Casirivimab/imdevimab reduced COVID-19 risk: real-time meta analysis of 34 studies

@CovidAnalysis, July 2025, Version 51
https://c19early.org/rmeta.html

Abstract

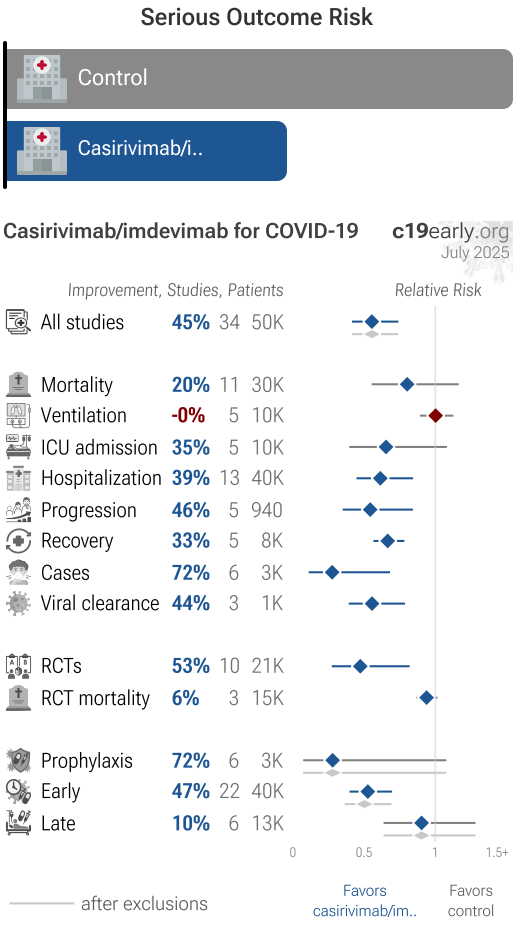
Significantly lower risk is seen for hospitalization, progression, recovery, cases, and viral clearance. 22 studies from 16 independent teams in 5 countries show significant benefit.

Meta analysis using the most serious outcome reported shows 45% [26-58%] lower risk. Results are similar for Randomized Controlled Trials and higher quality studies and slightly worse for peer-reviewed studies. Early treatment is more effective than late treatment.

Results are robust — in exclusion sensitivity analysis 12 of 34 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

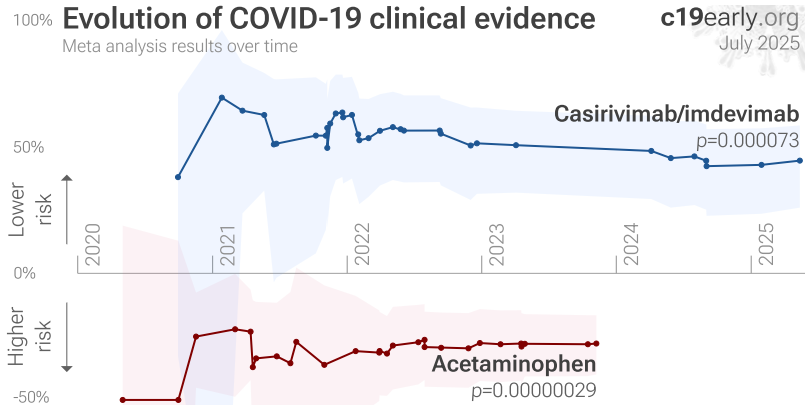
Efficacy is variant dependent. *In Vitro* studies suggest a lack of efficacy for many omicron variants [1-7]. ADE shown *In Vitro* [8]. mAb use may create new variants that spread globally [9-11], and may be associated with prolonged viral loads, clinical deterioration, and immune escape [10,12-14].

Prescription treatments have been preferentially used by patients at lower risk [15]. 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 is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. All data and sources to reproduce this analysis are in the appendix.

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



CASIRIVIMAB/IMDEVIMAB FOR COVID-19 — HIGHLIGHTS

Casirivimab/imdevimab reduces risk with very high confidence for hospitalization, progression, recovery, cases, viral clearance, and in pooled analysis, and low confidence for ICU admission.

Efficacy is variant dependent.

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

Early treatment and prophylaxis are more effective than late treatment.

18th treatment shown effective in March 2021, now with $p = 0.000073$ from 34 studies, recognized in 52 countries.

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

34 casirivimab/imdevimab COVID-19 studies

c19early.org
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	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
Shahnawaz	86%	0.14 [0.01-2.71]	death	0/85	3/84
Early treatment	47%	0.53 [0.40-0.70]		151/9,025	534/34,031

47% lower risk

$Tau^2 = 0.14$, $I^2 = 63.0\%$, $p < 0.0001$

	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)	3%	0.97 [0.56-1.69]	death	804 (n)	393 (n)
McCreary (PSM)	93%	0.07 [0.01-0.51]	death	1/652	29/1,304
Iustila-Maran (ICU)	-16%	1.16 [0.53-2.54]	death	14/50	7/29
Shah	-14%	1.14 [0.45-2.91]	death	8/50	7/50
Chua (PSM)	80%	0.20 [0.01-3.77]	ventilation	0/32	3/96
Late treatment	10%	0.90 [0.64-1.28]		966/6,427	1,075/6,818

ICU patients

10% lower risk

$Tau^2 = 0.06$, $I^2 = 37.9\%$, $p = 0.58$

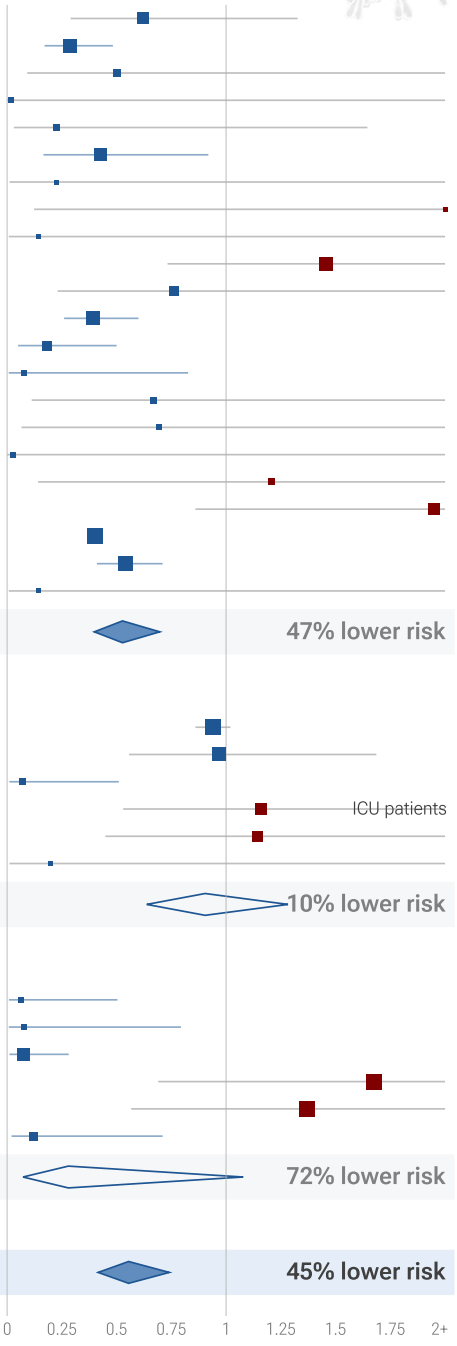
	Improvement	RR [CI]		Treatment	Control
Regeneron (RCT)	94%	0.06 [0.01-0.50]	symp. case	0/186	8/223
Regeneron (DB RCT)	92%	0.08 [0.01-0.79]	hosp.	0/841	6/842
Isa (DB RCT)	93%	0.07 [0.01-0.28]	symp. case	3/729	13/240
Bes-Berlandier	-67%	1.67 [0.69-4.06]	progression	5/17	13/74
Isa (RCT)	-37%	1.37 [0.57-3.32]	symp. case	35/245	5/48
Ohtani	88%	0.12 [0.02-0.71]	cases	14 (n)	38 (n)
Prophylaxis	72%	0.28 [0.07-1.08]		43/2,032	45/1,465

72% lower risk

$Tau^2 = 2.07$, $I^2 = 81.4\%$, $p = 0.064$

All studies	45%	0.55 [0.42-0.74]		1,160/17,484	1,654/42,314

45% lower risk



$Tau^2 = 0.33$, $I^2 = 91.7\%$, $p < 0.0001$

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

Favors casirivimab/im..

Favors control

A

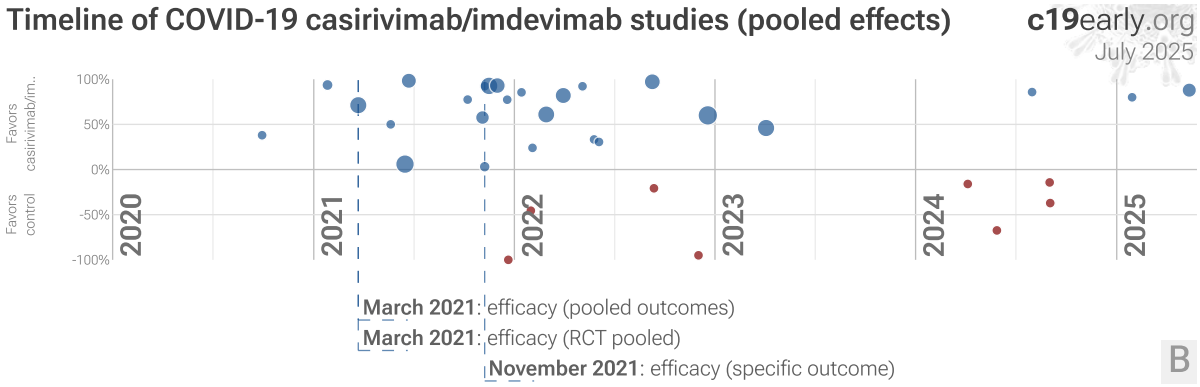


***Figure 1.* A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in 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 injury[18-30] and cognitive deficits[21,26], cardiovascular complications[31-35], organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits[36]—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Minimizing replication as early as possible is recommended.

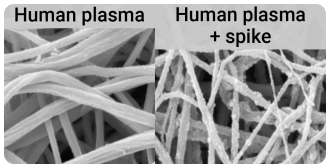


***Figure 2.* SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from[17].**

Many treatments are expected to modulate infection

SARS-CoV-2 infection and replication involves the complex interplay of 100+ host and viral proteins and other factors[A,37-44], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 9,000 compounds may reduce COVID-19 risk[45], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Monoclonal antibodies

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

Analysis

We analyze all significant controlled studies of 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 3 shows stages of possible treatment for COVID-19. Prophylaxis refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. Early Treatment refers to treatment immediately or soon after symptoms appear, while Late Treatment refers to more delayed treatment.

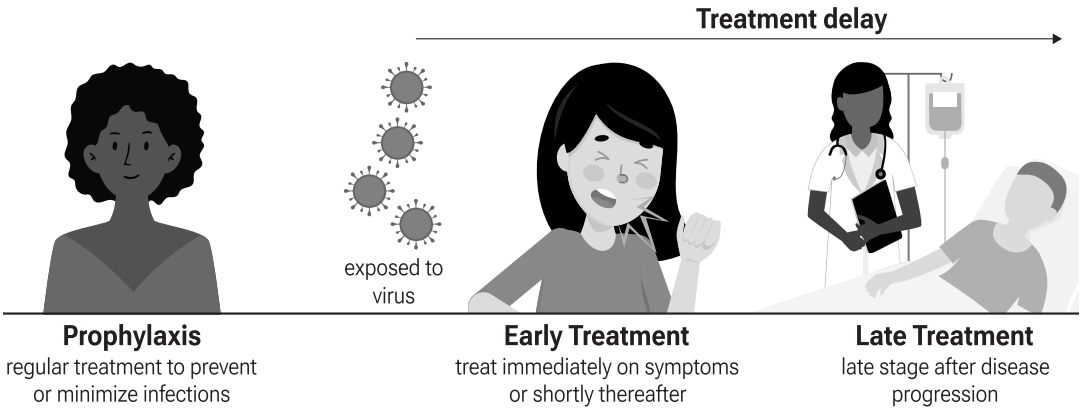


Figure 3. Treatment stages.

Variant Dependence

Extensive mutations in SARS-CoV-2 have resulted in variants that evade neutralizing antibodies from monoclonal antibody treatments [46,47], resulting in efficacy that is highly variant dependent. While the FDA has suspended the EUA for casirivimab/imdevimab due to a predicted lack of efficacy, it may retain efficacy for certain post-suspension variants [48]. Table 1 shows efficacy by variant for several monoclonal antibodies. This table covers earlier SARS-CoV-2 variants and has not been updated for more recent variants.

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

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

Results

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

	Relative Risk	Studies	Patients
All studies	0.55 [0.42-0.74] ****	34	50K
After exclusions	0.56 [0.42-0.74] ****	31	40K
Peer-reviewed	0.68 [0.47-0.97] *	22	40K
RCTs	0.47 [0.27-0.82] **	10	20K
Mortality	0.80 [0.55-1.16]	11	30K
Ventilation	1.00 [0.89-1.13]	5	10K
ICU admission	0.65 [0.40-1.08]	5	10K
Hospitalization	0.61 [0.45-0.84] **	13	40K
Recovery	0.67 [0.57-0.78] ****	5	8,277
Cases	0.28 [0.11-0.68] **	6	3,610
Viral	0.56 [0.39-0.79] **	3	1,878
RCT mortality	0.94 [0.87-1.02]	3	10K

Table 2. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes.** Results show the relative risk with treatment and the 95% confidence interval. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

	Early treatment	Late treatment	Prophylaxis
All studies	0.53 [0.40-0.70] ****	0.90 [0.64-1.28]	0.28 [0.07-1.08]
After exclusions	0.50 [0.36-0.69] ****	0.90 [0.64-1.28]	0.28 [0.07-1.08]
Peer-reviewed	0.51 [0.38-0.68] ****	0.94 [0.87-1.02]	1.51 [0.81-2.83]
RCTs	0.37 [0.24-0.58] ****	0.94 [0.87-1.02]	0.18 [0.02-1.32]
Mortality	0.32 [0.11-0.89] *	0.92 [0.65-1.31]	
Ventilation	0.50 [0.11-2.34]	1.01 [0.90-1.13]	
ICU admission	0.47 [0.22-1.00] *	0.69 [0.22-2.13]	
Hospitalization	0.61 [0.41-0.91] *	0.69 [0.41-1.14]	0.08 [0.01-0.79] *
Recovery	0.71 [0.63-0.81] ****	0.70 [0.52-0.94] *	0.38 [0.23-0.61] ***
Cases	0.67 [0.43-0.98] *		0.21 [0.07-0.65] **
Viral	0.66 [0.55-0.79] ****		0.31 [0.17-0.55] ****
RCT mortality	0.50 [0.09-2.72]	0.94 [0.87-1.02]	

Table 3. **Random effects meta-analysis results by treatment stage.** Results show the relative risk with treatment and the 95% confidence interval. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

