Casirivimab/imdevimab for COVID-19: real-time meta analysis of 27 studies

@CovidAnalysis, March 2024, Version 44
https://c19early.org/rmeta.html

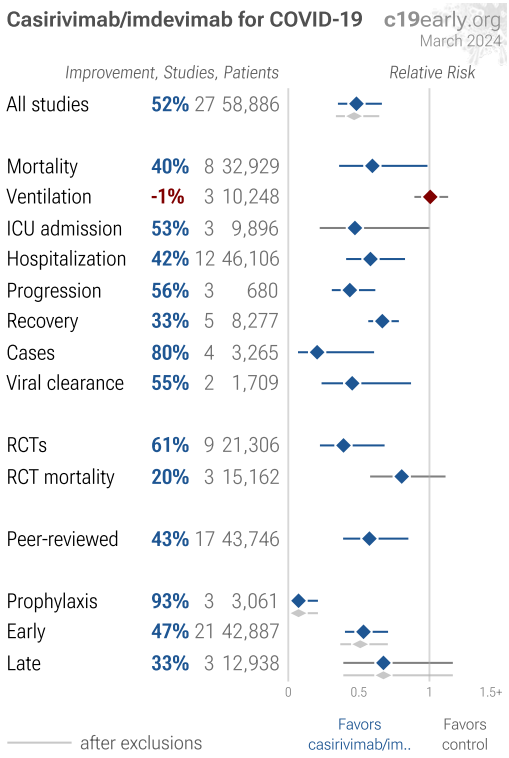
Abstract

Statistically significant lower risk is seen for mortality, hospitalization, progression, recovery, cases, and viral clearance. 20 studies from 14 independent teams in 4 countries show statistically significant improvements.

Meta analysis using the most serious outcome reported shows 52% [34-65%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies.

Results are robust — in exclusion sensitivity analysis 13 of 27 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

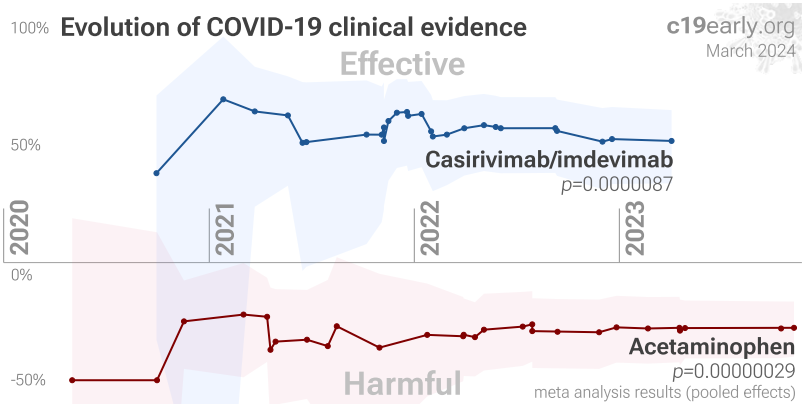
Efficacy is variant dependent. *In Vitro* studies suggest a lack of efficacy for many omicron variants *Haars, Liu, Pochtovyi, Sheward, Tatham, VanBlargan*. ADE shown *In Vitro* *Shimizu*. mAb use may create new variants that spread globally *Focosi, Leducq*, and may be associated with prolonged viral loads, clinical deterioration, and immune escape *Choudhary, Günther, Leducq*.



Prescription treatments have been preferentially used by patients at lower risk *Wilcock*. Retrospective studies may overestimate efficacy, for example patients with greater knowledge of effective treatments may be more likely to access prescription treatments but result in confounding because they are also more likely to use known beneficial non-prescription treatments.

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. *Wicaksono* present another meta analysis for casirivimab/imdevimab, showing significant improvements for mortality, hospital discharge, progression, and viral clearance.



HIGHLIGHTS

Casirivimab/imdevimab reduces risk for COVID-19 with very high confidence for hospitalization, progression, recovery, and in pooled analysis, high confidence for mortality and ICU admission, and low confidence for cases and viral clearance. Efficacy is variant dependent.

Casirivimab/imdevimab was the 17th treatment shown effective with ≥3 clinical studies in March 2021, now known with $p = 0.0000087$ from 27 studies, and recognized in 42 countries.

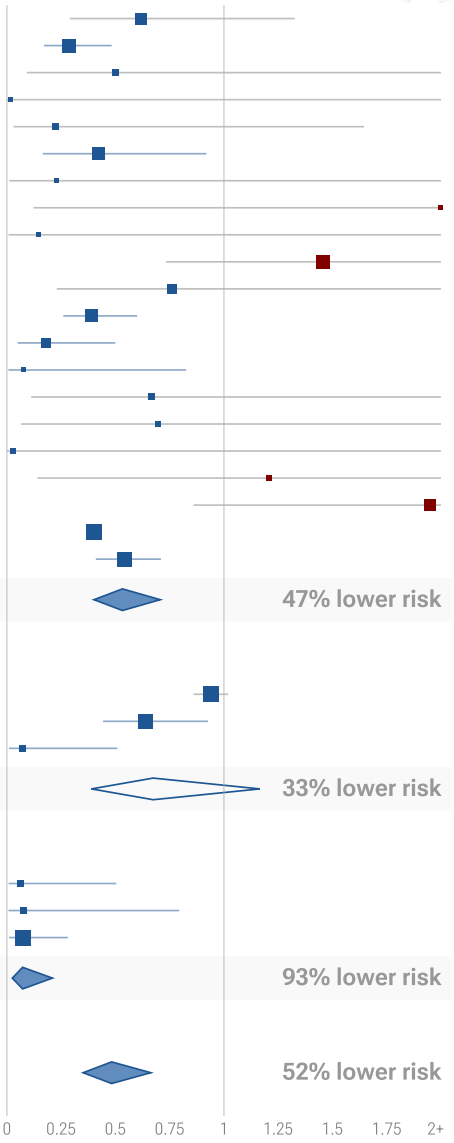
We show traditional outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor in COVID-19 studies.

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

27 casirivimab/imdevimab COVID-19 studies

c19early.org
March 2024

	Improvement	RR [CI]		Treatment	Control
Regeneron (RCT)	38%	0.62 [0.29-1.33]	recov. time	92 (n)	91 (n)
Regeneron (RCT)	71%	0.29 [0.17-0.48]	death/hosp.	18/1,355	62/1,341
Weinreich (RCT)	50%	0.50 [0.09-2.72]	death	2/2,091	4/2,089
Webb	98%	0.0 [0.00-2e+05]	death	0/115	57/5,536
Cooper	77%	0.23 [0.03-1.65]	death	1/1,148	33/8,534
Kakinoki	58%	0.42 [0.17-0.92]	progression	13/55	22/53
Komagamine	77%	0.23 [0.01-4.63]	ventilation	0/53	2/75
Suzuki (PSM)	-200%	3.00 [0.12-73.3]	death	1/222	0/222
O'Brien (DB RCT)	85%	0.15 [0.01-2.78]	hosp.	0/100	3/104
Shopen	-46%	1.46 [0.73-2.67]	severe case	24/116	26/243
Osugi	24%	0.76 [0.23-2.49]	hosp.	4/30	15/74
Wei	61%	0.39 [0.26-0.60]	death/hosp.	23/1,116	27/5,291
Wilden	82%	0.18 [0.05-0.50]	hosp.	n/a	n/a
Faraone	92%	0.08 [0.01-0.83]	death	0/11	8/23
Miyashita	33%	0.67 [0.11-3.97]	ventilation	2/461	3/461
Levey	31%	0.69 [0.07-7.37]	ICU	1/36	2/50
Kneidinger	97%	0.03 [0.00-264]	severe case	0/3	34/215
Williams	-21%	1.21 [0.14-9.86]	oxygen	1/88	6/676
Gershengorn	-95%	1.95 [0.86-4.18]	hosp.	369 (n)	5,915 (n)
Hussein (PSM)	60%	0.40 [0.38-0.42]	death/hosp.	population-based cohort	
Kip	46%	0.54 [0.41-0.71]	death/hosp.	61/1,479	227/2,954
Early treatment	47%	0.53 [0.40-0.71]		151/8,940	531/33,947
$Tau^2 = 0.15$, $I^2 = 64.4\%$, $p < 0.0001$					
	Improvement	RR [CI]		Treatment	Control
Horby (RCT)	6%	0.94 [0.86-1.02]	death	943/4,839	1,029/4,946
Somersa.. (DB RCT)	36%	0.64 [0.44-0.93]	death	59/804	45/393
McCreary (PSM)	93%	0.07 [0.01-0.51]	death	1/652	29/1,304
Late treatment	33%	0.67 [0.39-1.17]		1,003/6,295	1,103/6,643
$Tau^2 = 0.15$, $I^2 = 80.8\%$, $p = 0.16$					
	Improvement	RR [CI]		Treatment	Control
Regeneron (RCT)	94%	0.06 [0.01-0.50]	symp. case	0/186	8/223
Regeneron (DB RCT)	92%	0.08 [0.01-0.79]	hosp.	0/841	6/842
Isa (DB RCT)	93%	0.07 [0.01-0.28]	symp. case	3/729	13/240
Prophylaxis	93%	0.07 [0.03-0.21]		3/1,756	27/1,305
$Tau^2 = 0.00$, $I^2 = 0.0\%$, $p < 0.0001$					
All studies	52%	0.48 [0.35-0.66]		1,157/16,991	1,661/41,895

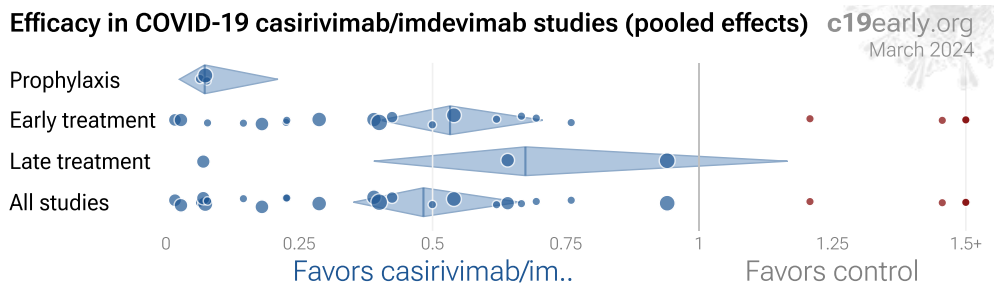


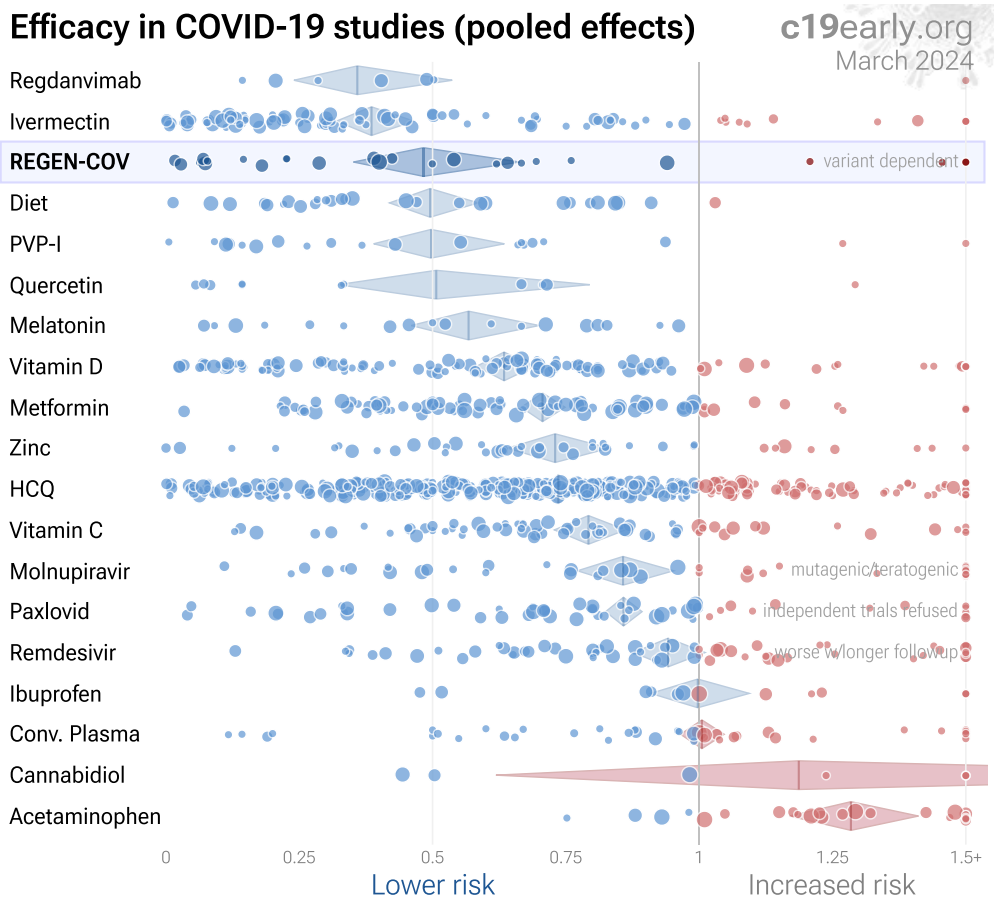
$Tau^2 = 0.32$, $I^2 = 93.0\%$, $p < 0.0001$

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

Favors casirivimab/im.. Favors control

A





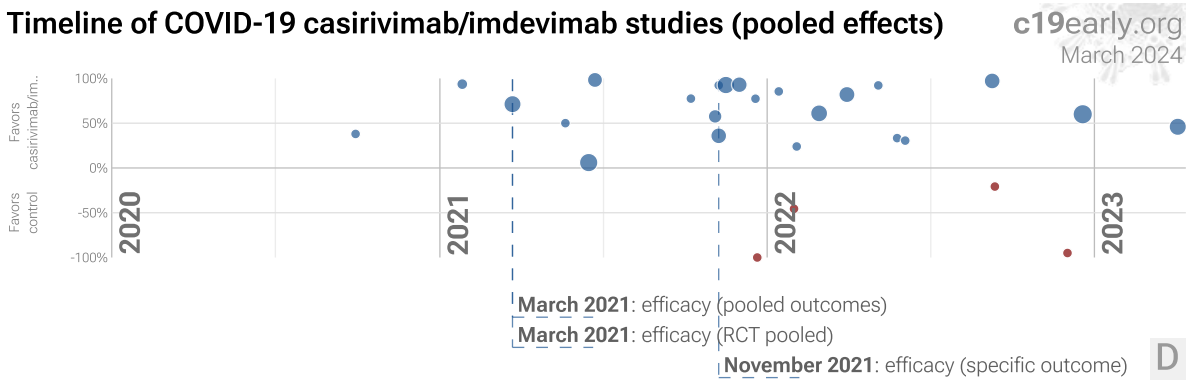


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the 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 casirivimab/imdevimab 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, and pooled outcomes in RCTs. Efficacy based on specific outcomes was delayed by 7.6 months, compared to using pooled outcomes.

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 casirivimab/imdevimab 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.

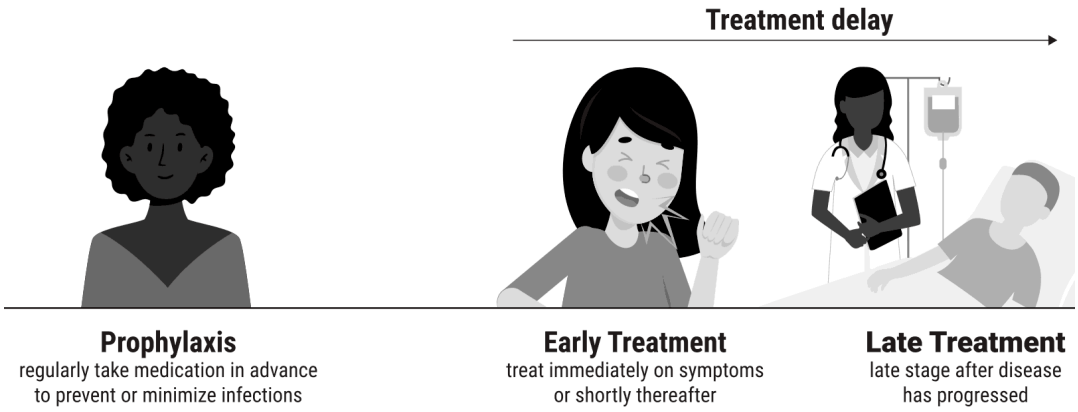


Figure 2. Treatment stages.

Variant Dependence

Efficacy for monoclonal antibodies is typically variant dependent. Table 1 shows efficacy by variant for several monoclonal antibodies.

