Budesonide reduces COVID-19 risk: real-time meta analysis of 15 studies

@CovidAnalysis, July 2025, Version 31
https://c19early.org/umeta.html

Abstract

Significantly lower risk is seen for mortality, ICU admission, hospitalization, progression, recovery, and cases. 11 studies from 11 independent teams in 7 countries show significant benefit.

Meta analysis using the most serious outcome reported shows 28% [18-36%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies. Early treatment is more effective than late treatment.

Results are very robust — in exclusion sensitivity analysis 11 of 15 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

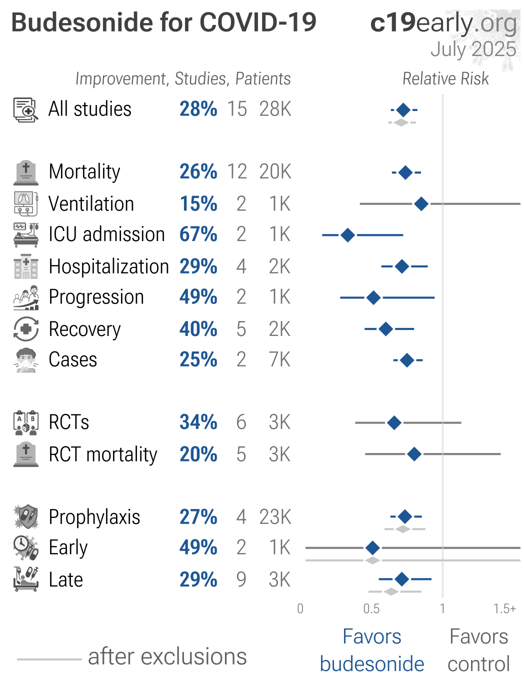
4 RCTs with 916 patients have not reported results (up to 5 years late).

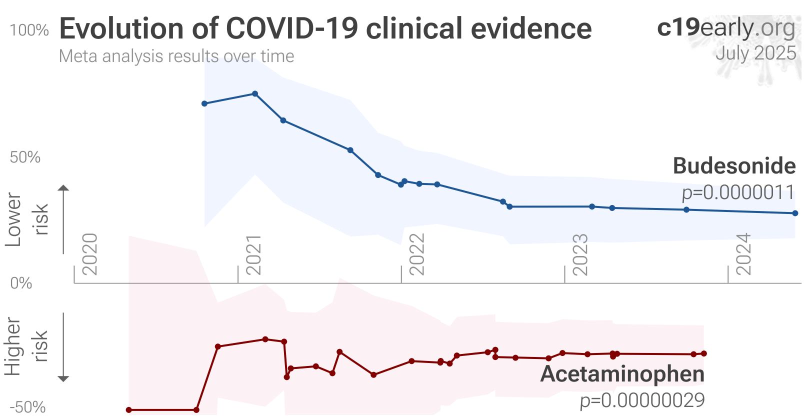
Inhaler technique and adherence may significantly affect outcomes[1].

No treatment is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. Other treatments are more effective. All data and sources to reproduce this analysis are in the appendix.

Other meta analyses show significant improvement with budesonide for recovery[2,3].

Serious Outcome Risk





BUDESONIDE FOR COVID-19 — HIGHLIGHTS

Budesonide reduces risk with very high confidence for mortality, hospitalization, recovery, and in pooled analysis, and low confidence for ICU admission, progression, and cases.

Early treatment is more effective than late treatment.

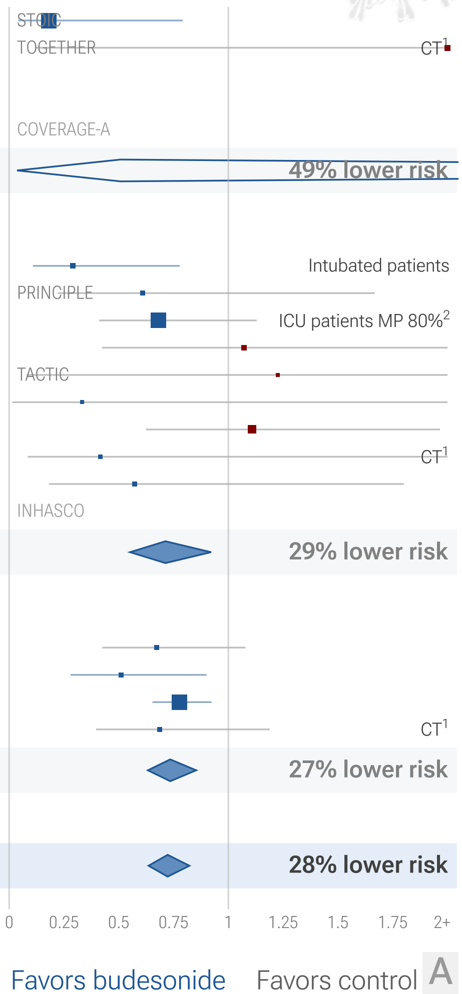
20th treatment shown effective in April 2021, now with *p* = 0.0000011 from 15 studies, recognized in 10 countries.

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.

15 budesonide COVID-19 studies (+4 unreported RCTs)

c19early.org July 2025

Study	Improvement	RR [CI]	Outcome	Treatment	Control
Ramakrish.. (RCT)	82%	0.18 [0.04-0.79]	hosp./ER	2/73	11/73
Reis (DB RCT)	-200%	3.00 [0.12-73.5]	death	1/738	0/738
Afazeli (DB RCT)	unknown, >5 years late			30 (est. total)	
Korea Un.. (DB RCT)	unknown, >2 years late			140 (est. total)	
Marcy (RCT)	unknown, >1.5 years late			600 (est. total)	
Early treatment	49%	0.51 [0.04-7.17]		3/811	11/811
Tau^2 = 2.32, I^2 = 58.9%, p = 0.63					
Ramlall (ICU)	71%	0.29 [0.11-0.78]	death	33 (n)	915 (n)
Yu (RCT)	39%	0.61 [0.22-1.67]	death	6/787	10/799
Al Sulaiman (ICU)	32%	0.68 [0.41-1.13]	death	30/64	31/64
Alsultan (RCT)	-7%	1.07 [0.42-2.71]	death	5/14	7/21
Agustí (RCT)	-23%	1.23 [0.08-19.0]	death	1/40	1/49
Bhandari	67%	0.33 [0.01-8.02]	death	0/60	1/60
Yang	-11%	1.11 [0.62-1.97]	death	30/125	13/60
Samajdar	58%	0.42 [0.08-2.05]	death	2/50	5/52
Dhanger (RCT)	43%	0.57 [0.18-1.80]	death	4/40	7/40
Taille (RCT)	unknown, >4 years late			146 (total)	
Late treatment	29%	0.71 [0.55-0.92]		78/1,213	75/2,060
Tau^2 = 0.00, I^2 = 0.0%, p = 0.0097					
Lee	33%	0.67 [0.42-1.08]	cases	19/1,674	95/5,345
Monserrat .. (PSM)	49%	0.51 [0.28-0.90]	death	n/a	n/a
Loucera	22%	0.78 [0.65-0.92]	death	1,047 (n)	14,921 (n)
Bai	31%	0.69 [0.40-1.19]	hosp.	71 (n)	241 (n)
Prophylaxis	27%	0.73 [0.63-0.85]		19/2,792	95/20,507
Tau^2 = 0.00, I^2 = 0.0%, p < 0.0001					
All studies	28%	0.72 [0.64-0.82]		100/4,816	181/23,378



[1] CT: study uses combined treatment
[2] MP: multiple medications, percentage budesonide shown

Tau^2 = 0.00, I^2 = 0.0%, p < 0.0001

Effect extraction pre-specified, see appendix

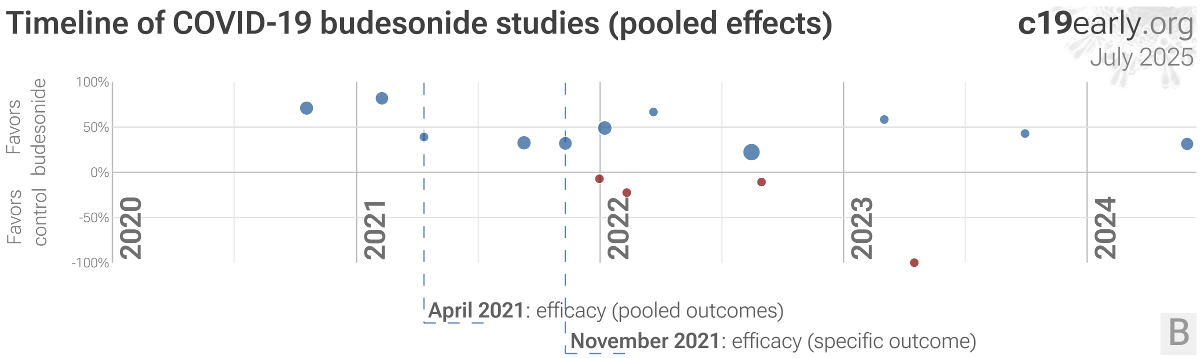


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in budesonide studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes and one or more specific outcome. Efficacy based on specific outcomes was delayed by 7.0 months, compared to using pooled outcomes.

Introduction

Immediate treatment recommended

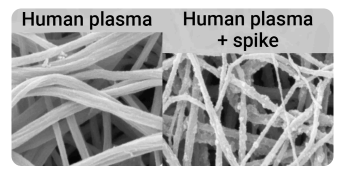


Figure 2. **SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from[4].**

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[5-17] and cognitive deficits[8,13], cardiovascular complications[18-22], organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits[23]—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Minimizing replication as early as possible is recommended.

Many treatments are expected to modulate infection

SARS-CoV-2 infection and replication involves the complex interplay of 100+ host and viral proteins and other factors[A,24-31], 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[32], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Analysis

We analyze all significant controlled studies of budesonide 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.

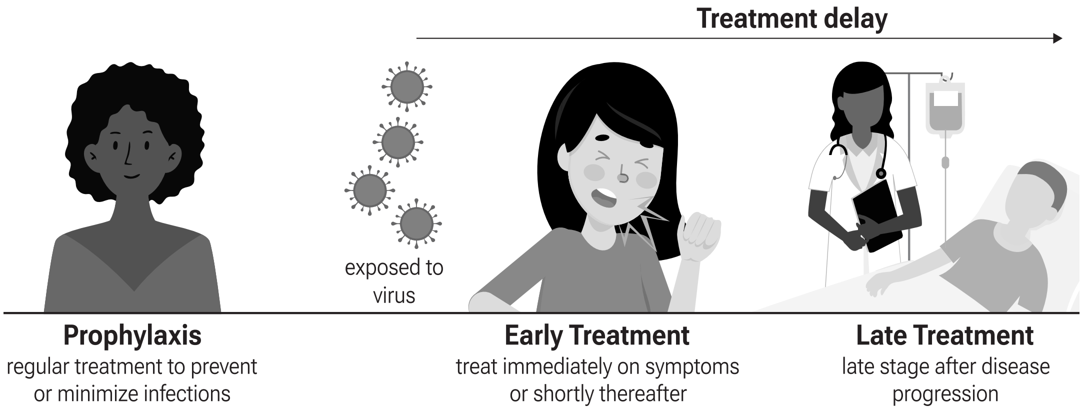


Figure 3. Treatment stages.

Preclinical Research

2 *In Vitro* studies support the efficacy of budesonide[33,34].

An *In Vivo* animal study supports the efficacy of budesonide[34].

Konduri investigate a novel formulation of budesonide that may be more effective for COVID-19.

Preclinical research is an important part of the development of treatments, however results may be very different in clinical trials. Preclinical results are not used in this paper.

Results

Table 1 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes. Table 2 shows results by treatment stage. Figure 4 plots individual results by treatment stage. Figure 5, 6, 7, 8, 9, 10, 11, 12, and 13 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, recovery, cases, and peer reviewed studies.

	Relative Risk	Studies	Patients
All studies	0.72 [0.64-0.82] ****	15	20K
After exclusions	0.71 [0.62-0.81] ****	13	20K
Peer-reviewed	0.74 [0.65-0.85] ****	13	20K
RCTs	0.66 [0.39-1.13]	6	3,412
Mortality	0.74 [0.64-0.85] ****	12	20K
Ventilation	0.85 [0.42-1.73]	2	1,662
ICU admission	0.33 [0.15-0.72] **	2	1,630
Hospitalization	0.71 [0.57-0.90] **	4	2,010
Recovery	0.60 [0.45-0.80] ***	5	2,297
Cases	0.75 [0.65-0.86] ****	2	7,331
RCT mortality	0.80 [0.46-1.41]	5	3,266

Table 1. **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<0.0001.

