

Tixagevimab/cilgavimab for COVID-19: real-time meta analysis of 15 studies

@CovidAnalysis, March 2024, Version 24

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

Abstract

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

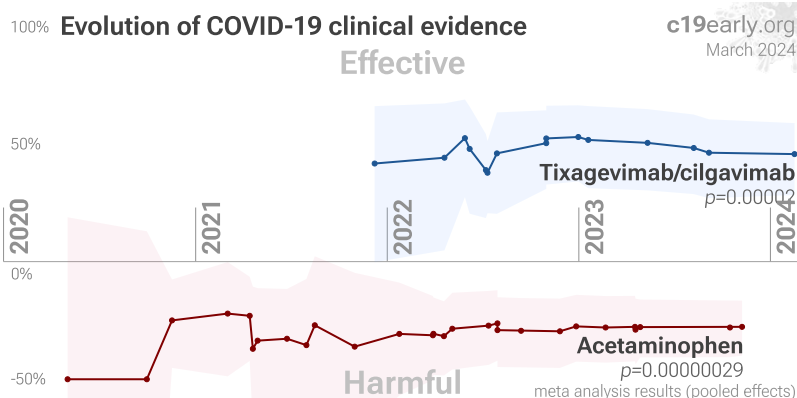
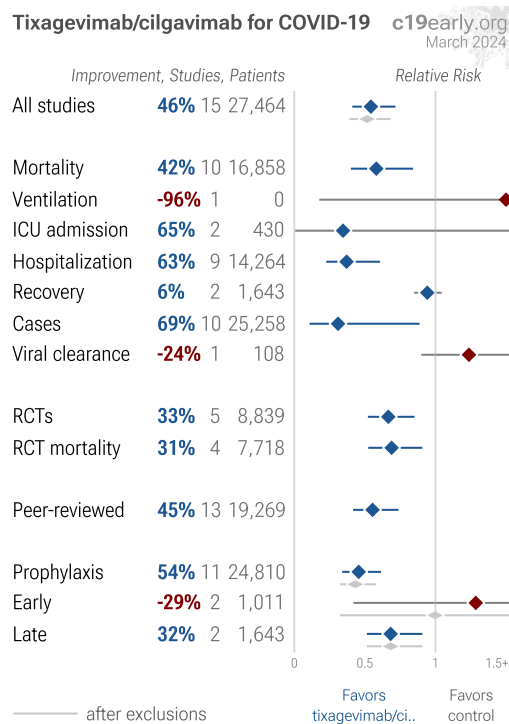
Meta analysis using the most serious outcome reported shows 46% [28-59%] lower risk. Results are similar for higher quality and peer-reviewed studies and slightly worse for Randomized Controlled Trials.

Results are robust — in exclusion sensitivity analysis 10 of 15 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 ^{Planas}, BA.5, BA.2.75, XBB ^{Haars}, XBB.1.9.1, XBB.1.9.3, XBB.1.5.24, XBB.1.16, XBB.2.9, BQ.1.1.45, CL.1, and CH.1.1 ^{Pochtovyi}. US EUA has been revoked. mAb use may create new variants that spread globally ^{Focosi}, ^{Leducq}, and may be associated with prolonged viral loads, clinical deterioration, and immune escape ^{Choudhary, Günther, Leducq}.

No treatment or intervention is 100% effective. All practical, effective, and safe means should be used based on risk/benefit analysis. Multiple treatments are typically used in combination, and other treatments may be more effective.

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



HIGHLIGHTS

Tixagevimab/cilgavimab reduces risk for COVID-19 with very high confidence for mortality, hospitalization, and in pooled analysis, and high confidence for cases, however increased risk is seen with very low confidence for ventilation and viral clearance. **Efficacy is variant dependent.**

Tixagevimab/cilgavimab was the 37th treatment shown effective with ≥ 3 clinical studies in May 2022, now known with $p = 0.00002$ from 15 studies, and recognized in 29 countries.

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

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

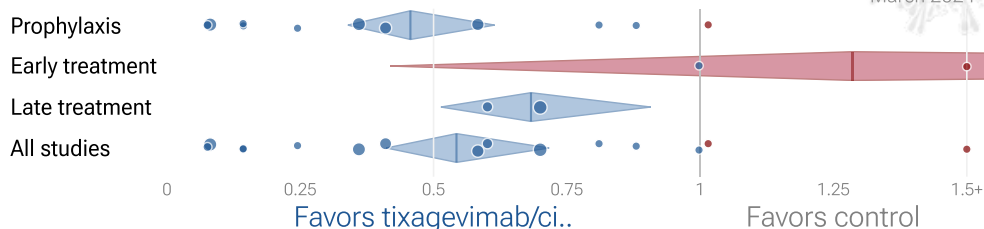
15 tixagevimab/cilgavimab COVID-19 studies

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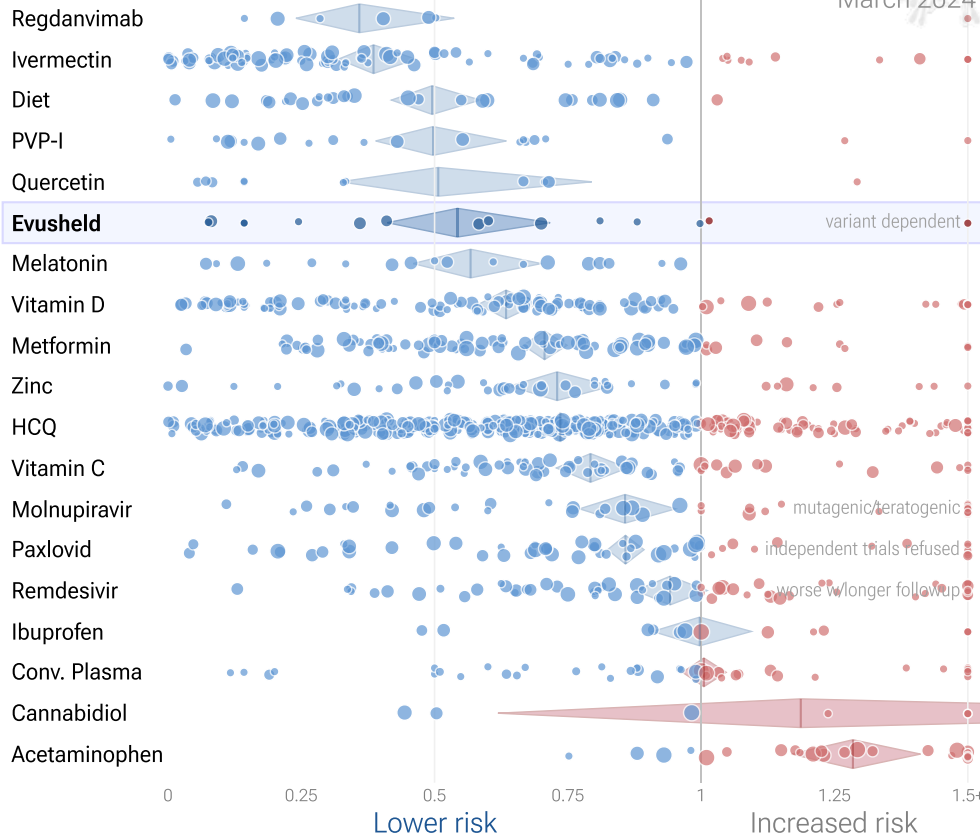
Efficacy in COVID-19 tixagevimab/cilgavimab studies (pooled effects)

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Efficacy in COVID-19 studies (pooled effects)

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Timeline of COVID-19 tixagevimab/cilgavimab studies (pooled effects)

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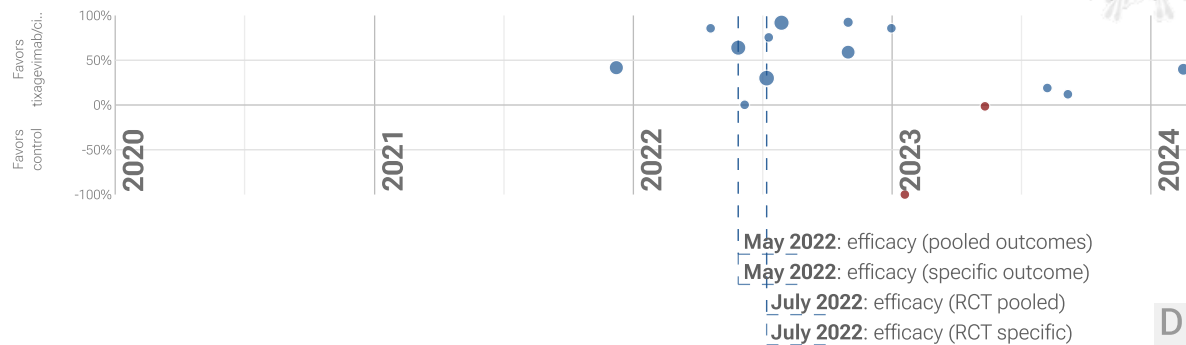


Figure 1. A. Random effects meta-analysis. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the [appendix](#). **B. Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis. **C. Results within the context of multiple COVID-19 treatments.** 0.6% of 6,686 proposed treatments show efficacy [c19early.org](#). **D. Timeline of results in tixagevimab/cilgavimab studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of $\geq 10\%$ from ≥ 3 studies for pooled outcomes, 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.