	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* **(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, 11, and 12 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.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	**52%** [34-65%] ****	27	58,886	402
After exclusions	**53%** [36-66%] ****	24	42,920	378
Peer-reviewed studies	**43%** [15-61%] **	17	43,746	260
Randomized Controlled Trials	**61%** [32-78%] ***	9	21,306	178
Mortality	**40%** [1-64%] *	8	32,929	216
Ventilation	**-1%** [-13-11%]	3	10,248	42
ICU admission	**53%** [-0-78%] *	3	9,896	19
Hospitalization	**42%** [17-59%] **	12	46,106	133
Recovery	**33%** [22-43%] ****	5	8,277	76
Cases	**80%** [39-93%] **	4	3,265	71
Viral	**55%** [13-76%] *	2	1,709	39
RCT mortality	**20%** [-11-42%]	3	15,162	105

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	**47%** [29-60%] ****	**33%** [-17-61%]	**93%** [79-97%] ****
After exclusions	**49%** [29-63%] ****	**33%** [-17-61%]	**93%** [79-97%] ****
Peer-reviewed studies	**49%** [31-62%] ****	**19%** [-17-44%]	
Randomized Controlled Trials	**63%** [42-76%] ****	**19%** [-17-44%]	**93%** [79-97%] ****
Mortality	**65%** [-6-88%]	**33%** [-17-61%]	
Ventilation	**50%** [-134-89%]	**-1%** [-14-10%]	
ICU admission	**53%** [-0-78%] *		
Hospitalization	**39%** [9-59%] *	**48%** [18-67%] **	**92%** [21-99%] *
Recovery	**29%** [19-37%] ****	**30%** [6-48%] *	**62%** [39-77%] ***
Cases	**33%** [2-57%] *		**85%** [74-91%] ****
Viral	**40%** [19-55%] **		**69%** [45-83%] ****
RCT mortality	**50%** [-172-91%]	**19%** [-17-44%]	

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. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

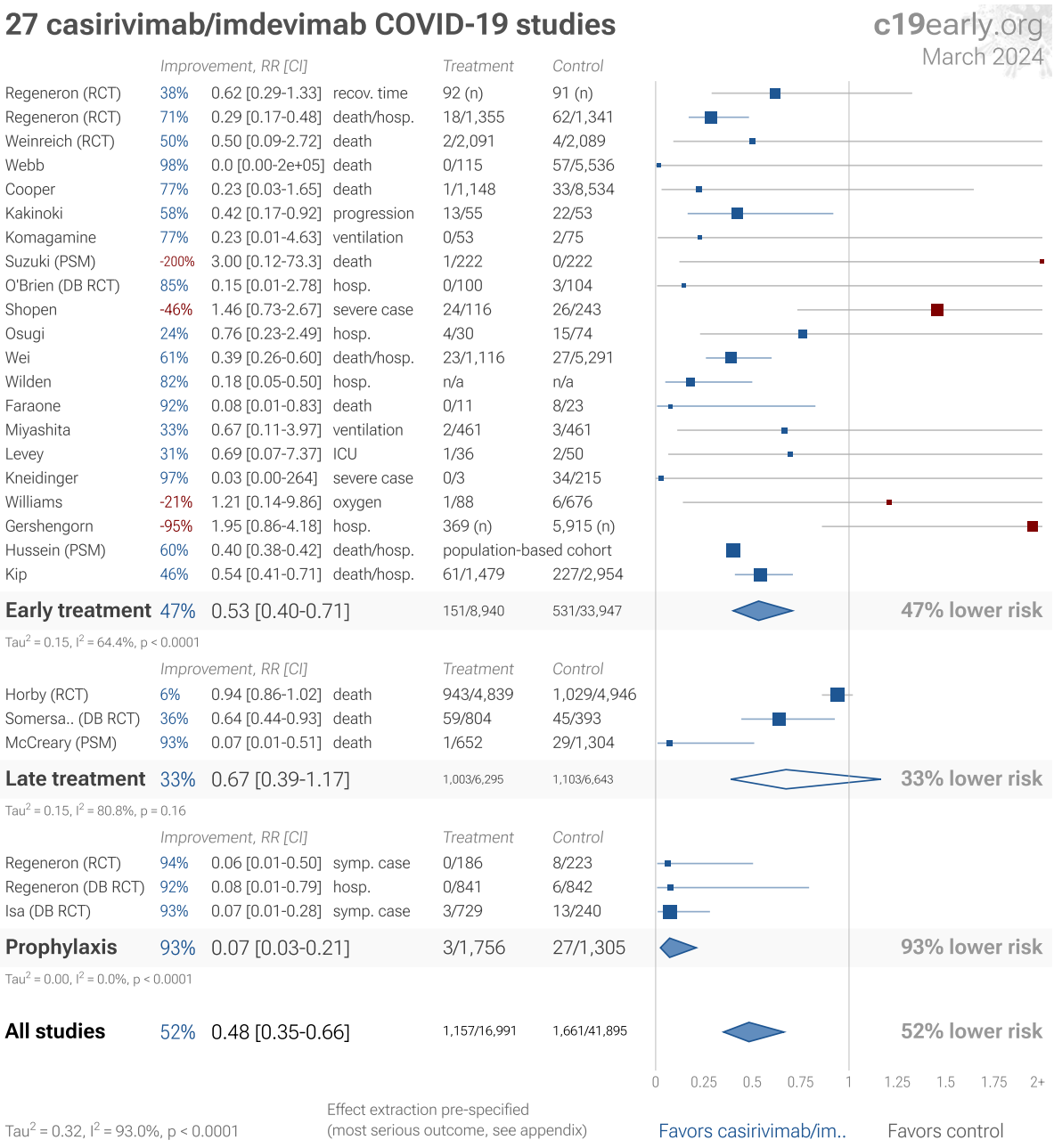


Figure 3. **Random effects meta-analysis for all studies with pooled effects.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details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

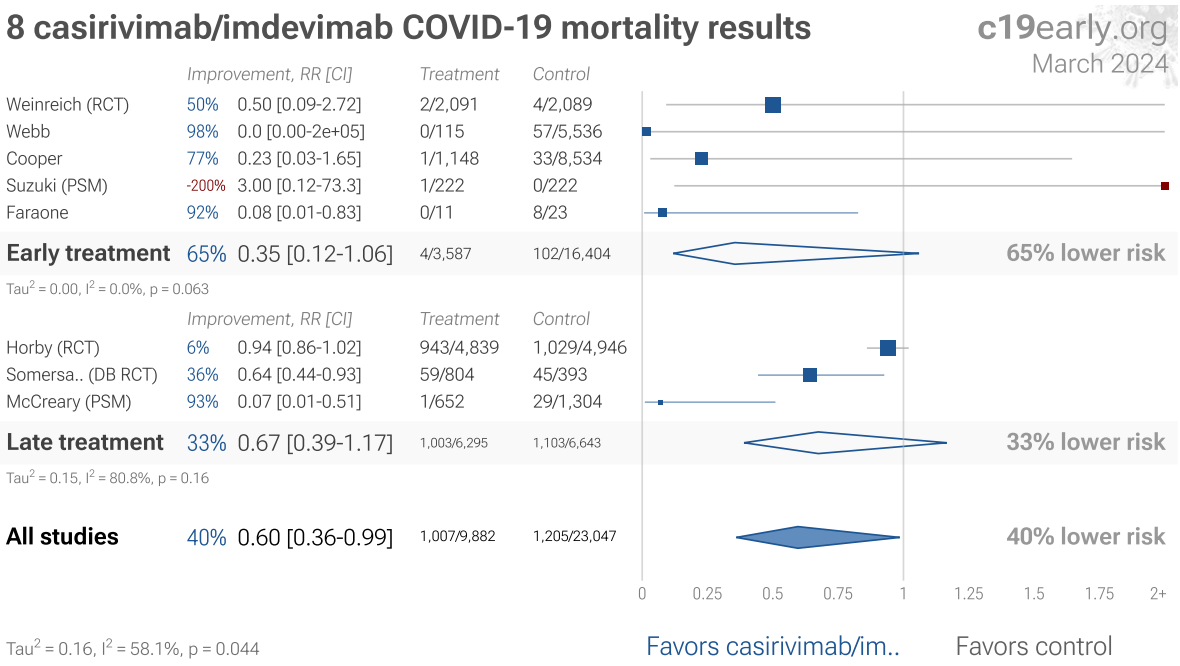


Figure 4. Random effects meta-analysis for mortality results.

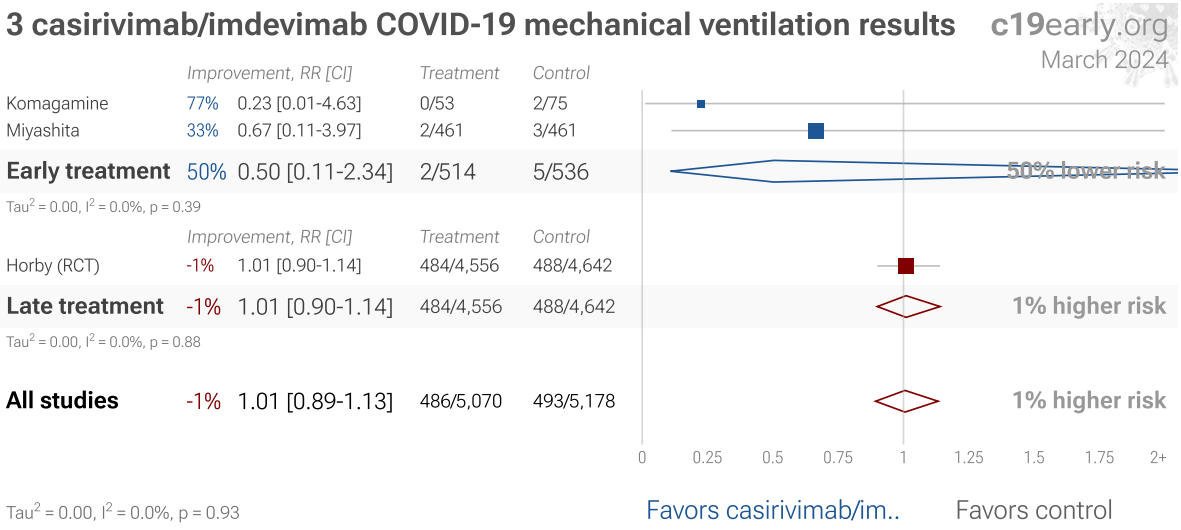


Figure 5. Random effects meta-analysis for ventilation.

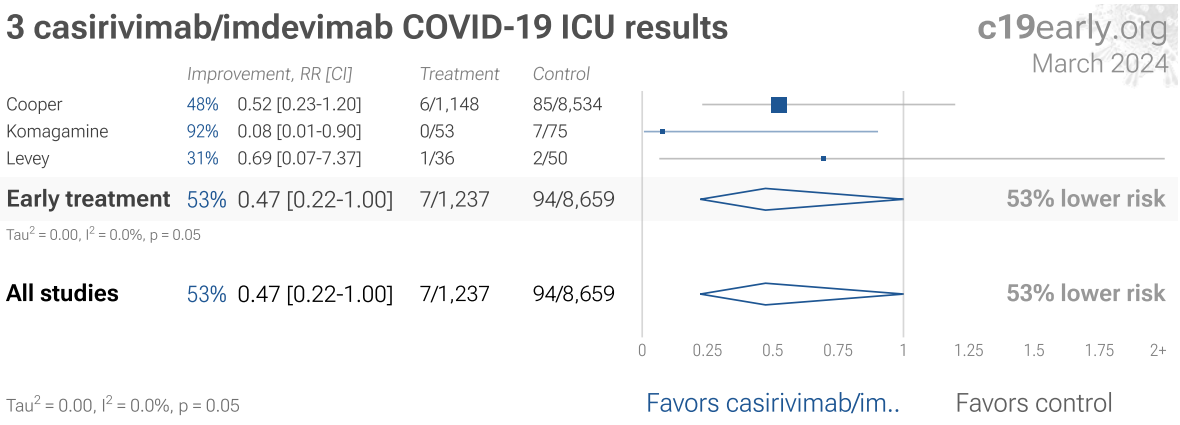


Figure 6. Random effects meta-analysis for ICU admission.

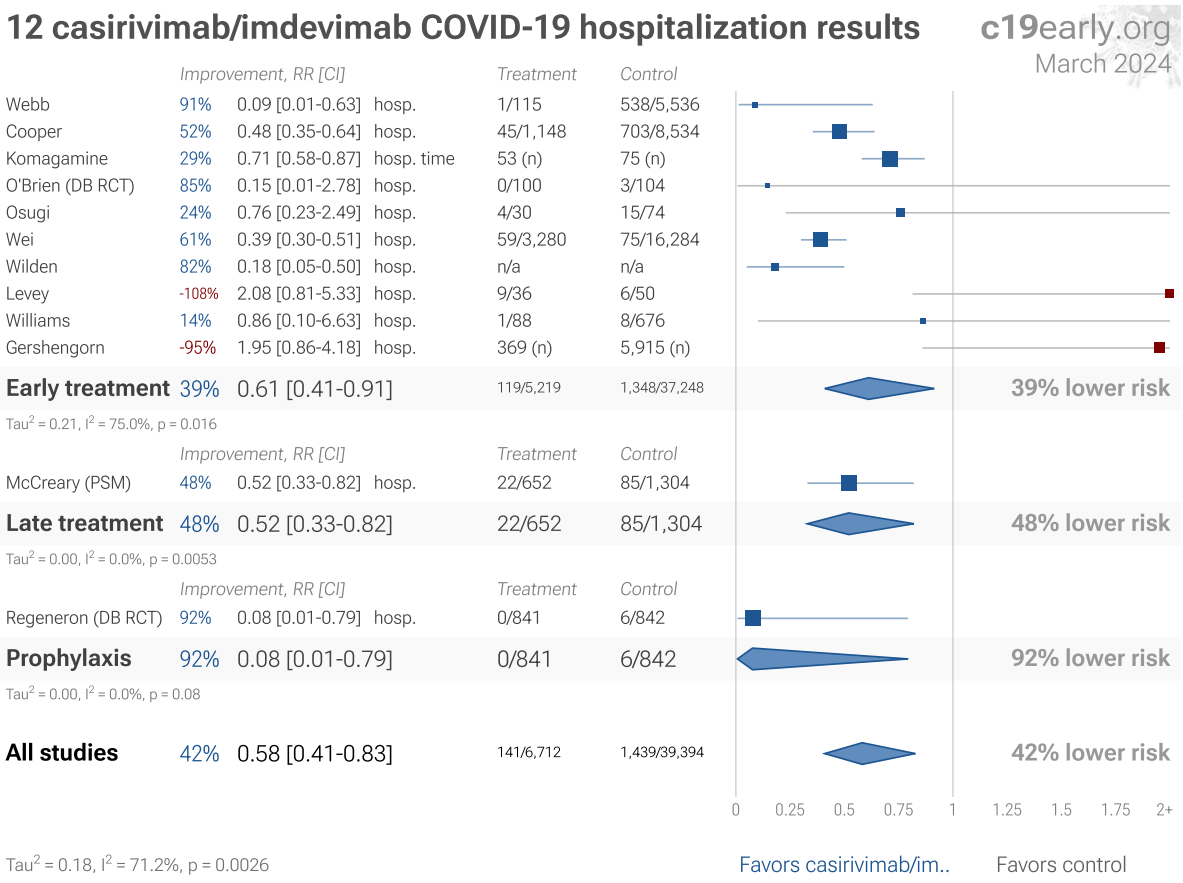


Figure 7. Random effects meta-analysis for hospitalization.

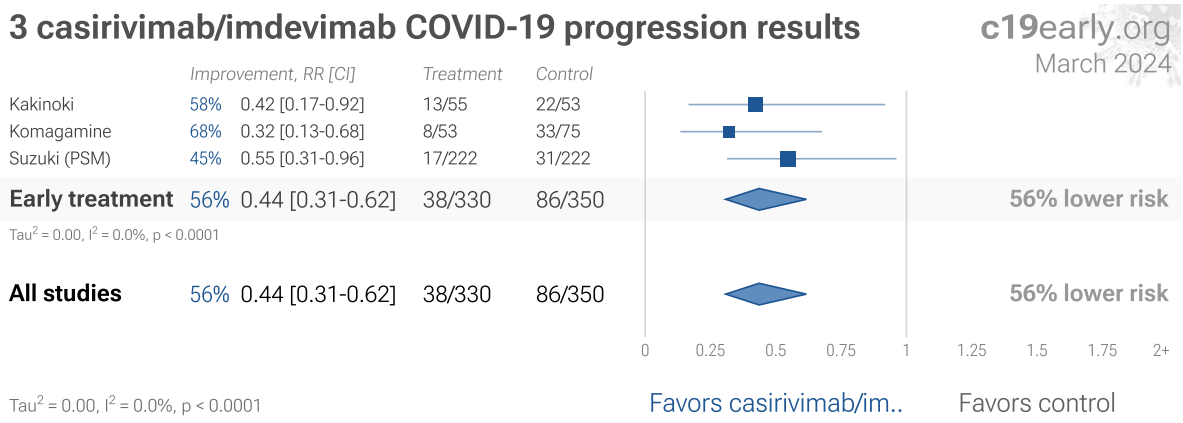


Figure 8. Random effects meta-analysis for progression.