	Early treatment	Late treatment	Prophylaxis
All studies	0.51 [0.04-7.17]	0.71 [0.55-0.92] **	0.73 [0.63-0.85] ****
After exclusions	0.51 [0.04-7.17]	0.64 [0.48-0.85] **	0.72 [0.59-0.88] **
Peer-reviewed	0.51 [0.04-7.17]	0.76 [0.58-0.99] *	0.73 [0.60-0.88] **
RCTs	0.51 [0.04-7.17]	0.77 [0.43-1.36]	
Mortality	3.00 [0.12-73.53]	0.71 [0.55-0.92] **	0.68 [0.46-1.00] *
Ventilation		0.85 [0.42-1.73]	
ICU admission		0.33 [0.15-0.72] **	
Hospitalization	0.88 [0.32-2.40]	0.60 [0.29-1.23]	0.69 [0.40-1.19]
Recovery	0.33 [0.15-0.72] **	0.65 [0.49-0.85] **	
Cases			0.75 [0.65-0.86] ****
RCT mortality	3.00 [0.12-73.53]	0.77 [0.43-1.36]	

Table 2. **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<0.0001.

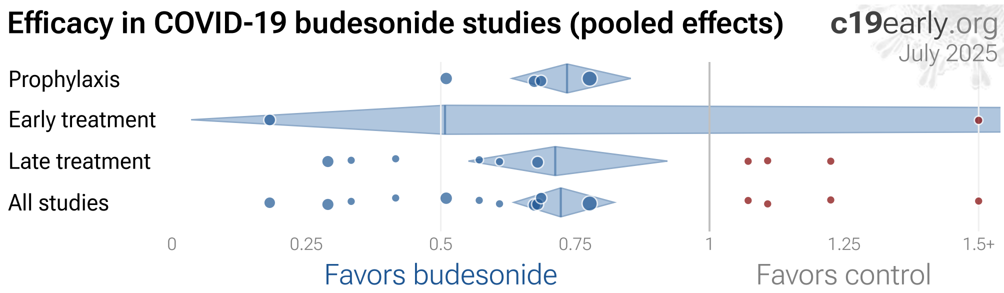


Figure 4. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

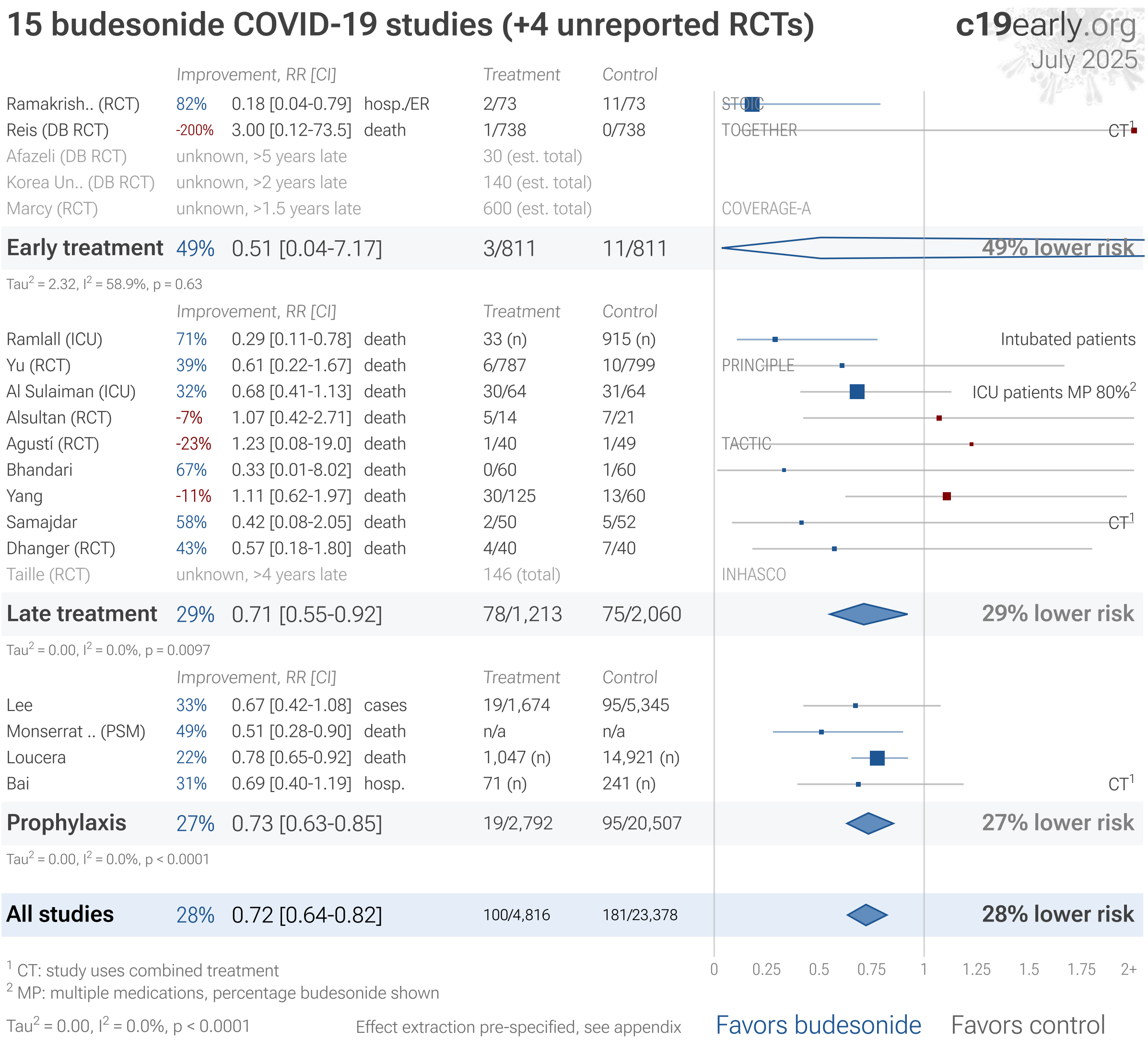


Figure 5. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For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

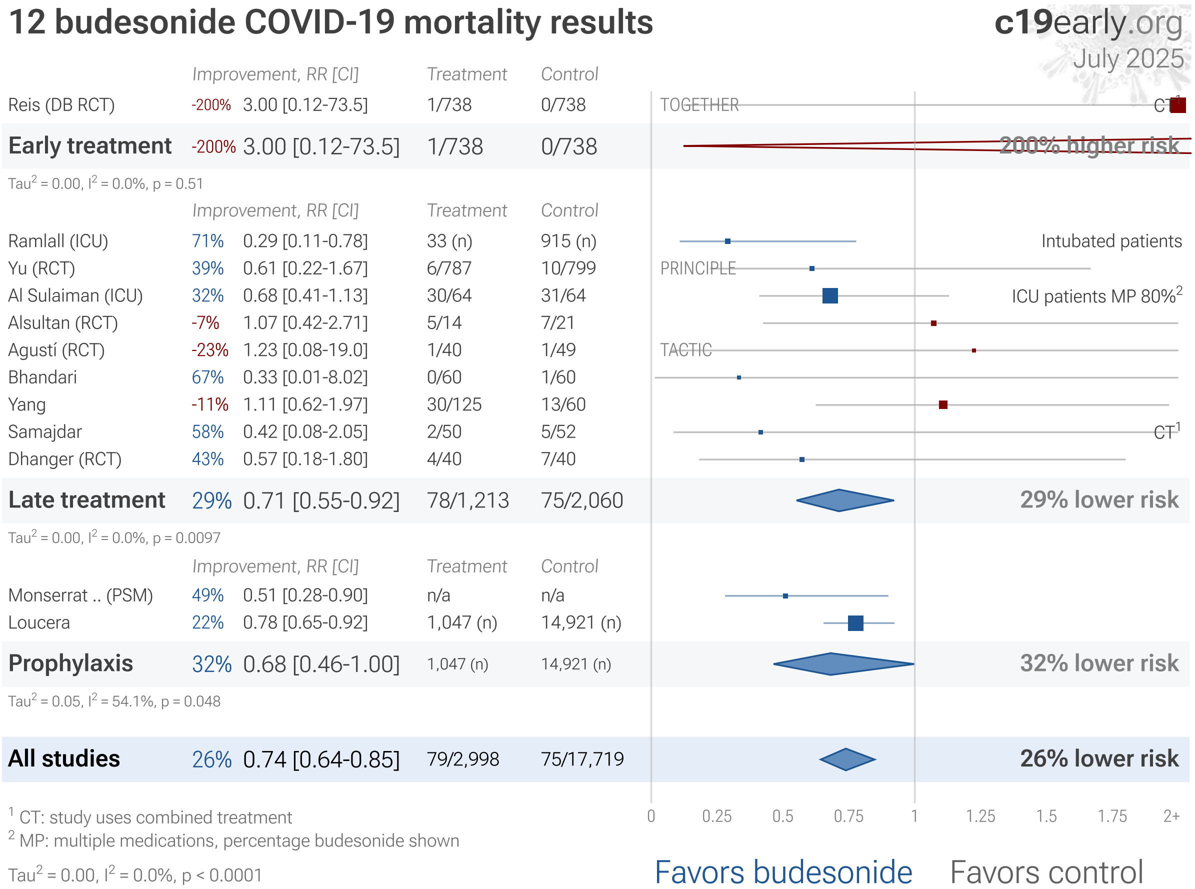


Figure 6. Random effects meta-analysis for mortality results.

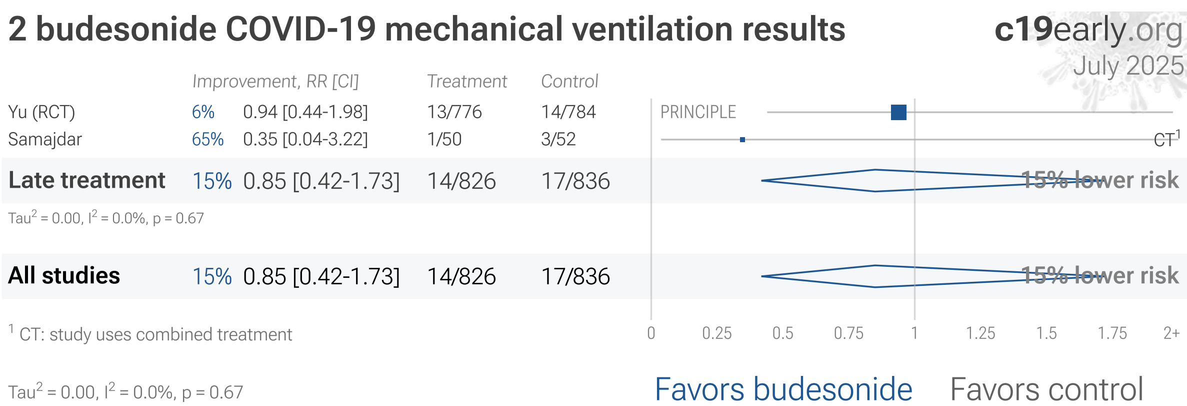


Figure 7. Random effects meta-analysis for ventilation.