Introduction

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

Many treatments are expected to modulate infection. SARS-CoV-2 infection and replication involves the complex interplay of 50+ host and viral proteins and other factors [Note A, Malone, Murigneux, Lv, Lui](#), providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 6,000 compounds may reduce COVID-19 risk [c19early.org \(B\)](#), either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

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

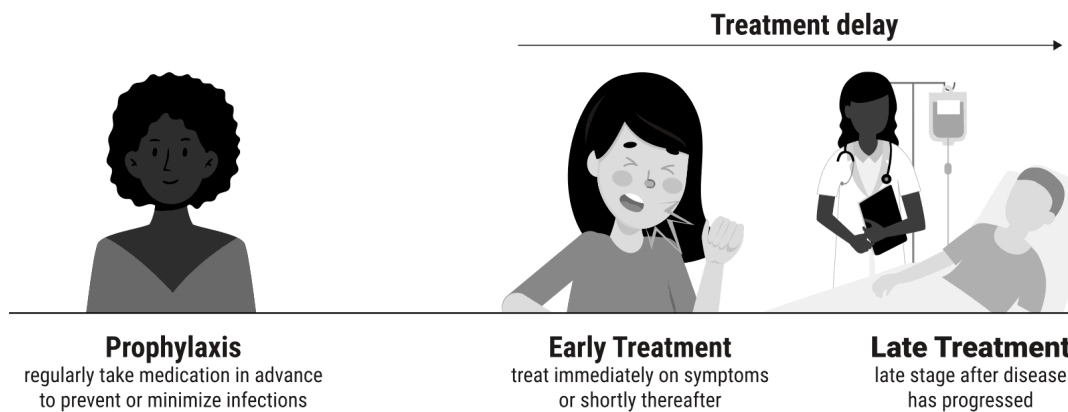


Figure 2. Treatment stages.

Variant Dependence

Efficacy is variant dependent, for example *in vitro* research suggests that tixagevimab/cilgavimab is not effective for omicron BA.4.6 and BQ.1.1 [Planas](#).

	<i>Bamlanivimab/ etesevimab</i>	<i>Casirivimab/ imdevimab</i>	<i>Sotrovimab</i>	<i>Bebtelovimab</i>	<i>Tixagevimab/ cilgavimab</i>
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* (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 3, 4, 5, 6, 7, 8, 9, 10, and 11 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, recovery, cases, viral clearance, and peer reviewed studies.

	<i>Improvement</i>	<i>Studies</i>	<i>Patients</i>	<i>Authors</i>
All studies	46% [28-59%] ****	15	27,464	375
After exclusions	48% [32-61%] ****	13	27,292	330
Peer-reviewed studies	45% [26-58%] ****	13	19,269	344
Randomized Controlled Trials	33% [15-48%] **	5	8,839	254
Mortality	42% [16-60%] **	10	16,858	311
ICU admission	65% [-2078-99%]	2	430	28
Hospitalization	63% [39-77%] ****	9	14,264	118
Recovery	6% [-4-15%]	2	1,643	189
Cases	69% [11-89%] *	10	25,258	121
RCT mortality	31% [9-48%] **	4	7,718	233

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 percentage improvement with treatment and the 95% confidence interval. * $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$ **** $p < 0.0001$.

	Early treatment	Late treatment	Prophylaxis
All studies	-29% [-295-58%]	32% [9-49%] **	54% [39-66%] ****
After exclusions	0% [-207-68%]	32% [9-49%] **	57% [42-68%] ****
Peer-reviewed studies	0% [-207-68%]	32% [9-49%] **	52% [31-67%] ****
Randomized Controlled Trials	0% [-207-68%]	32% [9-49%] **	44% [5-67%] *
Mortality	-29% [-295-58%]	32% [9-49%] **	67% [39-82%] ***
ICU admission			65% [-2078-99%]
Hospitalization	55% [24-74%] **		67% [35-83%] **
Recovery		6% [-4-15%]	
Cases			69% [11-89%] *
RCT mortality	0% [-207-68%]	32% [9-49%] **	86% [-198-99%]

Table 3. Random effects meta-analysis results by treatment stage. Results show the percentage improvement with treatment, the 95% confidence interval, and the number of studies for the stage. * $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$ **** $p < 0.0001$.

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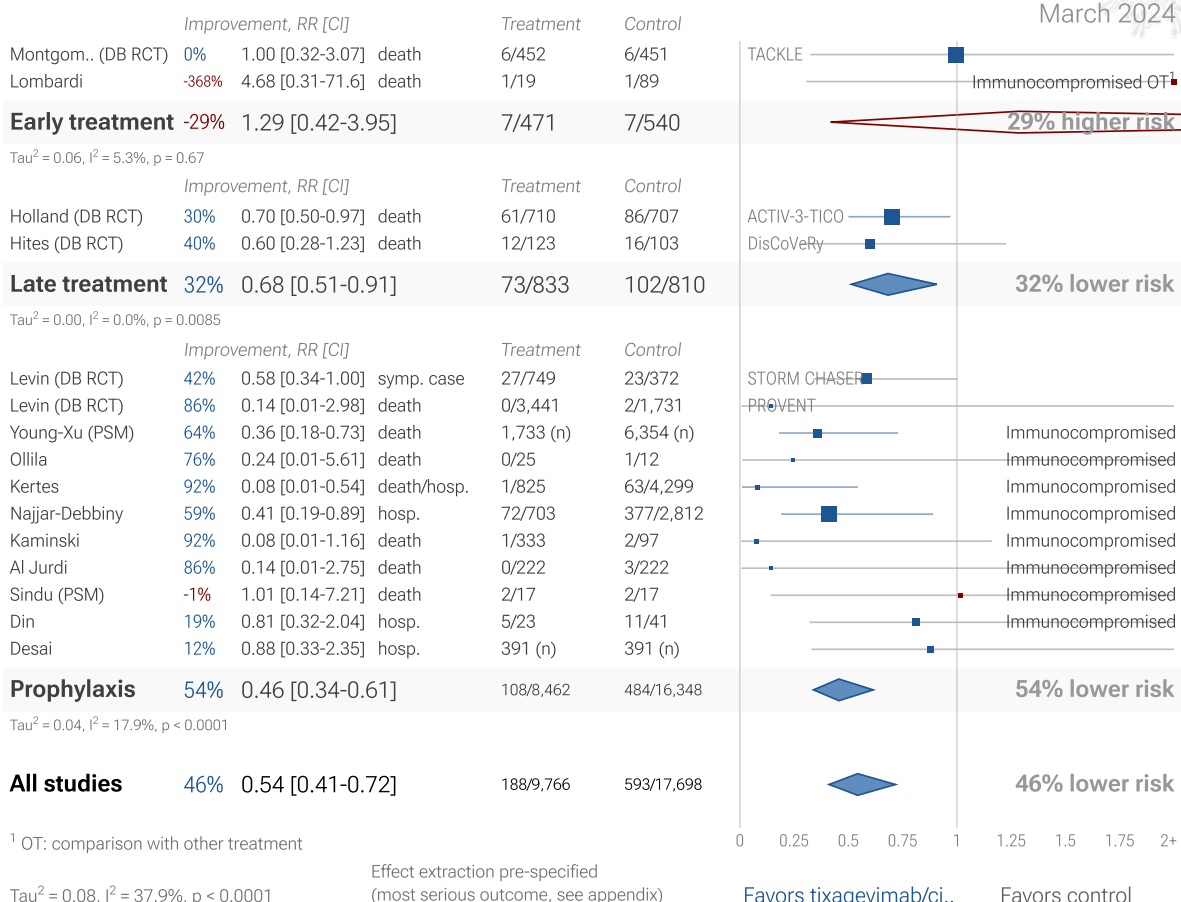


Figure 3. Random effects meta-analysis for all studies with pooled effects. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details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

10 tixagevimab/cilgavimab COVID-19 mortality results

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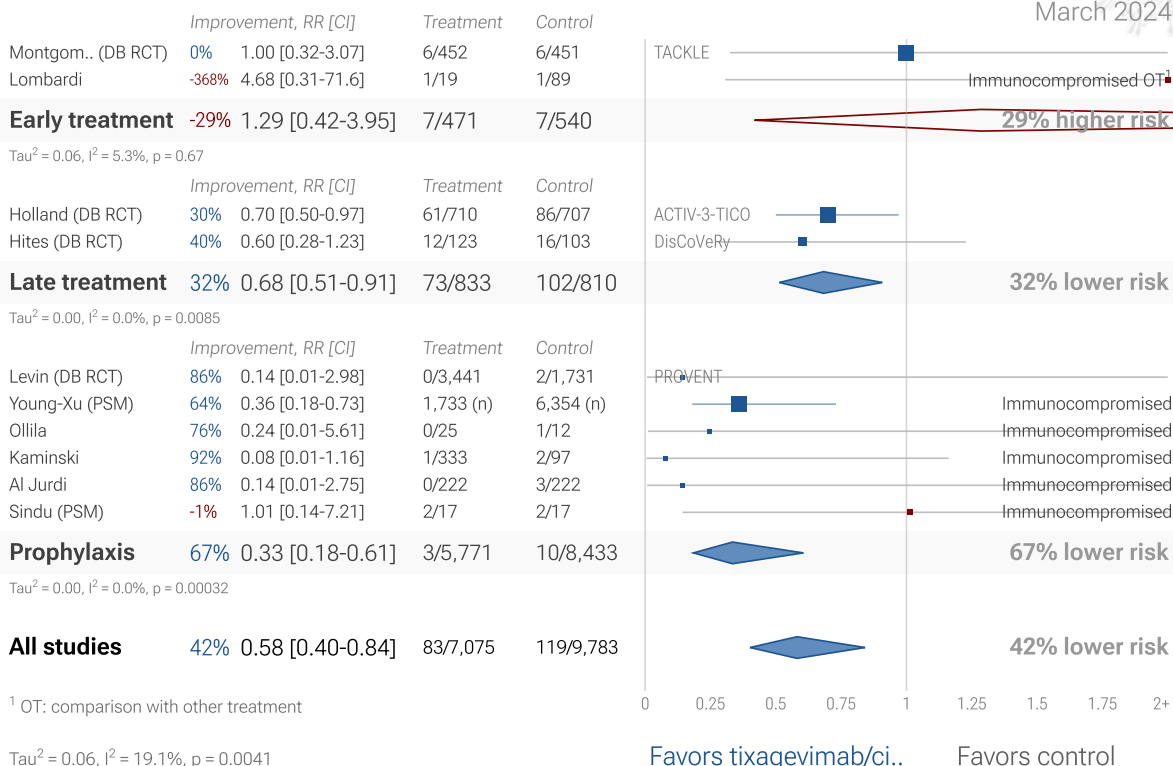


Figure 4. Random effects meta-analysis for mortality results.