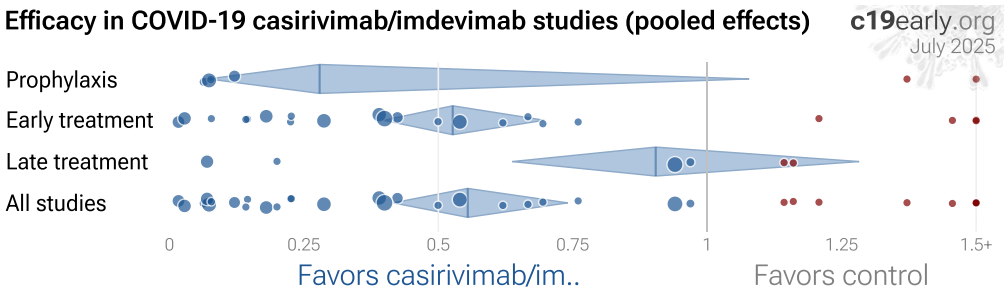


Figure 4. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

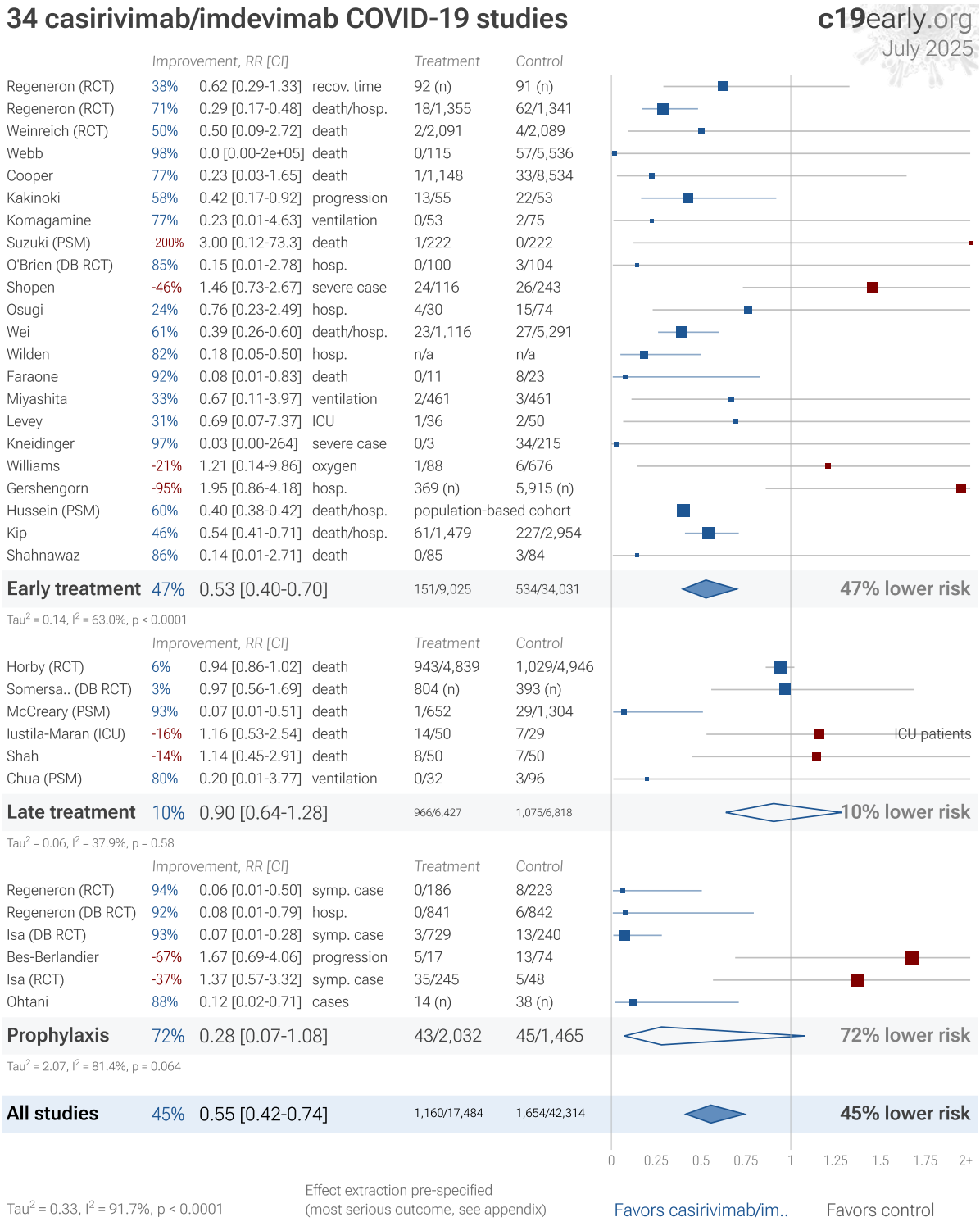


Figure 5. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For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

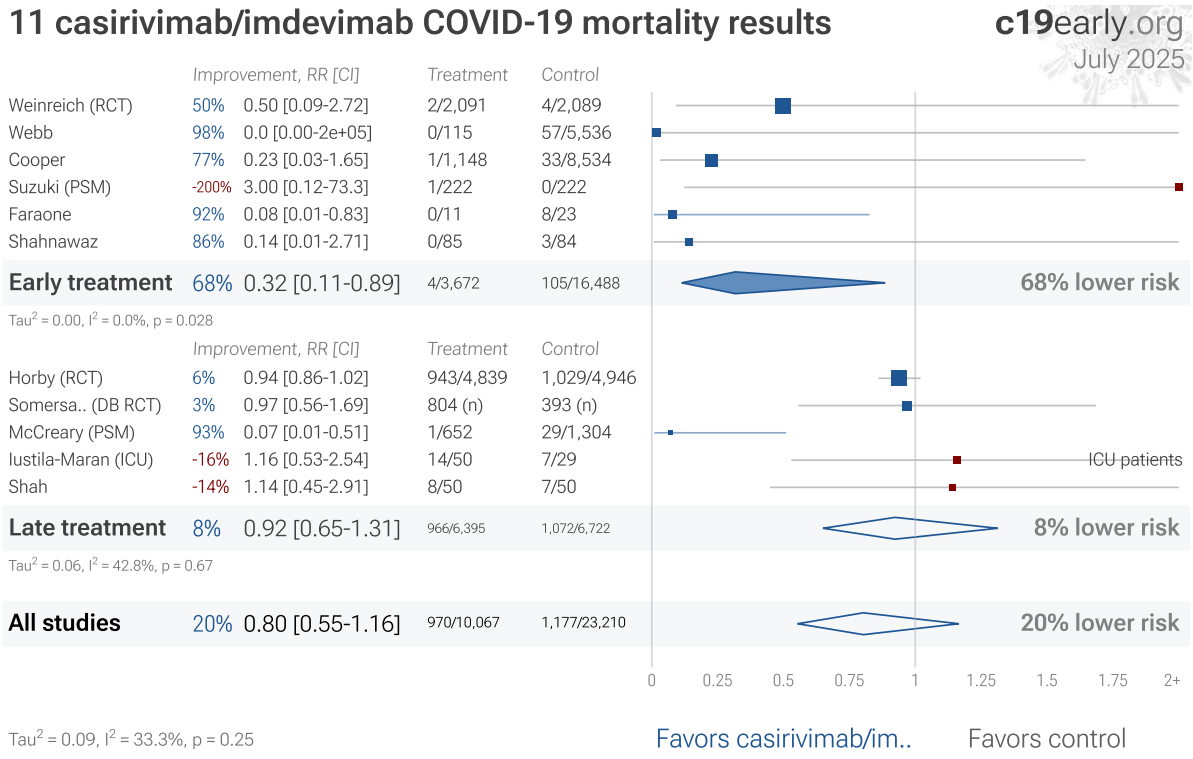


Figure 6. Random effects meta-analysis for mortality results.

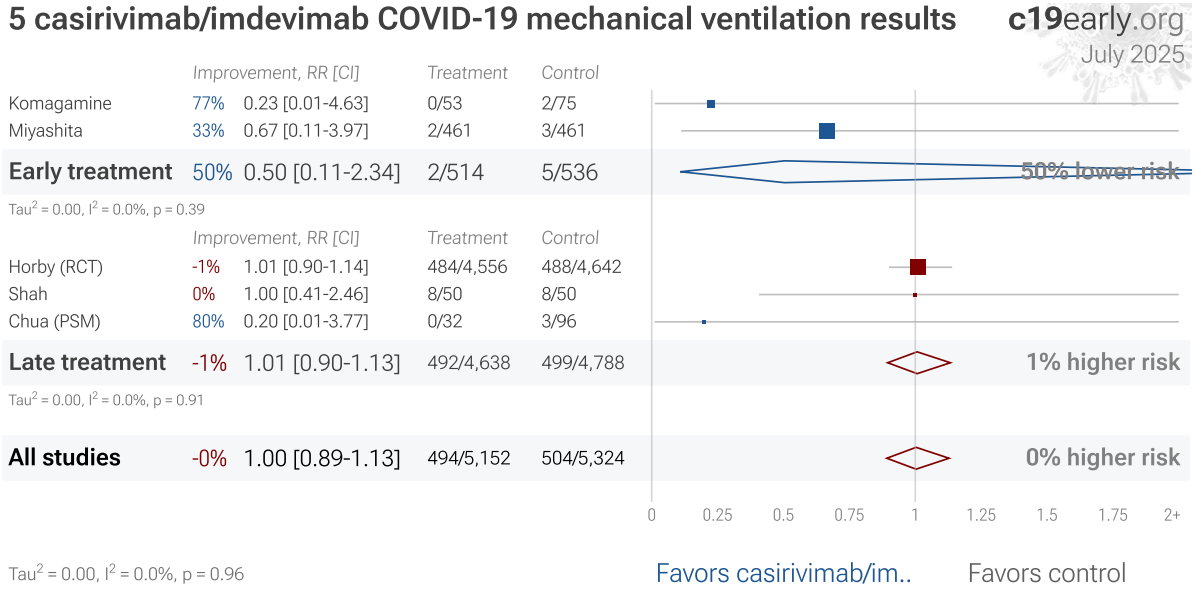


Figure 7. Random effects meta-analysis for ventilation.

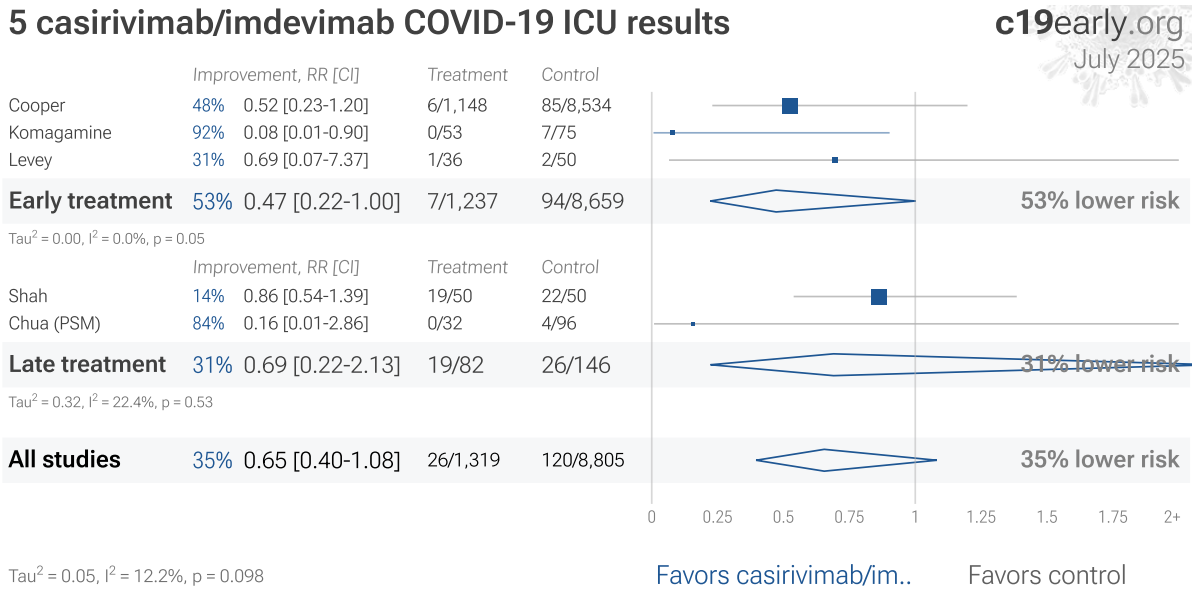


Figure 8. Random effects meta-analysis for ICU admission.

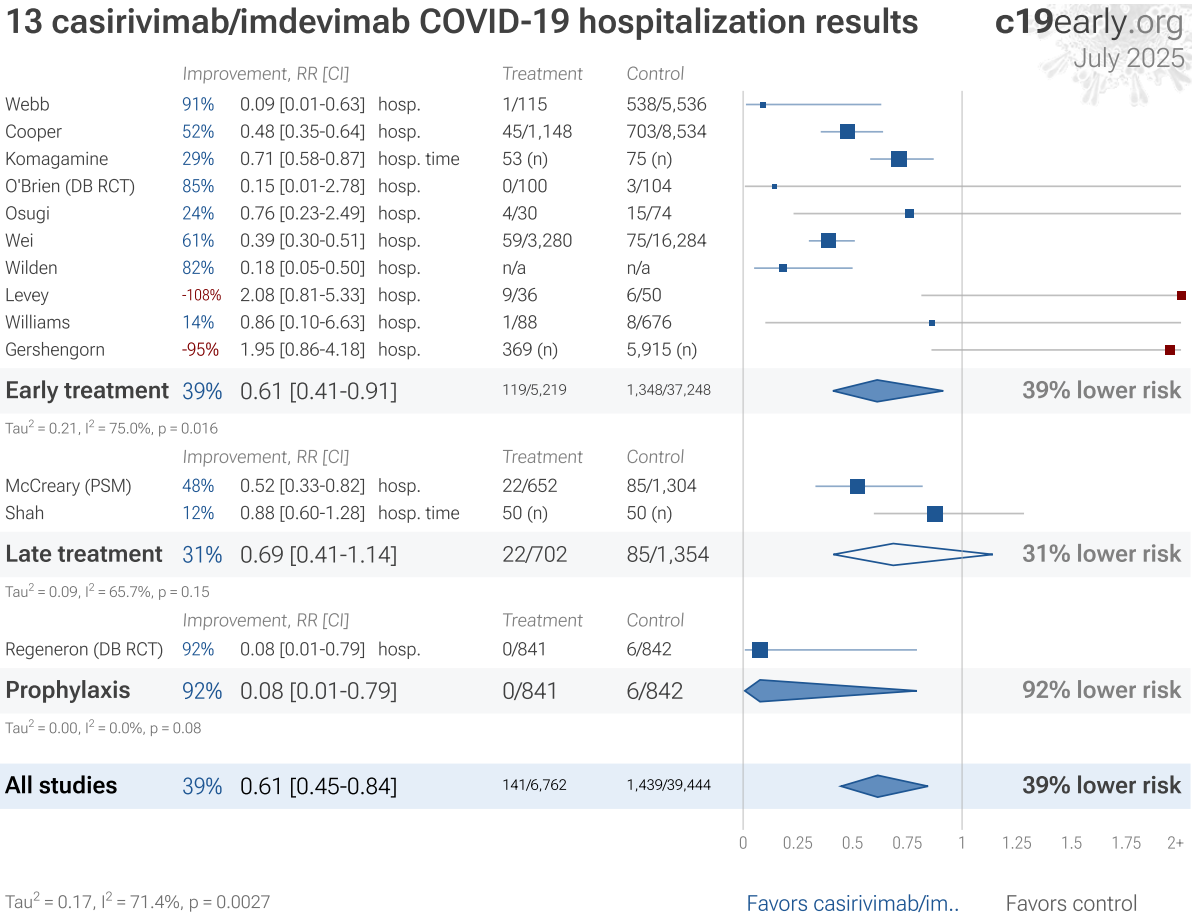


Figure 9. Random effects meta-analysis for hospitalization.

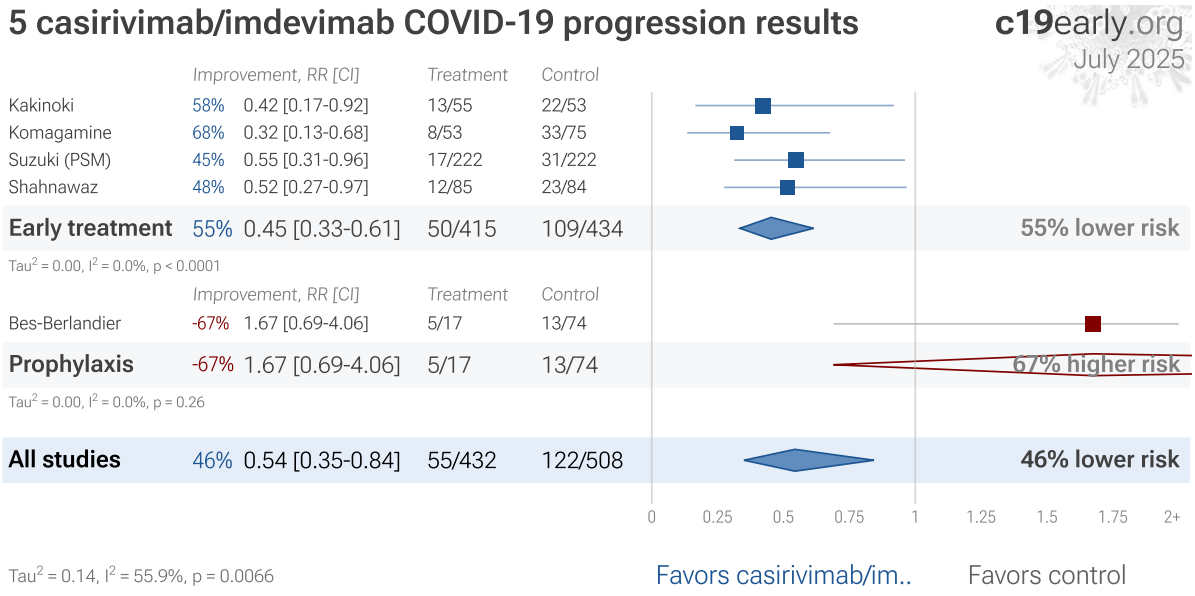


Figure 10. Random effects meta-analysis for progression.