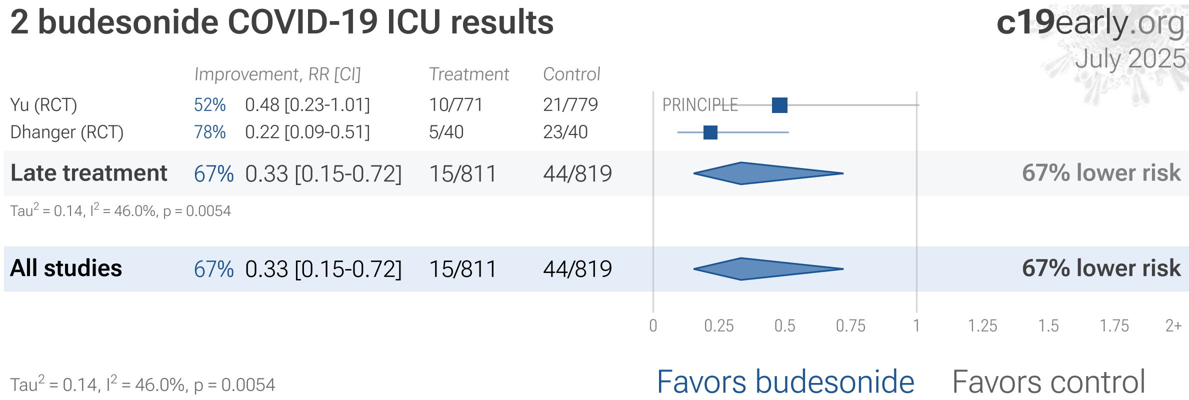


Figure 8. **Random effects meta-analysis for ICU admission.**

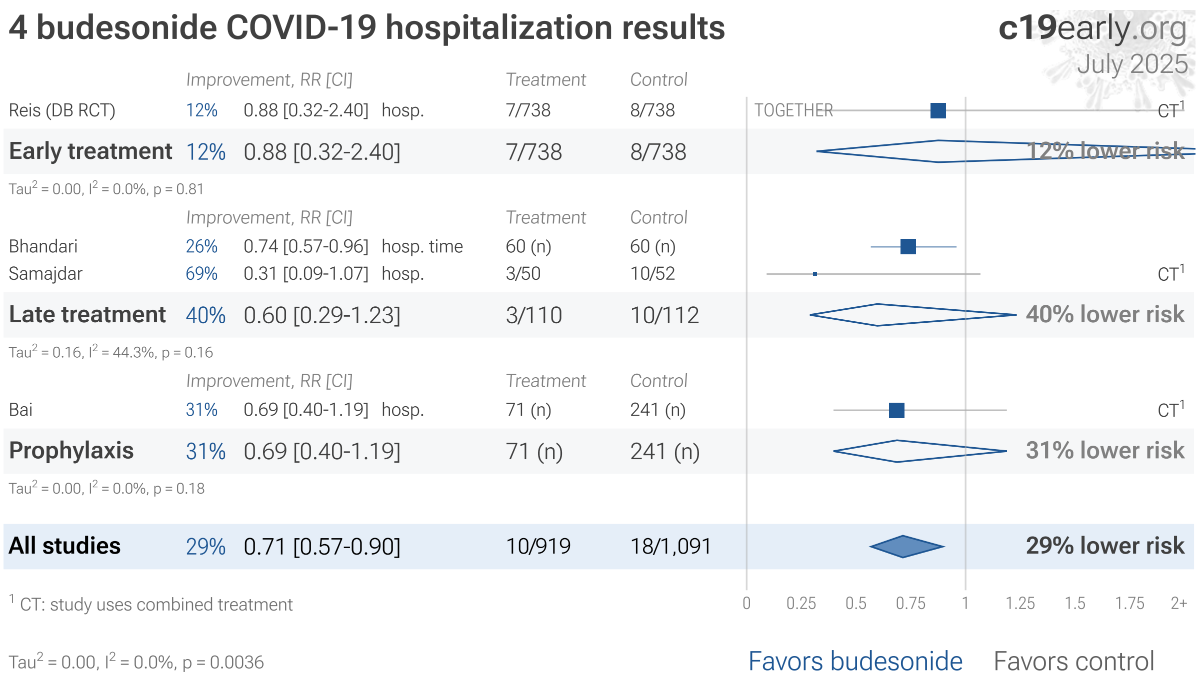


Figure 9. **Random effects meta-analysis for hospitalization.**

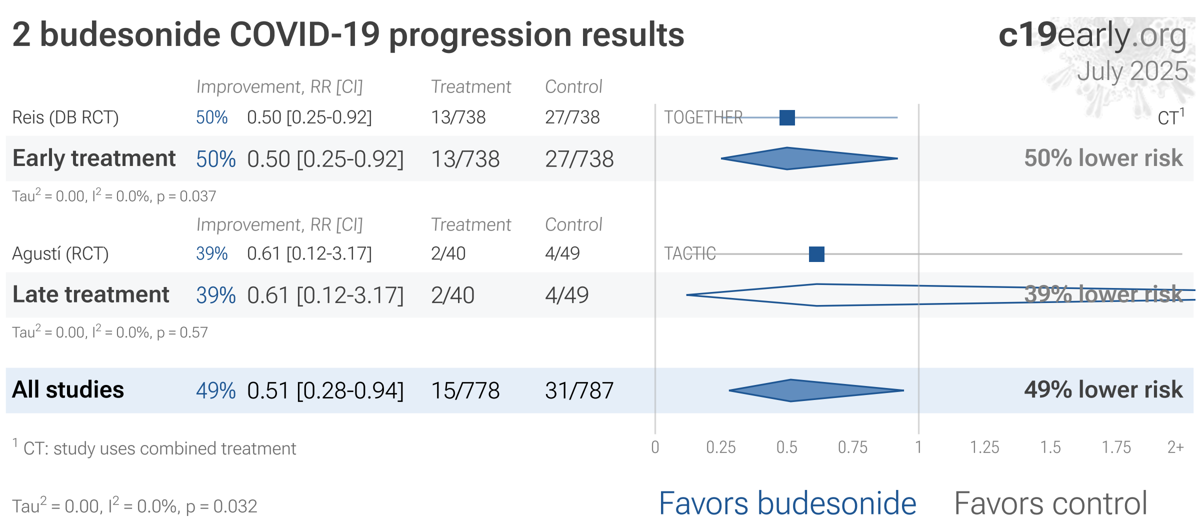


Figure 10. **Random effects meta-analysis for progression.**

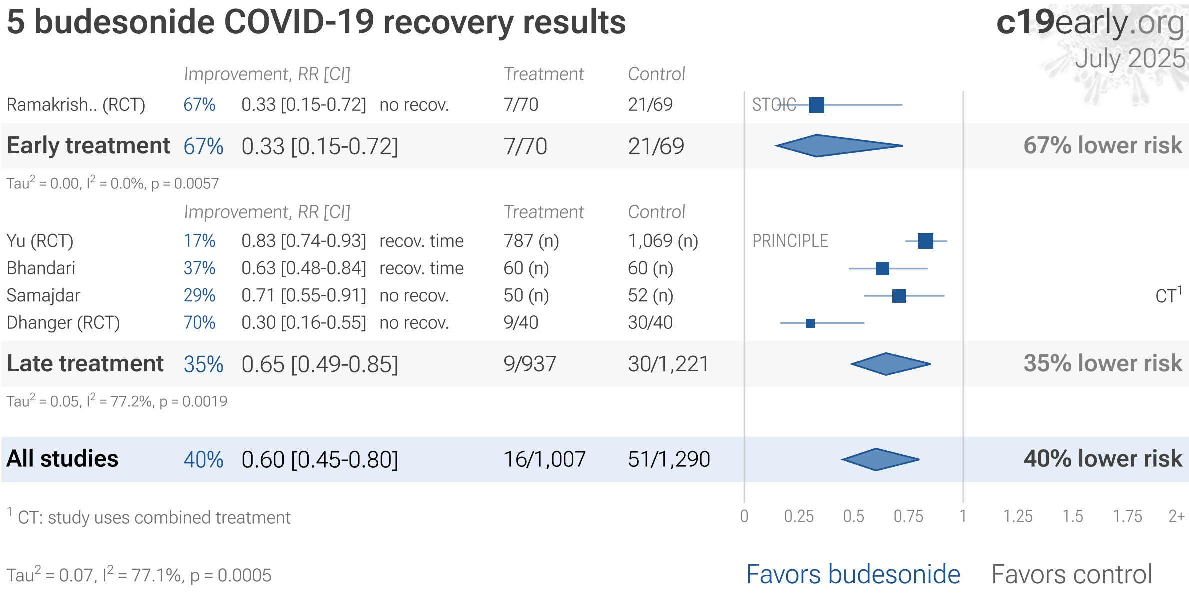


Figure 11. **Random effects meta-analysis for recovery.**

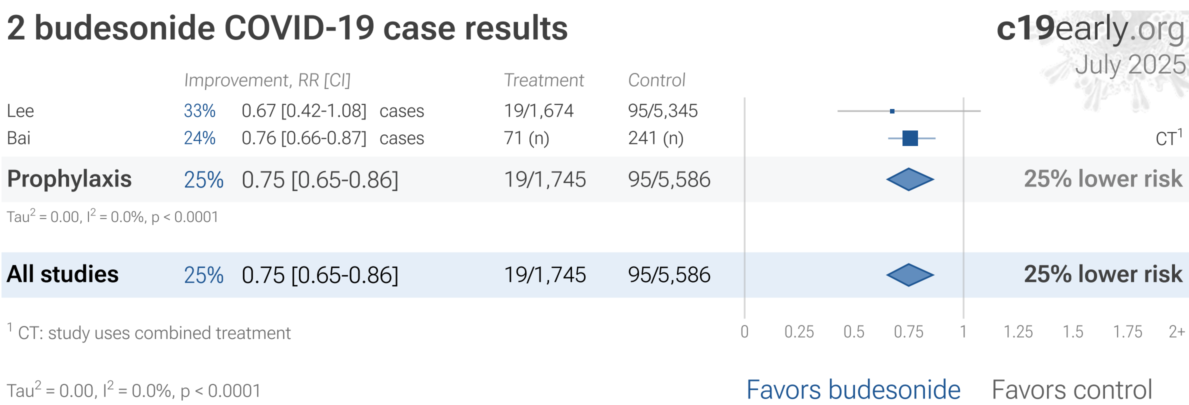


Figure 12. **Random effects meta-analysis for cases.**

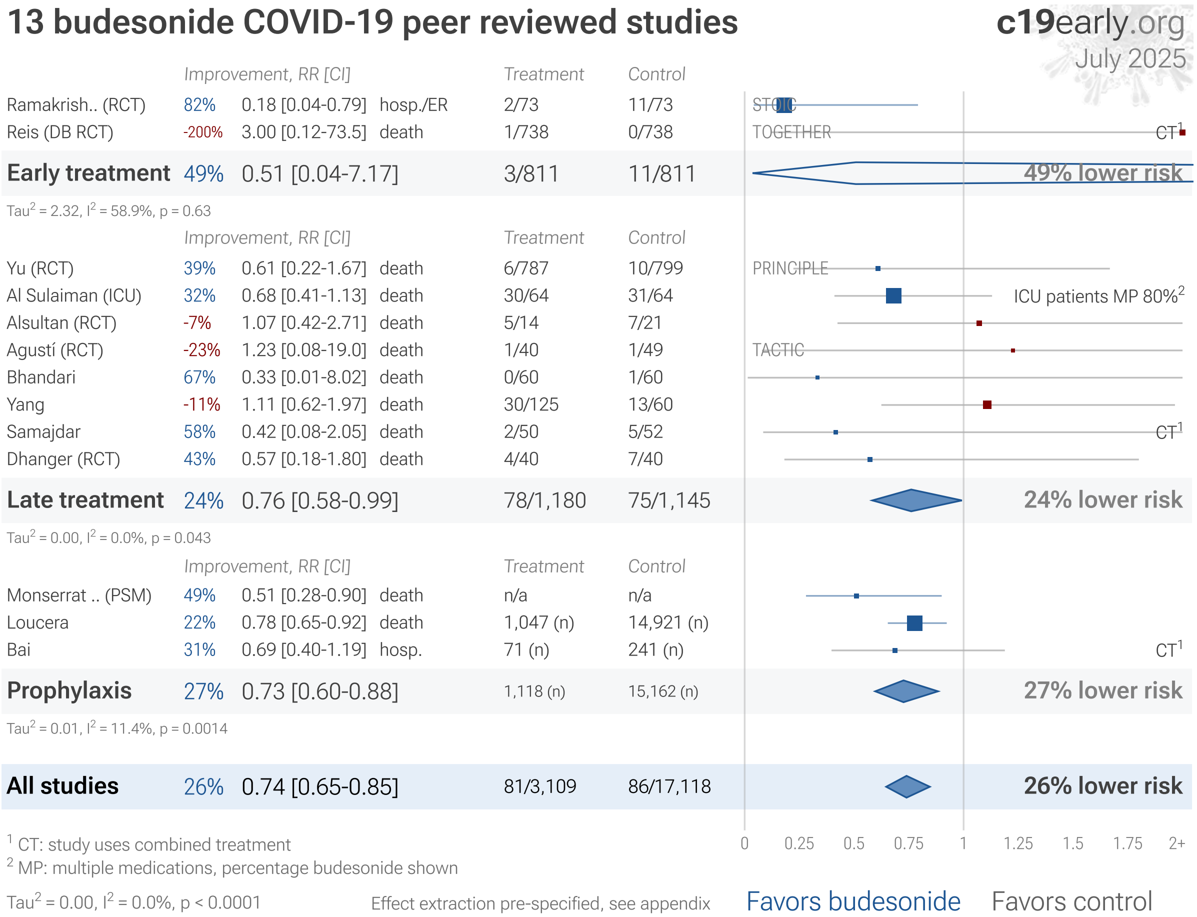


Figure 13. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding 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 14 shows a comparison of results for RCTs and observational studies. Random effects meta analysis of RCTs shows 34% improvement, compared to 29% for other studies. Figure 15 and 16 show forest plots for random effects meta-analysis of all Randomized Controlled Trials and RCT mortality results. RCT results are included in Table 1 and Table 2.

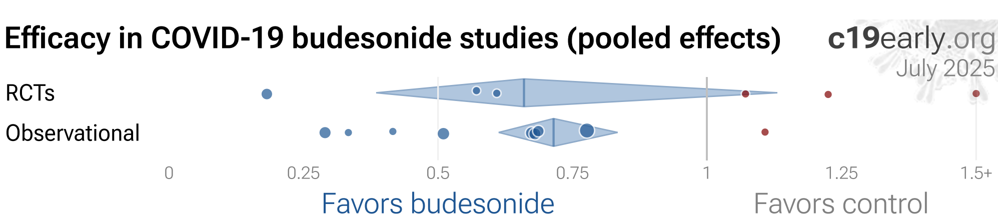


Figure 14. Results for RCTs and observational studies.

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 [37], and analysis of double-blind RCTs has identified extreme levels of bias [38]. 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] [43]. Similar results are found for all low-cost treatments, RR 1.00 [0.91-1.09]. High-cost treatments show a non-significant trend towards RCTs showing greater efficacy, RR 0.92 [0.84-1.02]. Details can be found in the supplementary data. *Lee et al.* showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases.