1 tixagevimab/cilgavimab COVID-19 mechanical ventilation result

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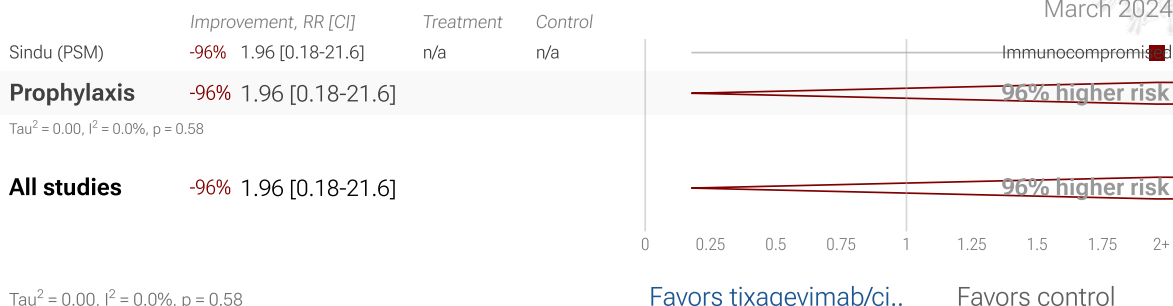


Figure 5. Random effects meta-analysis for ventilation.

2 tixagevimab/cilgavimab COVID-19 ICU results

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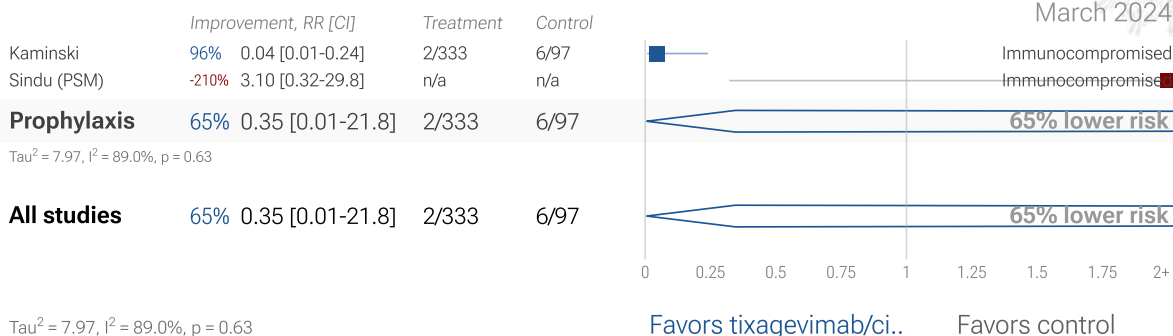


Figure 6. Random effects meta-analysis for ICU admission.

9 tixagevimab/cilgavimab COVID-19 hospitalization results

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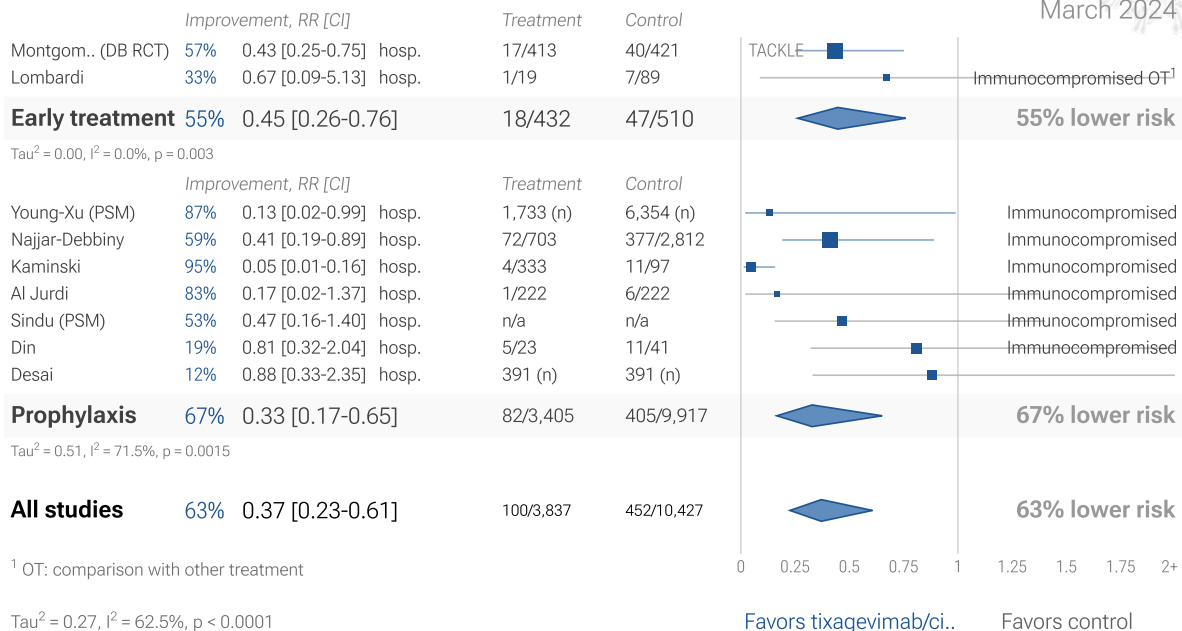


Figure 7. Random effects meta-analysis for hospitalization.

2 tixagevimab/cilgavimab COVID-19 recovery results

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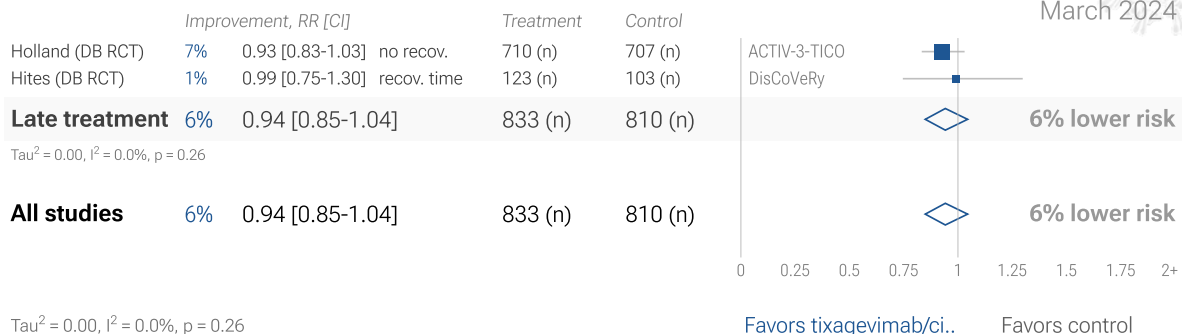


Figure 8. Random effects meta-analysis for recovery.

10 tixagevimab/cilgavimab COVID-19 case results

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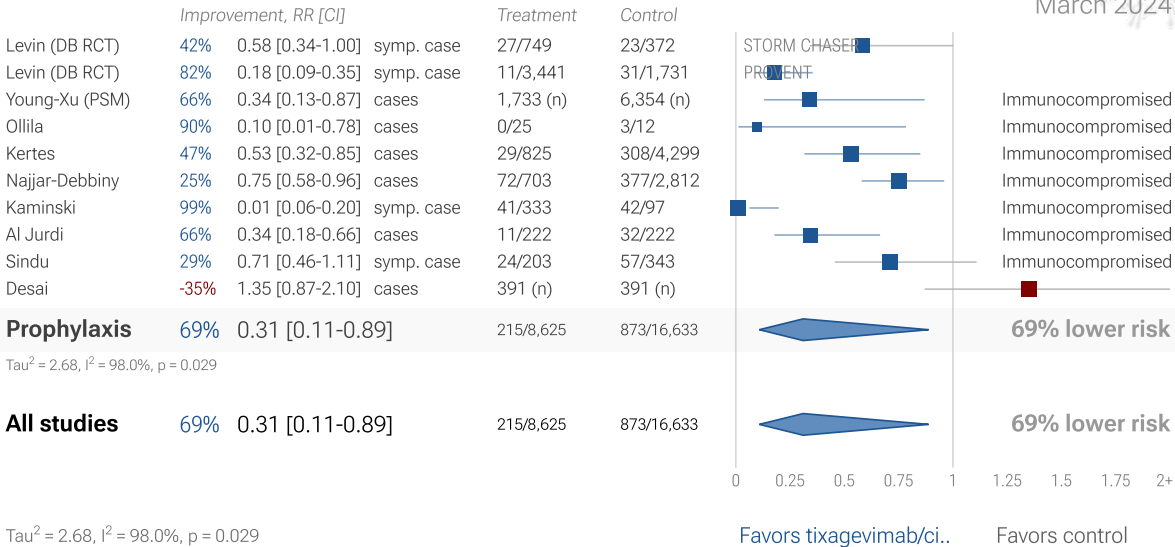


Figure 9. Random effects meta-analysis for cases.