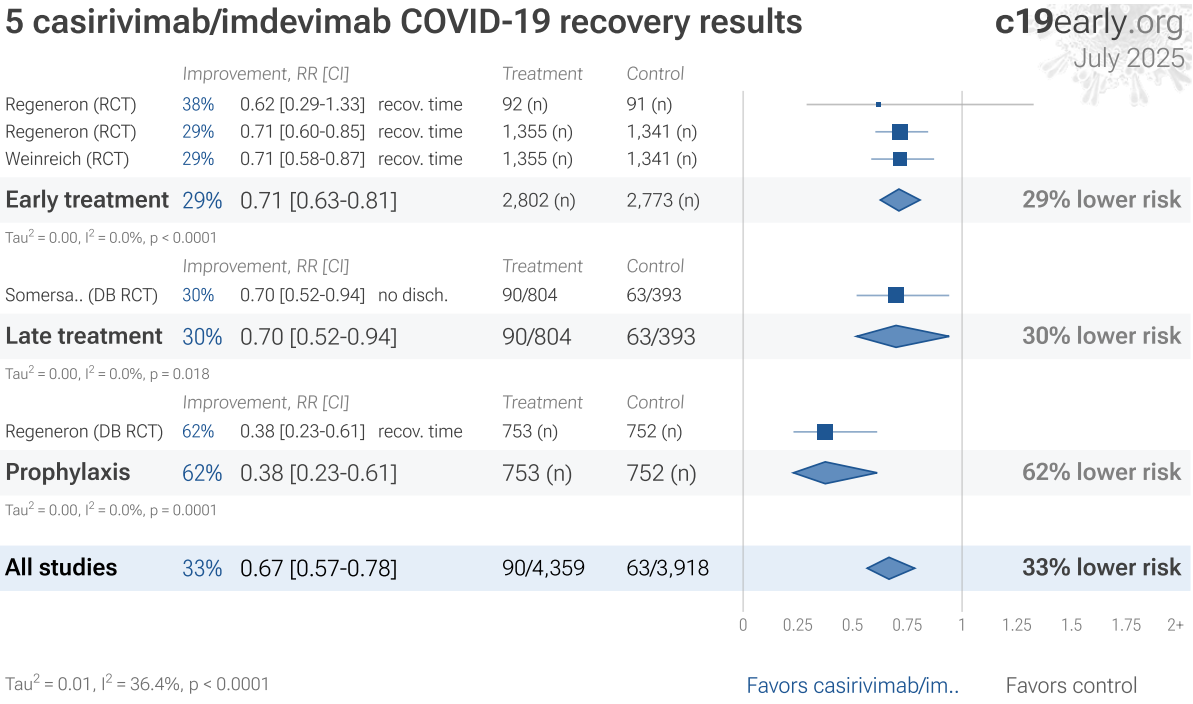


Figure 11. Random effects meta-analysis for recovery.

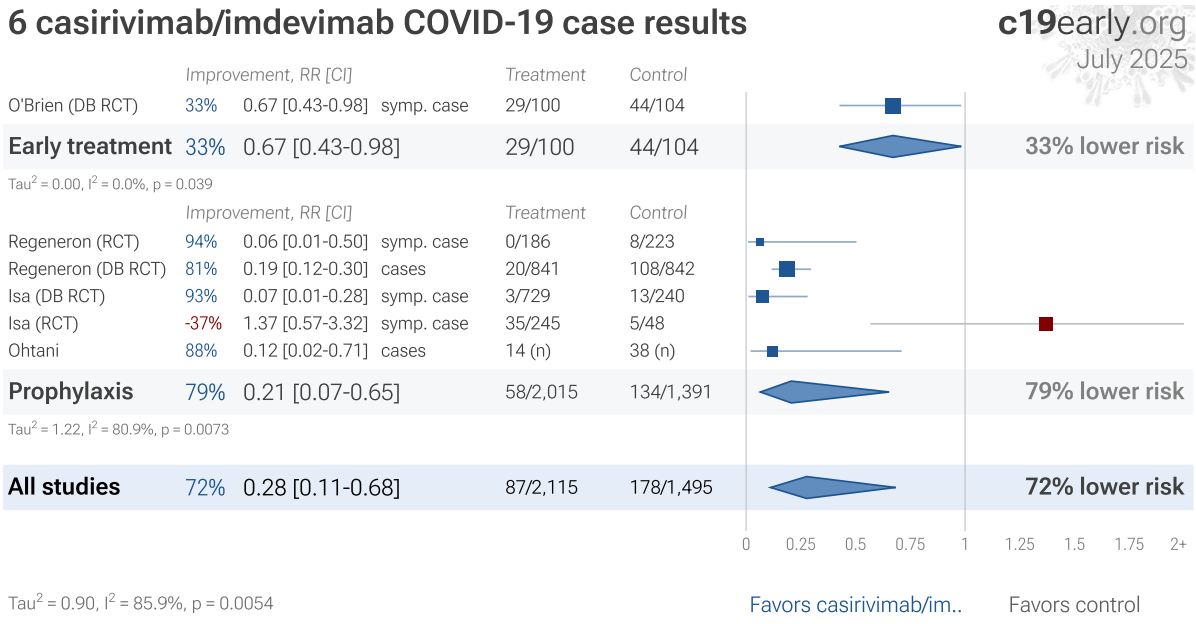


Figure 12. Random effects meta-analysis for cases.

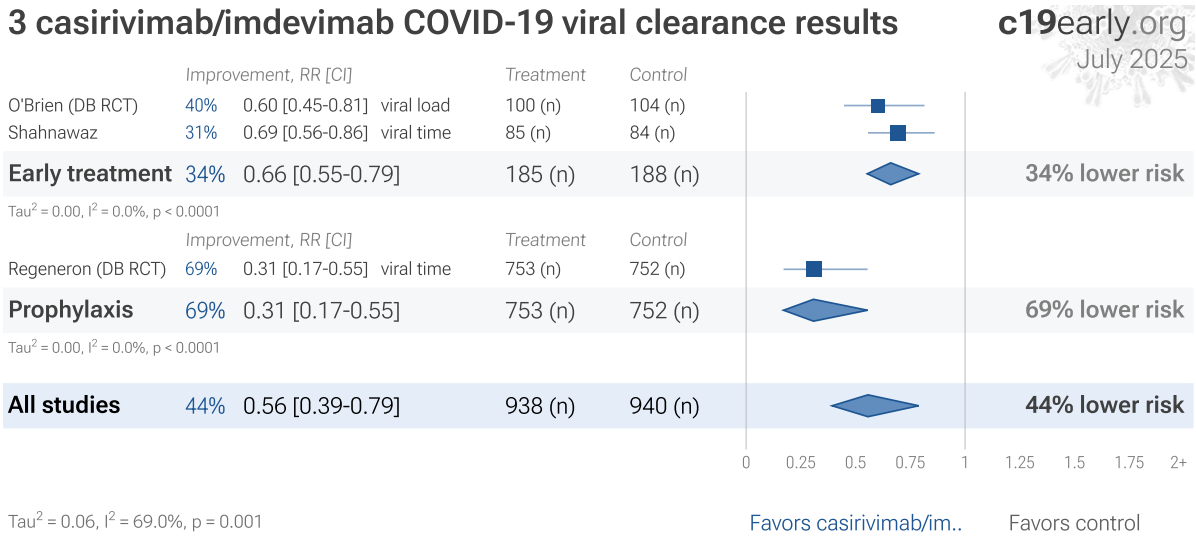


Figure 13. Random effects meta-analysis for viral clearance.

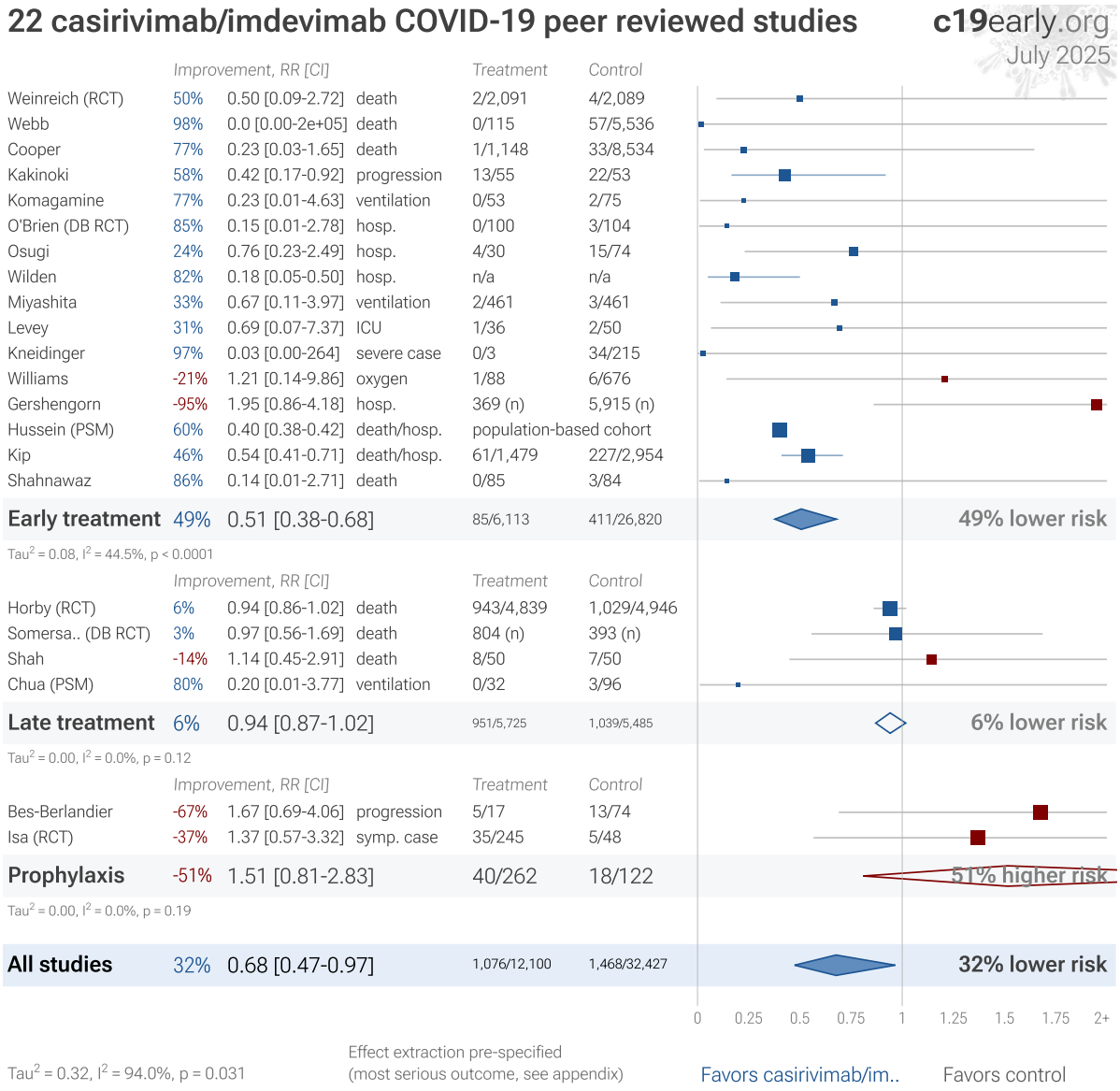


Figure 14. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. *Davidson et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

Randomized Controlled Trials (RCTs)

Figure 15 shows a comparison of results for RCTs and observational studies. Random effects meta analysis of RCTs shows 53% improvement, compared to 40% for other studies. Figure 16 and 17 show forest plots for random effects meta-analysis of all Randomized Controlled Trials and RCT mortality results. RCT results are included in Table 2 and Table 3.

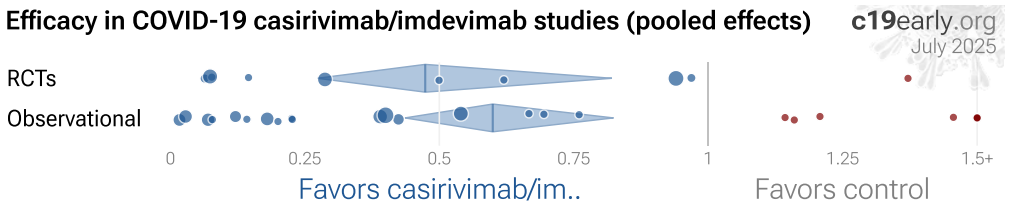


Figure 15. Results for RCTs and observational studies.

RCTs have many potential biases

RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases[52], and analysis of double-blind RCTs has identified extreme levels of bias[53]. For COVID-19, the overhead may delay treatment, dramatically compromising efficacy; they may encourage monotherapy for simplicity at the cost of efficacy which may rely on combined or synergistic effects; the participants that sign up may not reflect real world usage or the population that benefits most in terms of age, comorbidities, severity of illness, or other factors; standard of care may be compromised and unable to evolve quickly based on emerging research for new diseases; errors may be made in randomization and medication delivery; and investigators may have hidden agendas or vested interests influencing design, operation, analysis, reporting, and the potential for fraud. All of these biases have been observed with COVID-19 RCTs. There is no guarantee that a specific RCT provides a higher level of evidence.

Conflicts of interest for COVID-19 RCTs

RCTs are expensive and many RCTs are funded by pharmaceutical companies or interests closely aligned with pharmaceutical companies. For COVID-19, this creates an incentive to show efficacy for patented commercial products, and an incentive to show a lack of efficacy for inexpensive treatments. The bias is expected to be significant, for example *Als-Nielsen et al.* analyzed 370 RCTs from Cochrane reviews, showing that trials funded by for-profit organizations were 5 times more likely to recommend the experimental drug compared with those funded by nonprofit organizations. For COVID-19, some major philanthropic organizations are largely funded by investments with extreme conflicts of interest for and against specific COVID-19 interventions.

RCTs for novel acute diseases requiring rapid treatment

High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way. Every treatment RCT to date involves delayed treatment. Among the 172 treatments we have analyzed, 67% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments. They may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration.

Observational studies have been shown to be reliable

Evidence shows that observational studies can also provide reliable results. *Concato et al.* found that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. *Anglemyer et al.* analyzed reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. We performed a similar analysis across the 172 treatments we cover, showing no significant difference in the results of RCTs compared to observational studies, RR 0.98 [0.92-1.05][58]. Similar results are found for all low-cost treatments, RR 1.00 [0.91-1.09]. High-cost treatments show a non-significant trend towards RCTs showing greater efficacy, RR 0.92 [0.84-1.02]. Details can be found in the supplementary data. *Lee et al.* showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh

the benefits, for example excessive dosages, excessive treatment delays, or remote survey bias may have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see [60,61].