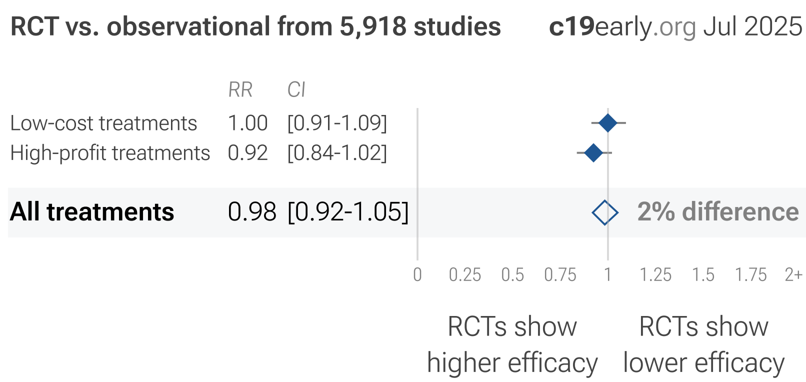


Figure 17. For COVID-19, observational study results do not systematically differ from RCTs, RR 0.98 [0.92-1.05] across 172 treatments [40].

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[45,46].

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.

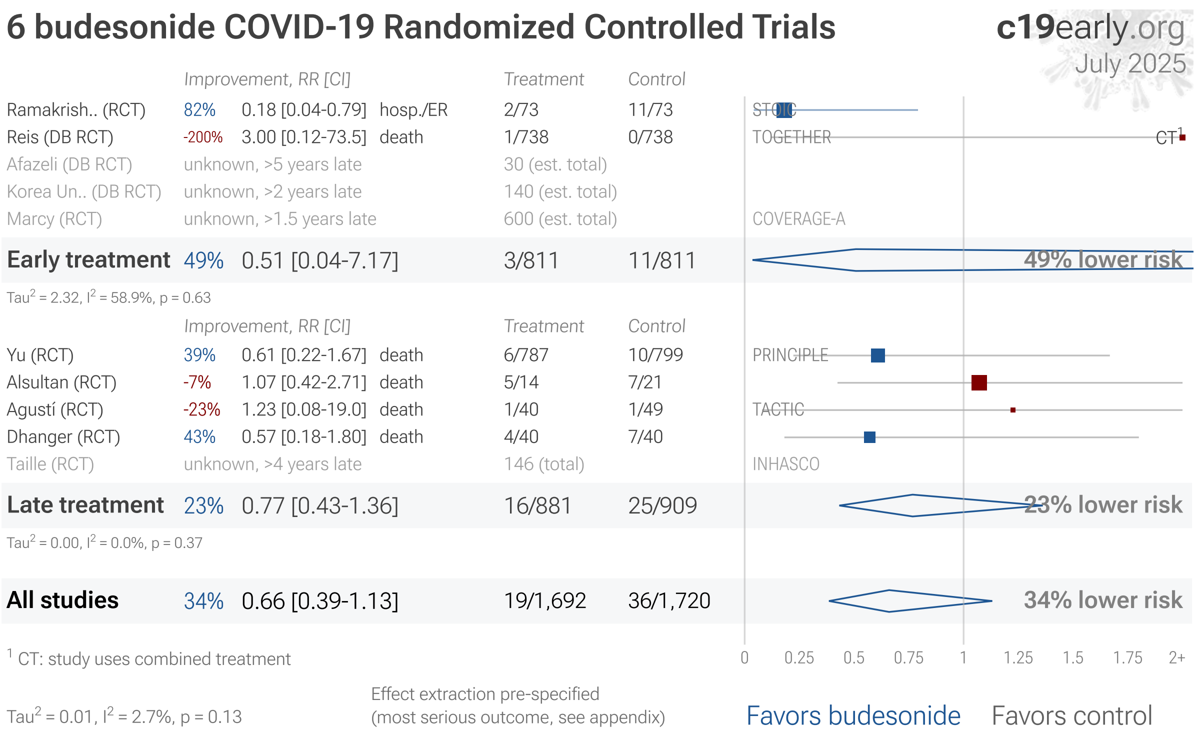


Figure 15. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

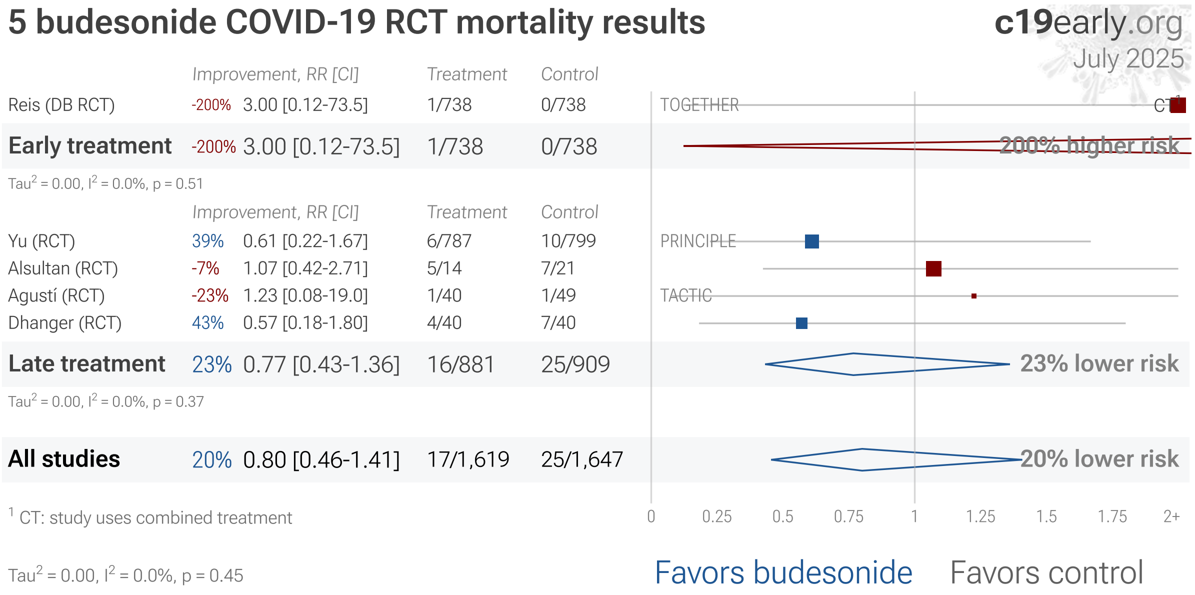


Figure 16. **Random effects meta-analysis for RCT mortality results.**

Unreported RCTs

4 budesonide RCTs have not reported results[47-50]. The trials report a total of 916 patients, with 1 trial having actual enrollment of 146, and the remainder estimated. The results are delayed from 1.5 years to over 5 years.

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

Bai, unadjusted results with minimal group details.

Yang (B), unadjusted results with no group details.

13 budesonide COVID-19 studies after exclusions

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	Improvement, RR [CI]			Treatment	Control
Ramakrish.. (RCT)	82%	0.18 [0.04-0.79]	hosp./ER	2/73	11/73
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Early treatment	49%	0.51 [0.04-7.17]		3/811	11/811
Tau² = 2.32, I² = 58.9%, p = 0.63					
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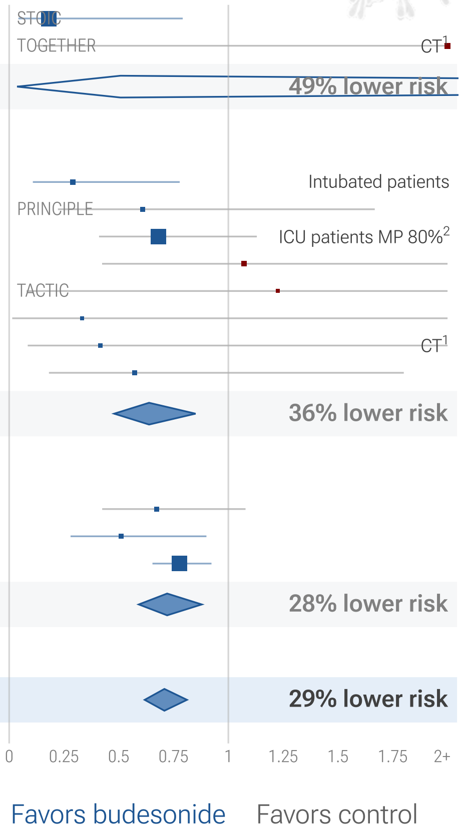
Al Sulaiman (ICU)	32%	0.68 [0.41-1.13]	death	30/64	31/64
Alsultan (RCT)	-7%	1.07 [0.42-2.71]	death	5/14	7/21
Agustí (RCT)	-23%	1.23 [0.08-19.0]	death	1/40	1/49
Bhandari	67%	0.33 [0.01-8.02]	death	0/60	1/60
Samajdar	58%	0.42 [0.08-2.05]	death	2/50	5/52
Dhanger (RCT)	43%	0.57 [0.18-1.80]	death	4/40	7/40
Late treatment	36%	0.64 [0.48-0.85]		48/1,088	62/2,000
Tau² = 0.00, I² = 0.0%, p = 0.0022					
	Improvement, RR [CI]			Treatment	Control
Lee	33%	0.67 [0.42-1.08]	cases	19/1,674	95/5,345
Monserrat .. (PSM)	49%	0.51 [0.28-0.90]	death	n/a	n/a
Loucera	22%	0.78 [0.65-0.92]	death	1,047 (n)	14,921 (n)
Prophylaxis	28%	0.72 [0.59-0.88]		19/2,721	95/20,266
Tau² = 0.01, I² = 14.0%, p = 0.0013					
All studies	29%	0.71 [0.62-0.81]		70/4,620	168/23,077



[1] CT: study uses combined treatment
[2] MP: multiple medications, percentage budesonide shown

Tau² = 0.00, I² = 0.0%, p < 0.0001

Effect extraction pre-specified, see appendix

Figure 18. **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[53,54]. 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 [55]
<24 hours	-33 hours symptoms [56]
24-48 hours	-13 hours symptoms [56]
Inpatients	-2.5 hours to improvement [57]

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

Figure 19 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 172 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

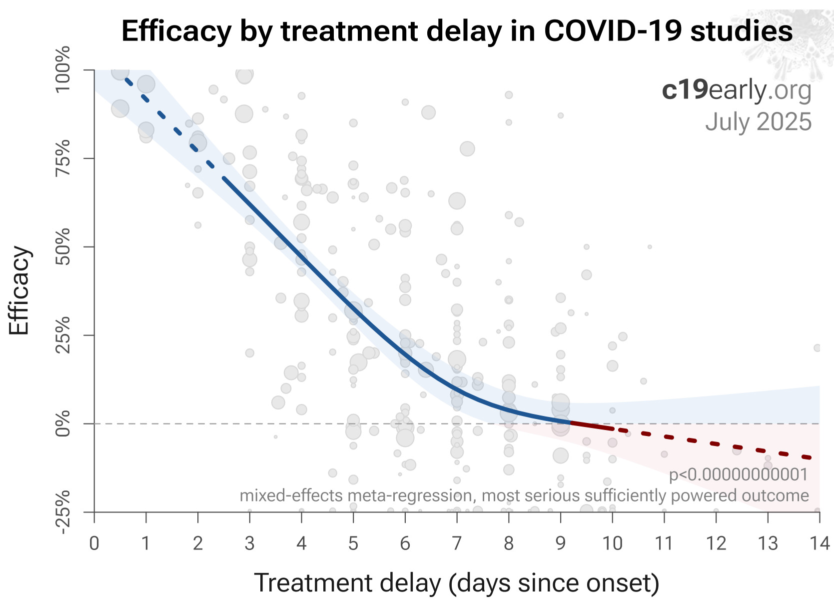


Figure 19. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 172 treatments.

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 [59], for example the Gamma variant shows significantly different characteristics [60-63]. 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 [64,65].

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 [68-84], 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 budesonide as of November 2021. Efficacy is now known based on specific outcomes. Efficacy based on specific outcomes was delayed by 7.0 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 20 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 21 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 22 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 $p = 0.0000000033$.

