomedicines, doi:10.3390/biomedicines12061147.
23. **Vashisht** et al., *Neurological Complications of COVID-19: Unraveling the Pathophysiological Underpinnings and Therapeutic Implications*, Viruses, doi:10.3390/v16081183.
24. **Ahmad** et al., *Neurological Complications and Outcomes in Critically Ill Patients With COVID-19: Results From International Neurological Study Group From the COVID-19 Critical Care Consortium*, The Neurohospitalist, doi:10.1177/19418744241292487.
25. **Wang** et al., *SARS-CoV-2 membrane protein induces neurodegeneration via affecting Golgi-mitochondria interaction*, Translational Neurodegeneration, doi:10.1186/s40035-024-00458-1.
26. **Eberhardt** et al., *SARS-CoV-2 infection triggers pro-atherogenic inflammatory responses in human coronary vessels*, Nature Cardiovascular Research, doi:10.1038/s44161-023-00336-5.
27. **Van Tin** et al., *Spike Protein of SARS-CoV-2 Activates Cardiac Fibrogenesis through NLRP3 Inflammasomes and NF-κB Signaling*, Cells, doi:10.3390/cells13161331.
28. **Borka Balas** et al., *COVID-19 and Cardiac Implications—Still a Mystery in Clinical Practice*, Reviews in Cardiovascular Medicine, doi:10.31083/j.rcm2405125.
29. **AlTaweel** et al., *An In-Depth Insight into Clinical, Cellular and Molecular Factors in COVID19-Associated Cardiovascular Ailments for Identifying Novel Disease Biomarkers, Drug Targets and Clinical Management Strategies*, Archives of Microbiology & Immunology, doi:10.26502/ami.936500177.
30. **Saha** et al., *COVID-19 beyond the lungs: Unraveling its vascular impact and cardiovascular complications—mechanisms and therapeutic implications*, Science Progress, doi:10.1177/00368504251322069.

31. **Trender** et al., *Changes in memory and cognition during the SARS-CoV-2 human challenge study*, eClinicalMedicine, doi:10.1016/j.eclinm.2024.102842.

32. **Dugied** et al., *Multimodal SARS-CoV-2 interactome sketches the virus-host spatial organization*, Communications Biology, doi:10.1038/s42003-025-07933-z.

33. **Malone** et al., *Structures and functions of coronavirus replication–transcription complexes and their relevance for SARS-CoV-2 drug design*, Nature Reviews Molecular Cell Biology, doi:10.1038/s41580-021-00432-z.

34. **Murigneux** et al., *Proteomic analysis of SARS-CoV-2 particles unveils a key role of G3BP proteins in viral assembly*, Nature Communications, doi:10.1038/s41467-024-44958-0.

35. **Lv** et al., *Host proviral and antiviral factors for SARS-CoV-2*, Virus Genes, doi:10.1007/s11262-021-01869-2.

36. **Lui** et al., *Nsp1 facilitates SARS-CoV-2 replication through calcineurin-NFAT signaling*, Virology, doi:10.1128/mbio.00392-24.

37. **Niarakis** et al., *Drug-target identification in COVID-19 disease mechanisms using computational systems biology approaches*, Frontiers in Immunology, doi:10.3389/fimmu.2023.1282859.

38. **Katiyar** et al., *SARS-CoV-2 Assembly: Gaining Infectivity and Beyond*, Viruses, doi:10.3390/v16111648.

39. **Wu** et al., *Decoding the genome of SARS-CoV-2: a pathway to drug development through translation inhibition*, RNA Biology, doi:10.1080/15476286.2024.2433830.

40. **c19early.org**, c19early.org/treatments.html.

41. **Hattab** et al., *SARS-CoV-2 journey: from alpha variant to omicron and its sub-variants*, Infection, doi:10.1007/s15010-024-02223-y.

42. **Focosi (B)**, D., *Monoclonal Antibody Therapies Against SARS-CoV-2: Promises and Realities*, Current Topics in Microbiology and Immunology, doi:10.1007/82_2024_268.

43. **Zhang** et al., *Virological Traits of the SARS-CoV-2 BA.2.87.1 Lineage*, Vaccines, doi:10.3390/vaccines12050487.