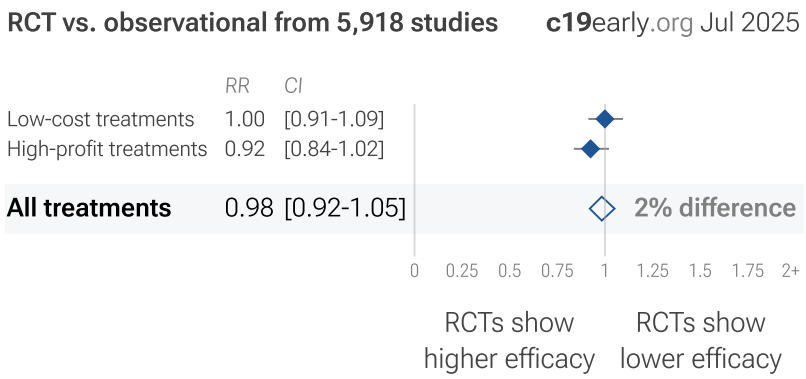


Figure 18. **For COVID-19, observational study results do not systematically differ from RCTs, RR 0.98 [0.92-1.05] across 172 treatments [55].**

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

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

Summary

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

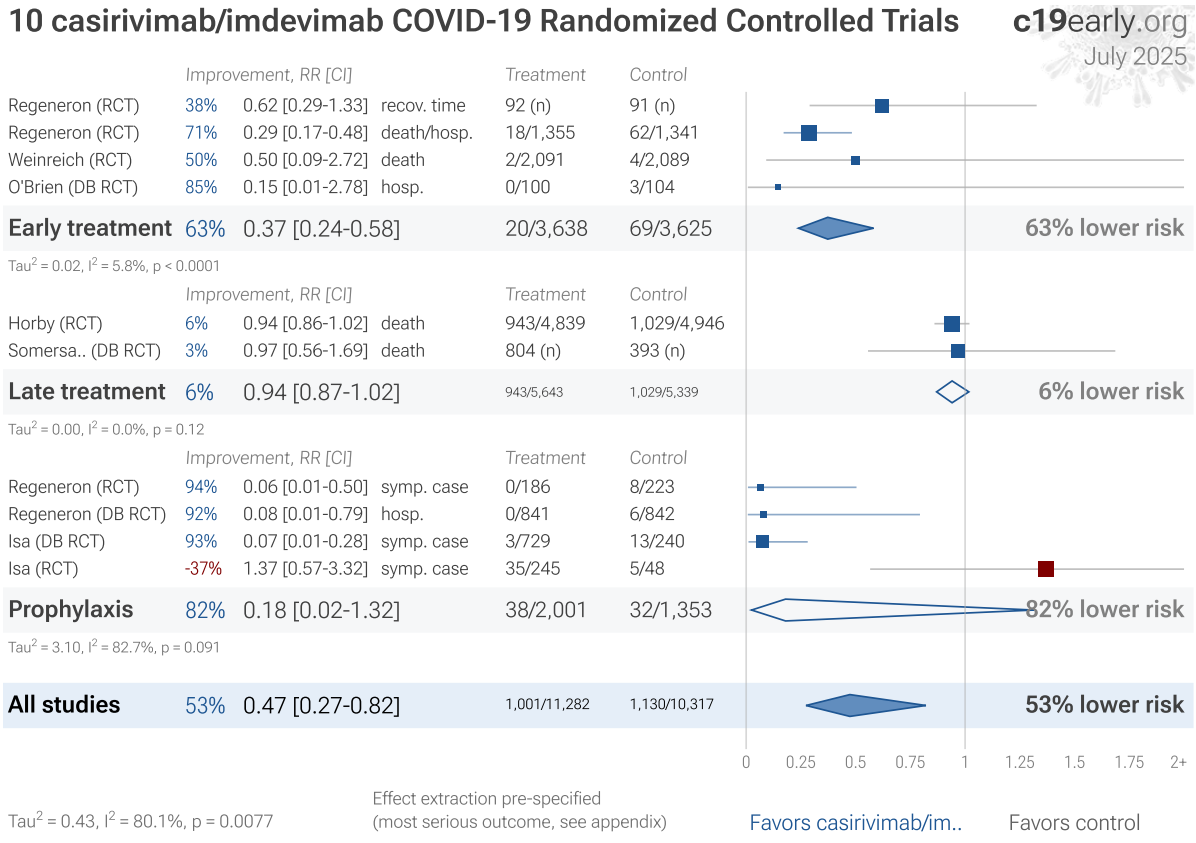


Figure 16. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious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

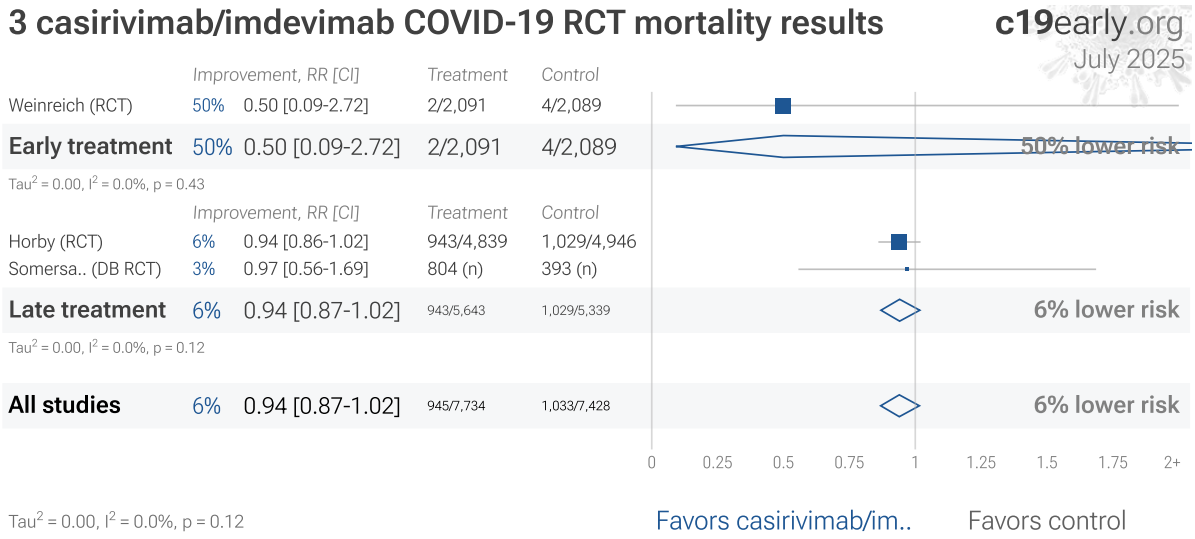


Figure 17. **Random effects meta-analysis for RCT mortality results.**

Exclusions

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

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

Cooper, unadjusted results with no group details.

Gershengorn, substantial unadjusted confounding by indication possible.

Hussein, substantial unadjusted confounding by indication possible.

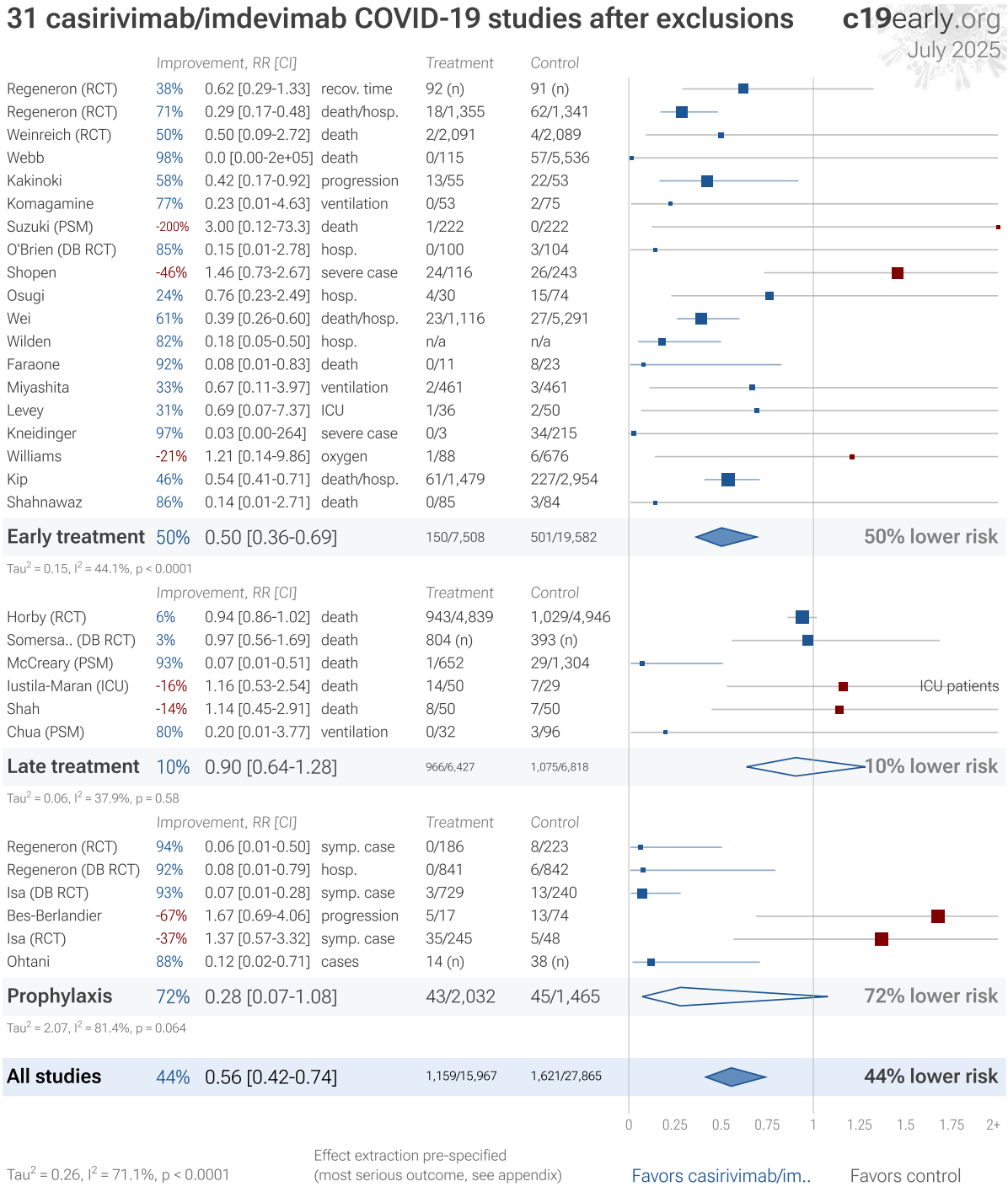


Figure 19. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome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

Heterogeneity

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

Treatment delay

The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours[65,66]. Baloxavir marboxil studies for influenza also show that treatment delay is critical — *Ikematsu et al.*

report an 86% reduction in cases for post-exposure prophylaxis, *Hayden et al.* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and *Kumar et al.* report only 2.5 hours improvement for inpatient treatment.

Treatment delay	*Result*
Post-exposure prophylaxis	86% fewer cases [67]
<24 hours	-33 hours symptoms [68]
24-48 hours	-13 hours symptoms [68]
Inpatients	-2.5 hours to improvement [69]

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

Figure 20 shows a mixed-effects meta-regression of efficacy as a function of treatment delay in COVID-19 casirivimab/imdevimab studies. For comparison, Figure 21 shows a meta-regression for all studies providing specific values across 172 treatments. Efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

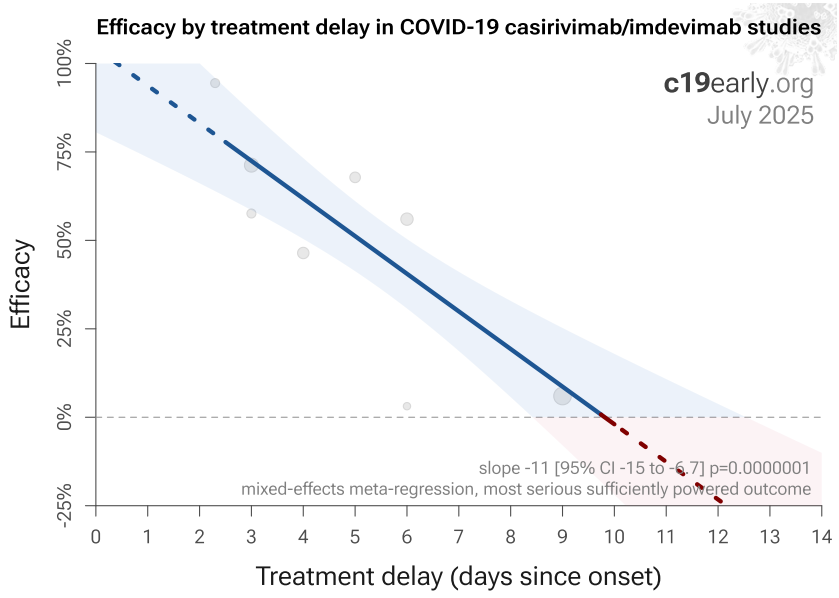


Figure 20. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 casirivimab/imdevimab studies.

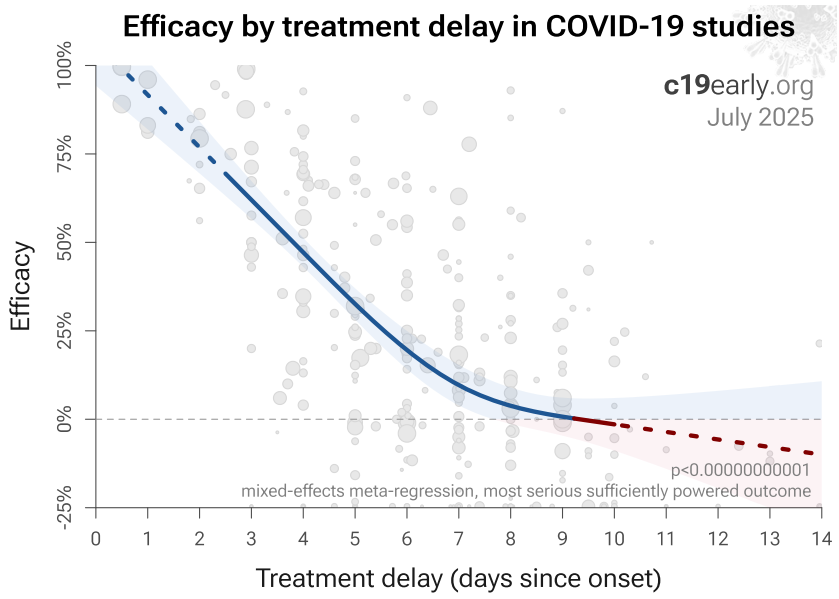


Figure 21. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 172 treatments.

Patient demographics

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

SARS-CoV-2 variants

Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants [71], for example the Gamma variant shows significantly different characteristics [72-75]. Different mechanisms of action may be more or less effective depending on variants, for example the degree to which TMPRSS2 contributes to viral entry can differ across variants [76,77].

Treatment regimen

Effectiveness may depend strongly on the dosage and treatment regimen.

Medication quality

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

Other treatments

The use of other treatments may significantly affect outcomes, including supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic [80-96], therefore efficacy may depend strongly on combined treatments.

Effect measured

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

Meta analysis

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

Pooled Effects

Pooled effects are no longer required to show efficacy as of November 2021

This section validates the use of pooled effects for COVID-19, which enables earlier detection of efficacy, however pooled effects are no longer required for casirivimab/imdevimab as of November 2021. Efficacy is now known based on specific outcomes. Efficacy based on specific outcomes was delayed by 7.6 months compared to using pooled outcomes.

Combining studies is required

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

Specific outcome and pooled analyses

We present both specific outcome and pooled analyses. In order to combine the results of studies reporting different outcomes we use the most serious outcome reported in each study, based on the thesis that improvement in the most serious outcome provides comparable measures of efficacy for a treatment. A critical advantage of this approach is simplicity and transparency. There are many other ways to combine evidence for different outcomes, along with additional evidence such as dose-response relationships, however these increase complexity.

Ethical and practical issues limit high-risk trials

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

Validating pooled outcome analysis for COVID-19

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

Analysis of the the association between different outcomes across studies from all 172 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 22 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 23 shows that improved recovery is very

strongly associated with lower mortality ($p < 0.000000000001$). Considering the extremes, *Singh et al.* show an association between viral clearance and hospitalization or death, with $p = 0.003$ after excluding one large outlier from a mutagenic treatment, and based on 44 RCTs including 52,384 patients. Figure 24 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to *Singh et al.*, with higher confidence due to the larger number of studies. As with *Singh et al.*, the confidence increases when excluding the outlier treatment, from $p = 0.000000082$ to $p = 0.0000000033$.