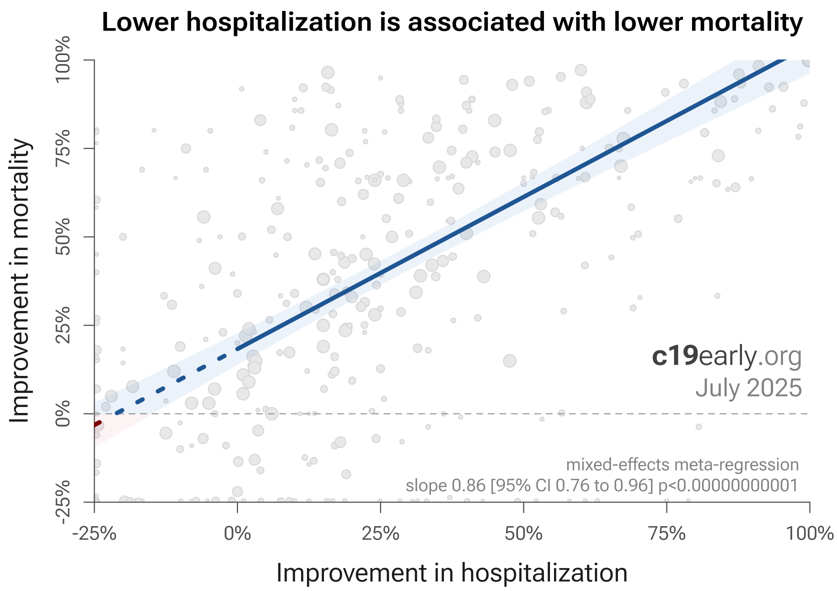


Figure 20. **Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.**

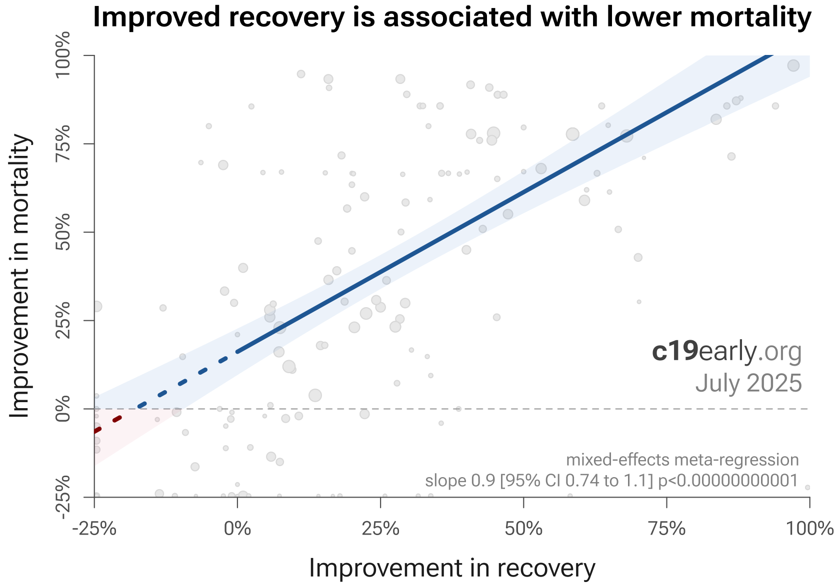


Figure 21. **Improved recovery is associated with lower mortality, supporting pooled outcome analysis.**

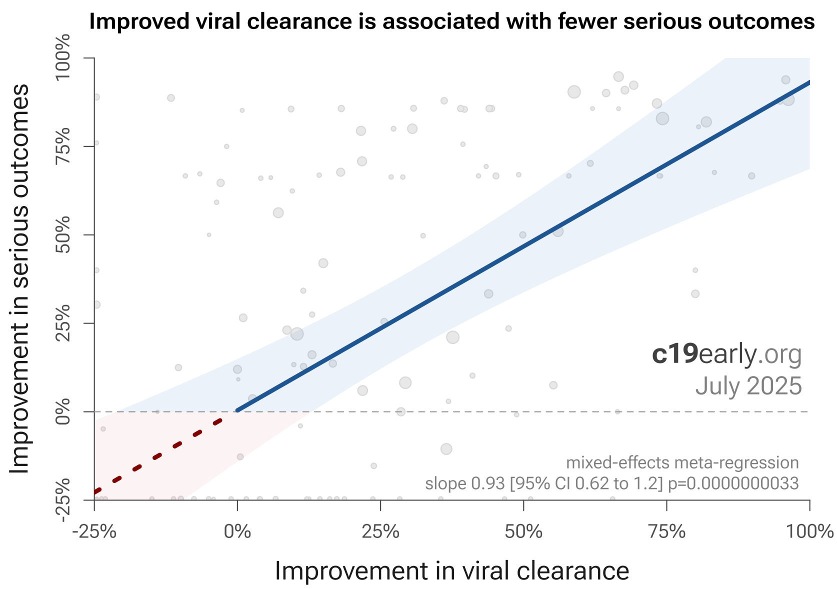


Figure 20. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

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

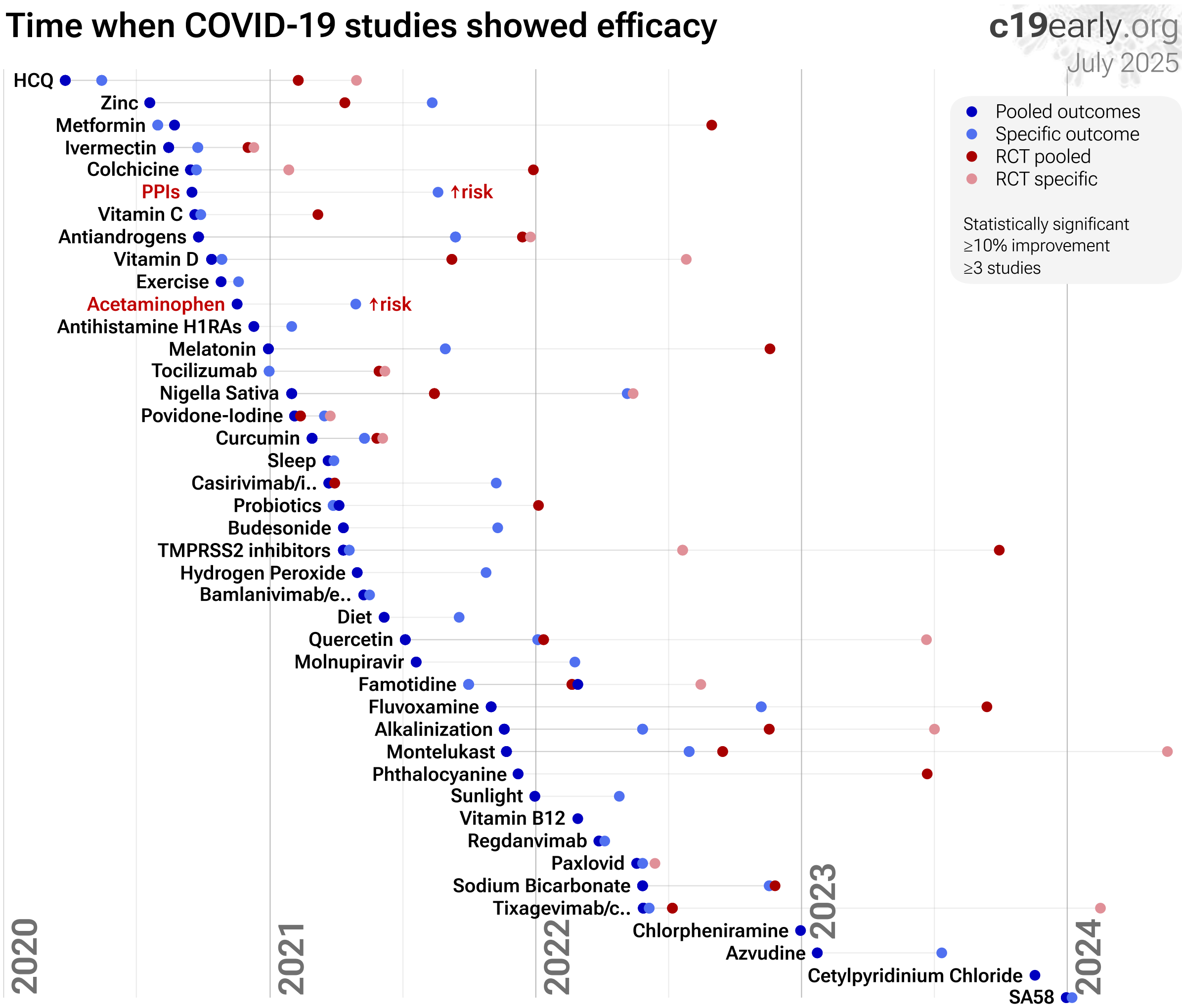


Figure 23. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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

Ciclesonide

Some analyses combine ciclesonide and budesonide studies. We have not done this due to significant differences. *Pharmacokinetics and pharmacodynamics*: budesonide has a more rapid onset of action and a shorter half-life, which can lead to a more immediate and potent anti-inflammatory effect. Ciclesonide is a prodrug that requires conversion to its active form, which may delay therapeutic effects. *Receptor affinity and potency*: budesonide has a higher affinity for glucocorticoid receptors and a higher potency compared to ciclesonide. This can result in more effective suppression of inflammation and immune modulation in the respiratory tract, potentially leading to better clinical outcomes. *Bioavailability*: budesonide typically has higher lung bioavailability compared to ciclesonide.

Publication bias

Publishing is often biased towards positive results, however evidence suggests that there may be a negative bias for inexpensive treatments for COVID-19. Both negative and positive results are very important for COVID-19, media in many countries prioritizes negative results for inexpensive treatments (inverting the typical incentive for scientists that value media recognition), and there are many reports of difficulty publishing positive results [86-89]. For budesonide, there is currently not enough data to evaluate publication bias with high confidence.

One method to evaluate bias is to compare prospective vs. retrospective studies. Prospective studies are more likely to be published regardless of the result, while retrospective studies are more likely to exhibit bias. For example, researchers may perform preliminary analysis with minimal effort and the results may influence their decision to continue. Retrospective studies also provide more opportunities for the specifics of data extraction and adjustments to influence results.

Figure 24 shows a scatter plot of results for prospective and retrospective studies. 71% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 75% of prospective studies, showing similar results. The median effect size for retrospective studies is 33% improvement, compared to 36% for prospective studies, showing similar results.

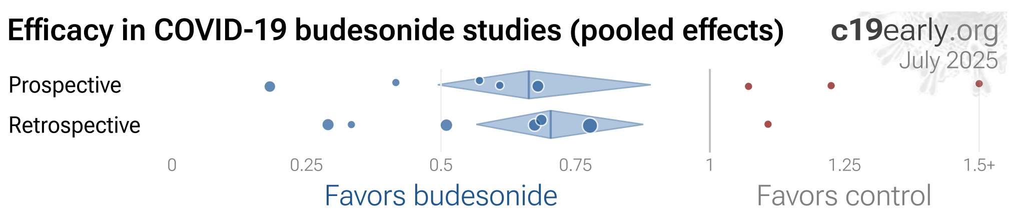


Figure 24. Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.

Late treatment bias

Studies for budesonide were mostly late treatment studies, in contrast with typical high-profit drugs that were more likely to be tested with early treatment.

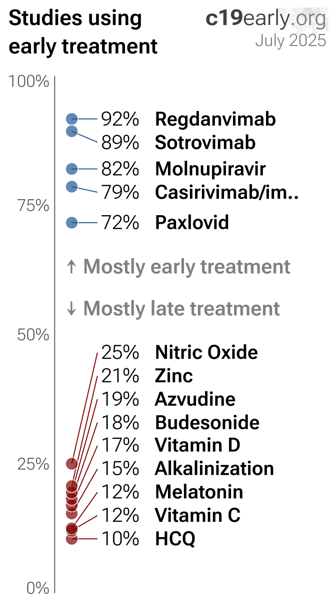


Figure 25. Early treatment was more common for high-profit drugs.

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 26 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ($p > 0.05$). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, $p < 0.0001$, with six variants of Egger's test all showing $p < 0.05$ [90-97]. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.

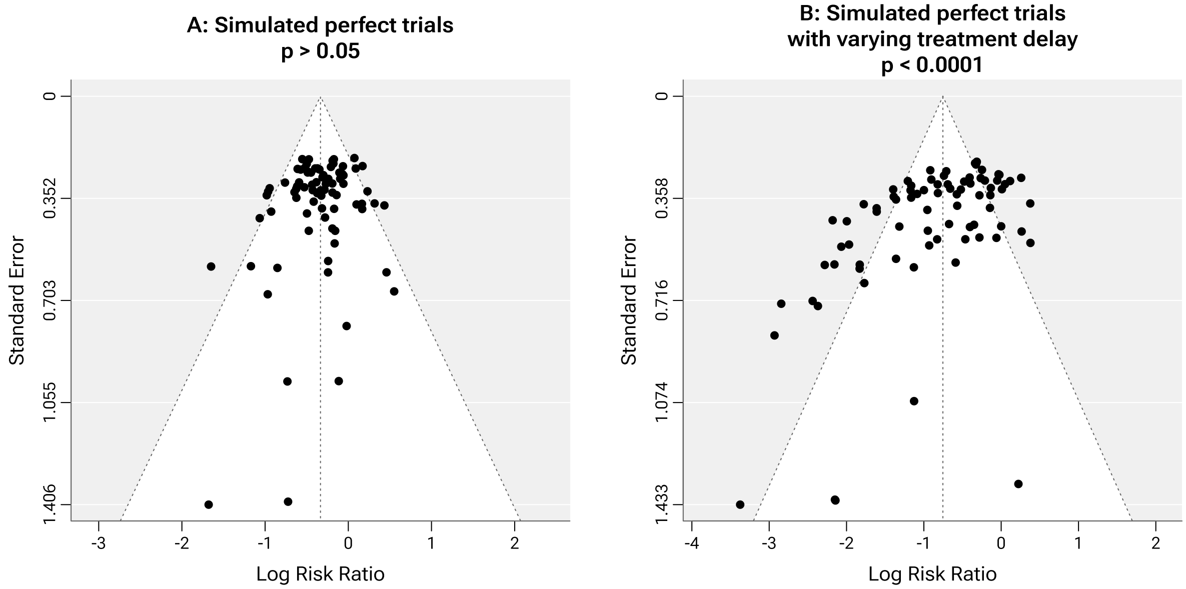


Figure 26. **Example funnel plot analysis for simulated perfect trials.**

Conflicts of interest

Pharmaceutical drug trials often have conflicts of interest whereby sponsors or trial staff have a financial interest in the outcome being positive. Budesonide for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 budesonide trials have been run by physicians on the front lines with the primary goal of finding the best methods to save human lives and minimize the collateral damage caused by COVID-19. While pharmaceutical companies are careful to run trials under optimal conditions (for example, restricting patients to those most likely to benefit, only including patients that can be treated soon after onset when necessary, and ensuring accurate dosing), not all budesonide trials represent the optimal conditions for efficacy.