1 tixagevimab/cilgavimab COVID-19 viral clearance result

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

13 tixagevimab/cilgavimab COVID-19 peer reviewed studies

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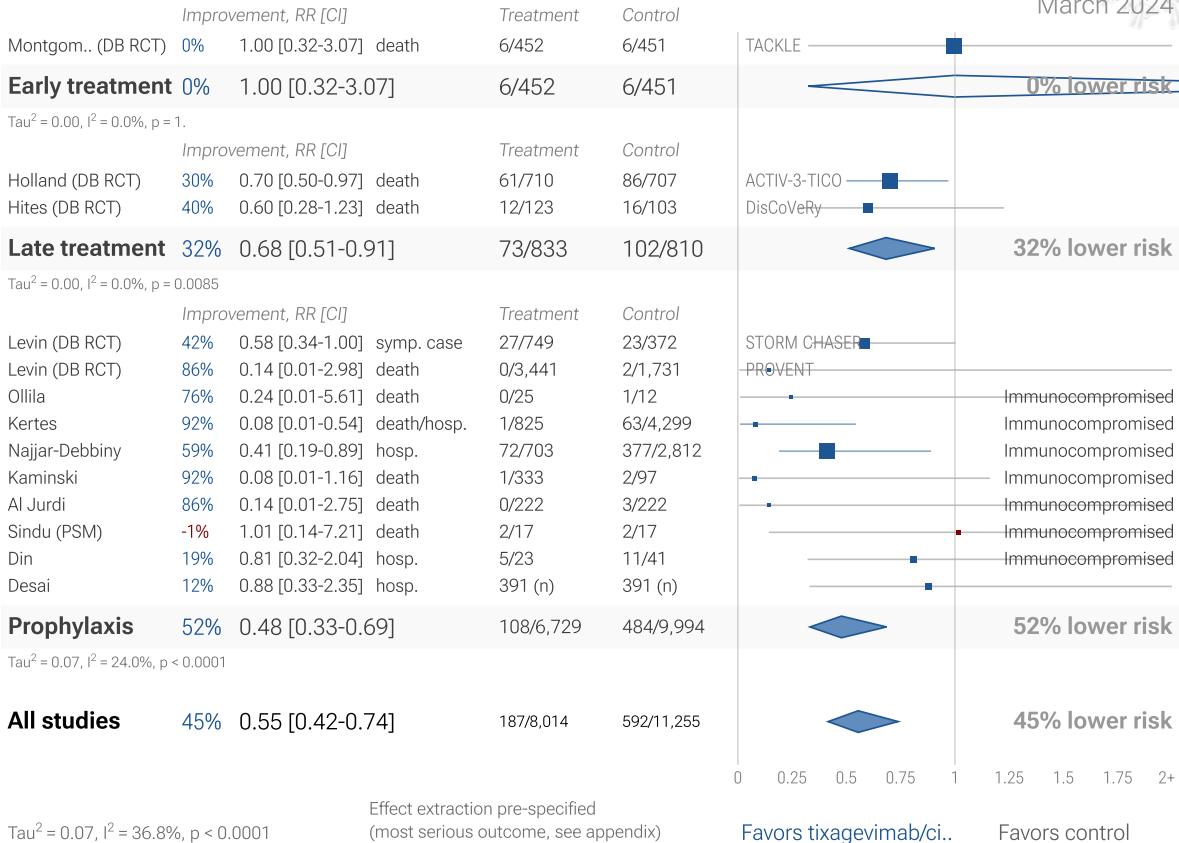


Figure 11. Random effects meta-analysis for peer reviewed studies. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Zeraatkar *et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. Davidson *et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

Randomized Controlled Trials (RCTs)

Figure 12 shows a comparison of results for RCTs and non-RCT studies. Figure 13 and 14 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.

RCTs have many potential biases. Bias in clinical research may be defined as something that tends to make conclusions differ systematically from the truth. RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases ^{Jadad}, and analysis of double-blind RCTs has identified extreme levels of bias ^{Gotzsche}. 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, 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 66 treatments we have analyzed, 63% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments (they may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration).

Non-RCT studies have been shown to be reliable. Evidence shows that non-RCT trials can also provide reliable results. *Concato et al.* found that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. *Anglemyer et al.* summarized reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. *Lee et al.* showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or Internet survey bias could have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see *Deaton, Nichol*.

Using all studies identifies efficacy 5.7+ months faster for COVID-19. Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as $\geq 10\%$ decreased risk or $>0\%$ increased risk from ≥ 3 studies. Of the 44 treatments with statistically significant efficacy/harm, 28 have been confirmed in RCTs, with a mean delay of 5.7 months. When considering only low cost treatments, 23 have been confirmed with a delay of 6.9 months. For the 16 unconfirmed treatments, 3 have zero RCTs to date. The point estimates for the remaining 13 are all consistent with the overall results (benefit or harm), with 10 showing $>20\%$. The only treatments showing $>10\%$ efficacy for all studies, but $<10\%$ for RCTs are sotrovimab and aspirin.

Summary. We need to evaluate each trial on its own merits. RCTs for a given medication and disease may be more reliable, however they may also be less reliable. For off-patent medications, very high conflict of interest trials may be more likely to be RCTs, and more likely to be large trials that dominate meta analyses.

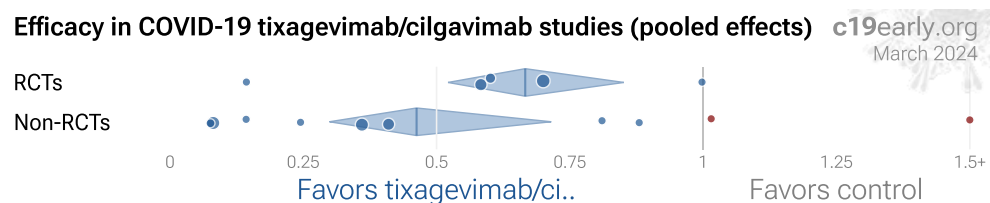


Figure 12. Results for RCTs and non-RCT studies.

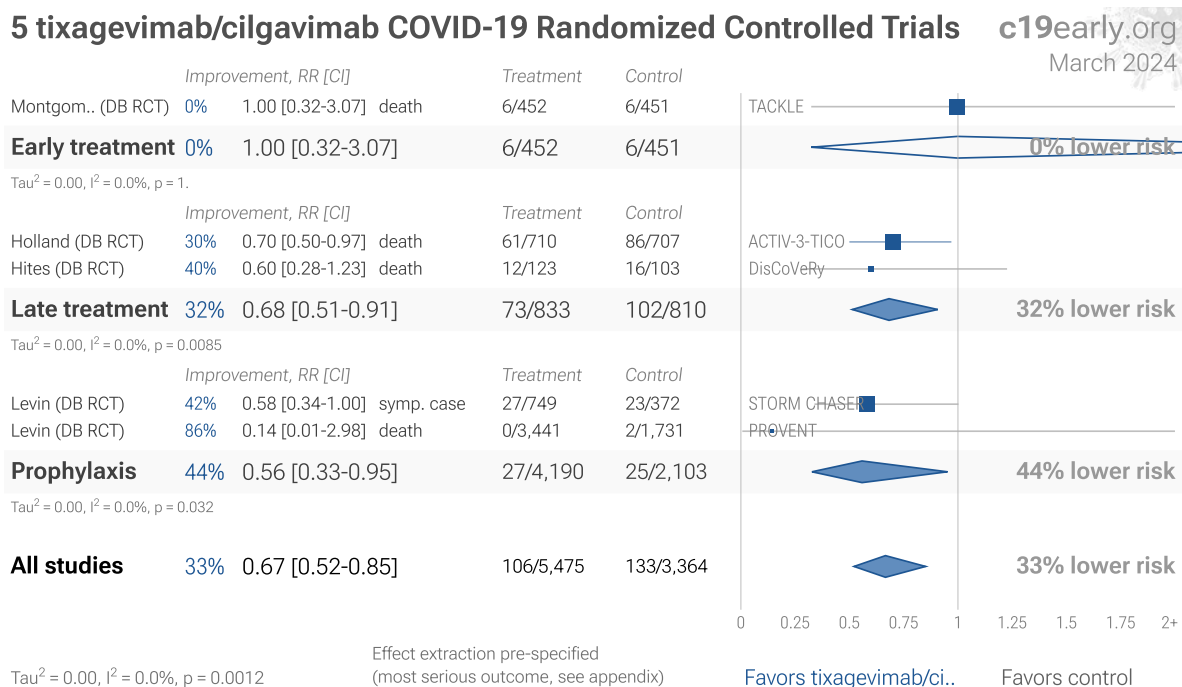


Figure 13. Random effects meta-analysis for all Randomized Controlled Trials. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

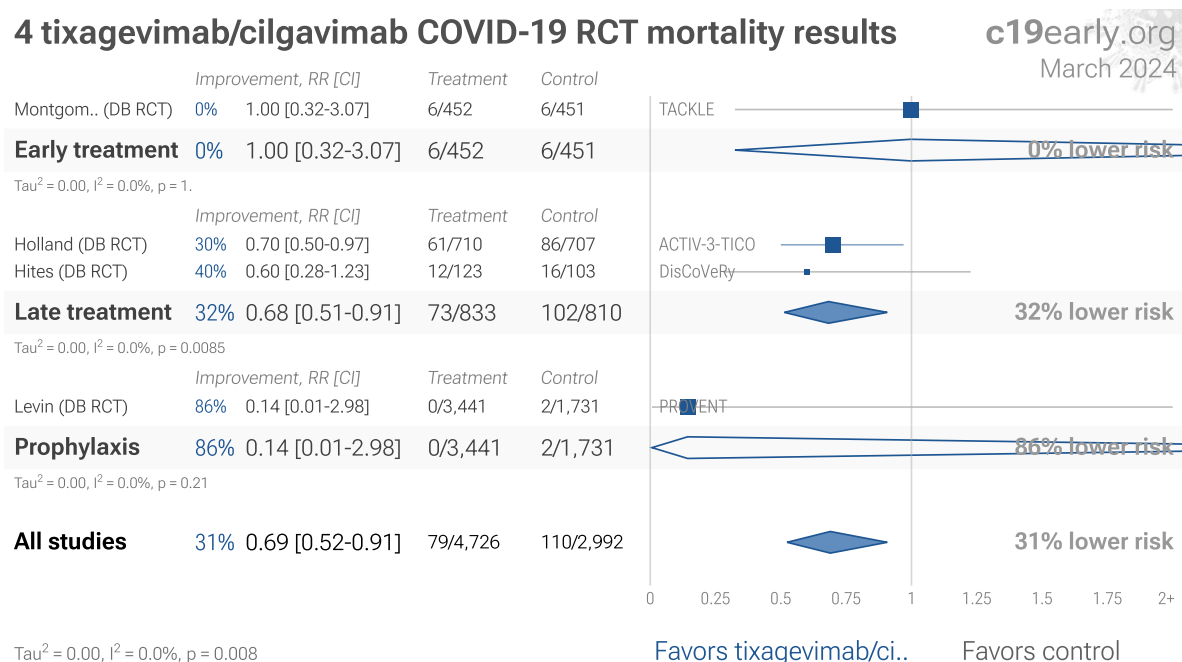


Figure 14. Random effects meta-analysis for RCT mortality results.