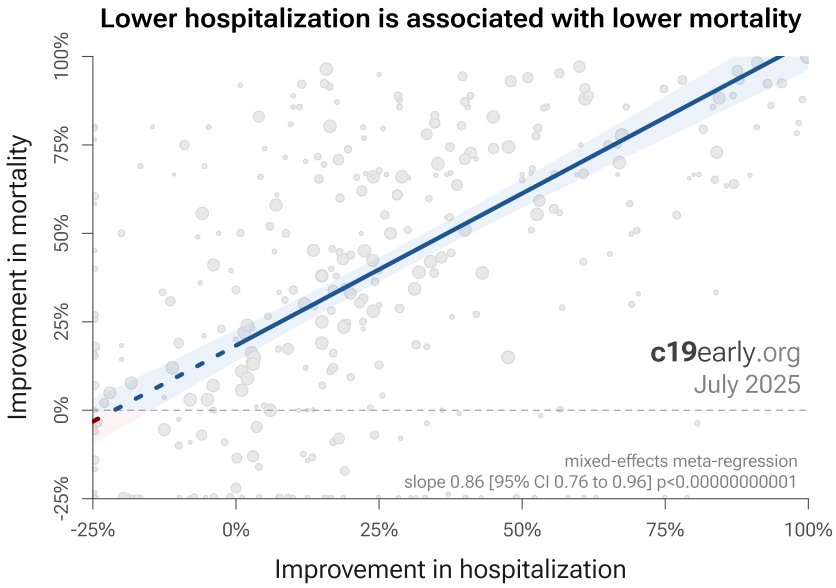


Figure 22. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

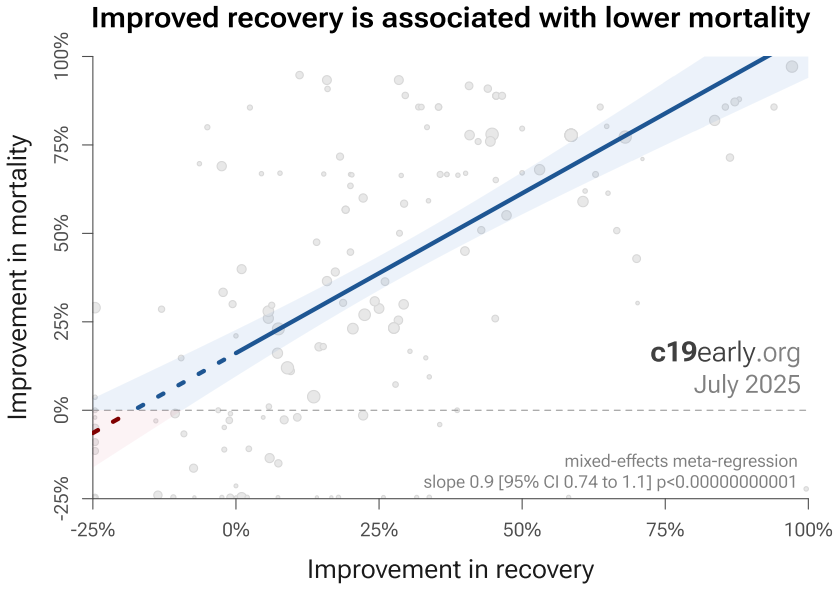


Figure 23. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

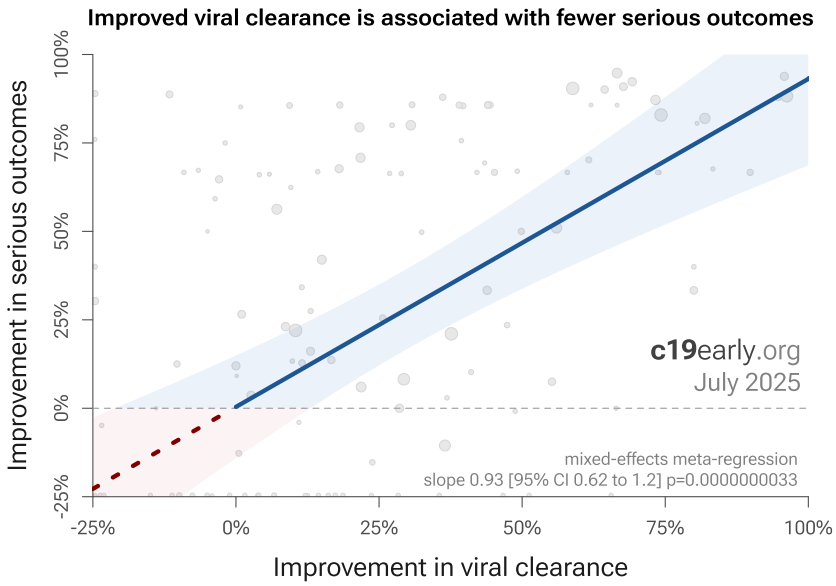


Figure 22. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

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

Currently, 55 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 88% of these have been confirmed with one or more specific outcomes, with a mean delay of 4.9 months. When restricting to RCTs only, 57% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 7.3 months. Figure 25 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

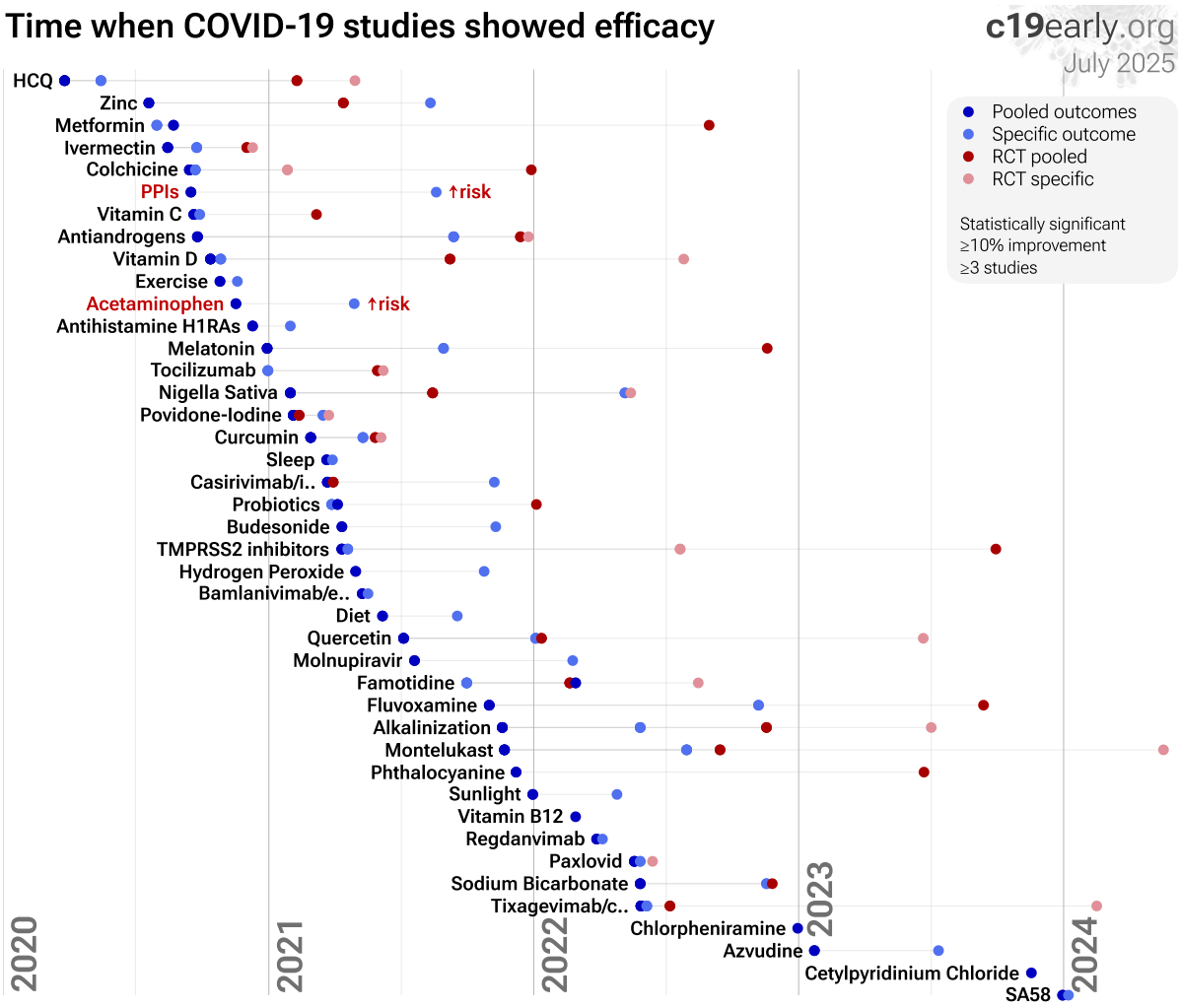


Figure 25. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

Limitations

Pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral clearance may show no efficacy if most studies only examine viral clearance. In practice, it is rare for a non-antiviral treatment to report viral clearance and to not report clinical outcomes; and in practice other sources of heterogeneity such as difference in treatment delay is more likely to hide efficacy.

Summary

Analysis validates the use of pooled effects and shows significantly faster detection of efficacy on average. However, as with all meta analyses, it is important to review the different studies included. We also present individual outcome analyses, which may be more informative for specific use cases.

Discussion

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 26 shows a scatter plot of results for prospective and retrospective studies. Prospective studies show 59% [29-76%] improvement in meta analysis, compared to 36% [12-54%] 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.

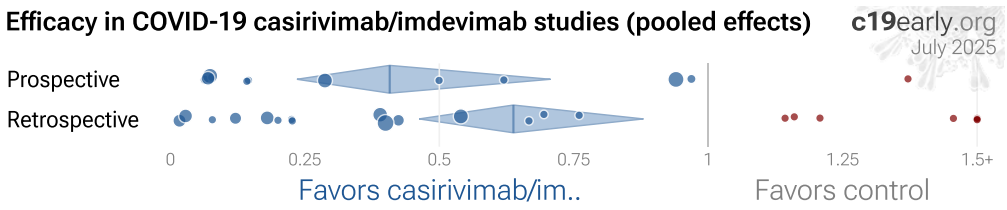


Figure 26. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

Early treatment was common

Studies for casirivimab/imdevimab were mostly early treatment studies, in contrast with typical low-cost treatments that were more likely to be tested with late treatment.

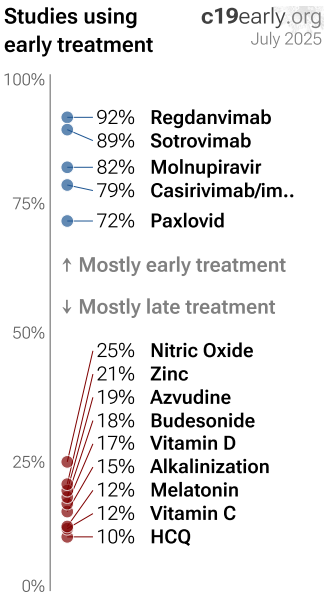


Figure 27. **Early treatment was more common for high-profit drugs.**

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 28 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 $p < 0.05$ [98-105]. 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.

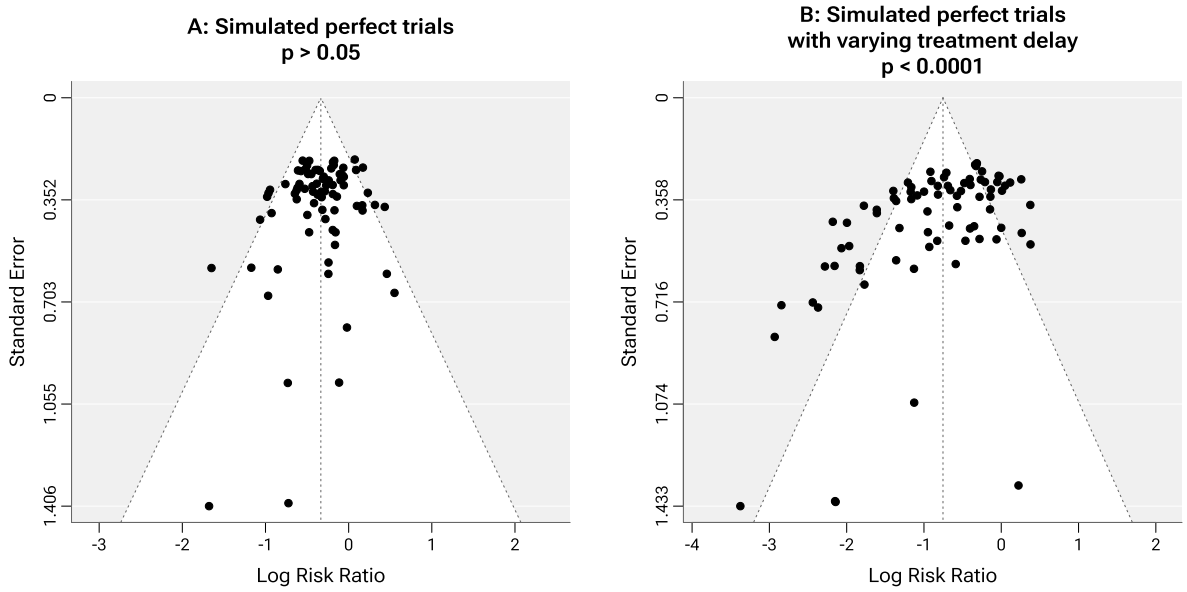


Figure 28. **Example funnel plot analysis for simulated perfect trials.**

Limitations

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

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

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

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

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

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone[80-96]. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

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

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

Notes

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

Reviews

Multiple reviews cover casirivimab/imdevimab for COVID-19, presenting additional background on mechanisms and related results, including [9,47,106].

Perspective

Results compared with other treatments

SARS-CoV-2 infection and replication involves a complex interplay of 100+ host and viral proteins and other factors [37-44], providing many therapeutic targets. Over 9,000 compounds have been predicted to reduce COVID-19 risk [45], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 29 shows an overview of the results for casirivimab/imdevimab in the context of multiple COVID-19 treatments, and Figure 30 shows a plot of efficacy vs. cost for COVID-19 treatments.

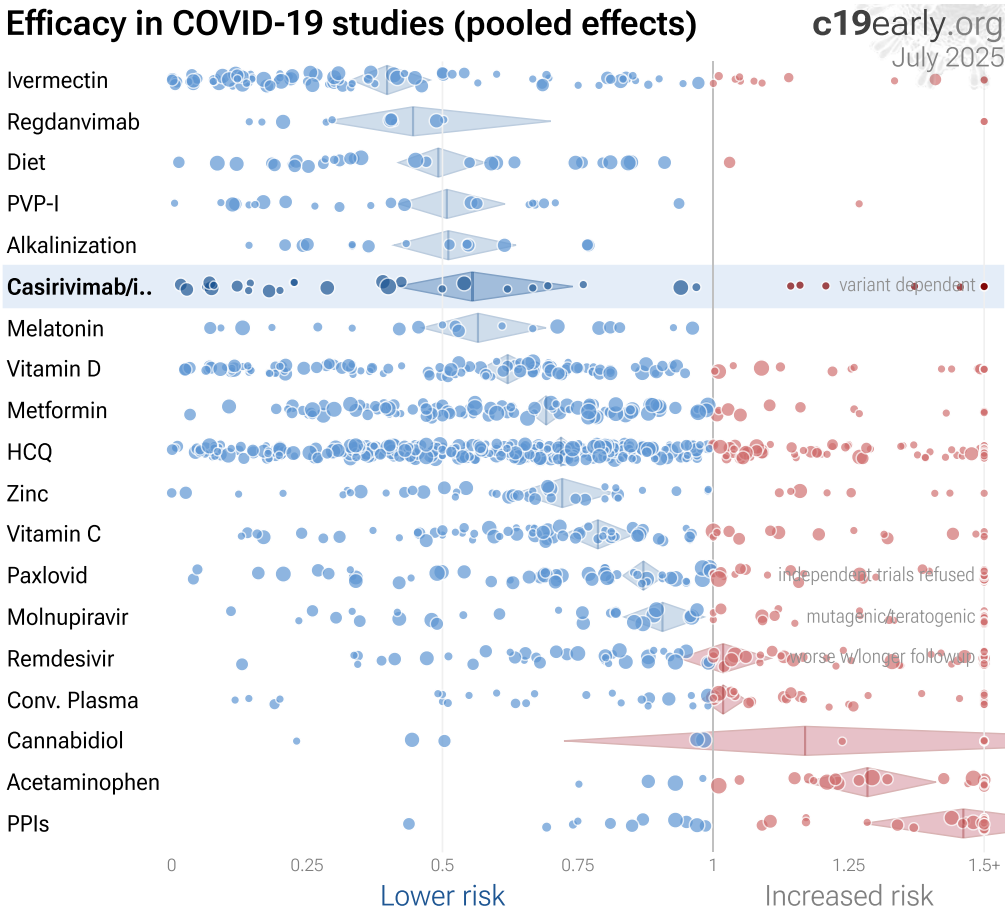


Figure 29. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy [107].