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[68-84]. 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

3 of 15 studies combine treatments. The results of budesonide alone may differ. 1 of 6 RCTs use combined treatment. Other meta analyses show significant improvement with budesonide for recovery[2,3].

Other studies

Additional preclinical or review papers suggesting potential benefits of budesonide for COVID-19 include[113-119]. We have not reviewed these studies in detail.

Perspective

Results compared with other treatments

SARS-CoV-2 infection and replication involves a complex interplay of 100+ host and viral proteins and other factors[24-31], providing many therapeutic targets. Over 9,000 compounds have been predicted to reduce COVID-19 risk[32], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 27 shows an overview of the results for budesonide in the context of multiple COVID-19 treatments, and Figure 28 shows a plot of efficacy vs. cost for COVID-19 treatments.

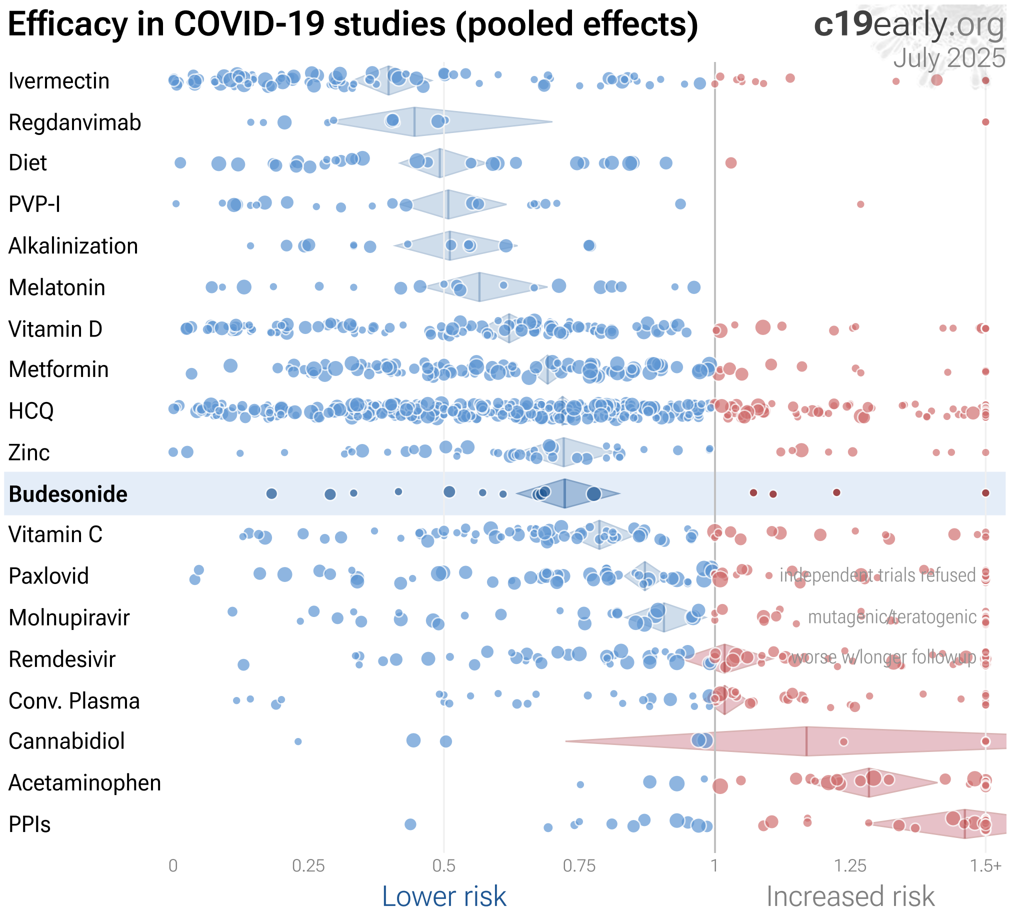


Figure 27. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy [120].

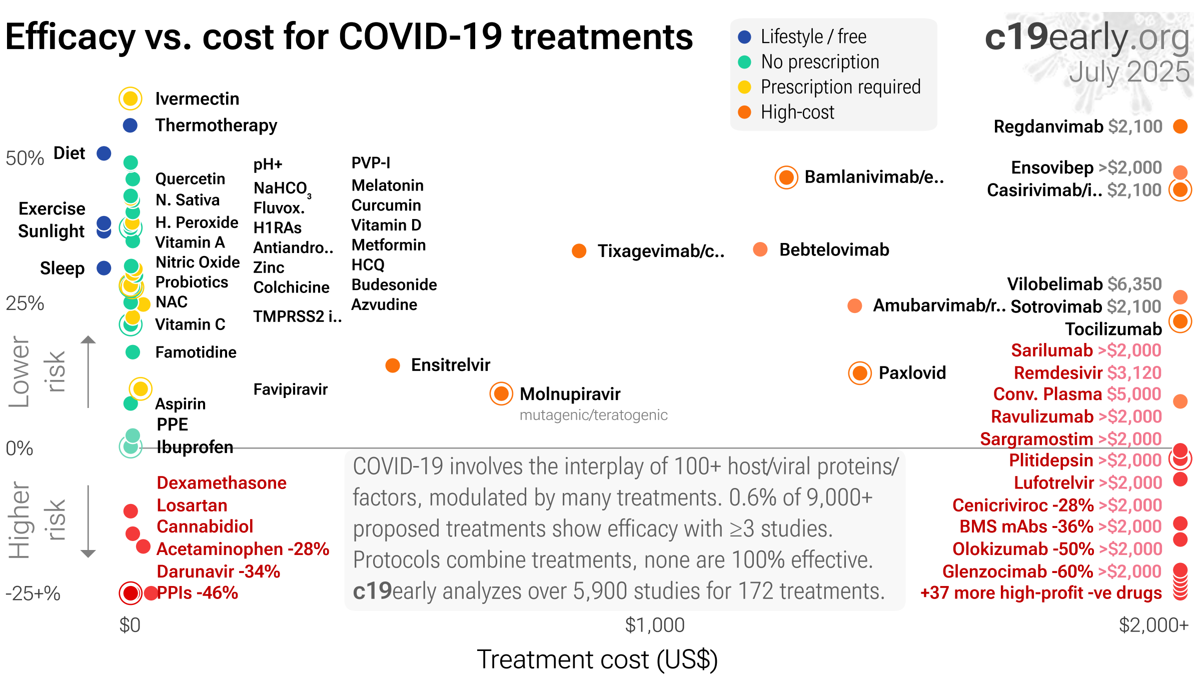


Figure 28. Efficacy vs. cost for COVID-19 treatments.

Conclusion

Budesonide is an effective treatment for COVID-19. Significantly lower risk is seen for mortality, ICU admission, hospitalization, progression, recovery, and cases. 11 studies from 11 independent teams in 7 countries show significant benefit. Meta analysis using the most serious outcome reported shows 28% [18-36%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies. Early treatment is more effective than late treatment. Results are very robust — in exclusion sensitivity analysis 11 of 15 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

Inhaler technique and adherence may significantly affect outcomes[1].

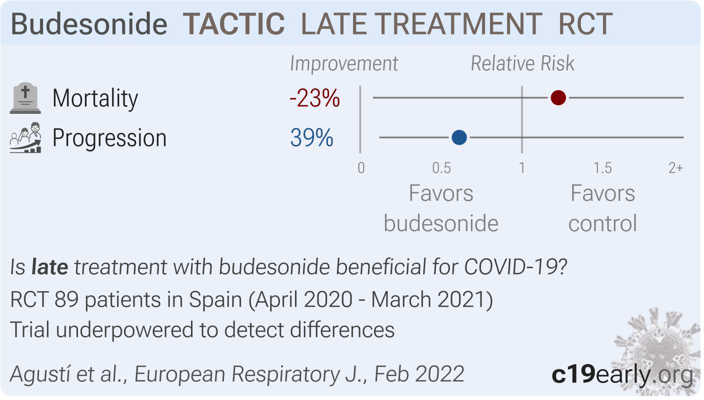
Other meta analyses show significant improvement with budesonide for recovery[2,3].

Study Notes

Afazeli

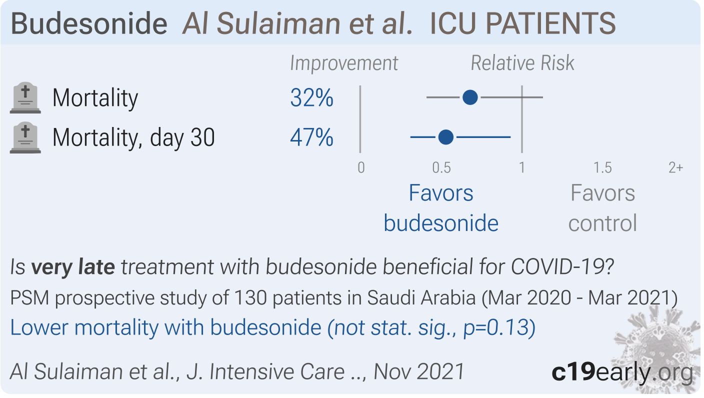
Estimated 30 patient budesonide early treatment RCT with results not reported over 5 years after estimated completion.

Agustí



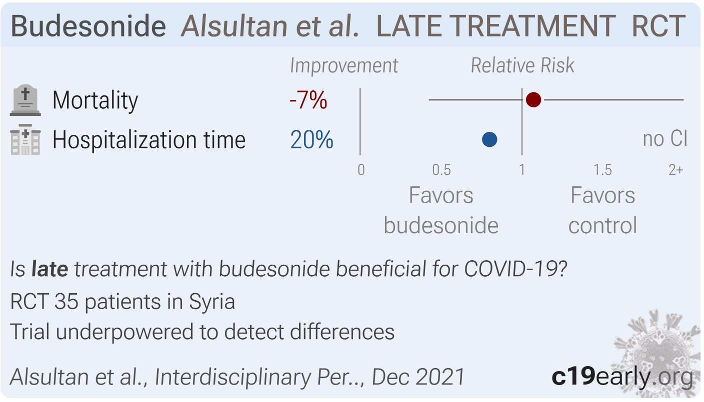
Small early-terminated RCT with 40 inhaled budesonide and 49 control patients, showing no significant differences. 400μg/12h via Pulmicort Turbuhaler.

Al Sulaiman



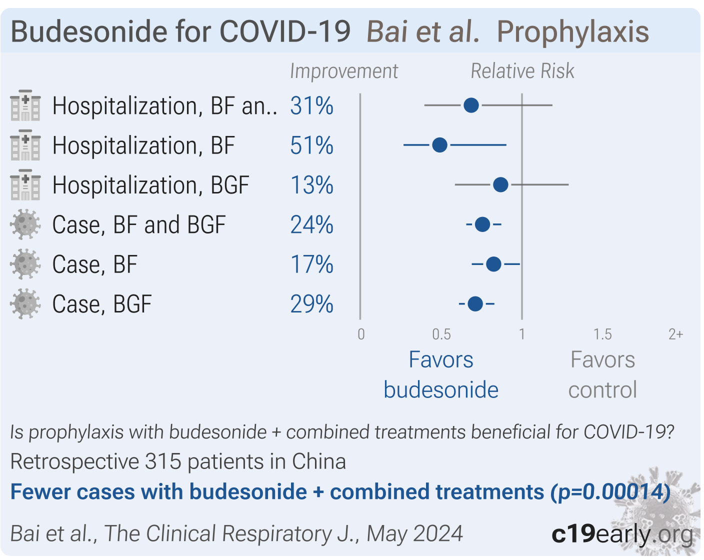
Combined retrospective (Mar-Jun 2020) and prospective (until Mar 2021) study of 954 COVID+ ICU patients in Saudi Arabia, 68 treated with ICS (80% budesonide or budesonide/formoterol, 20% fluticasone/salmeterol), showing lower mortality with treatment, statistically significant for 30-day but not in-hospital mortality.