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 may underemphasize serious issues not captured in the checklists, overemphasize issues unlikely to alter outcomes in specific cases (for example, lack of blinding for an objective mortality outcome, or certain specifics of randomization with a very large effect size), and can be easily influenced by potential bias.

The studies excluded are as below. Figure 15 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.

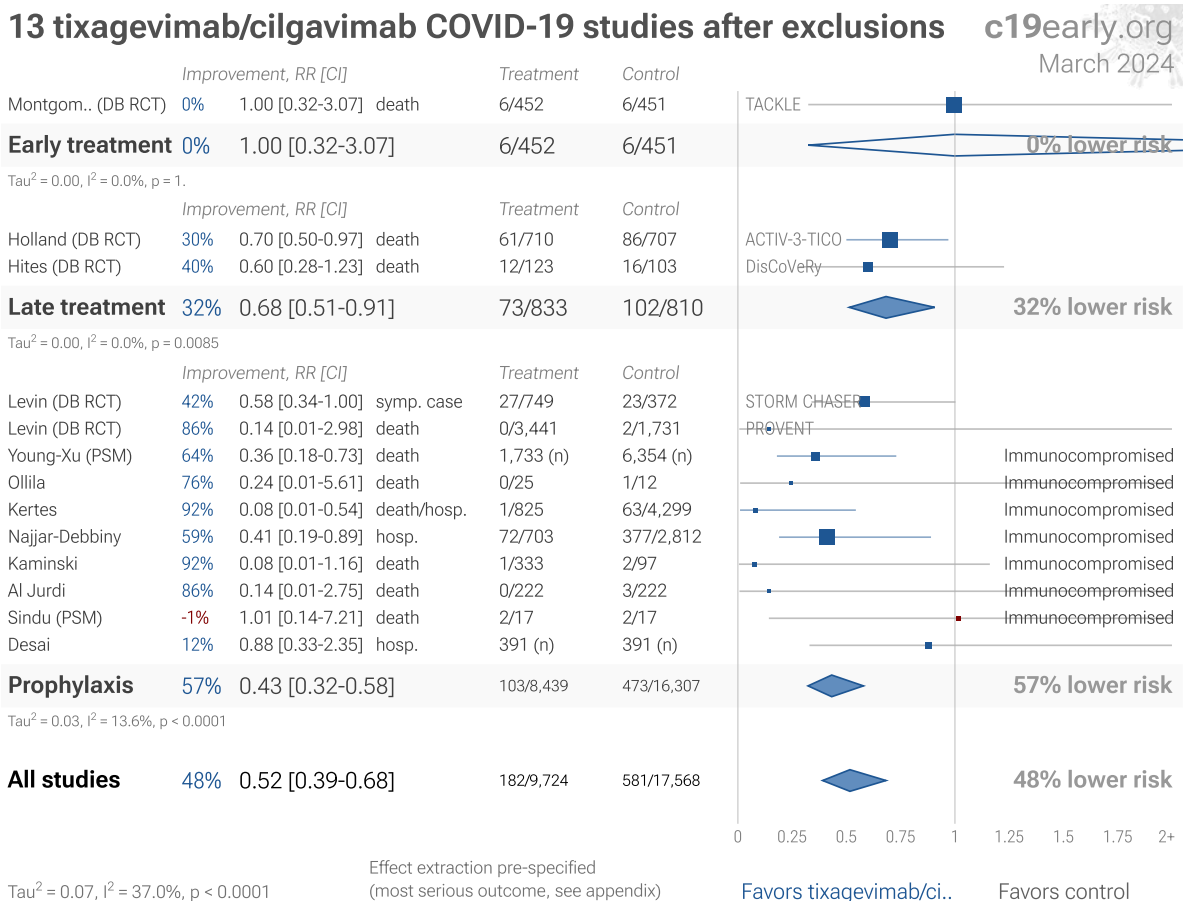


Figure 15. Random effects meta-analysis for all studies after exclusions. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

Heterogeneity

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

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

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

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

Figure 16 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 66 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

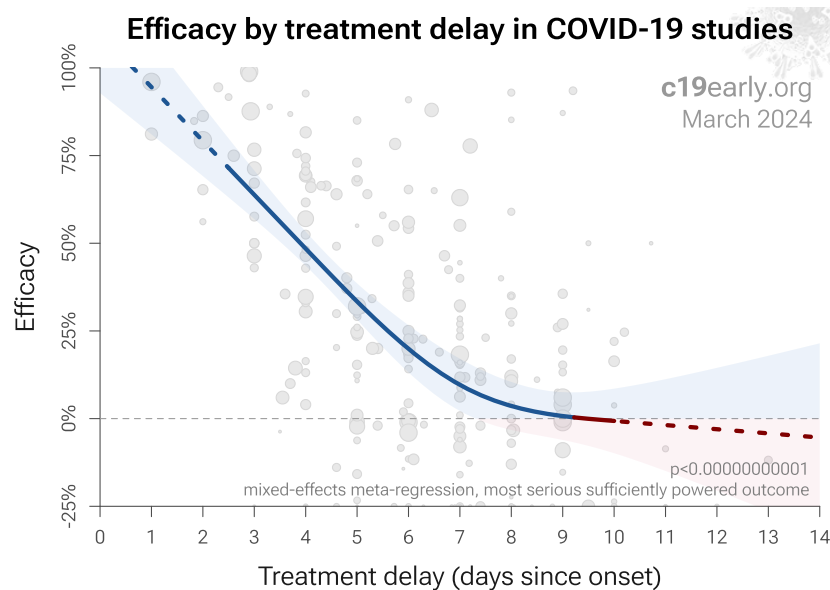


Figure 16. Early treatment is more effective. Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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

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

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

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

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

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

Pooled outcome analysis. We present both pooled analyses and specific outcome analyses. Notably, pooled analysis often results in earlier detection of efficacy as shown in Figure 17. For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, etc. An antiviral tested with a low-risk population may report zero mortality in both arms, however a reduction in severity and improved viral clearance may translate into lower mortality among a high-risk population, and including these results in pooled analysis allows faster detection of efficacy. Trials with high-risk patients may also be restricted due to ethical concerns for treatments that are known or expected to be effective.

Pooled analysis enables using more of the available information. While there is much more information available, for example dose-response relationships, the advantage of the method used here is simplicity and transparency. Note that pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral replication or early stage disease could show no efficacy in pooled analysis if most studies only examine viral clearance. While we present pooled results, we also present individual outcome analyses, which may be more informative for specific use cases.

Pooled outcomes identify efficacy faster. Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as $\geq 10\%$ decreased risk or $>0\%$ increased risk from ≥ 3 studies. 88% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 3.6 months. When restricting to RCTs only, 50% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.1 months.

Time when COVID-19 studies showed efficacy

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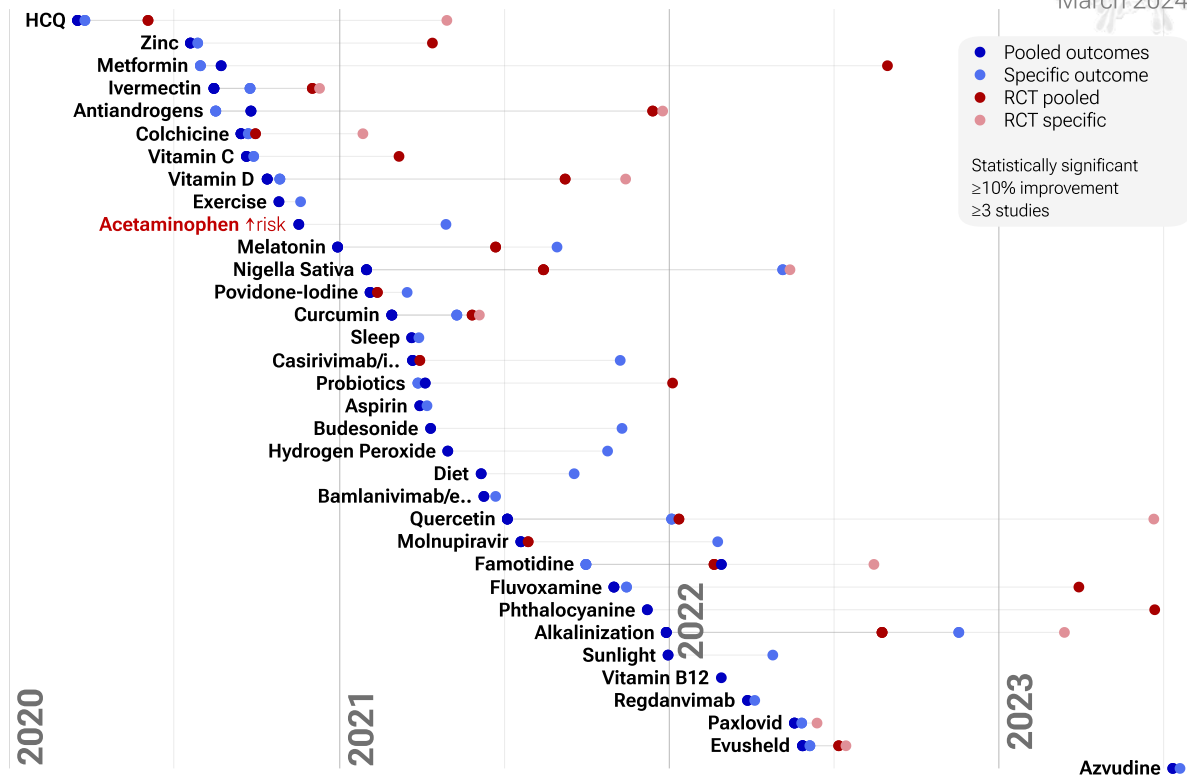


Figure 17. The time when studies showed that treatments were effective, defined as statistically significant improvement of $\geq 10\%$ from ≥ 3 studies. Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

Meta analysis. The distribution of studies will alter the outcome of a meta analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though early treatment is very effective. This may have a greater effect than pooling different outcomes such as mortality and hospitalization. For example a treatment may have 50% efficacy for mortality but only 40% for hospitalization when used within 48 hours. However efficacy could be 0% when used late.