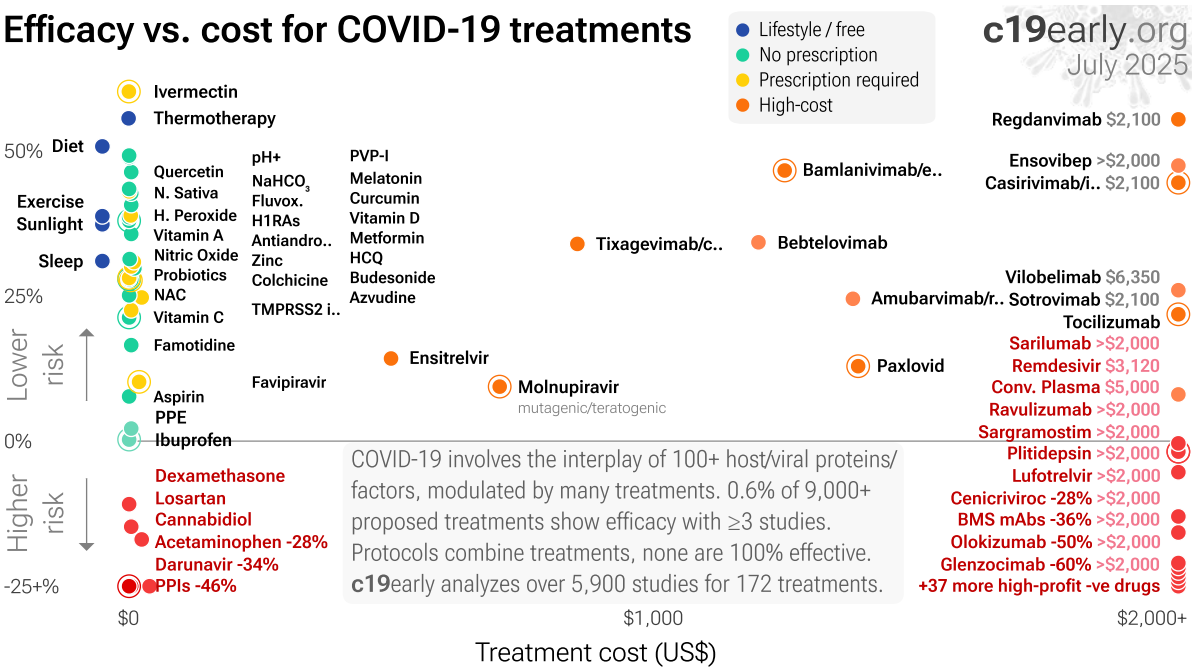


Figure 30. Efficacy vs. cost for COVID-19 treatments.

Conclusion

Casirivimab/imdevimab is an effective treatment for COVID-19. Significantly lower risk is seen for hospitalization, progression, recovery, cases, and viral clearance. 22 studies from 16 independent teams in 5 countries show significant benefit. Meta analysis using the most serious outcome reported shows 45% [26-58%] lower risk. Results are similar for Randomized Controlled Trials and higher quality studies and slightly worse for peer-reviewed studies. Early treatment is more effective than late treatment. Results are robust — in exclusion sensitivity analysis 12 of 34 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

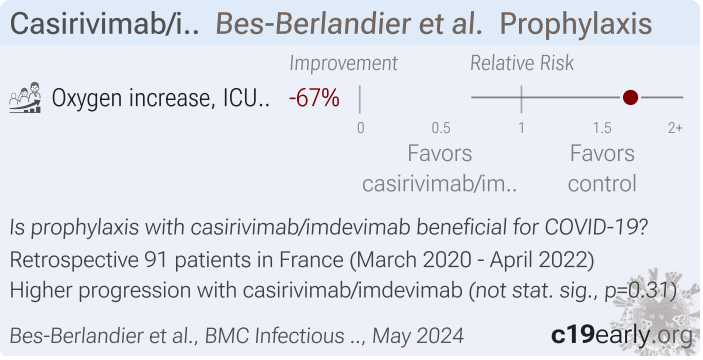
Efficacy is variant dependent. *In Vitro* studies suggest a lack of efficacy for many omicron variants[1-7]. ADE shown *In Vitro*[8]. mAb use may create new variants that spread globally[9-11], and may be associated with prolonged viral loads, clinical deterioration, and immune escape[10,12-14].

Wicaksono et al. 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[15]. 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.

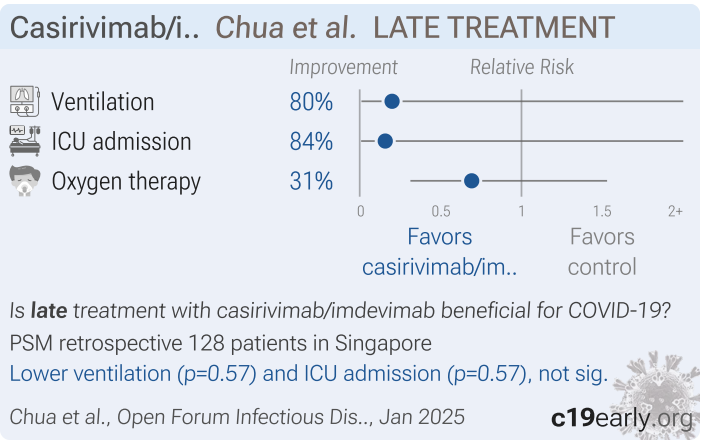
Study Notes

Bes-Berlandier



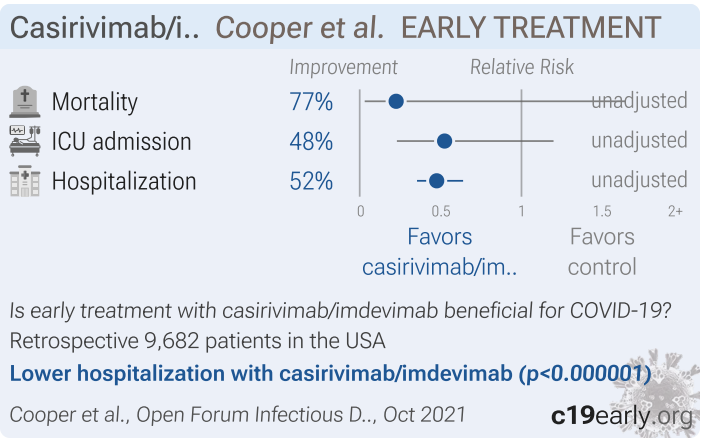
Retrospective 91 lung transplant recipients with COVID-19 showing no significant difference in poor outcomes with casirivimab/imdevimab or tixagevimab/cilgavimab prophylaxis in univariate analysis.

Chua



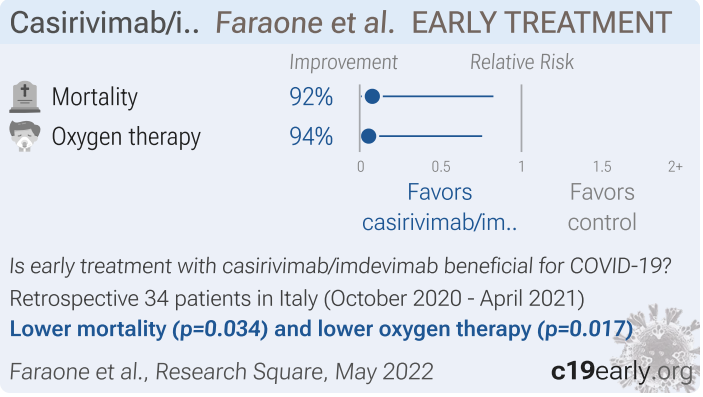
PSM retrospective 366 hospitalized COVID-19 patients in Singapore showing no statistically significant reduction in severe outcomes with monoclonal antibodies (mAbs), except for lower oxygen use in patients treated with sotrovimab during the Omicron wave. The 2021 numbers for sotrovimab do not appear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

Cooper



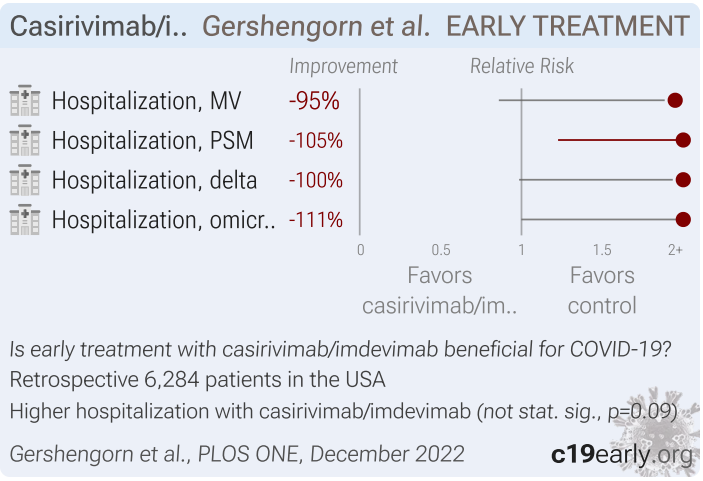
Retrospective 2,879 patients and matched controls in the USA, showing significantly lower mortality and hospitalization with bamlanivimab, bamlanivimab/etesevimab, and casirivimab/imdevimab. There was significantly lower hospitalization with casirivimab/imdevimab compared to bamlanivimab or bamlanivimab/etesevimab.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

Faraone



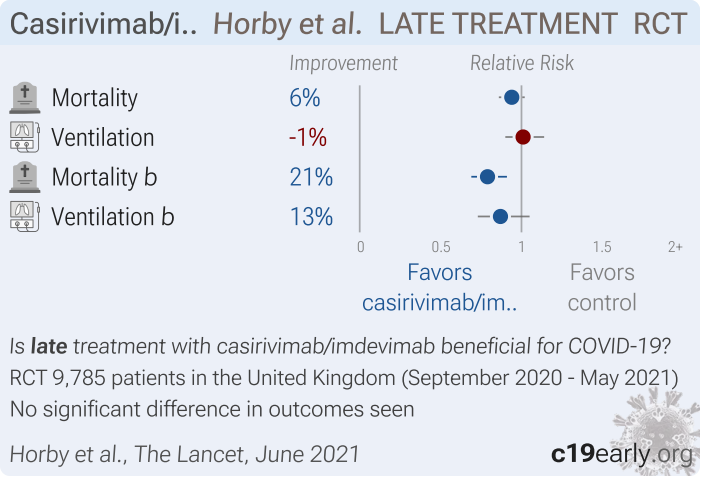
Retrospective 34 patients with hospital-acquired COVID-19, showing lower mortality and oxygen requirements with early casirivimab/imdevimab treatment.

Gershengorn



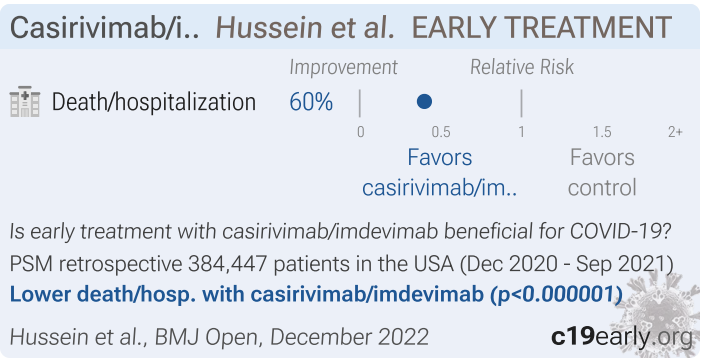
Retrospective 2,083 outpatients in the USA, showing higher risk of hospitalization with casirivimab/imdevimab, without statistical significance. There may be significant unadjusted confounding by indication.

Horby



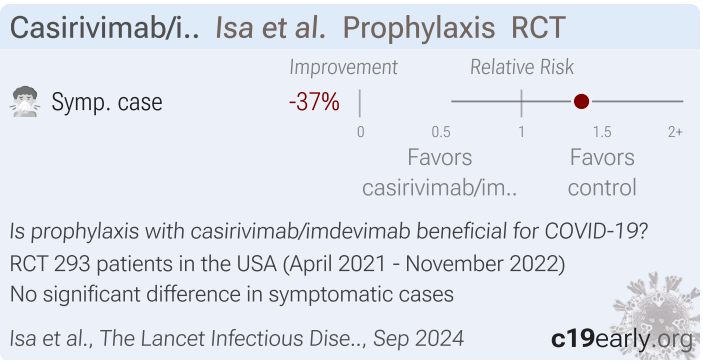
RCT 9,785 hospitalized patients in the UK showing lower mortality with casirivimab/imdevimab, with statistical significance reached for baseline seronegative patients.

Hussein



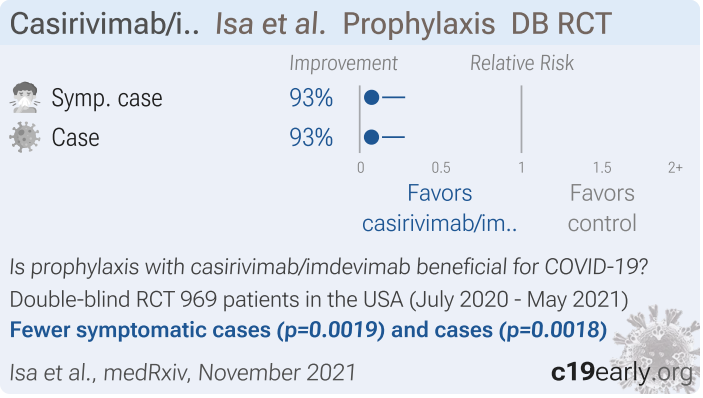
Retrospective 73,759 outpatients treated with casirivimab/imdevimab, showing lower mortality with treatment. This result is subject to potentially substantial confounding by indication - patients with more severe cases may be more likely to receive treatment, and severity information was unavailable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

Isa



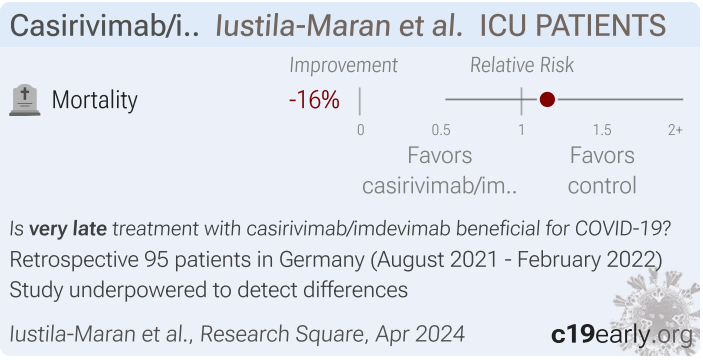
RCT 293 healthy adults focusing on the timing of casirivimab and imdevimab administration relative to mRNA-1273, but also showing the incidence of COVID-19 for each group, with higher incidence in the casirivimab and imdevimab groups (without statistical significance). Authors note the high prevalence of omicron variants which may explain the lack of efficacy seen.

Isa



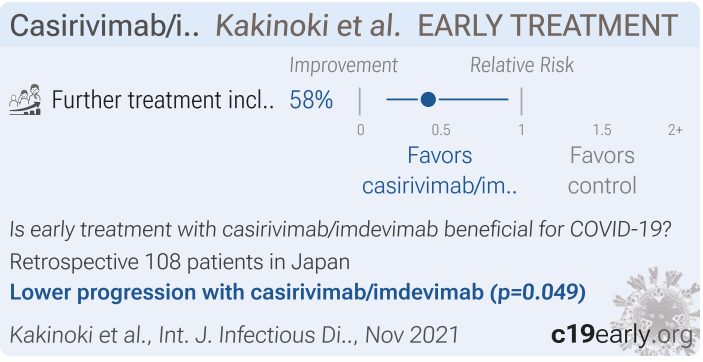
RCT 969 patients, 729 treated with monthly subcutaneous casirivimab/imdevimab, showing significantly lower risk of COVID-19 with treatment. There were no grade 3 injection site reactions or hypersensitivity reactions. Slightly more TEAEs were reported with treatment (54.9% vs. 48.3%), due to grade 1-2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

Iustila-Maran



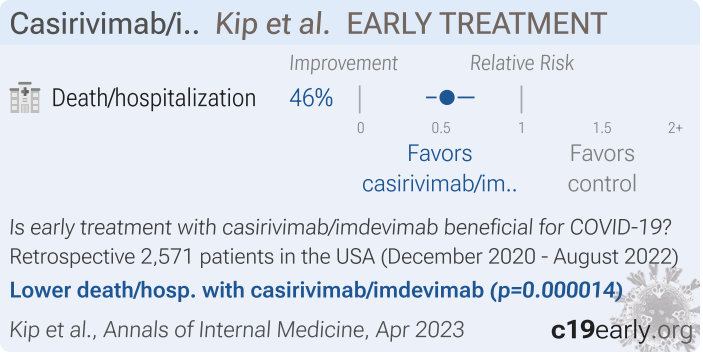
Retrospective 95 ICU patients showing no significant difference in mortality with casirivimab/imdevimab. There was significantly higher mortality with tocilizumab.

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.