Alsultan



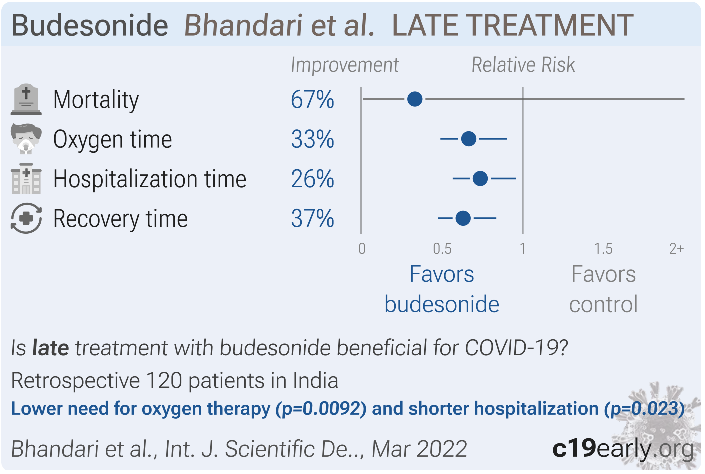
Small RCT 49 severe condition hospitalized patients in Syria, showing lower mortality with colchicine and shorter hospitalization time with both colchicine and budesonide (all of these are not statistically significant).

Bai



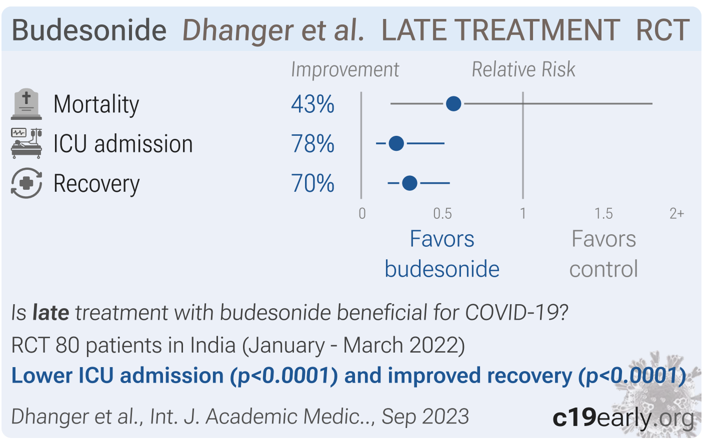
Retrospective 315 COPD patients in China showing significantly lower COVID-19 cases with budesonide/formoterol or budesonide/glycopyrronium/formoterol use. Note that Table 4 includes only infected patients, we show the COVID-19 hospitalization risk among all patients with known medication status. Minimal details are provided for the groups on these medications.

Bhandari



Retrospective 120 hospitalized COVID-19 patients with persistent cough in India, showing faster resolution of cough, shorter duration of oxygen support, and shorter hospitalization with inhaled budesonide treatment compared to standard of care alone.

Dhanger

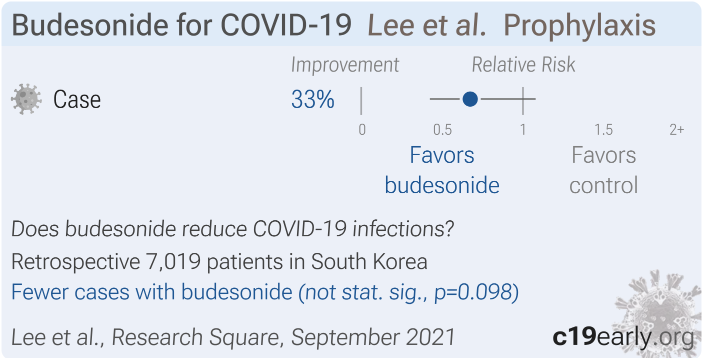


RCT inhaled budesonide with 80 moderate COVID-19 pneumonia patients. The budesonide group had significantly faster time to clinical improvement, fewer ICU admissions, shorter oxygen therapy duration, and lower mortality. Inhaled budesonide 400mcg twice daily for 14 days.

Korea United Pharm.

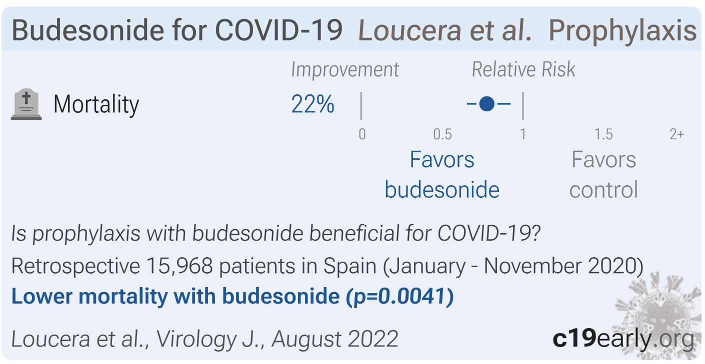
Estimated 140 patient budesonide early treatment RCT with results not reported over 2 years after estimated completion.

Lee



Retrospective 44,968 patients in South Korea, 7,019 on inhaled corticosteroids, showing no statistically significant differences in COVID-19 cases.

Loucera

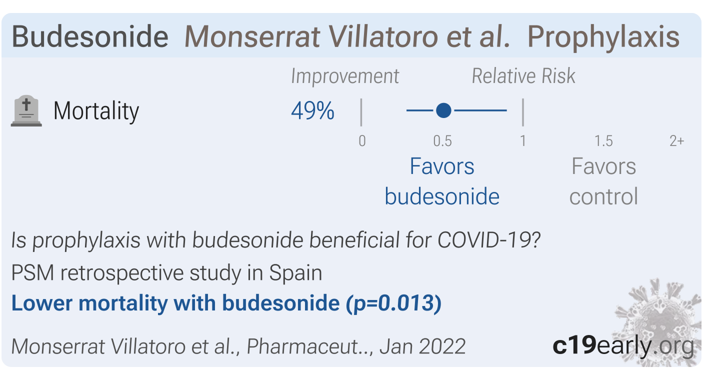


Retrospective 15,968 COVID-19 hospitalized patients in Spain, showing lower mortality with existing use of several medications including metformin, HCQ, azithromycin, aspirin, vitamin D, vitamin C, and budesonide. Since only hospitalized patients are included, results do not reflect different probabilities of hospitalization across treatments.

Marcy

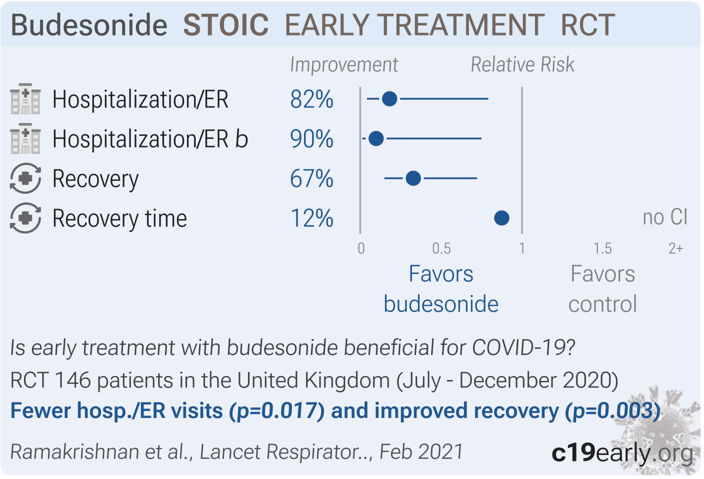
Estimated 600 patient budesonide early treatment RCT with results not reported over 1.5 years after estimated completion.

Monserrat Villatoro



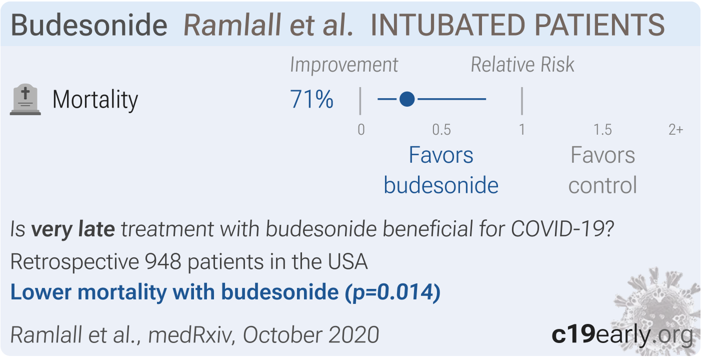
PSM retrospective 3,712 hospitalized patients in Spain, showing lower mortality with existing use of azithromycin, bemiparine, budesonide-formoterol fumarate, cefuroxime, colchicine, enoxaparin, ipratropium bromide, loratadine, mepyramine theophylline acetate, oral rehydration salts, and salbutamol sulphate, and higher mortality with acetylsalicylic acid, digoxin, folic acid, mirtazapine, linagliptin, enalapril, atorvastatin, and allopurinol.

Ramakrishnan



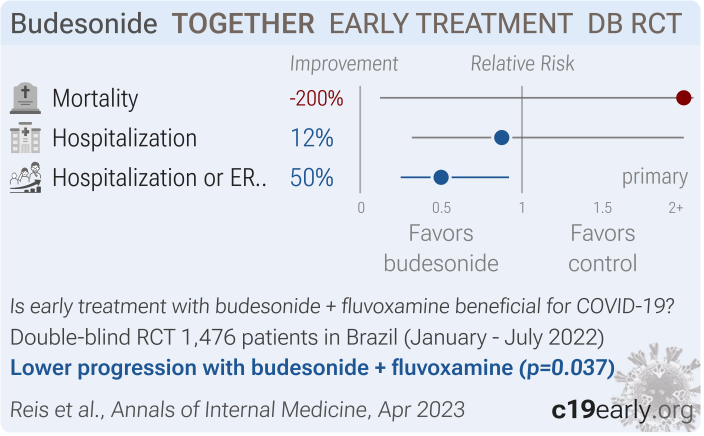
RCT with 73 budesonide patients and 73 control patients, showing significantly lower combined risk of an ER visit or hospitalization, and lower risk of no recovery at day 14.

Ramlall



Retrospective 948 intubated patients, 33 treated with budesonide, showing lower mortality with treatment.

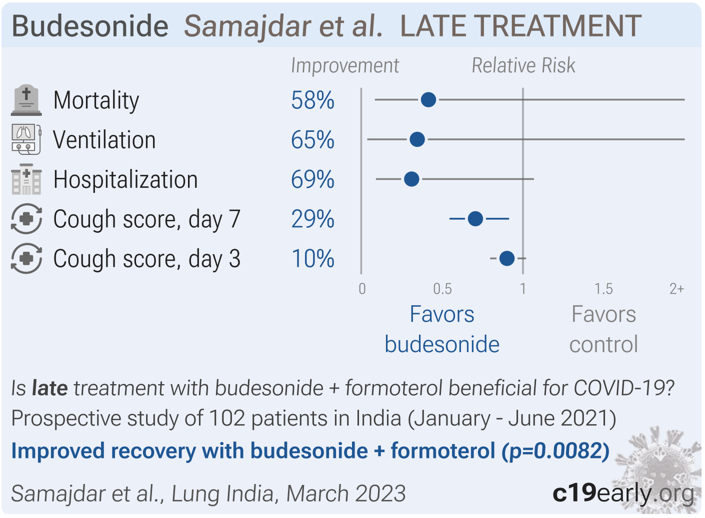
Reis



Low-risk (1% hospitalization) outpatient RCT with 738 fluvoxamine + budesonide patients and 738 placebo patients, showing significantly lower hospitalization/ER visits with treatment.

The TOGETHER trial has extreme COI, impossible data, blinding failure, randomization failure, uncorrected errors, and many protocol violations. Authors do not respond to these issues and they have refused to release the data as promised. Some issues may apply only to specific arms. For more details see [121-126].

Samajdar

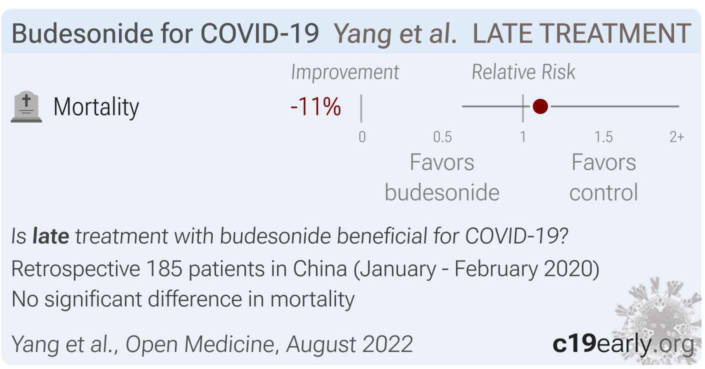


Prospective study of 102 patients in India, showing improved recovery of cough with budesonide+formoterol. Authors note better results with earlier treatment. Budesonide 800mcg + formoterol 12mcg bid for 7 days.