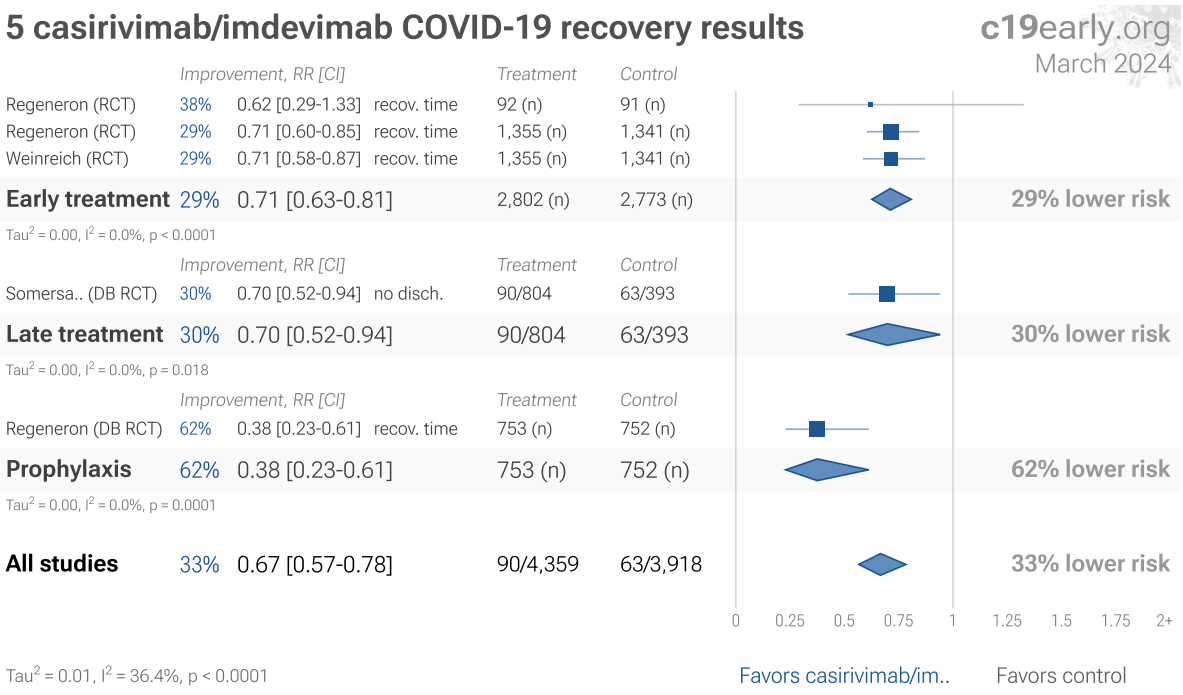


Figure 9. Random effects meta-analysis for recovery.

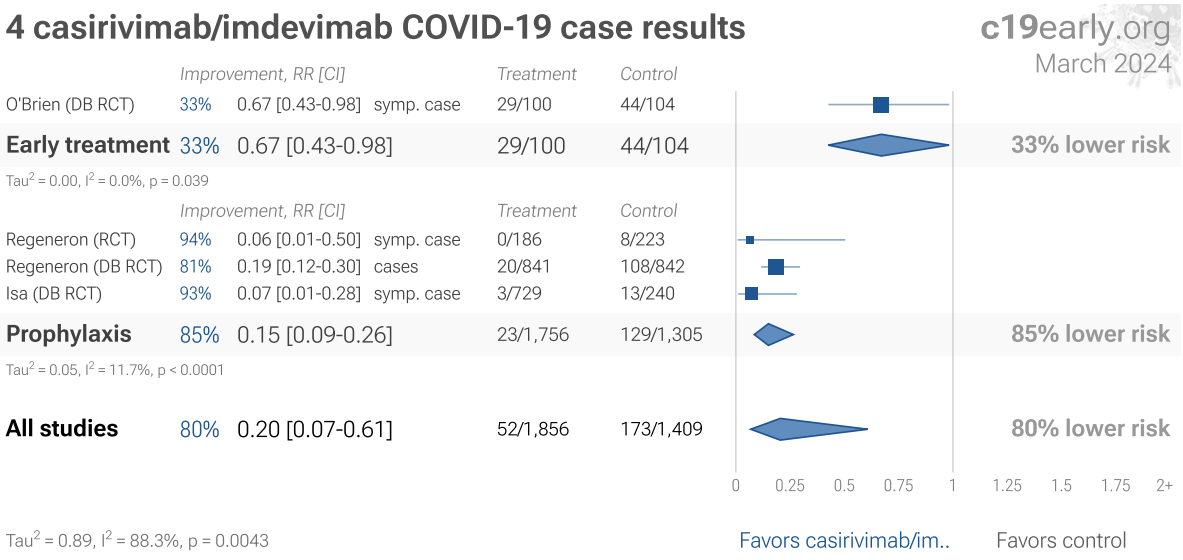


Figure 10. Random effects meta-analysis for cases.

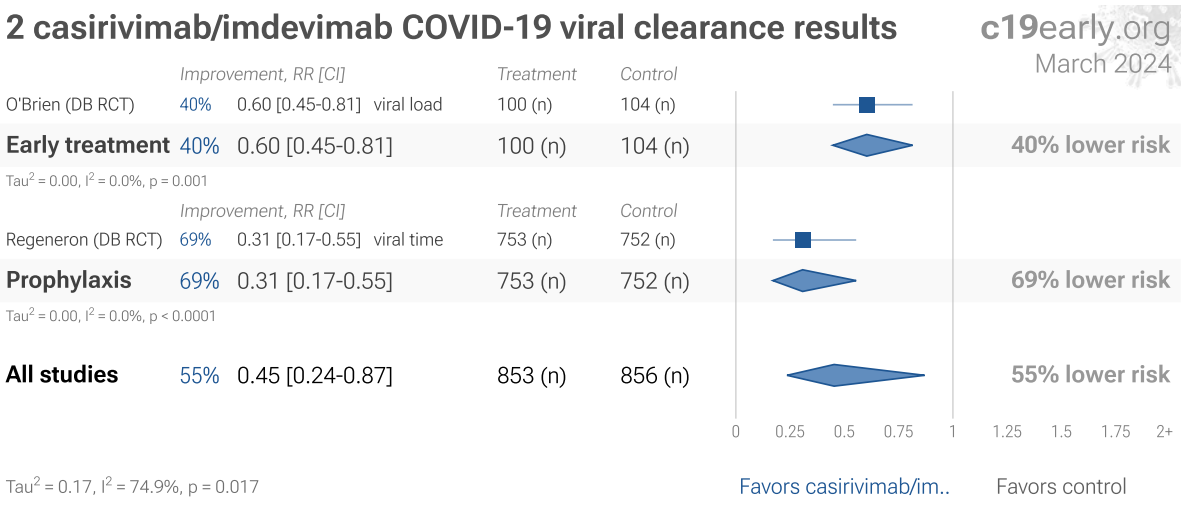


Figure 11. Random effects meta-analysis for viral clearance.

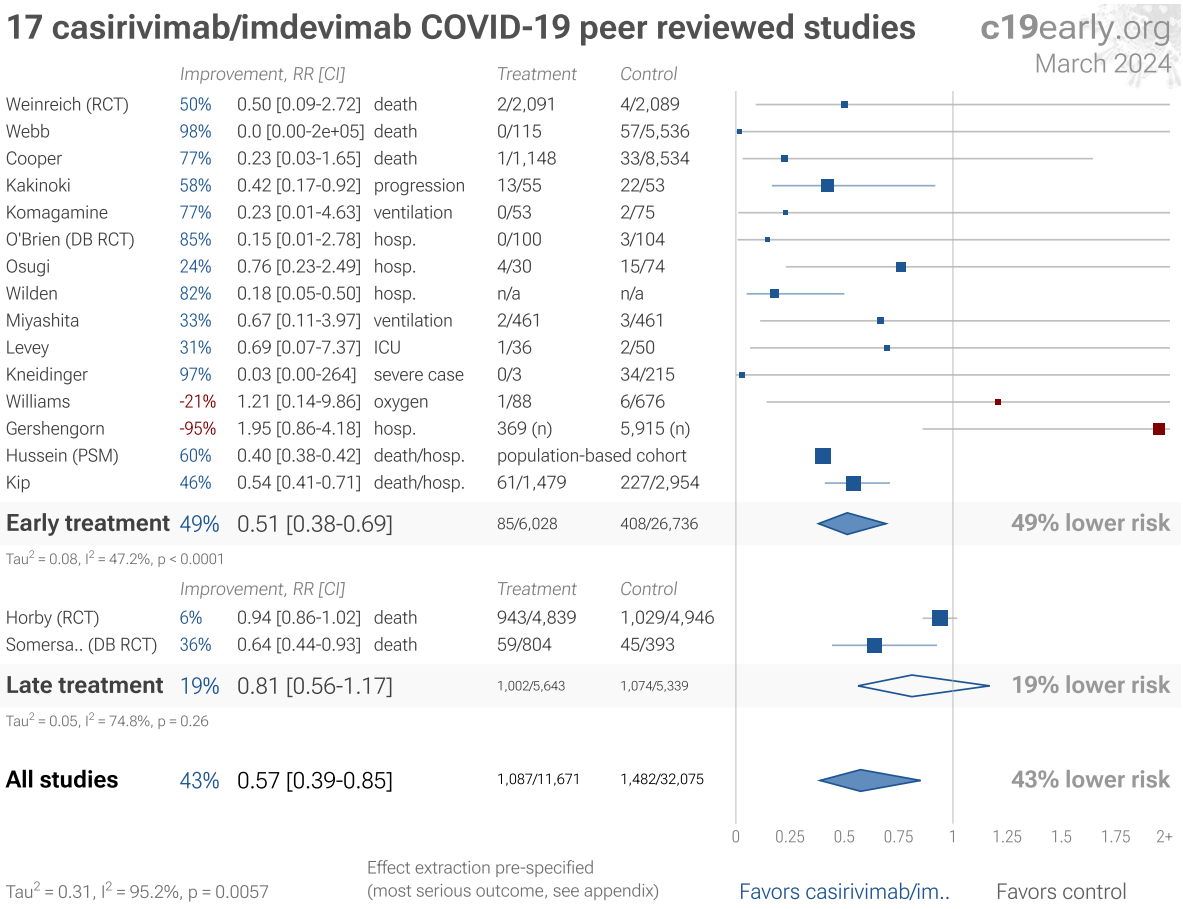


Figure 12. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with 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 13 shows a comparison of results for RCTs and non-RCT studies. The median effect size for RCTs is 71% improvement, compared to 59% for other studies. Figure 14 and 15 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 [Gøtzsche]. 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 ≥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.

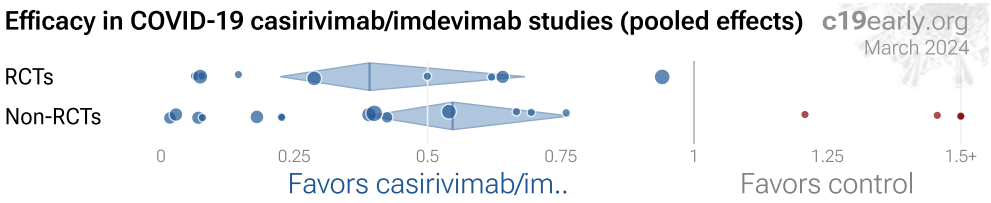


Figure 13. **Results for RCTs and non-RCT studies.**

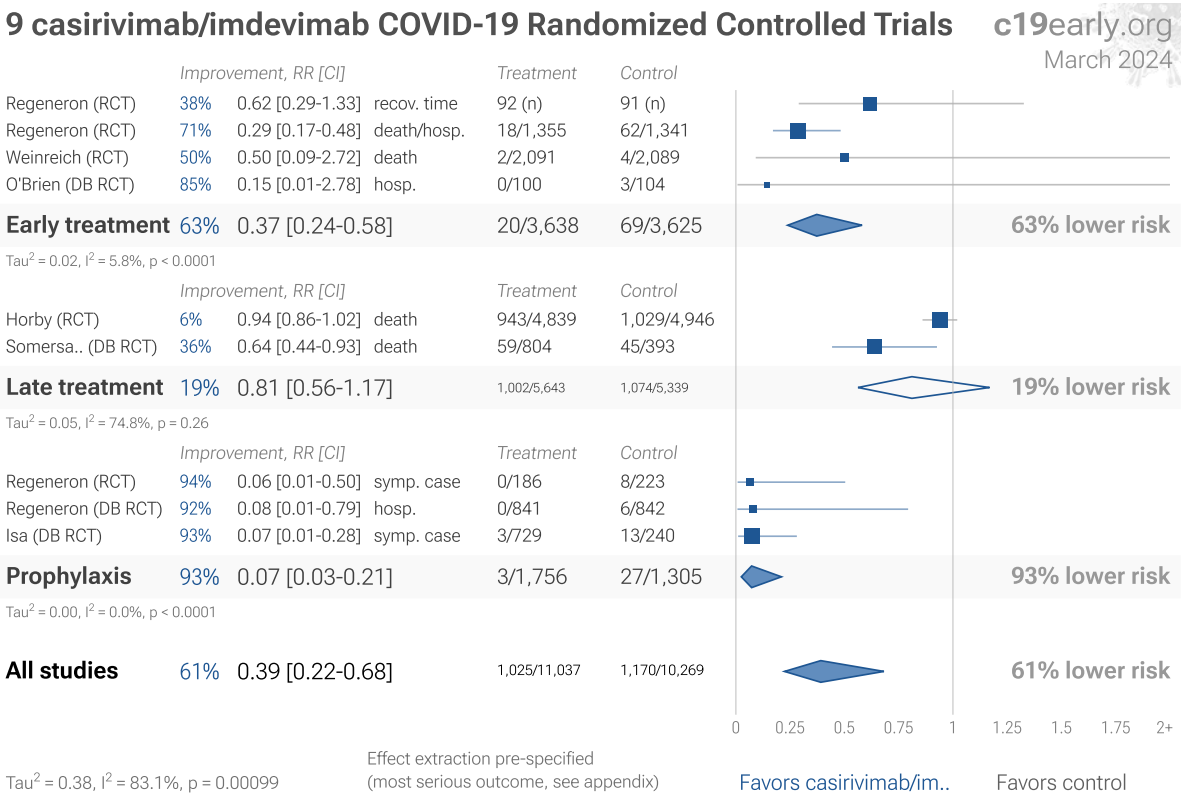


Figure 14. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

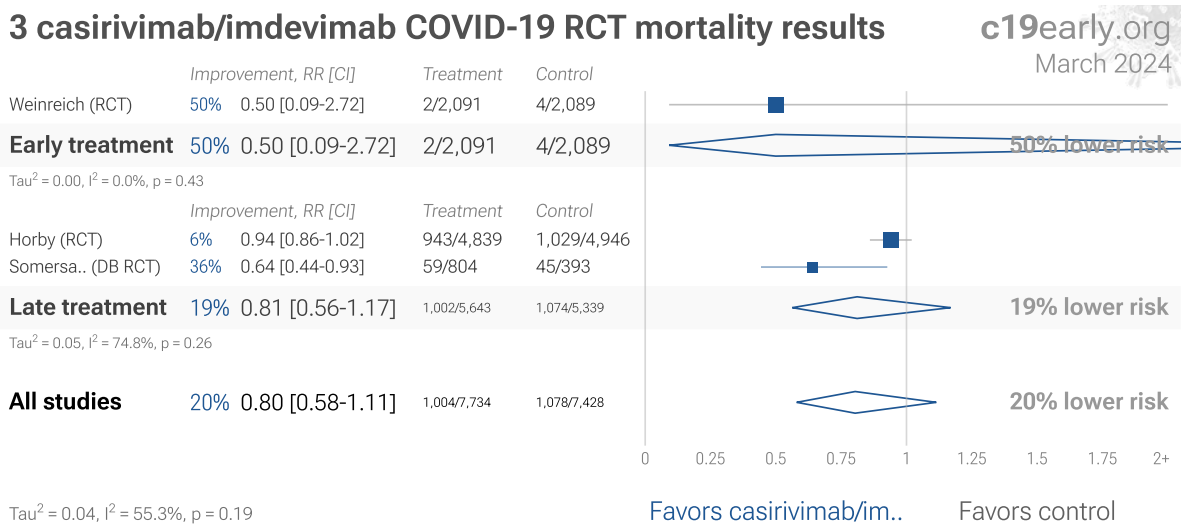


Figure 15. Random effects meta-analysis for RCT mortality results.