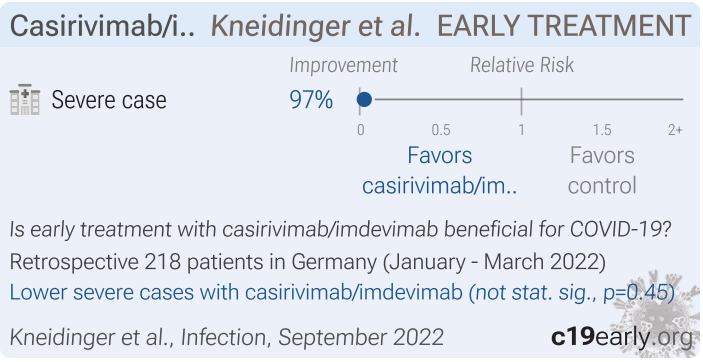
Kip



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.

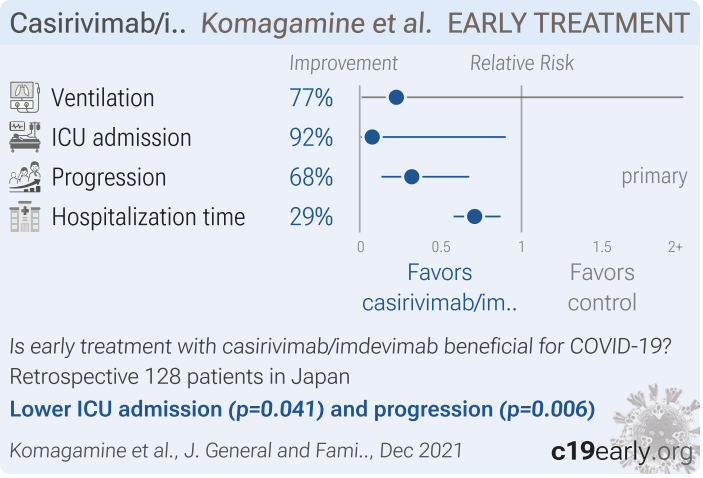
Confounding by treatment propensity. This study analyzes a population where only a fraction of eligible patients received the treatment. Patients receiving treatment may be more likely to follow other recommendations, more likely to receive additional care, and more likely to use additional treatments that are not tracked in the data (e.g., nasal/oral hygiene [108,109], vitamin D [110], 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



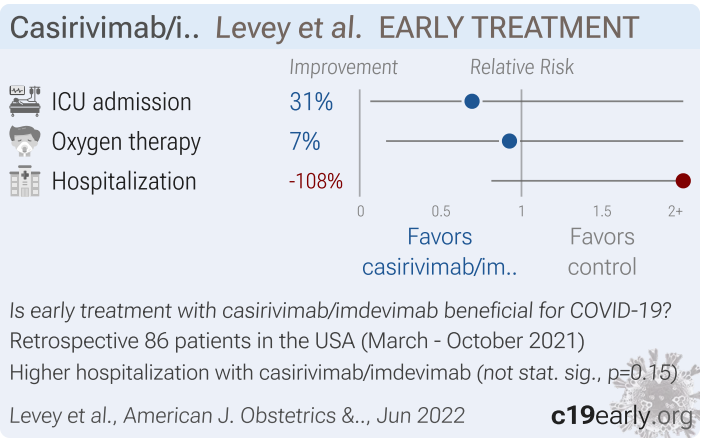
Retrospective 218 COVID+ lung transplant patients in Germany, showing no significant difference in severe cases with early casirivimab/imdevimab use.

Komagamine



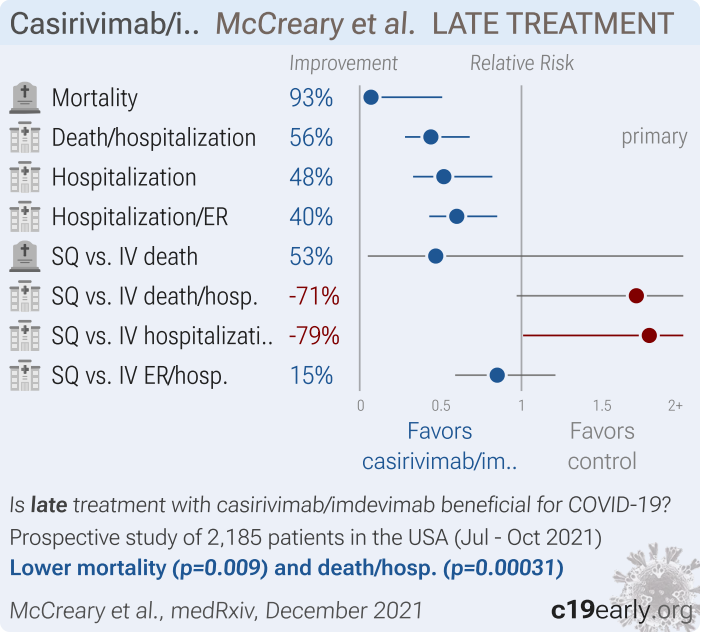
Combined retrospective/prospective study in Japan with 53 casirivimab/imdevimab patients and 75 control patients, showing significantly lower progression with treatment.

Levey



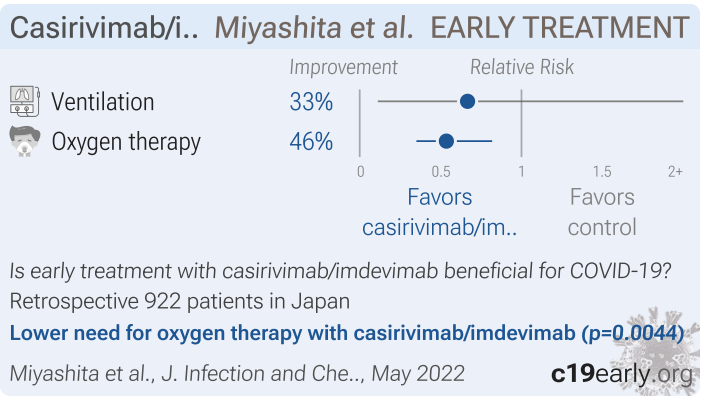
Retrospective 86 pregnant COVID-19 patients, 36 treated with casirivimab/imdevimab, showing no significant difference in COVID-19 outcomes with treatment.

McCreary



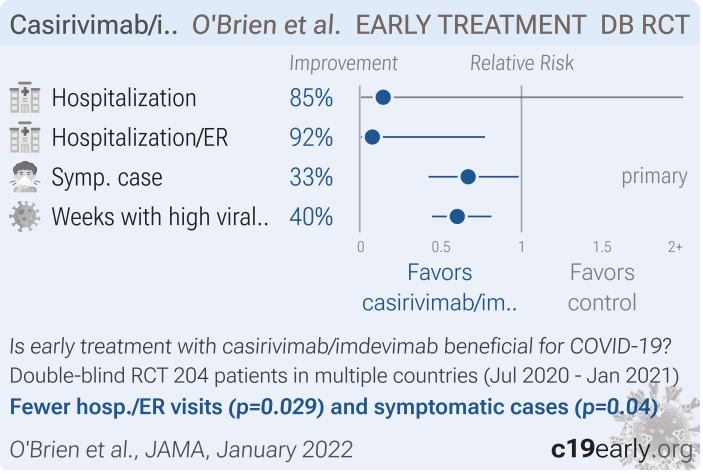
Prospective study comparing subcutaneous and intravenous casirivimab/imdevimab, and comparing to a PSM matched control set, showing significantly lower mortality and hospitalization with treatment. Controls were matched with EUA-eligible risk factors only, authors were unable to determine symptom severity.

Miyashita



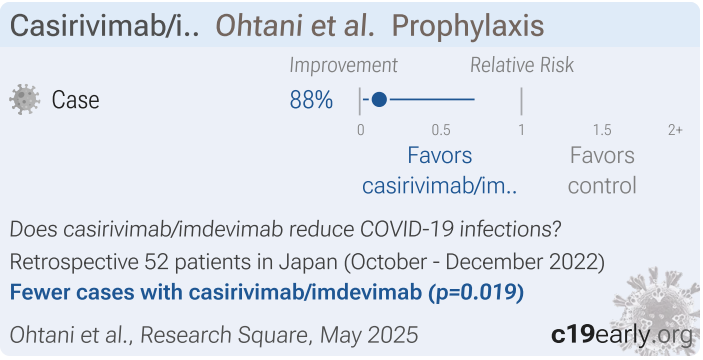
Retrospective 461 patients treated with casirivimab/imdevimab in Japan, and 461 matched controls, showing lower oxygen requirements with treatment.

O'Brien



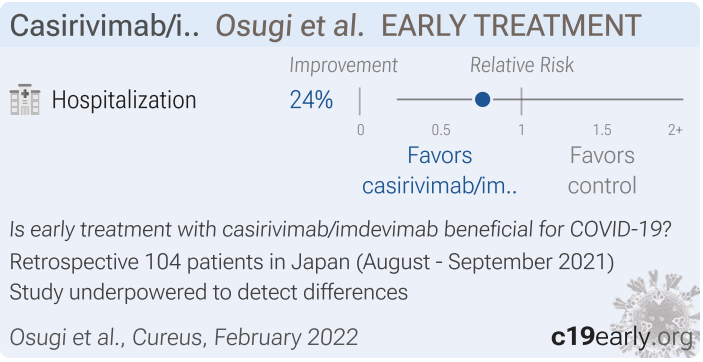
RCT 204 asymptomatic COVID+ patients, 100 treated with subcutaneous casirivimab/imdevimab, showing lower development of symptoms, lower hospitalization, and faster viral clearance with treatment. Study conducted prior to widespread circulation of delta and omicron in the study locations.

Ohtani



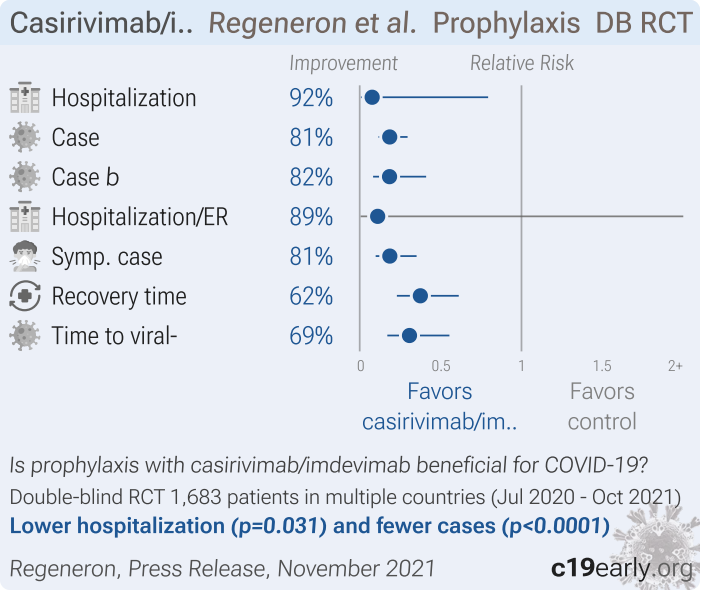
Retrospective study of 52 hospitalized patients showing significantly lower COVID-19 incidence with casirivimab/imdevimab for post-exposure prophylaxis during a period when Omicron BA.5 was dominant.

Osugi



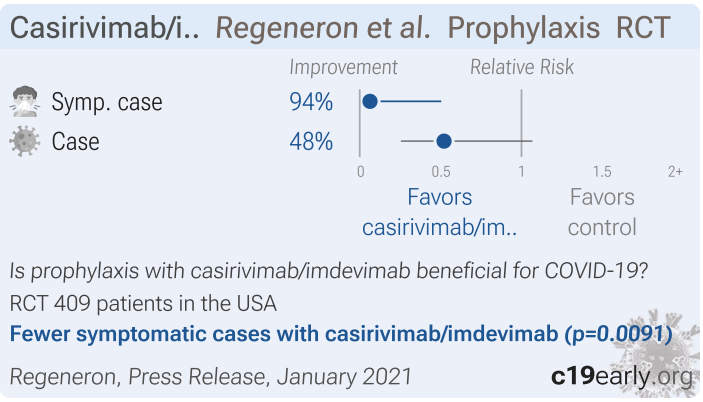
Retrospective 104 outpatients in Japan, 30 treated with casirivimab/imdevimab, showing no significant difference in hospitalization.

Regeneron



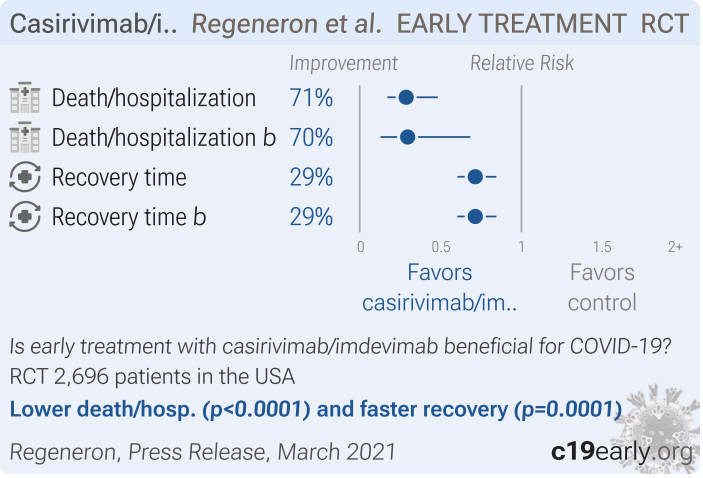
Long-term results for PEP RCT NCT04452318, with 841 baseline seronegative casirivimab/imdevimab patients and 842 placebo patients, showing significantly lower cases with treatment.

Regeneron



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).

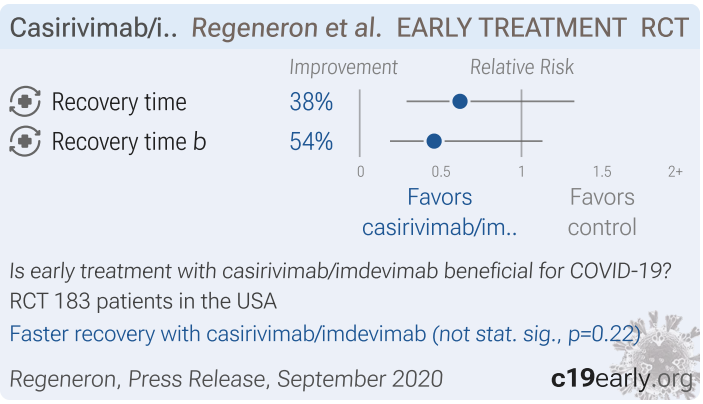
Regeneron



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[111].

Regeneron



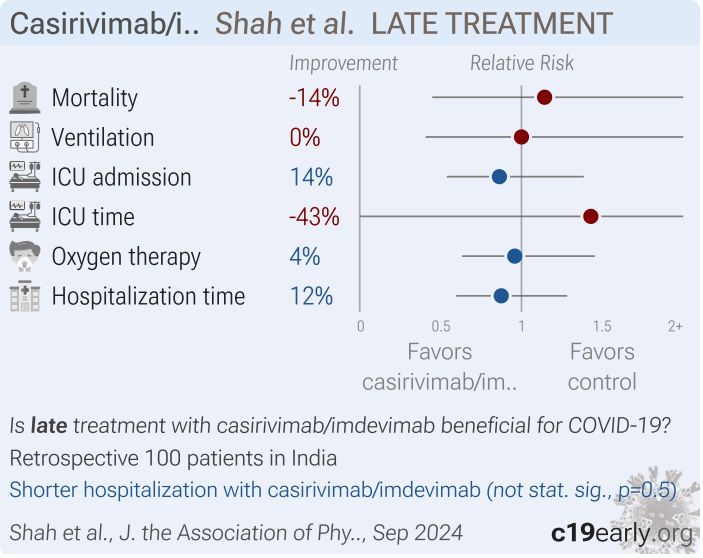
Analysis of the first 275 patients in a trial of the REGN-COV2 antibody cocktail showing reductions in viral load and the time to alleviate symptoms in non-hospitalized patients with COVID-19. Greatest improvements were seen with patients that had not mounted their own effective immune response prior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

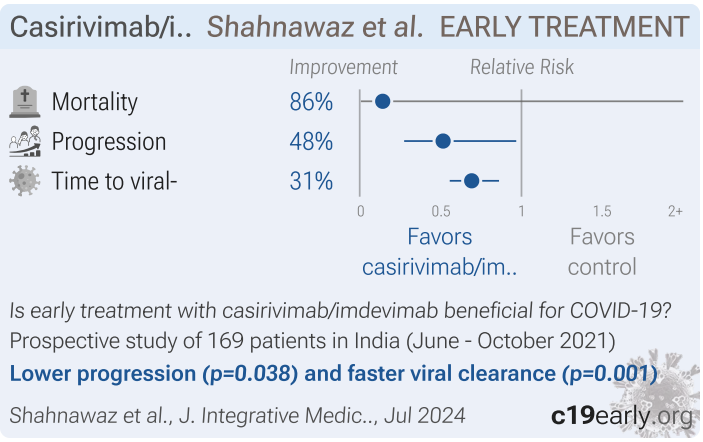
Adverse reactions were similar with treatment and placebo. There were no deaths.