44. **Davis** et al., *The Promise and Peril of Anti-SARS-CoV-2 Monoclonal Antibodies*, Clinical Infectious Diseases, doi:10.1093/cid/ciac902.

45. **Zeraatkar** et al., *Consistency of covid-19 trial preprints with published reports and impact for decision making: retrospective review*, BMJ Medicine, doi:10.1136/bmjmed-2022-0003091.

46. **Davidson** et al., *No evidence of important difference in summary treatment effects between COVID-19 preprints and peer-reviewed publications: a meta-epidemiological study*, Journal of Clinical Epidemiology, doi:10.1016/j.jclinepi.2023.08.011.

47. **Jadad** et al., *Randomized Controlled Trials: Questions, Answers, and Musings, Second Edition*, doi:10.1002/9780470691922.

48. **Gøtzsche**, P., *Bias in double-blind trials*, Doctoral Thesis, University of Copenhagen, www.scientificfreedom.dk/2023/05/16/bias-in-double-blind-trials-doctoral-thesis/.

49. **Als-Nielsen** et al., *Association of Funding and Conclusions in Randomized Drug Trials*, JAMA, doi:10.1001/jama.290.7.921.

50. **c19early.org (B)**, c19early.org/tcsupp.html#fig_rctobs.

51. **Concato** et al., NEJM, 342:1887-1892, doi:10.1056/NEJM200006223422507.

52. **Anglemyer** et al., *Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials*, Cochrane Database of Systematic Reviews 2014, Issue 4, doi:10.1002/14651858.MR000034.pub2.

53. **c19early.org (C)**, c19early.org/rctobs.html.

54. **Lee** et al., *Analysis of Overall Level of Evidence Behind Infectious Diseases Society of America Practice Guidelines*, Arch Intern Med., 2011, 171:1, 18-22, doi:10.1001/archinternmed.2010.482.

55. **Deaton** et al., *Understanding and misunderstanding randomized controlled trials*, Social Science & Medicine, 210, doi:10.1016/j.socscimed.2017.12.005.

56. **Nichol** et al., *Challenging issues in randomised controlled trials*, Injury, 2010, doi: 10.1016/j.injury.2010.03.033, www.injuryjournal.com/article/S0020-1383(10)00233-0/fulltext.

57. **Din** et al., *COVID-19 infection among CAR-T cell therapy recipients: A single center experience*, Hemasphere, doi:10.1097/01.HS9.0000973036.97124.6c.

58. **Lombardi** et al., *Preliminary Evidence of Good Safety Profile and Outcomes of Early Treatment With Tixagevimab/Cilgavimab Compared to Previously Employed Monoclonal Antibodies for COVID-19 in Immunocompromised Patients*, Preprints, doi:10.20944/preprints202301.0359.v1.

59. **Treanor** et al., *Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza: A Randomized Controlled Trial*, JAMA, 2000, 283:8, 1016-1024, doi:10.1001/jama.283.8.1016.

60. **McLean** et al., *Impact of Late Oseltamivir Treatment on Influenza Symptoms in the Outpatient Setting: Results of a Randomized Trial*, Open Forum Infect. Dis. September 2015, 2:3, doi:10.1093/ofid/ofv100.

61. **Ikematsu** et al., *Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts*, New England Journal of Medicine, doi:10.1056/NEJMoa1915341.

62. **Hayden** et al., *Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents*, New England Journal of Medicine, doi:10.1056/NEJMoa1716197.

63. **Kumar** et al., *Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza (FLAGSTONE): a randomised, parallel-group, double-blind, placebo-controlled, superiority trial*, The Lancet Infectious Diseases, doi:10.1016/S1473-3099(21)00469-2.

64. **López-Medina** et al., *Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial*, JAMA, doi:10.1001/jama.2021.3071.

65. **Korves** et al., *SARS-CoV-2 Genetic Variants and Patient Factors Associated with Hospitalization Risk*, medRxiv, doi:10.1101/2024.03.08.24303818.

66. **Faria** et al., *Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil*, Science, doi:10.1126/science.abh2644.

67. **Nonaka** et al., *SARS-CoV-2 variant of concern P.1 (Gamma) infection in young and middle-aged patients admitted to the intensive care units of a single hospital in Salvador, Northeast Brazil, February 2021*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2021.08.003.