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 16 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Cooper, unadjusted results with no group details.

Gershengorn, substantial unadjusted confounding by indication possible.

Hussein, substantial unadjusted confounding by indication possible.

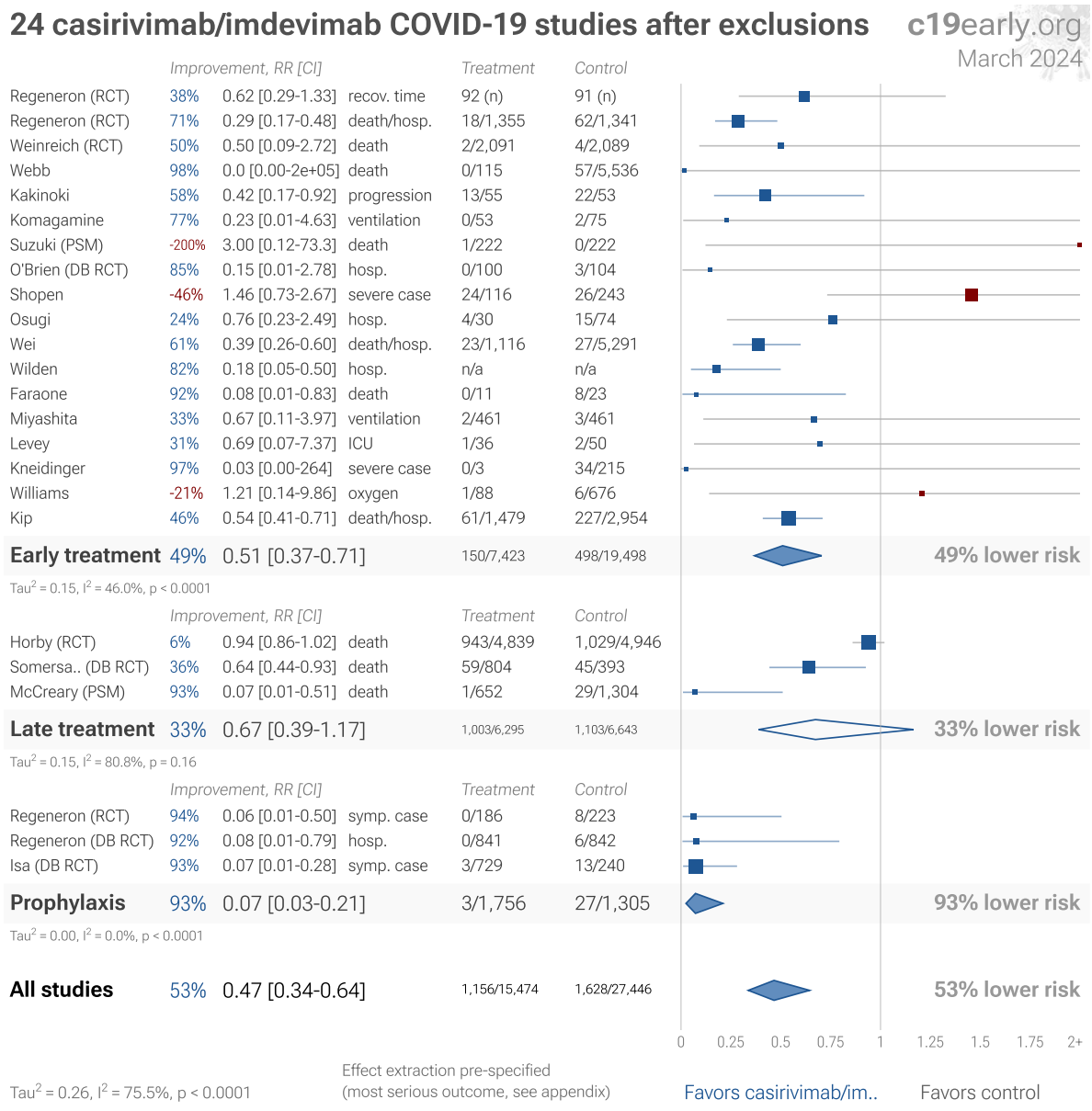


Figure 16. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details 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.

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

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

Figure 17 shows a mixed-effects meta-regression of efficacy as a function of treatment delay in COVID-19 casirivimab/imdevimab studies, with group estimates for early, late, and ICU studies that do not provide specific values. For comparison, Figure 18 shows a meta-regression for all studies providing specific values across 66 treatments. Efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

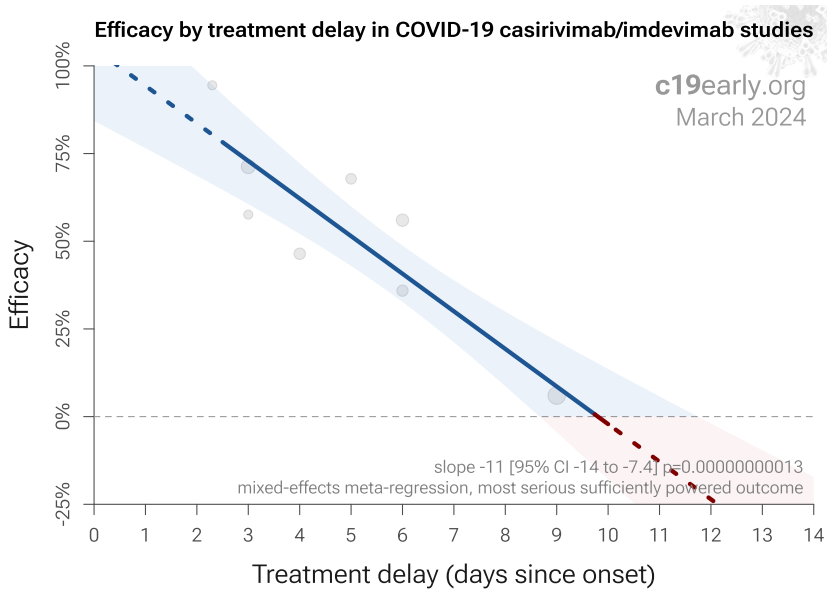


Figure 18. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 $casirivimab/imdevimab studies.

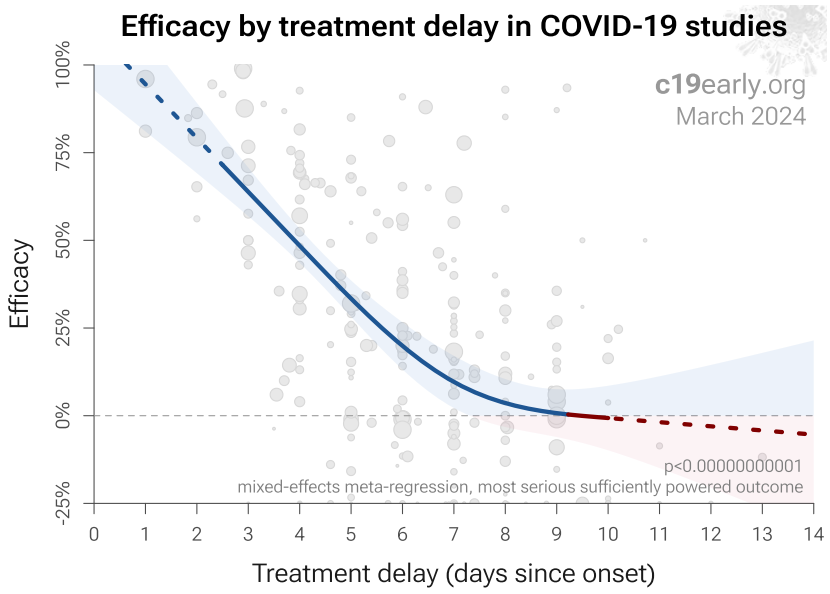


Figure 18. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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 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, etc. An antiviral tested with a low-risk population may report zero mortality in both arms, however a reduction in severity and improved viral clearance may translate into lower mortality among a high-risk population, and including these results in pooled analysis allows faster detection of efficacy. Trials with high-risk patients may also be restricted due to ethical concerns for treatments that are known or expected to be effective.

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

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

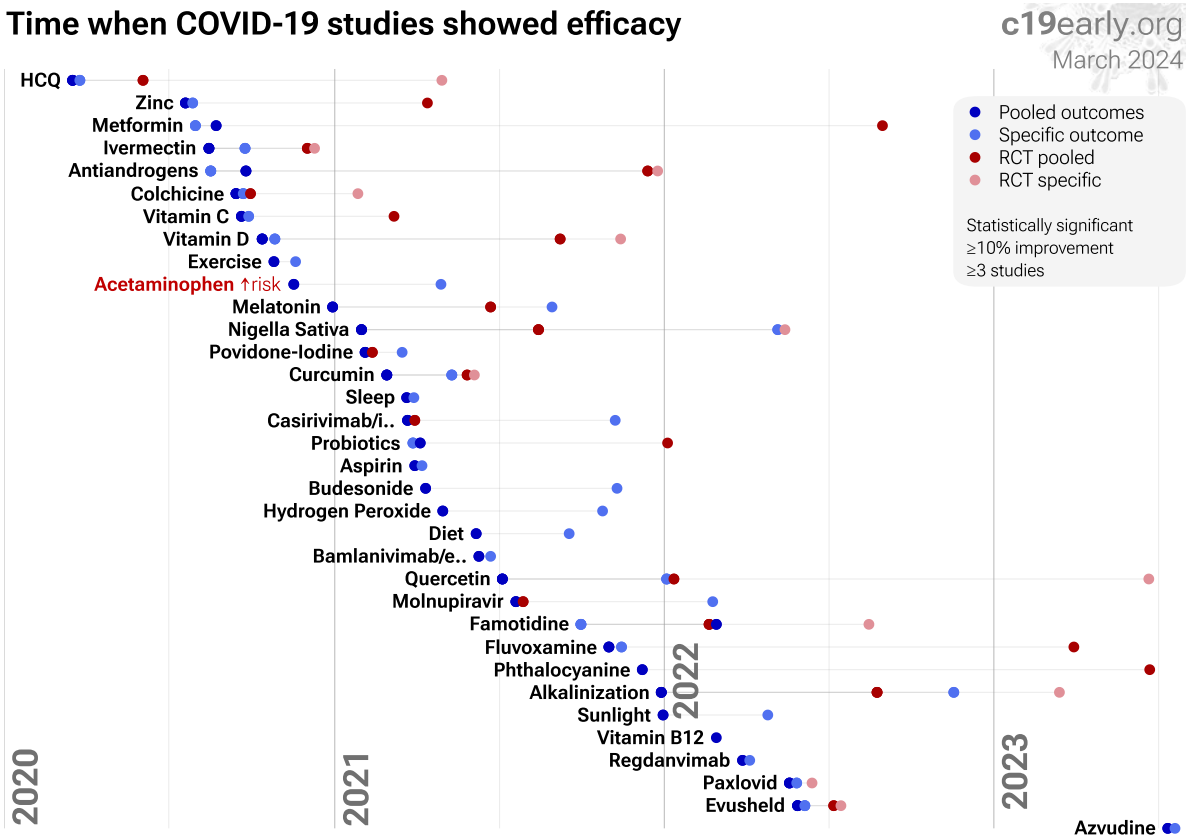


Figure 19. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

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

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

Discussion

Retrospective studies may overestimate efficacy. *Wilcock et al.* show that COVID-19 prescription treatments have been preferentially used by patients at lower risk. Retrospective studies may overestimate efficacy, and data for accurate adjustment may not be available. For example, patients with greater knowledge of effective treatments may be more likely to access prescription treatments but result in confounding because they are also more likely to use known beneficial non-prescription treatments.

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).

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 20 shows a scatter plot of results for prospective and retrospective studies. Prospective studies show 65% [39-80%] improvement in meta analysis, compared to 42% [19-59%] for retrospective studies, suggesting possible negative publication bias, with a non-significant trend towards retrospective studies reporting lower efficacy. However, many of the prospective studies for casirivimab/imdevimab have very high conflict of interest, which could also explain the improved results.

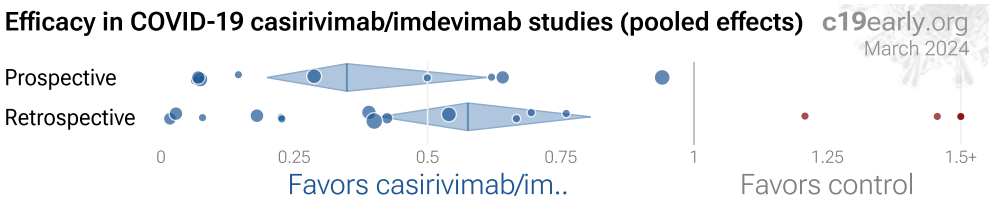


Figure 20. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

Early treatment bias. Studies for casirivimab/imdevimab were primarily for early treatment, in contrast with typical low cost treatments that were mostly tested with late treatment.

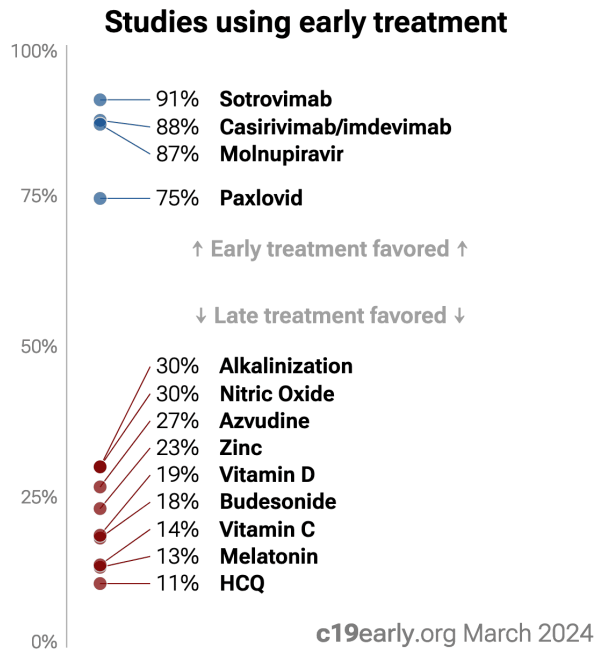


Figure 21. **Patented treatments received mostly early treatment studies, while low cost treatments were typically tested for late treatment.**

Funnel plot analysis. Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 22 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ($p > 0.05$). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, $p < 0.0001$, with six variants of Egger's test all showing $p < 0.05$ *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.

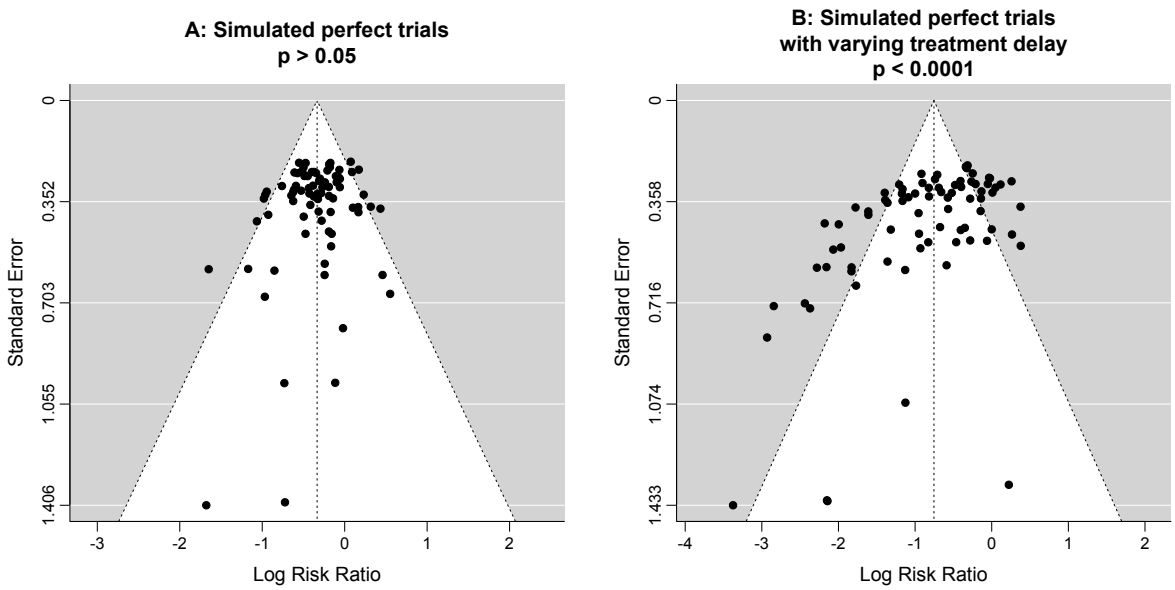


Figure 22. Example funnel plot analysis for simulated perfect trials.