All meta analyses combine heterogeneous studies, varying in population, variants, and potentially all factors above, and therefore may obscure efficacy by including studies where treatment is less effective. Generally, we expect the estimated effect size from meta analysis to be less than that for the optimal case. Looking at all studies is valuable for providing an overview of all research, important to avoid cherry-picking, and informative when a positive result is found despite combining less-optimal situations. However, the resulting estimate does not apply to specific cases such as early treatment in high-risk populations. While we present results for all studies, we also present treatment time and individual outcome analyses, which may be more informative for specific use cases.

Discussion

Publication bias. Publishing is often biased towards positive results. Trials with patented drugs may have a financial conflict of interest that results in positive studies being more likely to be published, or bias towards more positive results. For example with molnupiravir, trials with negative results remain unpublished to date (CTRI/2021/05/033864 and CTRI/2021/08/0354242). For 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 18 shows a scatter plot of results for prospective and retrospective studies. 60% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 60% of prospective studies, showing no difference. The median effect size for retrospective studies is 62% improvement, compared to 40% for prospective studies, suggesting a potential bias towards publishing results showing higher efficacy.

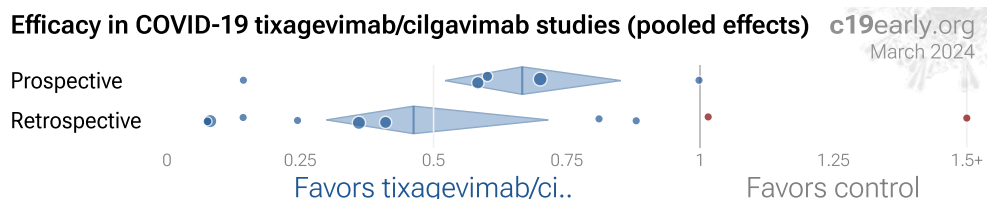


Figure 18. Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.

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 19 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ($p > 0.05$). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, $p < 0.0001$, with six variants of Egger's test all showing $p < 0.05$ *Egger, Harbord, Macaskill, Moreno, Peters, Rothstein, Rücker, Stanley*. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.

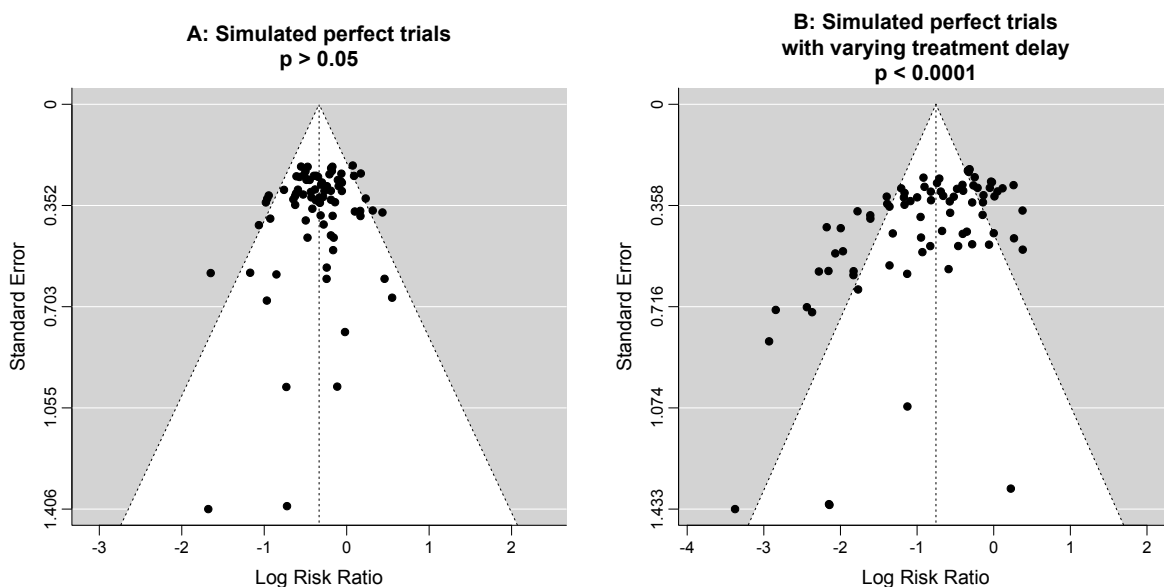


Figure 19. Example funnel plot analysis for simulated perfect trials.

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

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

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

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

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

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone *Alsaïdi, Andreani, De Forni, Fiaschi, Jeffreys, Jitobaom, Jitobaom (B), Ostrov, Said, Thairu, Wan*. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

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

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

Notes. 1 of the 15 studies compare against other treatments, which may reduce the effect seen.

Reviews. *Focosi (B) et al.* present a review covering tixagevimab/cilgavimab for COVID-19.

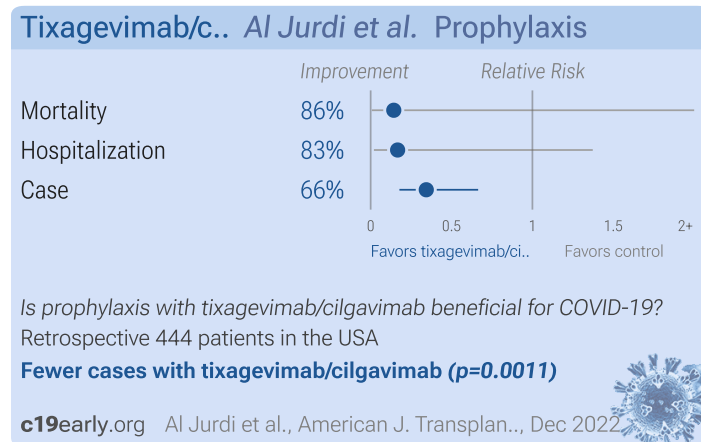
Conclusion

Tixagevimab/cilgavimab is an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality, hospitalization, and cases. 9 studies from 9 independent teams in 3 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 46% [28-59%] lower risk. Results are similar for higher quality and peer-reviewed studies and slightly worse for Randomized Controlled Trials. Results are robust — in exclusion sensitivity analysis 10 of 15 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 *Planas*, BA.5, BA.2.75, XBB *Haars*, XBB.1.9.1, XBB.1.9.3, XBB.1.5.24, XBB.1.16, XBB.2.9, BQ.1.1.45, CL.1, and CH.1.1 *Pochtovyi*. US EUA has been revoked. mAb use may create new variants that spread globally *Focosi, Leducq*, and may be associated with prolonged viral loads, clinical deterioration, and immune escape *Choudhary, Günther, Leducq*.

Study Notes

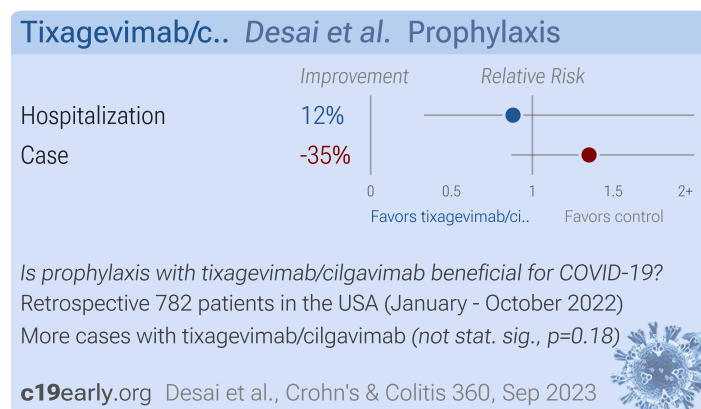
Al Jurdi



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 [c19early.org \(C\)](#), [c19early.org \(D\)](#), vitamin D [c19early.org \(E\)](#), 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.

Desai



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

Din

Tixagevimab/c.. for COVID-19 *Din et al.* Prophylaxis

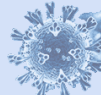


Is prophylaxis with tixagevimab/cilgavimab beneficial for COVID-19?

Retrospective 64 patients in the USA (June 2020 - February 2022)

Study underpowered to detect differences

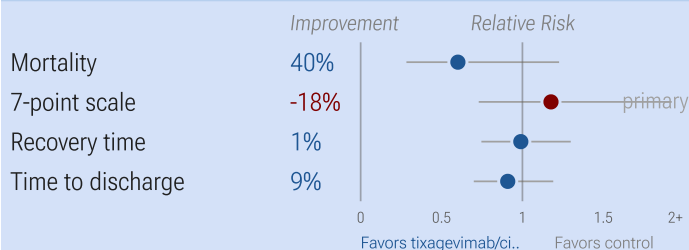
c19early.org Din et al., Hemasphere, August 2023



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

Hites

Tixagevimab/c.. DisCoVeRy LATE TREATMENT DB RCT



Is late treatment with tixagevimab/cilgavimab beneficial for COVID-19?