Taille

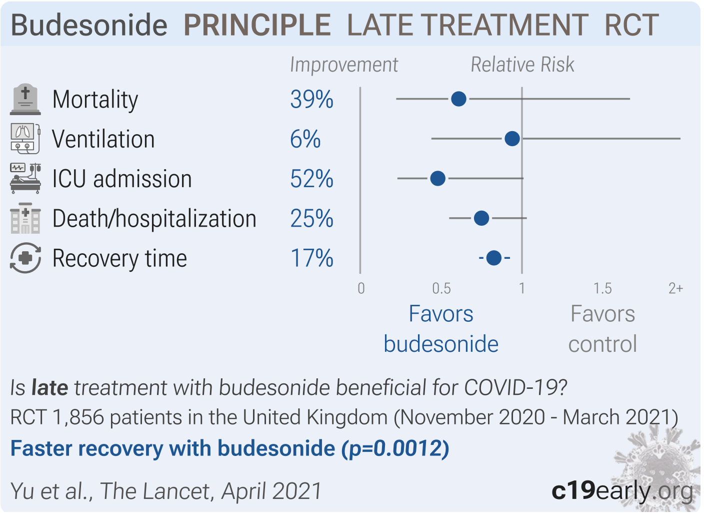
146 patient budesonide late treatment RCT with results not reported over 4 years after completion.

Yang



Retrospective 185 hospitalized COVID-19 patients in China, showing no significant difference in mortality with budesonide use in unadjusted results.

Yu



Results from the PRINCIPLE trial, 1,073 treated with budesonide starting a median of 6 days after symptom onset, showing lower hospitalization/death, and faster recovery with treatment.

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 budesonide 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 budesonide 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[127]. If only individual symptom data is available, the most serious

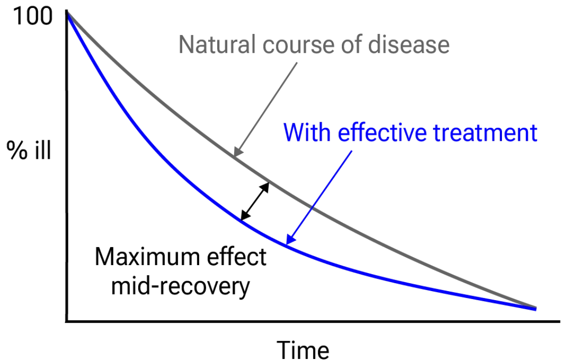


Figure 29. Mid-recovery results can more accurately reflect efficacy when almost all patients recover. *Mateja et al.* confirm that intermediate viral load results more accurately reflect hospitalization/death.

symptom has priority, for example difficulty breathing or low SpO_2 is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to Zhang et al. Reported confidence intervals and *p*-values are used when available, and adjusted values are used when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed Altman, Altman (B), and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 [131]. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.13.5) with scipy (1.16.0), pythonmeta (1.26), numpy (2.3.1), statsmodels (0.14.4), and plotly (6.2.0).

Forest plots are computed using PythonMeta [132] 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 [53,54].

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/umeta.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.

Afazeli, 5/20/2020, Double Blind Randomized Controlled Trial, Iran, trial NCT04331470 (history).	Estimated 30 patient RCT with results unknown and over 5 years late.
Korea United Pharm., 11/1/2022, Double Blind Randomized Controlled Trial, placebo-controlled, South Korea, trial NCT05055414 (history).	Estimated 140 patient RCT with results unknown and over 2 years late.
Marcy, 8/1/2023, Randomized Controlled Trial, multiple countries, trial NCT04920838 (history) (COVERAGE-A).	Estimated 600 patient RCT with results unknown and over 1.5 years late.
Ramakrishnan, 2/8/2021, Randomized Controlled Trial, United Kingdom, peer-reviewed, 24 authors, study period 16 July, 2020 - 9 December, 2020, average treatment delay 3.0 days, trial NCT04416399 (history) (STOIC).	risk of hospitalization/ER, 81.8% lower, RR 0.18, *p* = 0.02, treatment 2 of 73 (2.7%), control 11 of 73 (15.1%), NNT 8.1, ITT.
	risk of hospitalization/ER, 90.1% lower, RR 0.10, *p* = 0.004, treatment 1 of 70 (1.4%), control 10 of 69 (14.5%), NNT 7.7, PP.

	risk of no recovery, 67.1% lower, RR 0.33, *p* = 0.003, treatment 7 of 70 (10.0%), control 21 of 69 (30.4%), NNT 4.9, PP, day 14.
Reis, 4/17/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Brazil, peer-reviewed, 35 authors, study period 15 January, 2022 - 6 July, 2022, average treatment delay 3.0 days, this trial uses multiple treatments in the treatment arm (combined with fluvoxamine) - results of individual treatments may vary, trial NCT04727424 (history) (TOGETHER).	**risk of death, 200.0% higher, RR 3.00, *p* = 1.00**, treatment 1 of 738 (0.1%), control 0 of 738 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of hospitalization, 12.5% lower, RR 0.88, *p* = 1.00, treatment 7 of 738 (0.9%), control 8 of 738 (1.1%), NNT 738.
	hospitalization or ER >6hrs, 50.0% lower, RR 0.50, *p* = 0.04, treatment 13 of 738 (1.8%), control 27 of 738 (3.7%), NNT 53, adjusted per study, day 28, primary outcome.

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.

Agustí, 2/10/2022, Randomized Controlled Trial, Spain, peer-reviewed, 21 authors, study period 21 April, 2020 - 16 March, 2021, trial NCT04355637 (history) (TACTIC).	**risk of death, 22.5% higher, RR 1.23, *p* = 1.00**, treatment 1 of 40 (2.5%), control 1 of 49 (2.0%), day 90.
	risk of progression, 38.7% lower, RR 0.61, *p* = 0.69, treatment 2 of 40 (5.0%), control 4 of 49 (8.2%), NNT 32.
Al Sulaiman, 11/10/2021, prospective, Saudi Arabia, peer-reviewed, 80% of treatment patients used budesonide, mean age 61.4, 24 authors, study period 1 March, 2020 - 31 March, 2021.	**risk of death, 32.0% lower, HR 0.68, *p* = 0.13**, treatment 30 of 64 (46.9%), control 31 of 64 (48.4%), adjusted per study, in-hospital mortality, propensity score matching, multivariable, Cox proportional hazards.
	risk of death, 47.0% lower, HR 0.53, *p* = 0.03, treatment 25 of 65 (38.5%), control 29 of 65 (44.6%), adjusted per study, propensity score matching, multivariable, Cox proportional hazards, day 30.
Alsultan, 12/31/2021, Randomized Controlled Trial, Syria, peer-reviewed, 11 authors.	**risk of death, 7.1% higher, RR 1.07, *p* = 1.00**, treatment 5 of 14 (35.7%), control 7 of 21 (33.3%).
Bhandari, 3/22/2022, retrospective, India, peer-reviewed, 3 authors.	**risk of death, 66.7% lower, RR 0.33, *p* = 1.00**, treatment 0 of 60 (0.0%), control 1 of 60 (1.7%), NNT 60, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	oxygen time, 33.4% lower, relative time 0.67, *p* = 0.009, treatment mean 5.21 (±4.23) n=60, control mean 7.82 (±6.35) n=60.
	hospitalization time, 26.3% lower, relative time 0.74, *p* = 0.02, treatment mean 6.54 (±4.87) n=60, control mean 8.87 (±6.12) n=60.
	recovery time, 36.8% lower, relative time 0.63, *p* = 0.001, treatment mean 4.85 (±3.94) n=60, control mean 7.68 (±5.43) n=60, cough.
Dhanger, 9/30/2023, Randomized Controlled Trial, India, peer-reviewed, 4 authors, study period January 2022 - March 2022, trial REF/2021/09/046997.	**risk of death, 42.9% lower, RR 0.57, *p* = 0.52**, treatment 4 of 40 (10.0%), control 7 of 40 (17.5%), NNT 13.
	risk of ICU admission, 78.3% lower, RR 0.22, *p* < 0.001, treatment 5 of 40 (12.5%), control 23 of 40 (57.5%), NNT 2.2.

	risk of no recovery, 70.0% lower, RR 0.30, *p* < 0.001, treatment 9 of 40 (22.5%), control 30 of 40 (75.0%), NNT 1.9.
Ramlall, 10/18/2020, retrospective, USA, preprint, 3 authors.	risk of death, 71.0% lower, HR 0.29, *p* = 0.01, treatment 33, control 915, Cox proportional hazards.
Samajdar, 3/3/2023, prospective, India, peer-reviewed, mean age 47.2, 6 authors, study period January 2021 - June 2021, average treatment delay 5.98 days, this trial uses multiple treatments in the treatment arm (combined with formoterol) - results of individual treatments may vary.	risk of death, 58.4% lower, RR 0.42, *p* = 0.44, treatment 2 of 50 (4.0%), control 5 of 52 (9.6%), NNT 18.
	risk of mechanical ventilation, 65.3% lower, RR 0.35, *p* = 0.62, treatment 1 of 50 (2.0%), control 3 of 52 (5.8%), NNT 27.
	risk of hospitalization, 68.8% lower, RR 0.31, *p* = 0.07, treatment 3 of 50 (6.0%), control 10 of 52 (19.2%), NNT 7.6.
	cough score, 29.4% lower, RR 0.71, *p* = 0.008, treatment mean 2.14 (±1.24) n=50, control mean 3.03 (±1.99) n=52, day 7.
	cough score, 9.9% lower, RR 0.90, *p* = 0.10, treatment mean 4.66 (±1.42) n=50, control mean 5.17 (±1.65) n=52, day 3.
Taille, 5/28/2021, Randomized Controlled Trial, France, trial NCT04331054 (history) (INHASCO).	146 patient RCT with results unknown and over 4 years late.
Yang (B), 8/31/2022, retrospective, China, peer-reviewed, median age 62.0, 12 authors, study period 1 January, 2020 - 29 February, 2020, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 10.8% higher, RR 1.11, *p* = 0.85, treatment 30 of 125 (24.0%), control 13 of 60 (21.7%).
Yu (B), 4/12/2021, Randomized Controlled Trial, United Kingdom, peer-reviewed, 26 authors, study period 27 November, 2020 - 31 March, 2021, average treatment delay 6.0 days, trial ISRCTN86534580 (PRINCIPLE).	risk of death, 39.1% lower, RR 0.61, *p* = 0.45, treatment 6 of 787 (0.8%), control 10 of 799 (1.3%), NNT 204.
	risk of mechanical ventilation, 6.0% lower, RR 0.94, *p* = 1.00, treatment 13 of 776 (1.7%), control 14 of 784 (1.8%), NNT 905.
	risk of ICU admission, 52.0% lower, RR 0.48, *p* = 0.07, treatment 10 of 771 (1.3%), control 21 of 779 (2.7%), NNT 71.
	risk of death/hospitalization, 25.0% lower, RR 0.75, *p* = 0.96, treatment 72 of 787 (9.1%), control 116 of 1,069 (10.9%), NNT 59, adjusted per study, day 28.
	recovery time, 17.4% lower, relative time 0.83, *p* = 0.001, treatment 787, control 1,069, adjusted per study, inverted to make RR<1 favor treatment.

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.

Bai, 5/30/2024, retrospective, China, peer-reviewed, 8 authors, this trial uses multiple treatments in the treatment arm (combined with formoterol/glycopyrronium) - results of individual treatments may vary, excluded in exclusion analyses: unadjusted results with minimal group details.	risk of hospitalization, 31.4% lower, RR 0.69, *p* = 0.18, treatment 71, control 241, BF and BGF.
	risk of hospitalization, 50.8% lower, RR 0.49, *p* = 0.01, treatment 10 of 71 (14.1%), control 69 of 241 (28.6%), NNT 6.9, BF.
	risk of hospitalization, 13.1% lower, RR 0.87, *p* = 0.51, treatment 30 of 129 (23.3%), control 49 of 183 (26.8%), NNT 28, BF.

	risk of case, 24.4% lower, RR 0.76, *p* < 0.001, treatment 71, control 241, BF and BGF.
	risk of case, 17.5% lower, RR 0.83, *p* = 0.04, treatment 44 of 71 (62.0%), control 181 of 241 (75.1%), NNT 7.6, BF.
	risk of case, 28.8% lower, RR 0.71, *p* < 0.001, treatment 78 of 129 (60.5%), control 147 of 173 (85.0%), NNT 4.1, BGF.
Lee (B), 9/9/2021, retrospective, South Korea, preprint, 5 authors.	**risk of case, 32.6% lower, RR 0.67, *p* = 0.10**, treatment 19 of 1,674 (1.1%), control 95 of 5,345 (1.8%), NNT 156, adjusted per study, odds ratio converted to relative risk, multivariate.
Loucera, 8/16/2022, retrospective, Spain, peer-reviewed, 8 authors, study period January 2020 - November 2020.	**risk of death, 22.3% lower, HR 0.78, *p* = 0.004**, treatment 1,047, control 14,921, Cox proportional hazards, day 30.
Monserrat Villatoro, 1/8/2022, retrospective, propensity score matching, Spain, peer-reviewed, 18 authors.	**risk of death, 49.0% lower, OR 0.51, *p* = 0.01**, RR approximated with OR.

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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