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

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

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

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

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

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

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

No treatment, vaccine, or intervention is 100% available and effective for all current and future variants. Efficacy may vary significantly with different variants and within different populations. All treatments have potential side effects. Propensity to experience side effects may be predicted in advance by qualified physicians. We do not provide medical

advice. Before taking any medication, consult a qualified physician who can compare all options, provide personalized advice, and provide details of risks and benefits based on individual medical history and situations.

Notes. *Wicaksono* present another meta analysis for casirivimab/imdevimab, showing significant improvements for mortality, hospital discharge, progression, and viral clearance.

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

Conclusion

Casirivimab/imdevimab is an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality, hospitalization, progression, recovery, cases, and viral clearance. 20 studies from 14 independent teams in 4 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 52% [34-65%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies. Results are robust — in exclusion sensitivity analysis 13 of 27 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

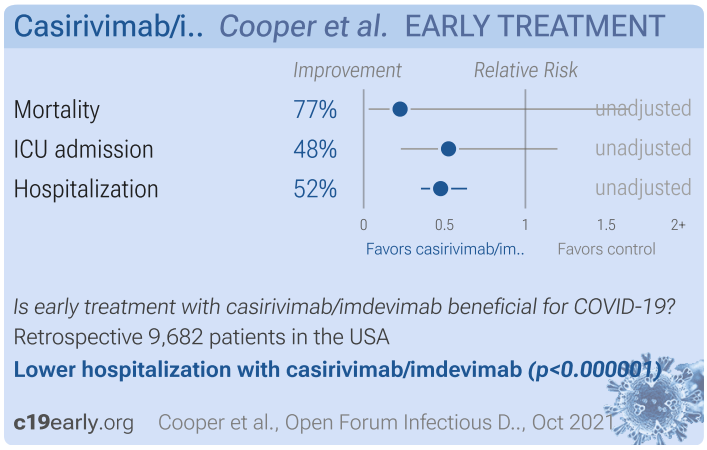
Efficacy is variant dependent. *In Vitro* studies suggest a lack of efficacy for many omicron variants *Haars, Liu, Pochtovyi, Sheward, Tatham, VanBlargan*. ADE shown *In Vitro* *Shimizu*. mAb use may create new variants that spread globally *Focosi, Leducq*, and may be associated with prolonged viral loads, clinical deterioration, and immune escape *Choudhary, Günther, Leducq*.

Wicaksono present another meta analysis for casirivimab/imdevimab, showing significant improvements for mortality, hospital discharge, progression, and viral clearance.

Prescription treatments have been preferentially used by patients at lower risk *Wilcock*. Retrospective studies may overestimate efficacy, for example patients with greater knowledge of effective treatments may be more likely to access prescription treatments but result in confounding because they are also more likely to use known beneficial non-prescription treatments.

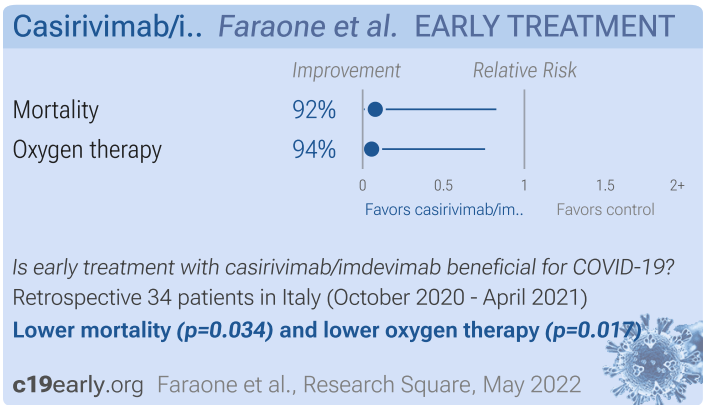
Study Notes

Cooper



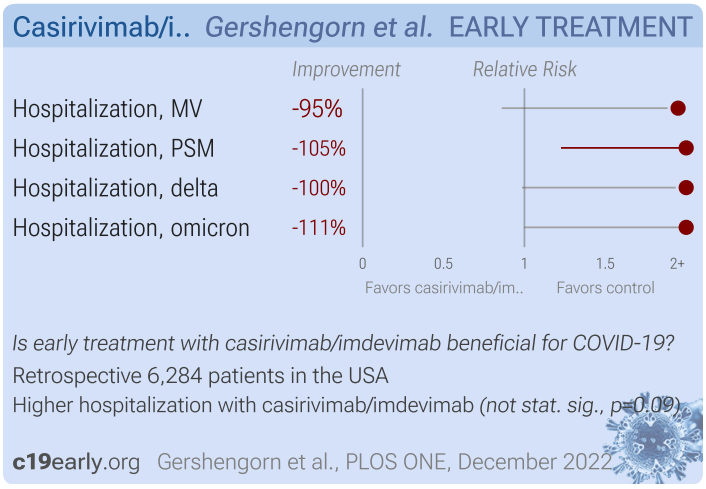
Cooper: Retrospective 2,879 patients and matched controls in the USA, showing significantly lower mortality and hospitalization with bamlanivimab, bamlanivimab/etesevimab, and casirivimab/imdevimab. There was significantly lower hospitalization with casirivimab/imdevimab compared to bamlanivimab or bamlanivimab/etesevimab. PSM and multivariate analysis is only provided for all treatments combined.

Faraone



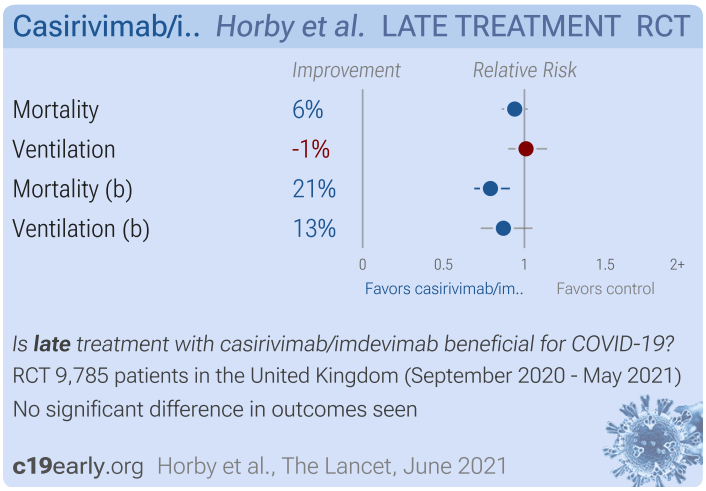
Faraone: Retrospective 34 patients with hospital-acquired COVID-19, showing lower mortality and oxygen requirements with early casirivimab/imdevimab treatment.

Gershengorn



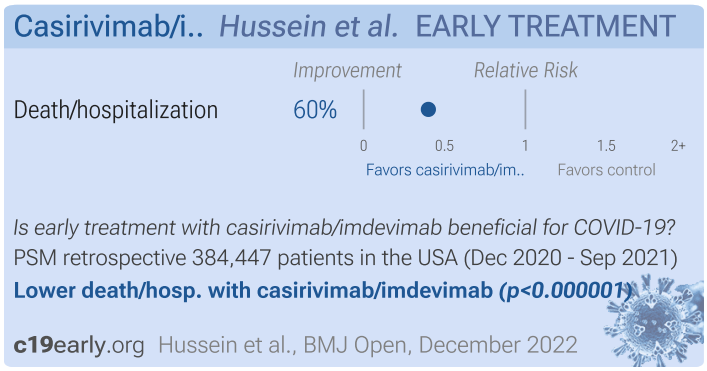
Gershengorn: Retrospective 2,083 outpatients in the USA, showing higher risk of hospitalization with casirivimab/imdevimab, without statistical significance. There may be significant unadjusted confounding by indication.

Horby



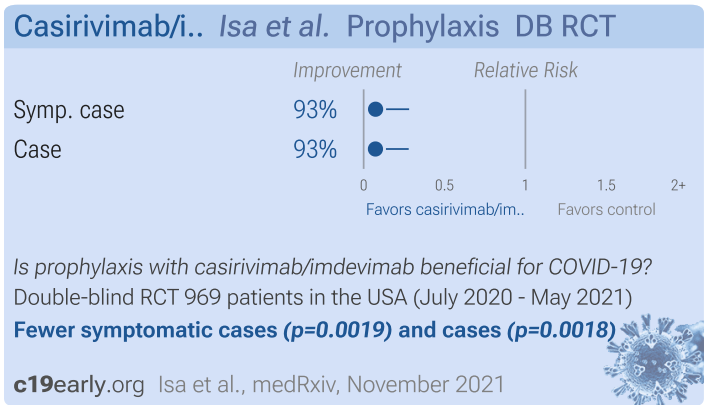
Horby: RCT 9,785 hospitalized patients in the UK showing lower mortality with casirivimab/imdevimab, with statistical significance reached for baseline seronegative patients.

Hussein



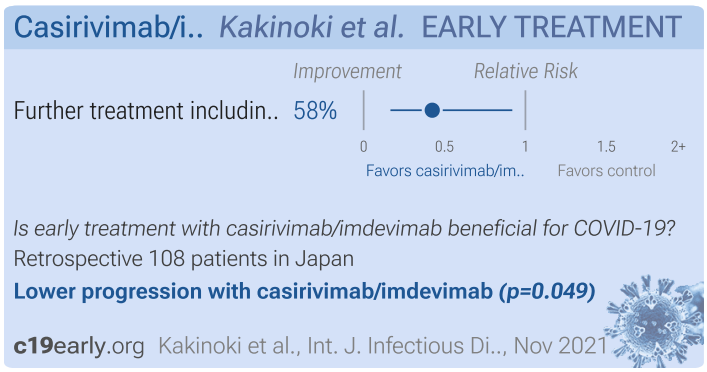
Hussein: Retrospective 73,759 outpatients treated with casirivimab/imdevimab, showing lower mortality with treatment. This result is subject to potentially substantial confounding by indication - patients with more severe cases may be more likely to receive treatment, and severity information was unavailable in the database.

Isa



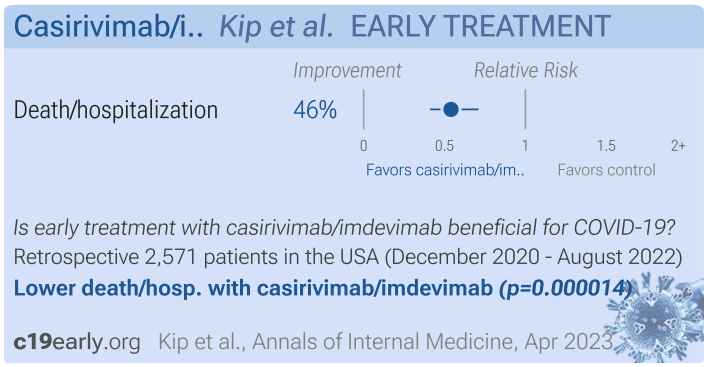
Isa: RCT 969 patients, 729 treated with monthly subcutaneous casirivimab/imdevimab, showing significantly lower risk of COVID-19 with treatment. There were no grade 3 injection site reactions or hypersensitivity reactions. Slightly more TEAEs were reported with treatment (54.9% vs. 48.3%), due to grade 1-2 ISRs. Serious adverse events were rare and occurred with similar percentages for treatment and control groups. There were no deaths. NCT04519437.

Kakinoki



Kakinoki: Retrospective 55 patients in Japan treated a median of 3 days from symptom onset with casirivimab/imdevimab, and 53 control patients, showing lower risk of further treatment including oxygen or antivirals.

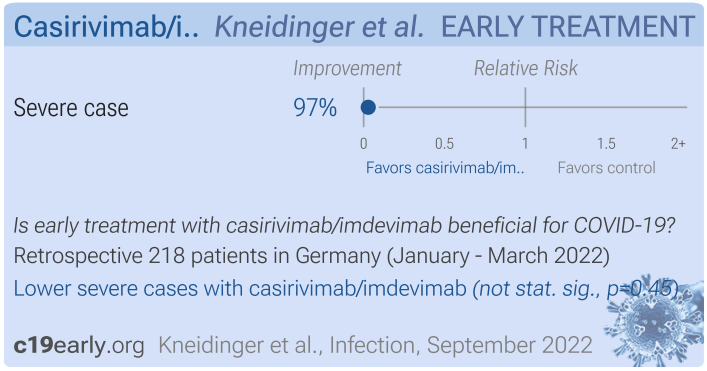
Kip



Kip: Retrospective 2,571 patients treated with mAbs in the USA, and 5,135 control patients, showing lower combined mortality/hospitalization for bamlanivimab, bamlanivimab/etesevimab, casirivimab/imdevimab, sotrovimab, and bebtelovimab, with statistical significance only for casirivimab/imdevimab.

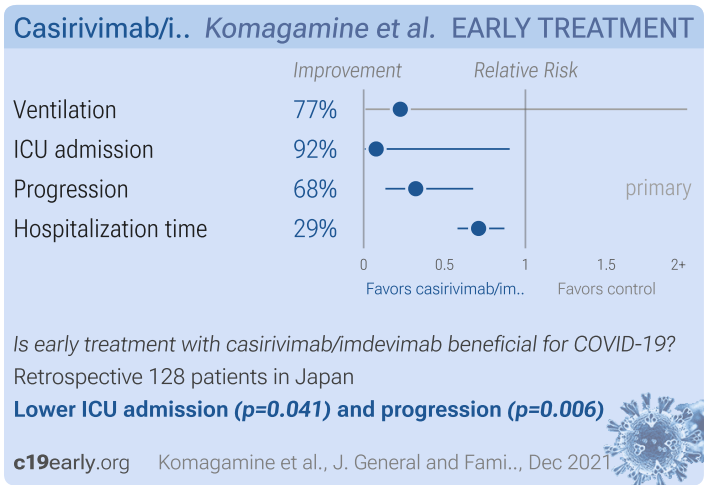
Confounding by treatment propensity. This study analyzes a population where only a fraction of eligible patients received the treatment. Patients receiving treatment may be more likely to follow other recommendations, more likely to receive additional care, and more likely to use additional treatments 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 casirivimab/imdevimab also recommended them, or because the patient seeking out casirivimab/imdevimab 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.

Kneidinger



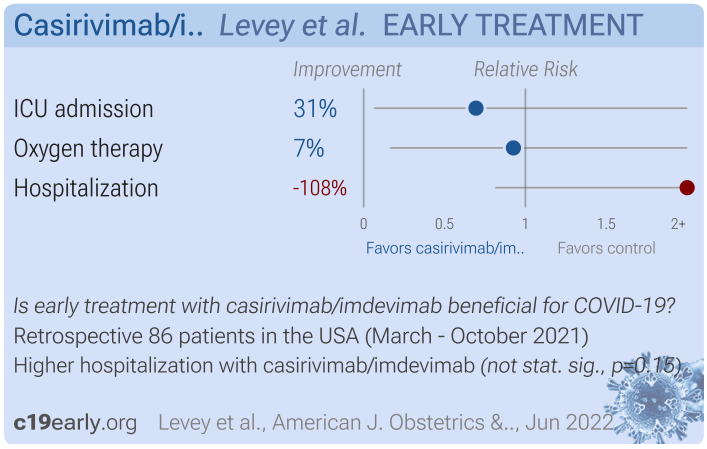
Kneidinger: Retrospective 218 COVID+ lung transplant patients in Germany, showing no significant difference in severe cases with early casirivimab/imdevimab use.

Komagamine



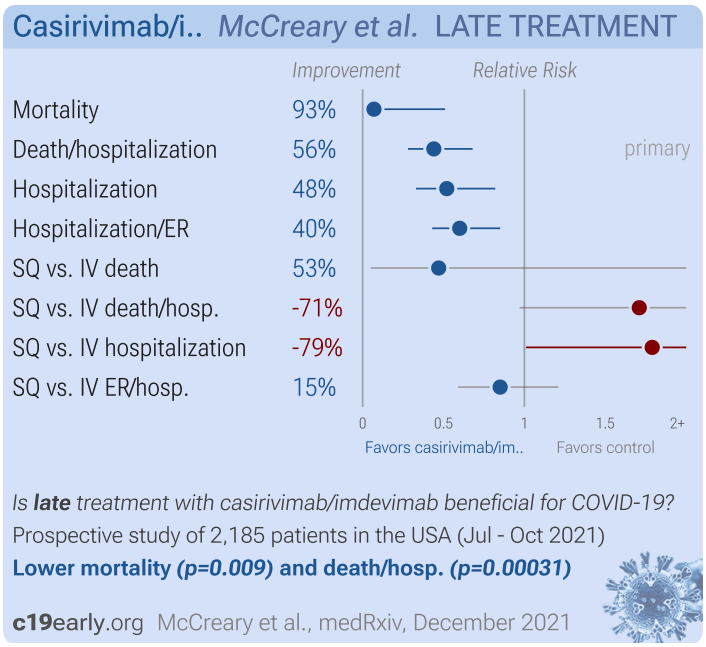
Komagamine: Combined retrospective/prospective study in Japan with 53 casirivimab/imdevimab patients and 75 control patients, showing significantly lower progression with treatment.