Double-blind RCT 226 patients in France

Lower mortality ($p=0.17$) and worse 7-point scale results ($p=0.52$), not sig.

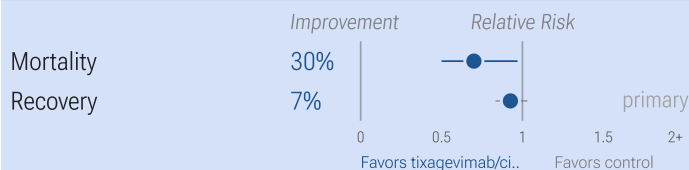
c19early.org Hites et al., J. Infection, February 2024



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

Tixagevimab/c.. ACTIV-3-TICO LATE TREATMENT DB RCT



Is late treatment with tixagevimab/cilgavimab beneficial for COVID-19?

Double-blind RCT 1,417 patients in the USA (February - September 2021)

Lower mortality with tixagevimab/cilgavimab ($p=0.032$)

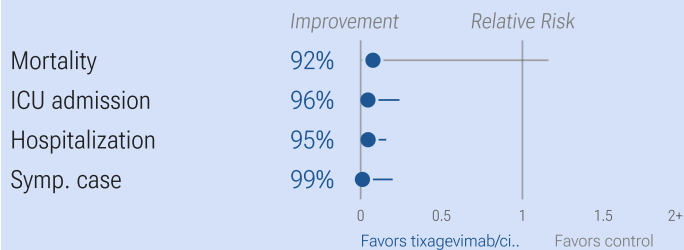
c19early.org Holland et al., The Lancet Respiratory., Jul 2022



Holland: RCT with 710 hospitalized patients treated with tixagevimab/cilgavimab, and 707 placebo patients, showing lower mortality with treatment.

Kaminski

Tixagevimab/c.. Kaminski et al. Prophylaxis



Is prophylaxis with tixagevimab/cilgavimab beneficial for COVID-19?
Retrospective 430 patients in France (December 2021 - February 2022)

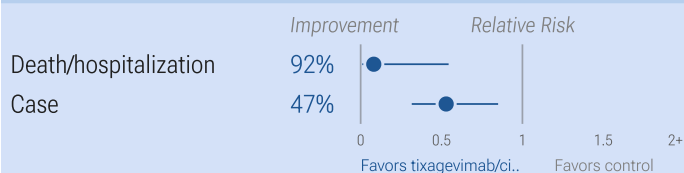
Lower ICU admission ($p=0.001$) and hospitalization ($p=0.001$)

c19early.org Kaminski et al., Kidney Int., October 2022

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

Tixagevimab/c.. Kertes et al. Prophylaxis



Is prophylaxis with tixagevimab/cilgavimab beneficial for COVID-19?
Retrospective 5,124 patients in Israel

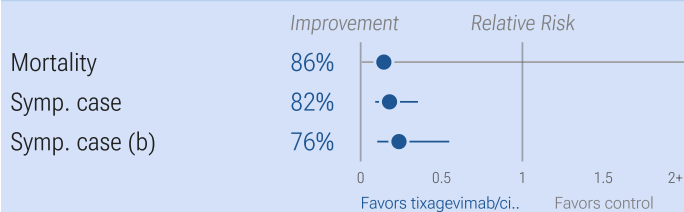
Lower death/hosp. ($p=0.013$) and fewer cases ($p=0.012$)

c19early.org Kertes et al., Clinical Infectious Dis., Jul 2022

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

Tixagevimab/c.. PROVENT Prophylaxis DB RCT



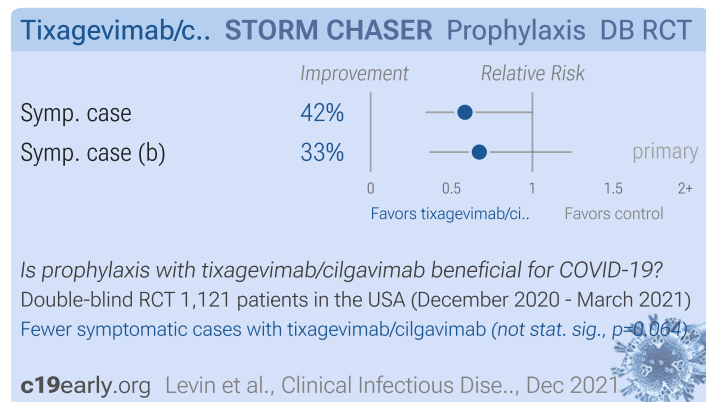
Is prophylaxis with tixagevimab/cilgavimab beneficial for COVID-19?
Double-blind RCT 5,172 patients in multiple countries (Nov 2020 - Mar 2021)

Fewer symptomatic cases with tixagevimab/cilgavimab ($p<0.000001$)

c19early.org Levin et al., New England J. Medicine, Apr 2022

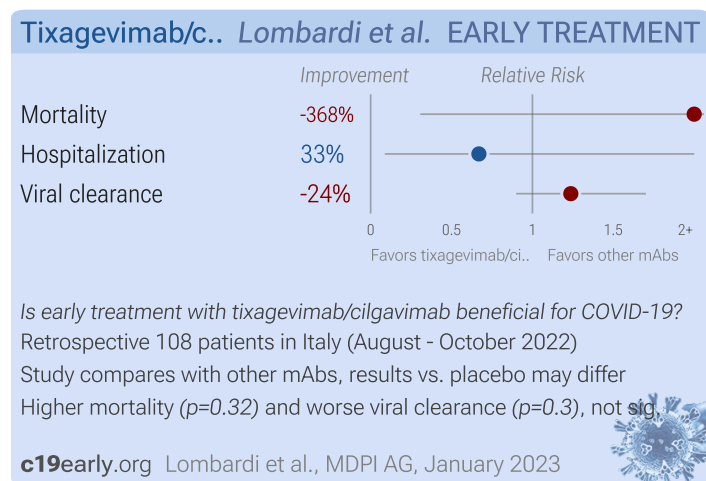
Levin: PrEP RCT with 3,441 tixagevimab/cilgavimab patients and 1,731 control patients, showing lower risk of symptomatic cases with treatment.

Levin



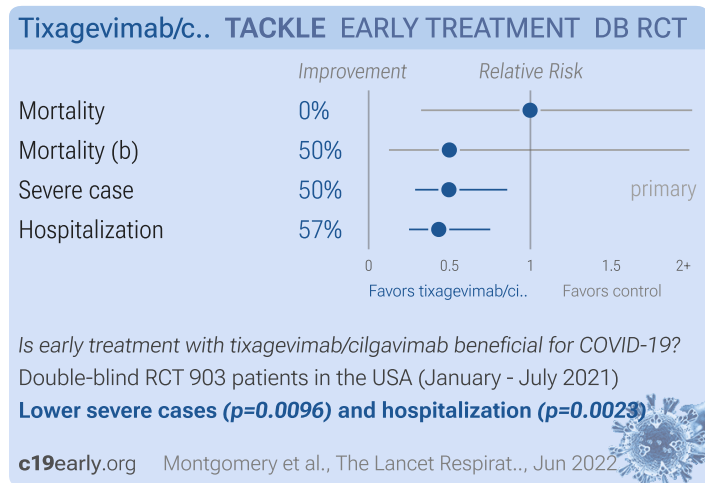
Levin (B): 1,121 patient PEP RCT showing lower symptomatic cases with tixagevimab/cilgavimab, without statistical significance.

Lombardi



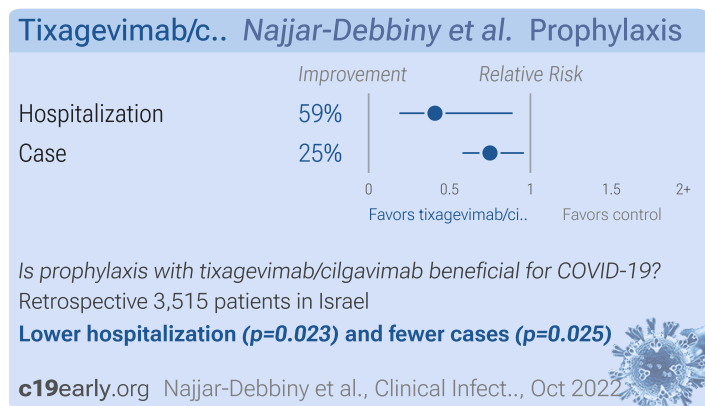
Lombardi: Retrospective immunocompromised patients, showing no significant difference between tixagevimab/cilgavimab and other mAbs.

Montgomery



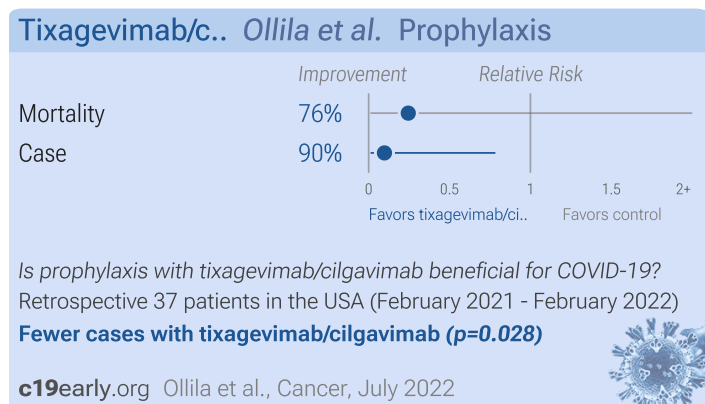
Montgomery: RCT 910 outpatients in the USA, 456 treated with tixagevimab/cilgavimab, showing significantly lower severe cases and hospitalization with treatment, but no difference in mortality.

Najjar-Debbiny



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.