Shah



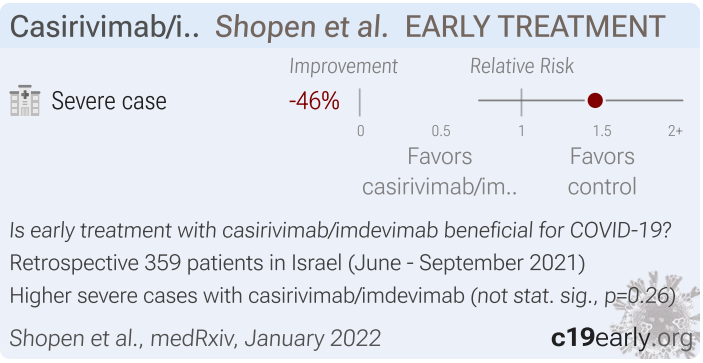
PSM retrospective 100 hospitalized COVID-19 patients in India showing no benefit with casirivimab/imdevimab treatment. There were no significant differences between groups in need for oxygen therapy, high-flow nasal cannula, noninvasive ventilation, invasive ventilation, ICU admission, hospital or ICU stay, or mortality.

Shahnawaz



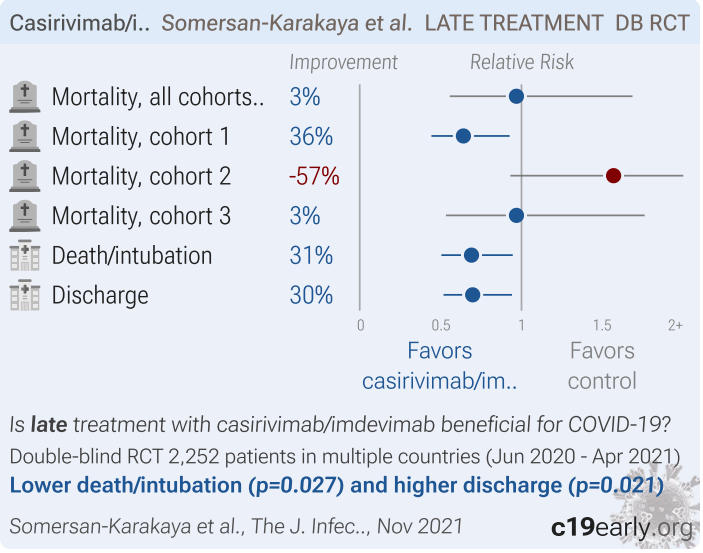
Prospective study of 169 non-hospitalized mild-to-moderate COVID-19 patients at high risk of progression in India, showing significantly lower progression and faster viral clearance with casirivimab/imdevimab.

Shopen



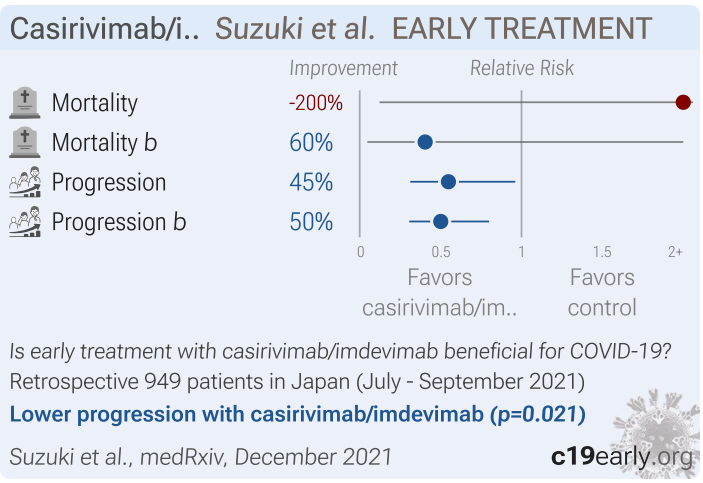
Retrospective 359 COVID+ patients in Israel, 116 treated with casirivimab/imdevimab, showing no significant difference with treatment in multivariable analysis.

Somersan-Karakaya



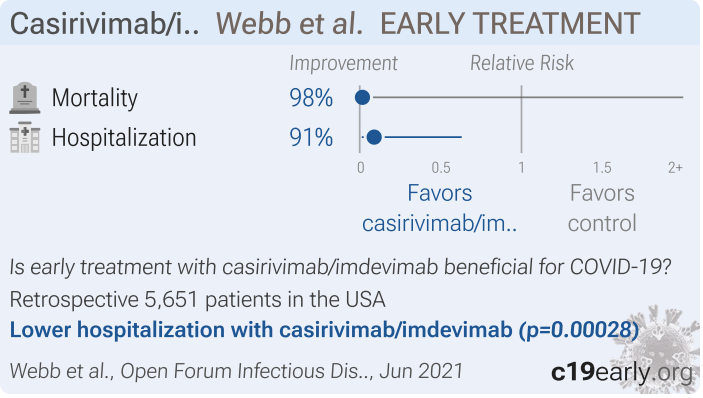
RCT 2,252 hospitalized patients. Results for 1,336 patients on low-flow or no supplemental oxygen are reported, showing lower mortality with casirivimab/imdevimab treatment. Cohorts 2&3 (high-intensity oxygen and mechanical ventilation) were paused mid-trial due to increased deaths in the treatment arm and only mortality results are reported.

Suzuki



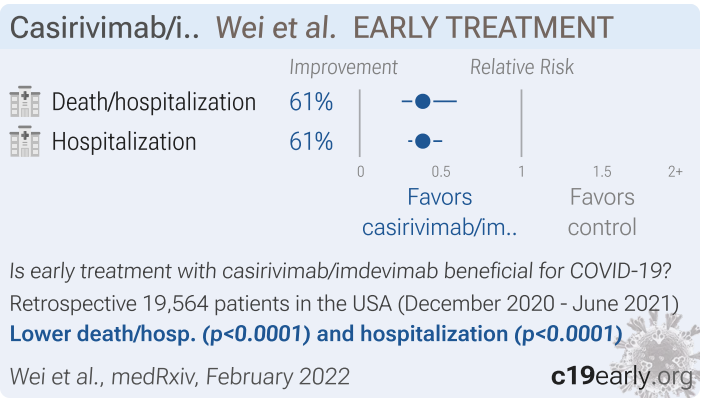
Retrospective 949 patients in Japan, 314 treated with casirivimab/imdevimab showing significantly lower risk of deterioration with treatment.

Webb



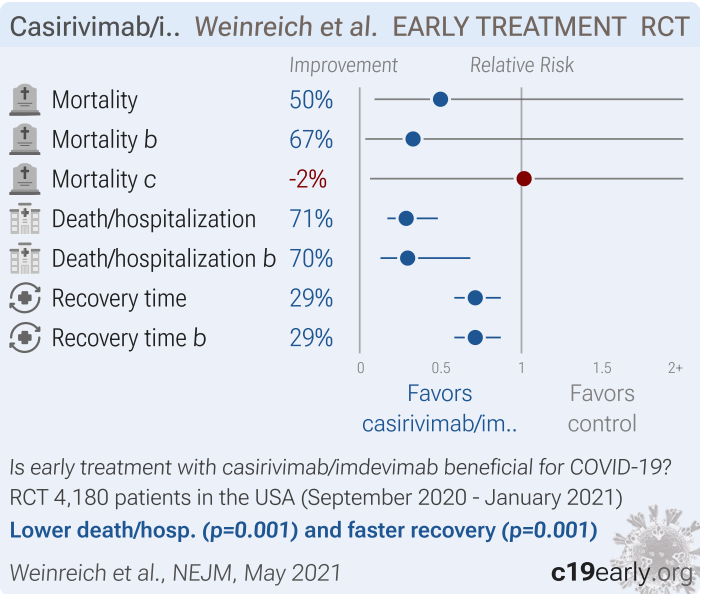
Retrospective 115 patients treated with casirivimab/imdevimab showing lower mortality, hospital admission, and emergency department visits with treatment. Authors incorrectly state that "no other COVID-19 therapies for ambulatory patients have proven effective".

Wei



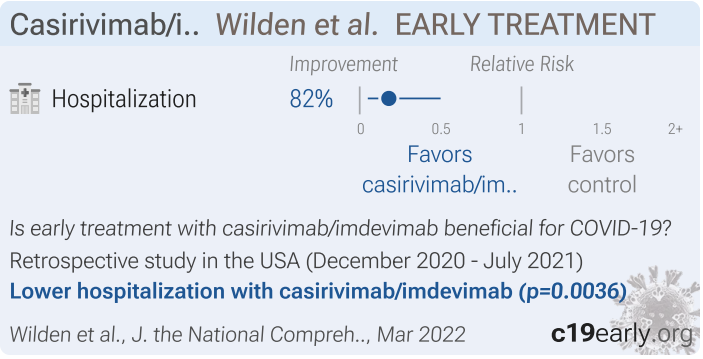
Retrospective 4,396 casirivimab/imdevimab patients in the USA, showing lower combined mortality/hospitalization (CDM database) and lower hospitalization (PMTX+ database) with treatment.

Weinreich



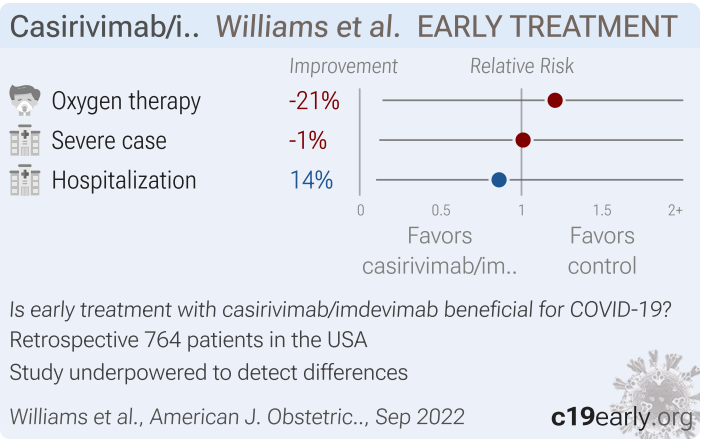
RCT 4,057 outpatients with >=1 risk factor for severe disease, showing significantly lower combined hospitalization/death, and significantly faster recovery with treatment. Median time from onset of symptoms 3 days.

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



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. Studies with major unexplained data issues, for example major outcome data that is impossible to be correct with no response from the authors, are excluded. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are reported then they are both used in specific outcome analyses, while mortality is used for pooled analysis. If symptomatic results are reported at multiple times, we use the latest time, for

example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral outcomes. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. An IPD meta-analysis confirms that intermediate viral load reduction is more closely associated with hospitalization/death than later viral load reduction [112]. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO_2 is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to *Zhang (B) et al.* Reported confidence intervals and *p*-values are used when available, and adjusted values are used when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 [116]. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.13.5) with scipy (1.16.0), pythonmeta (1.26), numpy (2.3.1), statsmodels (0.14.4), and plotly (6.2.0).

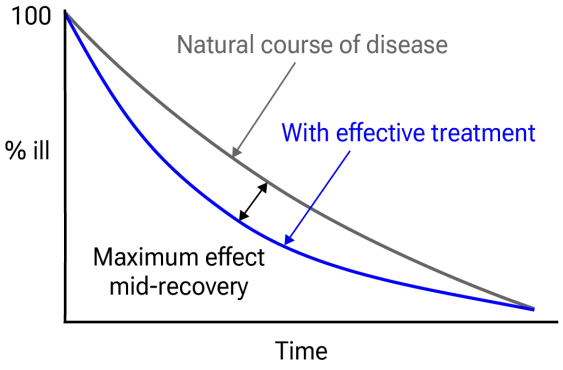


Figure 31. **Mid-recovery results can more accurately reflect efficacy when almost all patients recover.** *Mateja et al.* **confirm that intermediate viral load results more accurately reflect hospitalization/death.**

Forest plots are computed using PythonMeta [117] with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the I^2 statistic. Mixed-effects meta-regression results are computed with R (4.4.0) using the metafor (4.6-0) and rms (6.8-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a *p*-value less than 0.05 was considered statistically significant. Grobid 0.8.2 is used to parse PDF documents.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment (for example based on oxygen status or lung involvement), and treatment started within 5 days of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of patients contributing most to the events (for example, consider a study where most patients are treated early but late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective [65,66].

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.
Shahnawaz, 7/31/2024, prospective, India, peer-reviewed, mean age 62.4, 7 authors, study period June 2021 - October 2021.	risk of death, 85.8% lower, RR 0.14, $p = 0.12$, treatment 0 of 85 (0.0%), control 3 of 84 (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 progression, 48.4% lower, RR 0.52, $p = 0.04$, treatment 12 of 85 (14.1%), control 23 of 84 (27.4%), NNT 7.5.
	time to viral-, 30.8% lower, relative time 0.69, $p = 0.001$, treatment 85, control 84.
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, 40 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.

Chua, 1/29/2025, retrospective, Singapore, peer-reviewed, 9 authors.	**risk of mechanical ventilation, 80.0% lower, RR 0.20, p = 0.57**, treatment 0 of 32 (0.0%), control 3 of 96 (3.1%), NNT 32, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), propensity score matching.
	risk of ICU admission, 84.2% lower, RR 0.16, p = 0.57, treatment 0 of 32 (0.0%), control 4 of 96 (4.2%), NNT 24, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), propensity score matching.
	risk of oxygen therapy, 30.8% lower, RR 0.69, p = 0.48, treatment 6 of 32 (18.8%), control 26 of 96 (27.1%), NNT 12, propensity score matching.
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.
Iustila-Maran, 4/5/2024, retrospective, Germany, preprint, 4 authors, study period August 2021 - February 2022, trial NCT06233357 (history).	risk of death, 16.0% higher, RR 1.16, *p* = 0.80, treatment 14 of 50 (28.0%), control 7 of 29 (24.1%), C or C+T vs. N.
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.
Shah, 9/1/2024, retrospective, India, peer-reviewed, 5 authors.	risk of death, 14.3% higher, RR 1.14, *p* = 1.00, treatment 8 of 50 (16.0%), control 7 of 50 (14.0%).
	risk of mechanical ventilation, no change, RR 1.00, *p* = 1.00, treatment 8 of 50 (16.0%), control 8 of 50 (16.0%).
	risk of ICU admission, 13.6% lower, RR 0.86, *p* = 0.68, treatment 19 of 50 (38.0%), control 22 of 50 (44.0%), NNT 17.
	ICU time, 42.9% higher, relative time 1.43, *p* = 0.93, treatment 50, control 50.
	risk of oxygen therapy, 4.2% lower, RR 0.96, *p* = 1.00, treatment 23 of 50 (46.0%), control 24 of 50 (48.0%), NNT 50.
	hospitalization time, 12.5% lower, relative time 0.88, *p* = 0.50, treatment 50, control 50.
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, 3.1% lower, RR 0.97, *p* = 0.92, treatment 804, control 393, all cohorts combined.
	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, cohort 1.
	risk of death, 56.9% higher, RR 1.57, *p* = 0.08, treatment 44 of 110 (40.0%), control 13 of 51 (25.5%), cohort 2.
	risk of death, 3.1% lower, RR 0.97, *p* = 1.00, treatment 13 of 23 (56.5%), control 7 of 12 (58.3%), NNT 55, cohort 3.
	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, cohort 1.

	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, cohort 1.

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.

Bes-Berlandier, 5/28/2024, retrospective, France, peer-reviewed, median age 51.0, 10 authors, study period March 2020 - April 2022.	oxygen increase, ICU, or mortality, 67.4% higher, RR 1.67, p = 0.31, treatment 5 of 17 (29.4%), control 13 of 74 (17.6%).
Isa, 9/2/2024, Randomized Controlled Trial, USA, peer-reviewed, 40 authors, study period 29 April, 2021 - 21 November, 2022, trial NCT04852978 (history).	risk of symptomatic case, 37.1% higher, RR 1.37, p = 0.65, treatment 35 of 245 (14.3%), control 5 of 48 (10.4%).
Isa (B), 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.
Ohtani, 5/13/2025, retrospective, Japan, preprint, 13 authors, study period October 2022 - December 2022.	risk of case, 87.9% lower, OR 0.12, p = 0.02, treatment 14, control 38, adjusted per study, multivariable, RR approximated with OR.
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.

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