Levey



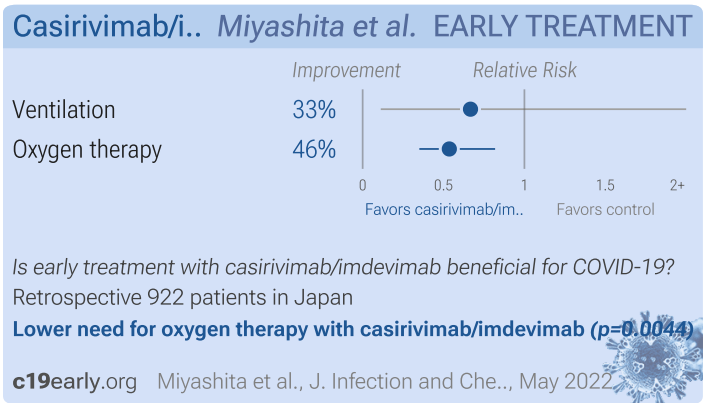
Levey: Retrospective 86 pregnant COVID-19 patients, 36 treated with casirivimab/imdevimab, showing no significant difference in COVID-19 outcomes with treatment.

McCreary



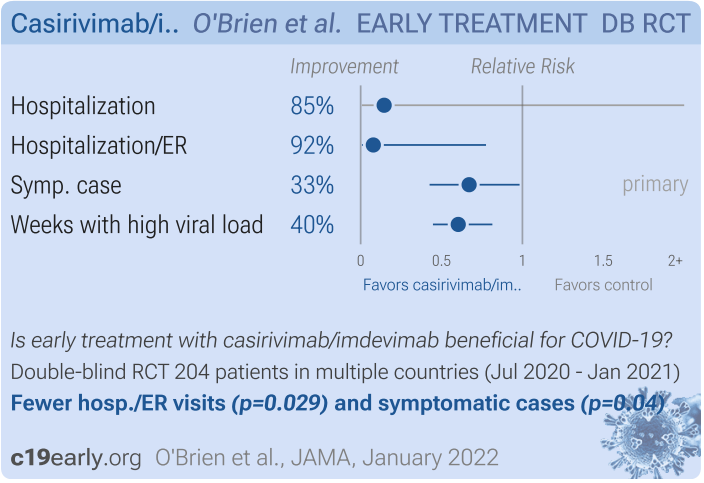
McCreary: Prospective study comparing subcutaneous and intravenous casirivimab/imdevimab, and comparing to a PSM matched control set, showing significantly lower mortality and hospitalization with treatment. Controls were matched with EUA-eligible risk factors only, authors were unable to determine symptom severity.

Miyashita



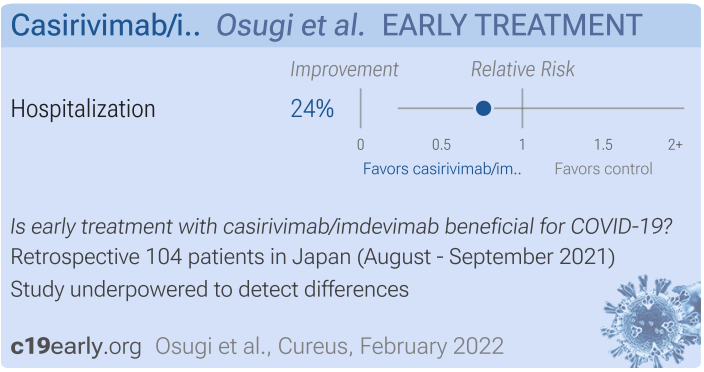
Miyashita: Retrospective 461 patients treated with casirivimab/imdevimab in Japan, and 461 matched controls, showing lower oxygen requirements with treatment.

O'Brien



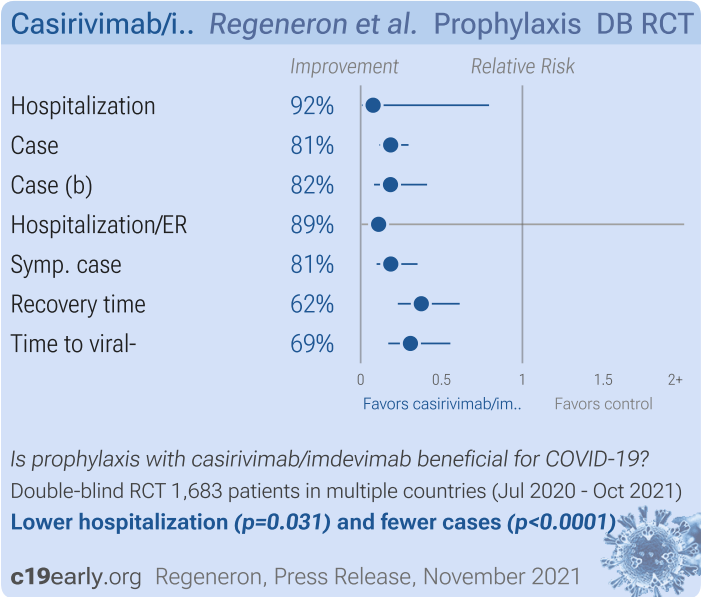
O'Brien: RCT 204 asymptomatic COVID+ patients, 100 treated with subcutaneous casirivimab/imdevimab, showing lower development of symptoms, lower hospitalization, and faster viral clearance with treatment. Study conducted prior to widespread circulation of delta and omicron in the study locations.

Osugi



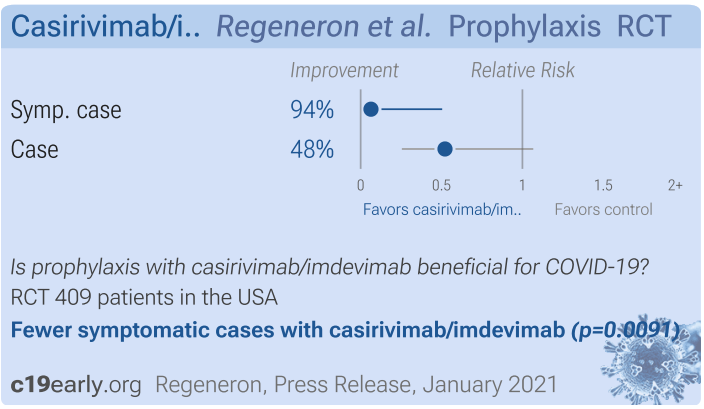
Osugi: Retrospective 104 outpatients in Japan, 30 treated with casirivimab/imdevimab, showing no significant difference in hospitalization.

Regeneron



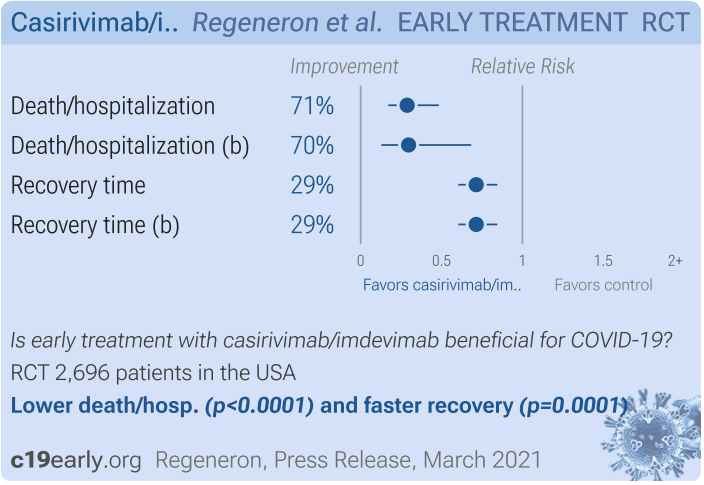
Regeneron (C): Long-term results for PEP RCT NCT04452318, with 841 baseline seronegative casirivimab/imdevimab patients and 842 placebo patients, showing significantly lower cases with treatment.

Regeneron



Regeneron (D): Interim results of REGEN-COV prophylaxis showing 100% prevention of symptomatic infection (8/223 placebo vs. 0/186 REGEN-COV), and approximately 50% lower overall rates of infection (symptomatic and asymptomatic) (23/223 placebo vs. 10/186 REGEN-COV).

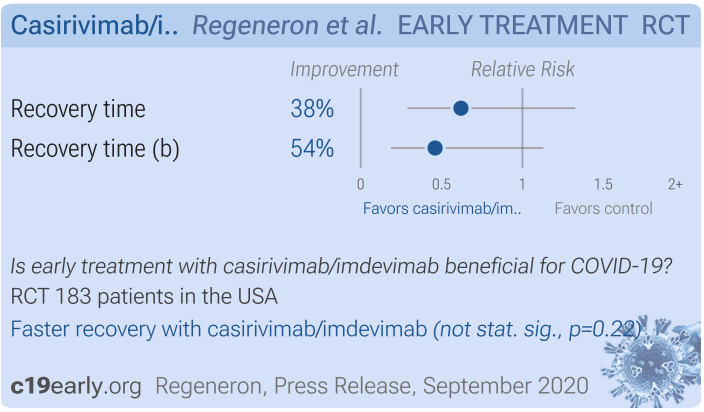
Regeneron



Regeneron: Press release for new phase III data showing lower hospitalization/mortality, and faster symptom resolution among the subset of patients with at least one risk factor.

Some variants may escape antibodies *cell.com*.

Regeneron



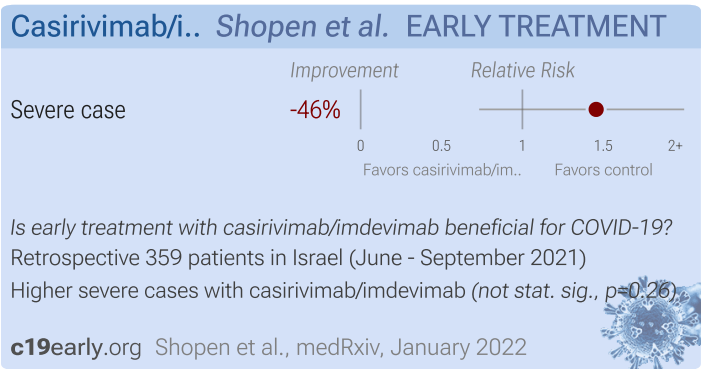
Regeneron (B): Analysis of the first 275 patients in a trial of the REGN-COV2 antibody cocktail showing reductions in viral load and the time to alleviate symptoms in non-hospitalized patients with COVID-19. Greatest improvements were seen with patients that had not mounted their own effective immune response prior to treatment.

The mean time-weighted-average change from baseline nasopharyngeal viral load through Day 7 in the seronegative (no measurable antiviral antibodies) group was a 0.60 log10 copies/mL greater reduction (p=0.03) in patients treated with high dose, and a 0.51 log10 copies/mL greater reduction (p=0.06) in patients treated with low dose, compared to placebo. In the overall population, there was a 0.51 log10 copies/mL greater reduction (p=0.0049) in patients treated with high dose, and a 0.23 log10 copies/mL greater reduction (p=0.20) in patients treated with low dose, compared to placebo.

Among seronegative patients, median time to symptom alleviation (defined as symptoms becoming mild or absent) was 13 days in placebo, 8 days in high dose (p=0.22), and 6 days in low dose (p=0.09).

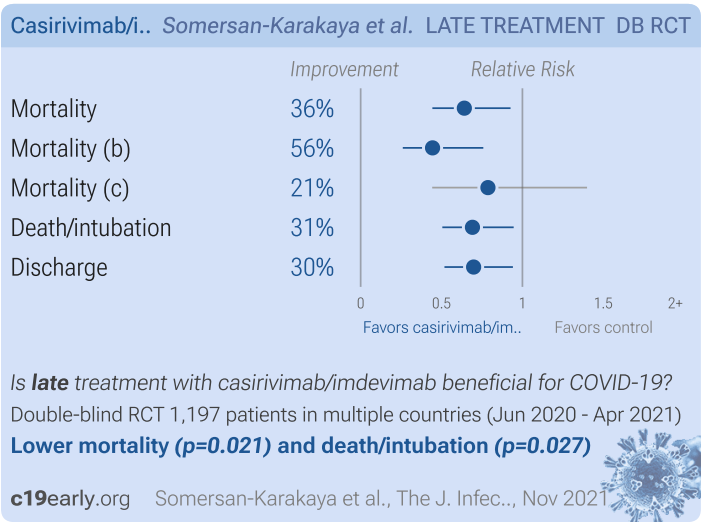
Adverse reactions were similar with treatment and placebo. There were no deaths.

Shopen



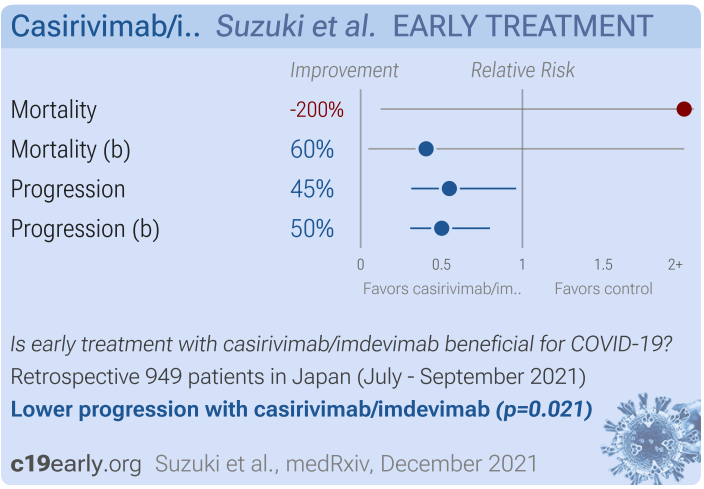
Shopen: Retrospective 359 COVID+ patients in Israel, 116 treated with casirivimab/imdevimab, showing no significant difference with treatment in multivariable analysis.

Somersan-Karakaya



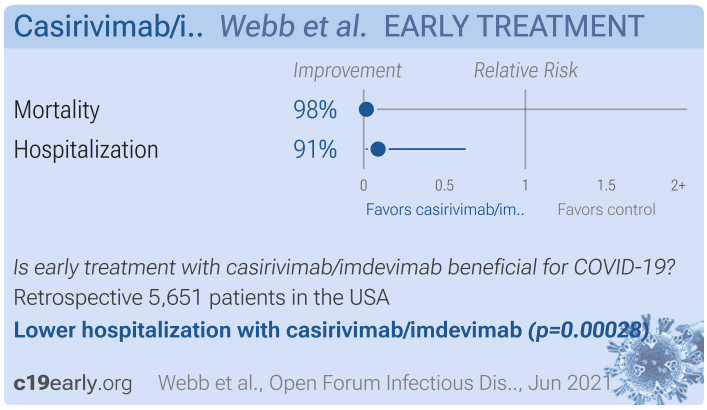
Somersan-Karakaya: RCT 1,336 hospitalized patients with symptom onset <=10 days on low-flow or no supplemental oxygen, showing lower mortality with treatment. Cohorts 2&3 were paused mid-trial due to increased deaths in the treatment arm and these results were not included. NCT04426695.

Suzuki



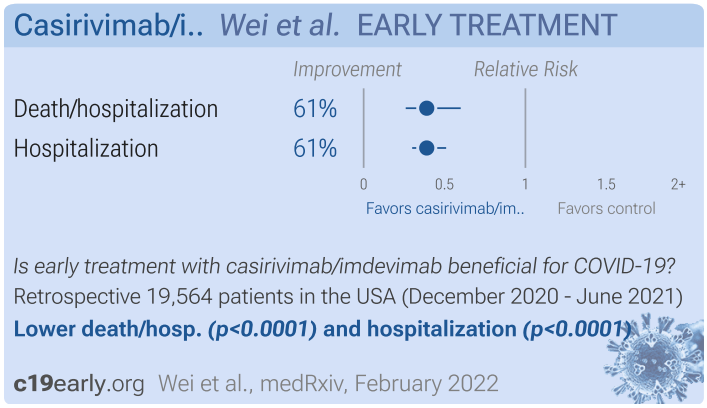
Suzuki: Retrospective 949 patients in Japan, 314 treated with casirivimab/imdevimab showing significantly lower risk of deterioration with treatment.