68. **Karita** et al., *Trajectory of viral load in a prospective population-based cohort with incident SARS-CoV-2 G614 infection*, medRxiv, doi:10.1101/2021.08.27.21262754.

69. **Zavascki** et al., *Advanced ventilatory support and mortality in hospitalized patients with COVID-19 caused by Gamma (P.1) variant of concern compared to other lineages: cohort study at a reference center in Brazil*, Research Square, doi:10.21203/rs.3.rs-910467/v1.

70. **Willett** et al., *The hyper-transmissible SARS-CoV-2 Omicron variant exhibits significant antigenic change, vaccine escape and a switch in cell entry mechanism*, medRxiv, doi:10.1101/2022.01.03.21268111.

71. **Peacock** et al., *The SARS-CoV-2 variant, Omicron, shows rapid replication in human primary nasal epithelial cultures and efficiently uses the endosomal route of entry*, bioRxiv, doi:10.1101/2021.12.31.474653.

72. **Williams**, T., *Not All Ivermectin Is Created Equal: Comparing The Quality of 11 Different Ivermectin Sources*, Do Your Own Research, doyourownresearch.substack.com/p/not-all-ivermectin-is-created-equal.

73. **Xu** et al., *A study of impurities in the repurposed COVID-19 drug hydroxychloroquine sulfate by UHPLC-Q/TOF-MS and LC-SPE-NMR*, Rapid Communications in Mass Spectrometry, doi:10.1002/rcm.9358.

74. **Jitobaom** et al., *Favipiravir and Ivermectin Showed in Vitro Synergistic Antiviral Activity against SARS-CoV-2*, Research Square, doi:10.21203/rs.3.rs-941811/v1.

75. **Jitobaom (B)** et al., *Synergistic anti-SARS-CoV-2 activity of repurposed anti-parasitic drug combinations*, BMC Pharmacology and Toxicology, doi:10.1186/s40360-022-00580-8.

76. **Jeffreys** et al., *Remdesivir-ivermectin combination displays synergistic interaction with improved in vitro activity against SARS-CoV-2*, International Journal of Antimicrobial Agents, doi:10.1016/j.ijantimicag.2022.106542.

77. **Ostrov** et al., *Highly Specific Sigma Receptor Ligands Exhibit Anti-Viral Properties in SARS-CoV-2 Infected Cells*, Pathogens, doi:10.3390/pathogens10111514.

78. **Alsaidi** et al., *Griffithsin and Carrageenan Combination Results in Antiviral Synergy against SARS-CoV-1 and 2 in a Pseudoviral Model*, Marine Drugs, doi:10.3390/md19080418.

79. **Andreani** et al., *In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect*, Microbial Pathogenesis, doi:10.1016/j.micpath.2020.104228.

80. **De Forni** et al., *Synergistic drug combinations designed to fully suppress SARS-CoV-2 in the lung of COVID-19 patients*, PLoS ONE, doi:10.1371/journal.pone.0276751.

81. **Wan** et al., *Synergistic inhibition effects of andrographolide and baicalin on coronavirus mechanisms by downregulation of ACE2 protein level*, Scientific Reports, doi:10.1038/s41598-024-54722-5.

82. **Said** et al., *The effect of Nigella sativa and vitamin D3 supplementation on the clinical outcome in COVID-19 patients: A randomized controlled clinical trial*, Frontiers in Pharmacology, doi:10.3389/fphar.2022.1011522.

83. **Fiaschi** et al., *In Vitro Combinatorial Activity of Direct Acting Antivirals and Monoclonal Antibodies against the Ancestral B.1 and BQ.1.1 SARS-CoV-2 Viral Variants*, Viruses, doi:10.3390/v16020168.

84. **Xing** et al., *Published anti-SARS-CoV-2 in vitro hits share common mechanisms of action that synergize with antivirals*, Briefings in Bioinformatics, doi:10.1093/bib/bbab249.

85. **Chen** et al., *Synergistic Inhibition of SARS-CoV-2 Replication Using Disulfiram/Ebselen and Remdesivir*, ACS Pharmacology & Translational Science, doi:10.1021/acsptsci.1c00022.

86. **Hempel** et al., *Synergistic inhibition of SARS-CoV-2 cell entry by otamixaban and covalent protease inhibitors: pre-clinical assessment of pharmacological and molecular properties*, Chemical Science, doi:10.1039/D1SC01494C.