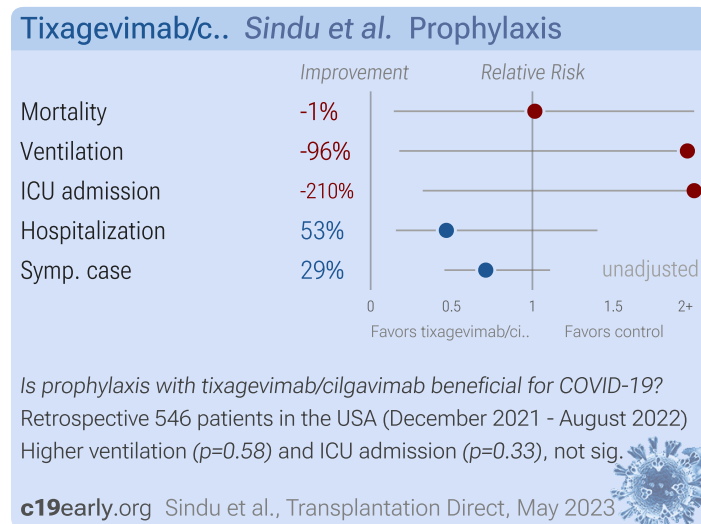
Ollila



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

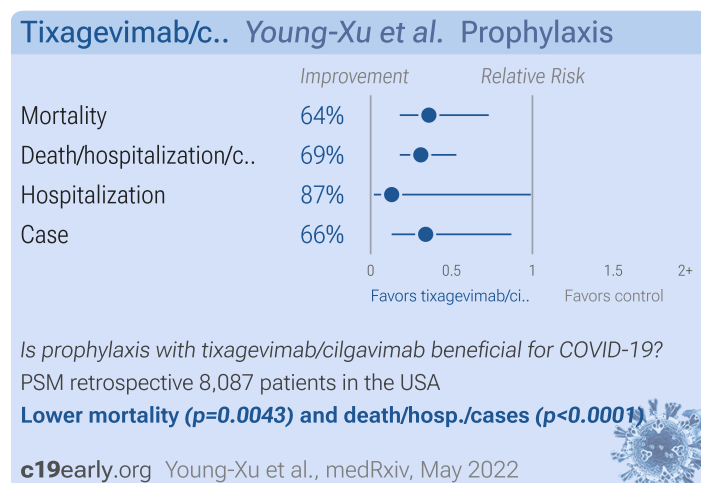
patients not receiving prophylaxis.

Sindu



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.

Young-Xu



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. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral test status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO₂ is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to *Zhang*. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 *Sweeting*. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.12.2) with scipy (1.12.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.1), and plotly (5.19.0).

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

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

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

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

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.

to placebo, excluded in exclusion analyses: study compares against another treatment showing significant efficacy.	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.
<i>Montgomery</i> , 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.

<i>Hites</i> , 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.
<i>Holland</i> , 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, 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 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.

<i>Al Jurdi</i> , 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.
<i>Desai</i> , 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.
<i>Din</i> , 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.
<i>Kaminski</i> , 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.
<i>Kertes</i> , 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.
<i>Levin</i> , 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.

	<p>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.</p>
<p><i>Levin (B)</i>, 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).</p>	<p>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.</p>
	<p>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.</p>
<p><i>Najjar-Debbiny</i>, 10/31/2022, retrospective, Israel, peer-reviewed, 5 authors.</p>	<p>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.</p>
	<p>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.</p>
<p><i>Ollila</i>, 7/11/2022, retrospective, USA, peer-reviewed, 13 authors, study period February 2021 - February 2022.</p>	<p>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).</p>
	<p>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).</p>
<p><i>Sindu</i>, 5/12/2023, retrospective, USA, peer-reviewed, median age 67.4, 7 authors, study period December 2021 - August 2022.</p>	<p>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.</p>
	<p>risk of mechanical ventilation, 95.8% higher, HR 1.96, $p = 0.58$, propensity score matching, Cox proportional hazards.</p>
	<p>risk of ICU admission, 209.6% higher, HR 3.10, $p = 0.33$, propensity score matching, Cox proportional hazards.</p>
	<p>risk of hospitalization, 53.2% lower, HR 0.47, $p = 0.17$, propensity score matching, Cox proportional hazards.</p>
	<p>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.</p>
<p><i>Young-Xu</i>, 5/29/2022, retrospective, propensity score matching, USA, preprint, 10 authors.</p>	<p>risk of death, 64.0% lower, HR 0.36, $p = 0.004$, treatment 1,733, control 6,354.</p>
	<p>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.</p>
	<p>risk of hospitalization, 87.0% lower, HR 0.13, $p = 0.04$, treatment 1,733, control 6,354.</p>

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. **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.
2. **Als-Nielsen** et al., *Association of Funding and Conclusions in Randomized Drug Trials*, JAMA, doi:10.1001/jama.290.7.921.
3. **Alsaïdi** 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.
4. **Altman**, D., *How to obtain the P value from a confidence interval*, BMJ, doi:10.1136/bmj.d2304.
5. **Altman (B)** et al., *How to obtain the confidence interval from a P value*, BMJ, doi:10.1136/bmj.d2090.
6. **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.
7. **Anglemeyer** 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.
8. **c19early.org**, c19early.org/timeline.html.
9. **c19early.org (B)**, c19early.org/treatments.html.
10. **c19early.org (C)**, c19early.org/p.
11. **c19early.org (D)**, c19early.org/ph.
12. **c19early.org (E)**, c19early.org/d.
13. **Choudhary** et al., *Emergence of SARS-CoV-2 Resistance with Monoclonal Antibody Therapy*, medRxiv, doi:10.1101/2021.09.03.21263105.
14. **Concato** et al., NEJM, 342:1887-1892, doi:10.1056/NEJM200006223422507.
15. **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.
16. **Davis** et al., *The Promise and Peril of Anti-SARS-CoV-2 Monoclonal Antibodies*, Clinical Infectious Diseases, doi:10.1093/cid/ciac902.
17. **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.

18. **Deaton** et al., *Understanding and misunderstanding randomized controlled trials*, Social Science & Medicine, 210, doi:10.1016/j.socscimed.2017.12.005.
19. **Deng**, H., *PyMeta*, Python module for meta-analysis, www.pymeta.com/.
20. **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.
21. **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.
22. **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.
23. **Egger** et al., *Bias in meta-analysis detected by a simple, graphical test*, BMJ, doi:10.1136/bmj.315.7109.629.
24. **Faria** et al., *Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil*, Science, doi:10.1126/science.abh2644.
25. **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.
26. **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.drug.2023.100991.
27. **Focosi (B)** 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.drug.2023.100991.
28. **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/.
29. **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.
30. **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.
31. **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.
32. **Hayden** et al., *Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents*, New England Journal of Medicine, doi:10.1056/NEJMoa1716197.
33. **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.
34. **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.
35. **Ikematsu** et al., *Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts*, New England Journal of Medicine, doi:10.1056/NEJMoa1915341.
36. **Jadad** et al., *Randomized Controlled Trials: Questions, Answers, and Musings, Second Edition*, doi:10.1002/9780470691922.
37. **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.
38. **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.
39. **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.
40. **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.

41. **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.
42. **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.
43. **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.
44. **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.
45. **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.
46. **Levin** et al., *Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of Covid-19*, New England Journal of Medicine, doi:10.1056/NEJMoa2116620.
47. **Levin (B)** et al., *AZD7442 (Tixagevimab/Cilgavimab) for Post-exposure Prophylaxis of Symptomatic COVID-19*, Clinical Infectious Diseases, doi:10.1093/cid/ciac899.
48. **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*, MDPI AG, doi:10.20944/preprints202301.0359.v1.
49. **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.
50. **Lui** et al., *Nsp1 facilitates SARS-CoV-2 replication through calcineurin-NFAT signaling*, Virology, doi:10.1128/mbio.00392-24.
51. **Lv** et al., *Host proviral and antiviral factors for SARS-CoV-2*, Virus Genes, doi:10.1007/s11262-021-01869-2.
52. **Macaskill** et al., *A comparison of methods to detect publication bias in meta-analysis*, Statistics in Medicine, doi:10.1002/sim.698.
53. **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.
54. **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.
55. **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.
56. **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.
57. **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.
58. **Najjar-Debbiny** et al., *Effectiveness of Evusheld in Immunocompromised Patients: Propensity Score-Matched Analysis*, Clinical Infectious Diseases, doi:10.1093/cid/ciac855.
59. **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.
60. **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.
61. **Ollila** et al., *Seroconversion and outcomes after initial and booster COVID-19 vaccination in adults with hematologic malignancies*, Cancer, doi:10.1002/cncr.34354.

62. **Ostrov** et al., *Highly Specific Sigma Receptor Ligands Exhibit Anti-Viral Properties in SARS-CoV-2 Infected Cells*, *Pathogens*, doi:10.3390/pathogens10111514.
63. **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.
64. **Peters**, J., *Comparison of Two Methods to Detect Publication Bias in Meta-analysis*, *JAMA*, doi:10.1001/jama.295.6.676.
65. **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.
66. **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.
67. **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.
68. **Rücker** et al., *Arcsine test for publication bias in meta-analyses with binary outcomes*, *Statistics in Medicine*, doi:10.1002/sim.2971.
69. **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.
70. **Scardua-Silva** et al., *Microstructural brain abnormalities, fatigue, and cognitive dysfunction after mild COVID-19*, *Scientific Reports*, doi:10.1038/s41598-024-52005-7.
71. **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.
72. **Stanley** et al., *Meta-regression approximations to reduce publication selection bias*, *Research Synthesis Methods*, doi:10.1002/jrsm.1095.
73. **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.
74. **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.
75. **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.
76. **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.
77. **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.
78. **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.
79. **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.
80. **Yang** et al., *SARS-CoV-2 infection causes dopaminergic neuron senescence*, *Cell Stem Cell*, doi:10.1016/j.stem.2023.12.012.
81. **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.
82. **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.
83. **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.

84. **Zhang** 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.