Webb



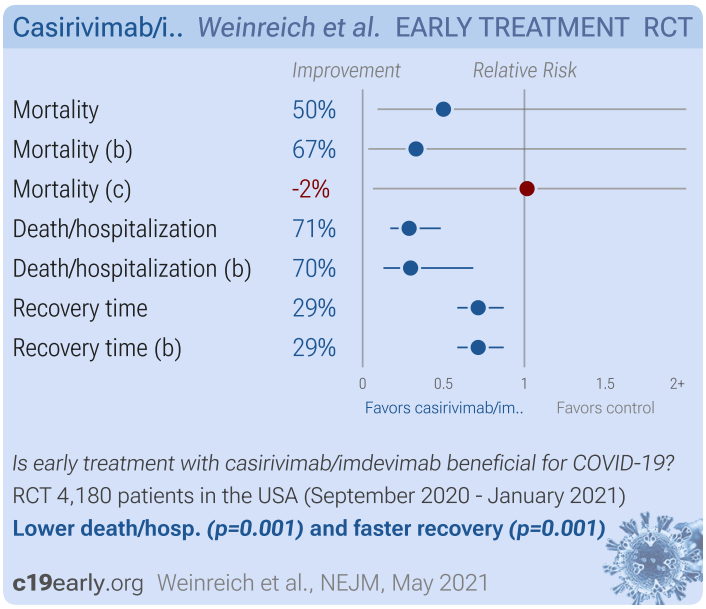
Webb: Retrospective 115 patients treated with casirivimab/imdevimab showing lower mortality, hospital admission, and emergency department visits with treatment. Authors incorrectly state that "no other COVID-19 therapies for ambulatory patients have proven effective".

Wei



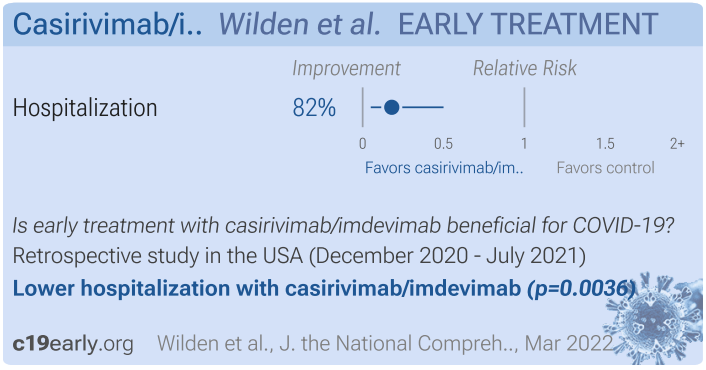
Wei: Retrospective 4,396 casirivimab/imdevimab patients in the USA, showing lower combined mortality/hospitalization (CDM database) and lower hospitalization (PMTX+ database) with treatment.

Weinreich



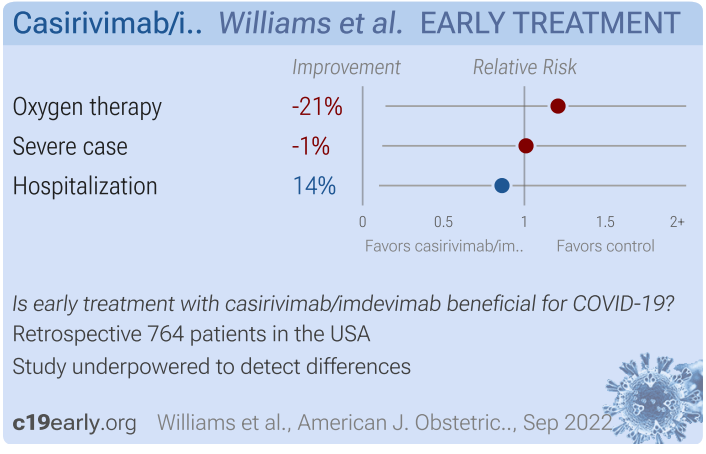
Weinreich: RCT 4,057 outpatients with >=1 risk factor for severe disease, showing significantly lower combined hospitalization/death, and significantly faster recovery with treatment. Median time from onset of symptoms 3 days. NCT04425629.

Wilden



Wilden: Retrospective 395 patients in the USA receiving casirivimab/imdevimab or bamlanivimab, showing lower risk of hospitalization with treatment, statistically significant for casirivimab/imdevimab.

Williams



Williams (B): Retrospective 764 pregnant patients with COVID-19 in the USA, 88 treated with casirivimab/imdevimab, showing no significant difference in outcomes.

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 casirivimab, imdevimab, REGEN-COV 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 casirivimab/imdevimab 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 SpO_2 is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to *Zhang*. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 *Sweeting*. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.12.2) with scipy (1.12.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.1), and plotly (5.19.0).

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

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

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

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

Cooper, 10/8/2021, retrospective, USA, peer-reviewed, 9 authors, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 77.5% lower, RR 0.23, $p = 0.18$, treatment 1 of 1,148 (0.1%), control 33 of 8,534 (0.4%), NNT 334, unadjusted.
	risk of ICU admission, 47.5% lower, RR 0.52, $p = 0.14$, treatment 6 of 1,148 (0.5%), control 85 of 8,534 (1.0%), NNT 211, unadjusted.
	risk of hospitalization, 52.4% lower, RR 0.48, $p < 0.001$, treatment 45 of 1,148 (3.9%), control 703 of 8,534 (8.2%), NNT 23, unadjusted.
Faraone, 5/5/2022, retrospective, Italy, preprint, 12 authors, study period 25 October, 2020 - 30 April, 2021, average treatment delay 2.3 days.	risk of death, 92.2% lower, RR 0.08, $p = 0.03$, treatment 0 of 11 (0.0%), control 8 of 23 (34.8%), NNT 2.9, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of oxygen therapy, 94.5% lower, RR 0.06, $p = 0.02$, treatment 0 of 11 (0.0%), control 15 of 23 (65.2%), NNT 1.5, odds ratio converted to relative risk, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
Gershengorn, 12/2/2022, retrospective, USA, peer-reviewed, 6 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication possible.	risk of hospitalization, 95.0% higher, OR 1.95, $p = 0.09$, treatment 369, control 5,915, adjusted per study, multivariable, day 30, RR approximated with OR.
	risk of hospitalization, 104.9% higher, RR 2.05, $p = 0.009$, treatment 21 of 369 (5.7%), control 41 of 1,476 (2.8%), propensity score matching, day 30, Figure 2, PSM cohort.
	risk of hospitalization, 100% higher, RR 2.00, $p = 0.07$, treatment 11 of 213 (5.2%), control 22 of 852 (2.6%), delta, propensity score matching, day 30, Figure 2, PSM cohort.
	risk of hospitalization, 110.5% higher, RR 2.11, $p = 0.06$, treatment 10 of 156 (6.4%), control 19 of 624 (3.0%), omicron, propensity score matching, day 30, Figure 2, PSM cohort.
Hussein, 12/19/2022, retrospective, USA, peer-reviewed, 9 authors, study period 1 December, 2020 - 30 September, 2021, excluded in exclusion analyses: substantial unadjusted confounding by indication possible.	risk of death/hospitalization, 60.0% lower, HR 0.40, $p < 0.001$, NNT 35, propensity score matching, Cox proportional hazards, day 30.

Kakinoki, 11/4/2021, retrospective, Japan, peer-reviewed, 16 authors, average treatment delay 3.0 days.	risk of further treatment including oxygen or antivirals, 57.6% lower, RR 0.42, $p = 0.049$, treatment 13 of 55 (23.6%), control 22 of 53 (41.5%), NNT 5.6, adjusted per study, odds ratio converted to relative risk, multivariable.
Kip, 4/4/2023, retrospective, USA, peer-reviewed, 16 authors, study period 8 December, 2020 - 31 August, 2022.	risk of death/hospitalization, 46.0% lower, RR 0.54, $p < 0.001$, treatment 61 of 1,479 (4.1%), control 227 of 2,954 (7.7%), NNT 28, mainly delta variant, day 28.
Kneidinger, 9/9/2022, retrospective, Germany, peer-reviewed, 11 authors, study period 1 January, 2022 - 20 March, 2022, lung transplant patients.	risk of severe case, 97.2% lower, RR 0.03, $p = 0.45$, treatment 0 of 3 (0.0%), control 34 of 215 (15.8%), NNT 6.3, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
Komagamine, 12/19/2021, retrospective, Japan, peer-reviewed, 4 authors, average treatment delay 5.0 days.	risk of mechanical ventilation, 77.3% lower, RR 0.23, $p = 0.51$, treatment 0 of 53 (0.0%), control 2 of 75 (2.7%), NNT 38, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of ICU admission, 92.3% lower, RR 0.08, $p = 0.04$, treatment 0 of 53 (0.0%), control 7 of 75 (9.3%), NNT 11, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of progression, 67.8% lower, RR 0.32, $p = 0.006$, treatment 8 of 53 (15.1%), control 33 of 75 (44.0%), NNT 3.5, adjusted per study, odds ratio converted to relative risk, multivariable, primary outcome.
	hospitalization time, 28.9% lower, relative time 0.71, $p < 0.001$, treatment 53, control 75.
Levey, 6/4/2022, retrospective, USA, peer-reviewed, 6 authors, study period March 2021 - October 2021.	risk of ICU admission, 30.6% lower, RR 0.69, $p = 1.00$, treatment 1 of 36 (2.8%), control 2 of 50 (4.0%), NNT 82.
	risk of oxygen therapy, 7.4% lower, RR 0.93, $p = 1.00$, treatment 2 of 36 (5.6%), control 3 of 50 (6.0%), NNT 225.
	risk of hospitalization, 108.3% higher, RR 2.08, $p = 0.15$, treatment 9 of 36 (25.0%), control 6 of 50 (12.0%).
Miyashita, 5/26/2022, retrospective, Japan, peer-reviewed, 6 authors, average treatment delay 4.0 days.	risk of mechanical ventilation, 33.3% lower, RR 0.67, $p = 1.00$, treatment 2 of 461 (0.4%), control 3 of 461 (0.7%), NNT 461.
	risk of oxygen therapy, 46.4% lower, RR 0.54, $p = 0.004$, treatment 30 of 461 (6.5%), control 56 of 461 (12.1%), NNT 18.
O'Brien, 1/14/2022, Double Blind Randomized Controlled Trial, placebo-controlled, multiple countries, peer-reviewed, 38 authors, study period 13 July, 2020 - 28 January, 2021.	risk of hospitalization, 85.5% lower, RR 0.15, $p = 0.25$, treatment 0 of 100 (0.0%), control 3 of 104 (2.9%), NNT 35, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization/ER, 92.2% lower, RR 0.08, $p = 0.03$, treatment 0 of 100 (0.0%), control 6 of 104 (5.8%), NNT 17, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).

	risk of symptomatic case, 33.0% lower, RR 0.67, *p* = 0.04, treatment 29 of 100 (29.0%), control 44 of 104 (42.3%), NNT 7.5, odds ratio converted to relative risk, day 14, primary outcome.
	relative weeks with high viral load, 39.7% better, RR 0.60, *p* = 0.001, treatment 100, control 104.
Osugi, 2/3/2022, retrospective, Japan, peer-reviewed, mean age 47.8, 5 authors, study period 31 August, 2021 - 27 September, 2021.	risk of hospitalization, 24.0% lower, HR 0.76, *p* = 0.65, treatment 4 of 30 (13.3%), control 15 of 74 (20.3%), adjusted per study, multivariable, Cox proportional hazards.
Regeneron, 3/23/2021, Randomized Controlled Trial, USA, preprint, 1 author.	risk of death/hospitalization, 71.3% lower, RR 0.29, *p* < 0.001, treatment 18 of 1,355 (1.3%), control 62 of 1,341 (4.6%), NNT 30, 2,400mg IV, >=1 risk factor.
	risk of death/hospitalization, 70.4% lower, RR 0.30, *p* = 0.003, treatment 7 of 736 (1.0%), control 24 of 748 (3.2%), NNT 44, 1,200mg IV, >=1 risk factor.
	recovery time, 28.6% lower, relative time 0.71, *p* < 0.001, treatment 1,355, control 1,341, 2,400mg IV, >=1 risk factor.
	recovery time, 28.6% lower, relative time 0.71, *p* < 0.001, treatment 736, control 748, 1,200mg IV, >=1 risk factor.
Regeneron (B), 9/29/2020, Randomized Controlled Trial, USA, preprint, 1 author.	recovery time, 38.0% lower, relative time 0.62, *p* = 0.22, treatment 92, control 91, high dose median time to recovery, group sizes estimated because they were not supplied.
	recovery time, 54.0% lower, relative time 0.46, *p* = 0.09, treatment 92, control 91, low dose median time to recovery, group sizes estimated because they were not supplied.
Shopen, 1/31/2022, retrospective, Israel, preprint, 11 authors, study period June 2021 - September 2021.	risk of severe case, 45.6% higher, RR 1.46, *p* = 0.26, treatment 24 of 116 (20.7%), control 26 of 243 (10.7%), adjusted per study, odds ratio converted to relative risk.
Suzuki, 12/21/2021, retrospective, Japan, preprint, 49 authors, study period 24 July, 2021 - 30 September, 2021.	risk of death, 200.0% higher, RR 3.00, *p* = 1.00, treatment 1 of 222 (0.5%), control 0 of 222 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), propensity score matching.
	risk of death, 59.6% lower, RR 0.40, *p* = 0.67, treatment 1 of 314 (0.3%), control 5 of 635 (0.8%), NNT 213, unadjusted.
	risk of progression, 45.2% lower, RR 0.55, *p* = 0.02, treatment 17 of 222 (7.7%), control 31 of 222 (14.0%), NNT 16, propensity score matching.
	risk of progression, 49.9% lower, RR 0.50, *p* = 0.002, treatment 34 of 314 (10.8%), control 70 of 365 (19.2%), NNT 12, odds ratio converted to relative risk, multivariate.
Webb, 6/23/2021, retrospective, USA, peer-reviewed, 14 authors.	risk of death, 98.3% lower, RR 0.02, *p* = 0.63, treatment 0 of 115 (0.0%), control 57 of 5,536 (1.0%), NNT 97, relative risk is not 0 because of continuity correction due to zero events (with

	reciprocal of the contrasting arm).
	risk of hospitalization, 91.1% lower, RR 0.09, $p < 0.001$, treatment 1 of 115 (0.9%), control 538 of 5,536 (9.7%), NNT 11.
Wei, 2/28/2022, retrospective, database analysis, USA, preprint, 8 authors, study period December 2020 - June 2021.	risk of death/hospitalization, 61.0% lower, HR 0.39, $p < 0.001$, treatment 23 of 1,116 (2.1%), control 27 of 5,291 (0.5%), Optum CDM, Cox proportional hazards.
	risk of hospitalization, 61.0% lower, HR 0.39, $p < 0.001$, treatment 59 of 3,280 (1.8%), control 75 of 16,284 (0.5%), IQVIA PMTX+, Cox proportional hazards.
Weinreich, 5/21/2021, Randomized Controlled Trial, USA, peer-reviewed, 39 authors, study period 24 September, 2020 - 17 January, 2021, average treatment delay 3.0 days, trial NCT04425629 (history).	risk of death, 50.0% lower, RR 0.50, $p = 0.45$, treatment 2 of 2,091 (0.1%), control 4 of 2,089 (0.2%), NNT 1044, Table S9.
	risk of death, 67.0% lower, RR 0.33, $p = 0.37$, treatment 1 of 1,355 (0.1%), control 3 of 1,341 (0.2%), NNT 667, 2400mg,Table S9.
	risk of death, 1.6% higher, RR 1.02, $p = 1.00$, treatment 1 of 736 (0.1%), control 1 of 748 (0.1%), 1200mg,Table S9.
	risk of death/hospitalization, 71.3% lower, RR 0.29, $p < 0.001$, treatment 18 of 1,355 (1.3%), control 62 of 1,341 (4.6%), NNT 30, 2400mg.
	risk of death/hospitalization, 70.4% lower, RR 0.30, $p = 0.002$, treatment 7 of 736 (1.0%), control 24 of 748 (3.2%), NNT 44, 1200mg.
	recovery time, 28.6% lower, relative time 0.71, $p < 0.001$, treatment 1,355, control 1,341, 2400mg.
	recovery time, 28.6% lower, relative time 0.71, $p < 0.001$, treatment 736, control 748, 1200mg.
Wilden, 3/31/2022, retrospective, USA, peer-reviewed, 9 authors, study period December 2020 - July 2021.	risk of hospitalization, 82.0% lower, OR 0.18, $p = 0.004$, adjusted per study, multivariable, RR approximated with OR.
Williams (B), 9/12/2022, retrospective, USA, peer-reviewed, 6 authors.	risk of oxygen therapy, 20.8% higher, RR 1.21, $p = 0.87$, treatment 1 of 88 (1.1%), control 6 of 676 (0.9%), odds ratio converted to relative risk.
	risk of severe case, 1.0% higher, RR 1.01, $p = 0.99$, treatment 1 of 88 (1.1%), control 7 of 676 (1.0%), odds ratio converted to relative risk.
	risk of hospitalization, 13.9% lower, RR 0.86, $p = 0.90$, treatment 1 of 88 (1.1%), control 8 of 676 (1.2%), NNT 2125, odds ratio converted to relative risk.