87. **Schultz** et al., *Pyrimidine inhibitors synergize with nucleoside analogues to block SARS-CoV-2*, Nature, doi:10.1038/s41586-022-04482-x.

88. **Ohashi** et al., *Potential anti-COVID-19 agents, cepharanthine and nelfinavir, and their usage for combination treatment*, iScience, doi:10.1016/j.isci.2021.102367.

89. **Al Krad** et al., *The protease inhibitor Nirmatrelvir synergizes with inhibitors of GRP78 to suppress SARS-CoV-2 replication*, bioRxiv, doi:10.1101/2025.03.09.642200.

90. **Thairu** et al., *A Comparison of Ivermectin and Non Ivermectin Based Regimen for COVID-19 in Abuja: Effects on Virus Clearance, Days-to-discharge and Mortality*, Journal of Pharmaceutical Research International, doi:10.9734/jpri/2022/v34i44A36328.

91. **Singh** et al., *The relationship between viral clearance rates and disease progression in early symptomatic COVID-19: a systematic review and meta-regression analysis*, Journal of Antimicrobial Chemotherapy, doi:10.1093/jac/dkae045.

92. **Rothstein**, H., *Publication Bias in Meta-Analysis: Prevention, Assessment and Adjustments*, www.wiley.com/en-ae/Publication+Bias+in+Meta+Analysis:+Prevention,+Assessment+and+Adjustments-p-9780470870143.

93. **Stanley** et al., *Meta-regression approximations to reduce publication selection bias*, Research Synthesis Methods, doi:10.1002/jrsm.1095.

94. **Rücker** et al., *Arcsine test for publication bias in meta-analyses with binary outcomes*, Statistics in Medicine, doi:10.1002/sim.2971.

95. **Peters**, J., *Comparison of Two Methods to Detect Publication Bias in Meta-analysis*, JAMA, doi:10.1001/jama.295.6.676.

96. **Moreno** et al., *Assessment of regression-based methods to adjust for publication bias through a comprehensive simulation study*, BMC Medical Research Methodology, doi:10.1186/1471-2288-9-2.

97. **Macaskill** et al., *A comparison of methods to detect publication bias in meta-analysis*, Statistics in Medicine, doi:10.1002/sim.698.

98. **Egger** et al., *Bias in meta-analysis detected by a simple, graphical test*, BMJ, doi:10.1136/bmj.315.7109.629.

99. **Harbord** et al., *A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints*, Statistics in Medicine, doi:10.1002/sim.2380.

100. **Vukovikj** et al., *Impact of SARS-CoV-2 variant mutations on susceptibility to monoclonal antibodies and antiviral drugs: a non-systematic review, April 2022 to October 2024*, Eurosurveillance, doi:10.2807/1560-7917.ES.2025.30.10.2400252.

101. **Enyeji** et al., *Effective Treatment of COVID-19 Infection with Repurposed Drugs: Case Reports*, Viral Immunology, doi:10.1089/vim.2024.0034.

102. **Keam**, S., *Tixagevimab + Cilgavimab: First Approval*, Drugs, doi:10.1007/s40265-022-01731-1.

103. **c19early.org (D)**, c19early.org/timeline.html.

104. **c19early.org (E)**, c19early.org/p.

105. **c19early.org (F)**, c19early.org/ph.

106. **c19early.org (G)**, c19early.org/d.

107. **Mourad** et al., *Long-term outcomes of passive immunotherapy for COVID-19: a pooled analysis of a large multinational platform randomized clinical trial*, Clinical Microbiology and Infection, doi:10.1016/j.cmi.2025.02.002.

108. **Mateja** et al., *The choice of viral load endpoint in early phase trials of COVID-19 treatments aiming to reduce 28-day hospitalization and/or death*, The Journal of Infectious Diseases, doi:10.1093/infdis/jiaf282.

109. **Zhang (B)** et al., *What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes*, JAMA, 80:19, 1690, doi:10.1001/jama.280.19.1690.

110. **Altman**, D., *How to obtain the P value from a confidence interval*, BMJ, doi:10.1136/bmj.d2304.

111. **Altman (B)** et al., *How to obtain the confidence interval from a P value*, BMJ, doi:10.1136/bmj.d2090.

112. **Sweeting** et al., *What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data*, Statistics in Medicine, doi:10.1002/sim.1761.

113. **Deng**, H., *PyMeta, Python module for meta-analysis*, www.pymeta.com/.

114. **Montgomery** et al., *Efficacy and safety of intramuscular administration of tixagevimab–cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial*, The Lancet Respiratory Medicine, doi:10.1016/S2213-2600(22)00180-1.

115. **Chua** et al., *Evaluating the use of Monoclonal Antibodies - Sotrovimab, Casirivimab/Imedvimab (REGEN-COV) and Tixagevimab/Cilgavimab (EVUSHELD) for COVID-19 Treatment in Singapore*, Open Forum Infectious Diseases, doi:10.1093/ofid/ofae631.2172.

116. **Hites** et al., *Tixagevimab-cilgavimab (AZD7442) for the treatment of patients hospitalized with COVID-19 (DisCoVeRy): a phase 3, randomized, double-blind, placebo-controlled trial*, Journal of Infection, doi:10.1016/j.jinf.2024.106120.

117. **Holland** et al., *Tixagevimab–cilgavimab for treatment of patients hospitalised with COVID-19: a randomised, double-blind, phase 3 trial*, The Lancet Respiratory Medicine, doi:10.1016/S2213-2600(22)00215-6.

118. **Al Jurdi** et al., *Tixagevimab/cilgavimab pre-exposure prophylaxis is associated with lower breakthrough infection risk in vaccinated solid organ transplant recipients during the omicron wave*, American Journal of Transplantation, doi:10.1111/ajt.17128.

119. **Bes-Berlandier** et al., *Management of immunosuppression in lung transplant recipients and COVID-19 outcomes: an observational retrospective cohort-study*, BMC Infectious Diseases, doi:10.1186/s12879-024-09269-1.

120. **Desai** et al., *Tixagevimab and Cilgavimab (Evusheld) as Pre-exposure Prophylaxis for COVID-19 in Patients With Inflammatory Bowel Disease: A Propensity Matched Cohort Study*, Crohn's & Colitis 360, doi:10.1093/crocol/otad047.

121. **Dluzynski** et al., *Dose-dependent impact of tixagevimab–cilgavimab as primary prevention against SARS-CoV-2 in immunocompromised individuals*, Scientific Reports, doi:10.1038/s41598-025-02240-3.

122. **Kaminski** et al., *COVID-19 morbidity decreases with tixagevimab–cilgavimab preexposure prophylaxis in kidney transplant recipient nonresponders or low-vaccine responders*, Kidney International, doi:10.1016/j.kint.2022.07.008.

123. **Kertes** et al., *Association between AZD7442 (tixagevimab-cilgavimab) administration and SARS-CoV-2 infection, hospitalization and mortality*, Clinical Infectious Diseases, doi:10.1093/cid/ciac625.

124. **Levin** et al., *Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of Covid-19*, New England Journal of Medicine, doi:10.1056/NEJMoa2116620.

125. **Levin (B)** et al., *AZD7442 (Tixagevimab/Cilgavimab) for Post-exposure Prophylaxis of Symptomatic COVID-19*, Clinical Infectious Diseases, doi:10.1093/cid/ciac899.

126. **Najjar-Debbiny** et al., *Effectiveness of Evusheld in Immunocompromised Patients: Propensity Score-Matched Analysis*, Clinical Infectious Diseases, doi:10.1093/cid/ciac855.

127. **Ollila** et al., *Seroconversion and outcomes after initial and booster COVID-19 vaccination in adults with hematologic malignancies*, Cancer, doi:10.1002/cncr.34354.

128. **Sindu** et al., *Pre-exposure Prophylaxis with Tixagevimab-cilgavimab did not Reduce Severity of COVID-19 in Lung Transplant Recipients with Breakthrough Infection*, Transplantation Direct, doi:10.1097/txd.0000000000001485.

129. **Solera** et al., *Longitudinal outcomes of COVID-19 in solid organ transplant recipients from 2020 to 2023*, American Journal of Transplantation, doi:10.1016/j.ajt.2024.03.011.

130. **Young-Xu** et al., *Tixagevimab/Cilgavimab for Prevention of COVID-19 during the Omicron Surge: Retrospective Analysis of National VA Electronic Data*, medRxiv, doi:10.1101/2022.05.28.22275716.