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.

Horby, 6/16/2021, Randomized Controlled Trial, United Kingdom, peer-reviewed, 32 authors, study period 18 September, 2020 - 22 May, 2021, average treatment delay 9.0 days.	**risk of death, 6.0% lower, RR 0.94, $p = 0.16$**, treatment 943 of 4,839 (19.5%), control 1,029 of 4,946 (20.8%), NNT 76, all patients.
	risk of mechanical ventilation, 1.0% higher, RR 1.01, $p = 0.88$, treatment 484 of 4,556 (10.6%), control 488 of 4,642 (10.5%), all patients.
	risk of death, 21.0% lower, RR 0.79, $p = 0.001$, treatment 396 of 1,633 (24.2%), control 452 of 1,520 (29.7%), NNT 18, seronegative patients.
	risk of mechanical ventilation, 13.0% lower, RR 0.87, $p = 0.13$, treatment 190 of 1,599 (11.9%), control 202 of 1,484 (13.6%), NNT 58, seronegative patients.
McCreary, 12/1/2021, prospective, USA, preprint, 27 authors, study period 14 July, 2021 - 26 October, 2021, average treatment delay 6.0 days.	**risk of death, 93.0% lower, RR 0.07, $p = 0.009$**, treatment 1 of 652 (0.2%), control 29 of 1,304 (2.2%), NNT 48, propensity score matching.
	risk of death/hospitalization, 56.0% lower, RR 0.44, $p < 0.001$, treatment 22 of 652 (3.4%), control 101 of 1,304 (7.7%), NNT 23, propensity score matching, primary outcome.
	risk of hospitalization, 48.0% lower, RR 0.52, $p = 0.005$, treatment 22 of 652 (3.4%), control 85 of 1,304 (6.5%), NNT 32, propensity score matching.
	risk of hospitalization/ER, 40.0% lower, RR 0.60, $p = 0.003$, treatment 40 of 652 (6.1%), control 133 of 1,304 (10.2%), NNT 25, propensity score matching.
Somersan-Karakaya, 11/8/2021, Double Blind Randomized Controlled Trial, placebo-controlled, multiple countries, peer-reviewed, median age 62.0, 34 authors, study period 10 June, 2020 - 9 April, 2021, average treatment delay 6.0 days, trial NCT04426695 (history), conflicts of interest: research funding from the drug patent holder, employee of the drug patent holder.	**risk of death, 35.9% lower, RR 0.64, $p = 0.02$**, treatment 59 of 804 (7.3%), control 45 of 393 (11.5%), NNT 24, day 28, mFAS.
	risk of death, 55.6% lower, RR 0.44, $p = 0.005$, treatment 24 of 360 (6.7%), control 24 of 160 (15.0%), NNT 12, seronegative, day 28, mFAS.
	risk of death, 21.3% lower, RR 0.79, $p = 0.42$, treatment 26 of 369 (7.0%), control 18 of 201 (9.0%), NNT 52, seropositive, day 28, mFAS.
	risk of death/intubation, 30.9% lower, RR 0.69, $p = 0.03$, treatment 82 of 804 (10.2%), control 58 of 393 (14.8%), NNT 22, day 1-29, mFAS.
	risk of no hospital discharge, 30.2% lower, RR 0.70, $p = 0.02$, treatment 90 of 804 (11.2%), control 63 of 393 (16.0%), NNT 21, day 1-29, mFAS.

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.

Isa, 11/16/2021, Double Blind Randomized Controlled Trial, USA, preprint, 31 authors, study period 26 July, 2020 - 21 May, 2021, trial NCT04519437 (history), conflicts of interest: employee of the drug patent holder.	risk of symptomatic case, 92.6% lower, RR 0.07, $p = 0.002$, treatment 3 of 729 (0.4%), control 13 of 240 (5.4%), NNT 20, odds ratio converted to relative risk.
	risk of case, 92.7% lower, RR 0.07, $p = 0.002$, treatment 0 of 729 (0.0%), control 10 of 240 (4.2%), NNT 24, odds ratio converted to relative risk, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), seroconversion.
Regeneron (C), 11/8/2021, Double Blind Randomized Controlled Trial, multiple countries, preprint, 1 author, study period 13 July, 2020 - 4 October, 2021, trial NCT04452318 (history).	risk of hospitalization, 92.3% lower, RR 0.08, $p = 0.03$, treatment 0 of 841 (0.0%), control 6 of 842 (0.7%), NNT 140, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), 8 months.
	risk of case, 81.5% lower, RR 0.19, $p < 0.001$, treatment 20 of 841 (2.4%), control 108 of 842 (12.8%), NNT 9.6, months 1-8.
	risk of case, 81.6% lower, RR 0.18, $p < 0.001$, treatment 7 of 841 (0.8%), control 38 of 842 (4.5%), NNT 27, months 2-8.
	risk of hospitalization/ER, 88.9% lower, RR 0.11, $p = 0.06$, treatment 0 of 753 (0.0%), control 4 of 752 (0.5%), NNT 188, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 29.
	risk of symptomatic case, 81.4% lower, RR 0.19, $p < 0.001$, treatment 11 of 753 (1.5%), control 59 of 752 (7.8%), NNT 16, day 29.
	recovery time, 62.5% lower, relative time 0.37, $p < 0.001$, treatment 753, control 752, short-term followup, relative time with symptoms.
	time to viral-, 69.2% lower, relative time 0.31, $p < 0.001$, treatment 753, control 752, short-term followup, relative time with high viral load.
Regeneron (D), 1/26/2021, Randomized Controlled Trial, USA, preprint, 1 author.	risk of symptomatic case, 93.6% lower, RR 0.06, $p = 0.009$, treatment 0 of 186 (0.0%), control 8 of 223 (3.6%), NNT 28, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of case, 47.9% lower, RR 0.52, $p = 0.07$, treatment 10 of 186 (5.4%), control 23 of 223 (10.3%), NNT 20.

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. **Als-Nielsen** et al., *Association of Funding and Conclusions in Randomized Drug Trials*, JAMA, doi:10.1001/jama.290.7.921.
2. **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.
3. **Altman**, D., *How to obtain the P value from a confidence interval*, BMJ, doi:10.1136/bmj.d2304.
4. **Altman (B)** et al., *How to obtain the confidence interval from a P value*, BMJ, doi:10.1136/bmj.d2090.
5. **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.
6. **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.
7. ***c19early.org***, c19early.org/timeline.html.
8. ***c19early.org (B)***, c19early.org/treatments.html.
9. ***c19early.org (C)***, c19early.org/p.
10. ***c19early.org (D)***, c19early.org/ph.
11. ***c19early.org (E)***, c19early.org/d.
12. ***cell.com***, www.cell.com/cell/fulltext/S0092-8674(21)00367-6.
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. **Cooper** et al., *Real-world Assessment of 2,879 COVID-19 Patients Treated with Monoclonal Antibody Therapy: A Propensity Score-Matched Cohort Study*, Open Forum Infectious Diseases, doi:10.1093/ofid/ofab512.
16. **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.
17. **Davis** et al., *The Promise and Peril of Anti-SARS-CoV-2 Monoclonal Antibodies*, Clinical Infectious Diseases, doi:10.1093/cid/ciac902.
18. **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.
19. **Deaton** et al., *Understanding and misunderstanding randomized controlled trials*, Social Science & Medicine, 210, doi:10.1016/j.socscimed.2017.12.005.
20. **Deng**, H., *PyMeta, Python module for meta-analysis*, www.pymeta.com/.

21. **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.

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

23. **Faraone** et al., *REGEN-COV antibody cocktail (casirivimab/imdevimab) for the treatment of inpatients with early hospital-acquired COVID-19: a single center experience*, Research Square, doi:10.21203/rs.3.rs-1170976/v1.

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.drup.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.drup.2023.100991.

28. **Gershengorn** et al., *The clinical effectiveness of REGEN-COV in SARS-CoV-2 infection with Omicron versus Delta variants*, PLOS ONE, doi:10.1371/journal.pone.0278770.

29. **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/.

30. **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.

31. **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.

32. **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.

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

34. **Horby** et al., *Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial*, The Lancet, doi:10.1016/S0140-6736(22)00163-5.

35. **Hussein** et al., *Real-world effectiveness of casirivimab and imdevimab among patients diagnosed with COVID-19 in the ambulatory setting: a retrospective cohort study using a large claims database*, BMJ Open, doi:10.1136/bmjopen-2022-064953.

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

37. **Isa** et al., *Repeat Subcutaneous Administration of REGEN-COV® in Adults is Well-Tolerated and Prevents the Occurrence of COVID-19*, medRxiv, doi:10.1101/2021.11.10.21265889.

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

39. **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.

40. **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.

41. **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.

42. **Kakinoki** et al., *Impact of Antibody Cocktail Therapy Combined with Casirivimab and Imdevimab on Clinical Outcome for Covid-19 patients in A Real-Life Setting: A Single Institute Analysis*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2022.01.067.

43. **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.

44. **Kip** et al., *Evolving Real-World Effectiveness of Monoclonal Antibodies for Treatment of COVID-19*, Annals of Internal Medicine, doi:10.7326/M22-1286.

45. **Kneidinger** et al., *Outcome of lung transplant recipients infected with SARS-CoV-2/Omicron/B.1.1.529: a Nationwide German study*, Infection, doi:10.1007/s15010-022-01914-8.

46. **Komagamine** et al., *The effect of casirivimab with imdevimab on disease progression in nonsevere COVID-19 patients in a single hospital in Japan*, Journal of General and Family Medicine, doi:10.1002/jgf2.516.

47. **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.

48. **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.

49. **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.

50. **Levey** et al., *Outcomes of pregnant patients treated with REGEN-COV during the COVID-19 pandemic*, American Journal of Obstetrics & Gynecology MFM, doi:10.1016/j.ajogmf.2022.100673.

51. **Liu** et al., *Striking Antibody Evasion Manifested by the Omicron Variant of SARS-CoV-2*, bioRxiv, doi:10.1101/2021.12.14.472719.

52. **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.

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

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

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

56. **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.

57. **McCreary** et al., *Association of subcutaneous or intravenous route of administration of casirivimab and imdevimab monoclonal antibodies with clinical outcomes in COVID-19*, medRxiv, doi:10.1101/2021.11.30.21266756.

58. **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.

59. **Miyashita** et al., *Clinical efficacy of casirivimab-imdevimab antibody combination treatment in patients with COVID-19 Delta variant*, Journal of Infection and Chemotherapy, doi:10.1016/j.jiac.2022.05.012.

60. **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.

61. **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.

62. **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.

63. **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.

64. **O'Brien** et al., *Effect of Subcutaneous Casirivimab and Imdevimab Antibody Combination vs Placebo on Development of Symptomatic COVID-19 in Early Asymptomatic SARS-CoV-2 Infection: A Randomized Clinical Trial*, JAMA, doi:10.1001/jama.2021.24939768.

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

66. **Osugi** et al., *Clinical Prognosis of Patients With Mild COVID-19 Treated With Casirivimab/Imdevimab in Japan*, Cureus, doi:10.7759/cureus.21882.

67. **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.

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

69. **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.

70. **Regeneron**, *New phase III data shows investigational antibody cocktail casirivimab and imdevimab reduced hospitalisation or death by 70% in non-hospitalised patients with COVID-19*, Press Release, www.roche.com/media/releases/med-cor-2021-03-23.htm.

71. **Regeneron (B)**, *Regeneron's REGN-COV2 antibody cocktail reduced viral levels and improved symptoms in non-hospitalized COVID-19 patients*, Press Release, investor.regeneron.com/news-releases/news-release-details/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and.

72. **Regeneron (C)**, *New phase 3 analyses show that a single dose of REGEN-COV® (casirivimab and imdevimab) provides long-term protection against COVID-19*, Press Release, newsroom.regeneron.com/news-releases/news-release-details/new-phase-3-analyses-show-single-dose-regen-covr-casirivimab-and.

73. **Regeneron (D)**, *Regeneron Reports Positive Interim Data with REGEN-COV™ Antibody Cocktail used as Passive Vaccine to Prevent COVID-19*, Press Release, www.prnewswire.com/news-releases/regeneron-reports-positive-interim-data-with-regen-cov-antibody-cocktail-used-as-passive-vaccine-to-prevent-covid-19-301214619.html.

74. **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.

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

76. **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.

77. **Scardua-Silva** et al., *Microstructural brain abnormalities, fatigue, and cognitive dysfunction after mild COVID-19*, Scientific Reports, doi:10.1038/s41598-024-52005-7.

78. **Sheward** et al., *Variable loss of antibody potency against SARS-CoV-2 B.1.1.529 (Omicron)*, bioRxiv, doi:10.1101/2021.12.19.473354.

79. **Shimizu** et al., *Reevaluation of antibody-dependent enhancement of infection in anti-SARS-CoV-2 therapeutic antibodies and mRNA-vaccine antisera using FcR- and ACE2-positive cells*, Scientific Reports, doi:10.1038/s41598-022-19993-w.

80. **Shopen** et al., *Doubtful Clinical Benefit of Casirivimab-Imdevimab Treatment for Disease Severity Outcome of High-Risk Patients with SARS-CoV-2 Delta Variant Infection*, medRxiv, doi:10.1101/2022.01.29.22270090.

81. **Somersan-Karakaya** et al., *Casirivimab and Imdevimab for the Treatment of Hospitalized Patients With COVID-19*, The Journal of Infectious Diseases, doi:10.1093/infdis/jiac320.

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

83. **Suzuki** et al., *Real-world clinical outcomes of treatment with casirivimab-imdevimab among patients with mild-to-moderate coronavirus disease 2019 during the Delta variant pandemic*, medRxiv, doi:10.1101/2021.12.19.21268078.

84. **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.

85. **Tatham** et al., *Lack of Ronapreve (REGN-CoV; casirivimab and imdevimab) virological efficacy against the SARS-CoV 2 Omicron variant (B.1.1.529) in K18-hACE2 mice*, bioRxiv, doi:10.1101/2022.01.23.477397.

86. **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.

87. **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.

88. **VanBlargan** et al., *An infectious SARS-CoV-2 B.1.1.529 Omicron virus escapes neutralization by several therapeutic monoclonal antibodies*, bioRxiv, doi:10.1101/2021.12.15.472828.

89. **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.

90. **Webb** et al., *Real-World Effectiveness and Tolerability of Monoclonal Antibody Therapy for Ambulatory Patients with Early COVID-19*, Open Forum Infectious Diseases, doi:10.1093/ofid/ofab331.

91. **Wei** et al., *Real-world Effectiveness of Casirivimab and Imdevimab in Patients With COVID-19 in the Ambulatory Setting: An Analysis of Two Large US National Claims Databases*, medRxiv, doi:10.1101/2022.02.28.22270796.

92. **Weinreich** et al., *REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19*, NEJM, doi:10.1056/NEJMoa2108163.

93. **Wicaksono** et al., *Efficacy and safety of casirivimab-imdevimab combination on COVID-19 patients: A systematic review and meta-analysis randomized controlled trial*, Heliyon, doi:10.1016/j.heliyon.2023.e22839.

94. **Wilcock** et al., *Clinical Risk and Outpatient Therapy Utilization for COVID-19 in the Medicare Population*, JAMA Health Forum, doi:10.1001/jamahealthforum.2023.5044.

95. **Wilden** et al., *Real World Outcomes of Cancer Patients With SARS-CoV-2 Infection Receiving Monoclonal Antibodies*, Journal of the National Comprehensive Cancer Network, doi:10.6004/jnccn.2021.7309.

96. **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.

97. **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.

98. **Williams (B)** et al., *Effectiveness of REGEN-COV combination monoclonal antibody infusion to reduce risk of COVID-19 hospitalization in pregnancy: A retrospective cohort study*, American Journal of Obstetrics and Gynecology, doi:10.1016/j.ajog.2022.09.017.

99. **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.

100. **Yang** et al., *SARS-CoV-2 infection causes dopaminergic neuron senescence*, Cell Stem Cell, doi:10.1016/j.stem.2023.12.012.

101. **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.

102. **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.

103. **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.