

# Budesonide for COVID-19: real-time meta analysis of 14 studies

@CovidAnalysis, March 2024, Version 30

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

## Abstract

Statistically significant lower risk is seen for mortality, ICU admission, hospitalization, progression, and recovery. 10 studies from 10 independent teams in 7 countries show statistically significant improvements.

Meta analysis using the most serious outcome reported shows 29% [17-39%] 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 robust — in exclusion sensitivity analysis 10 of 14 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

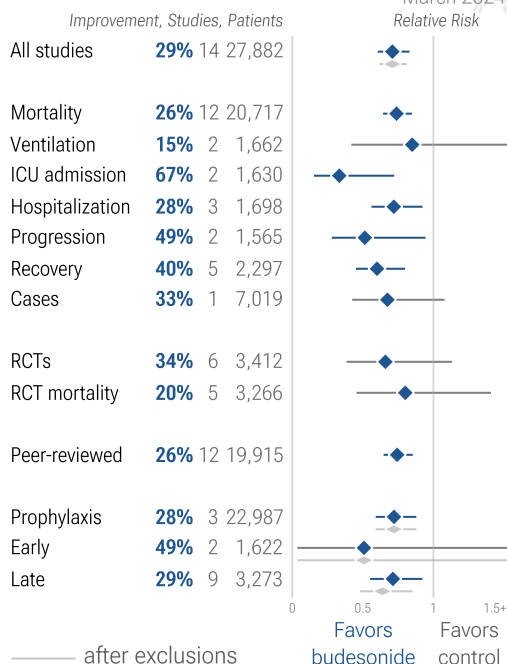
4 RCTs with 916 patients have not reported results (up to 3 years late).

Inhaler technique and adherence may significantly affect outcomes *Tichopád*.

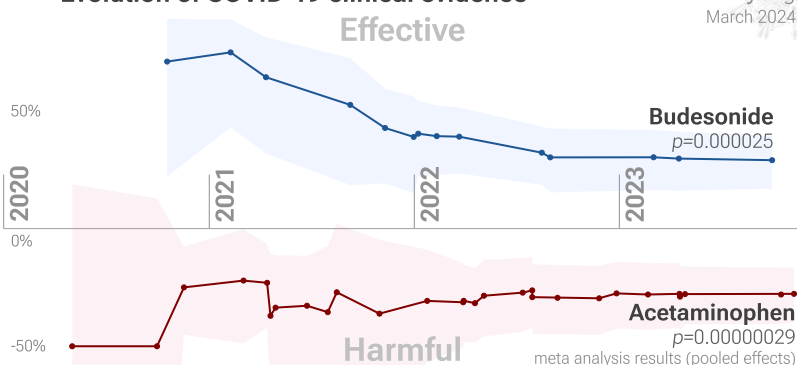
No treatment or intervention is 100% effective. All practical, effective, and safe means should be used based on risk/benefit analysis. Multiple treatments are typically used in combination, and other treatments are more effective.

All data to reproduce this paper and sources are in the appendix. *Yu* present another meta analysis for budesonide, showing significant improvement for recovery.

## Budesonide for COVID-19



## Evolution of COVID-19 clinical evidence



## HIGHLIGHTS

Budesonide reduces risk for COVID-19 with very high confidence for mortality, hospitalization, recovery, and in pooled analysis, and low confidence for ICU admission, progression, and cases.

Budesonide was the 20th treatment shown effective with  $\geq 3$  clinical studies in April 2021, now known with  $p = 0.000025$  from 14 studies, and recognized in 8 countries.

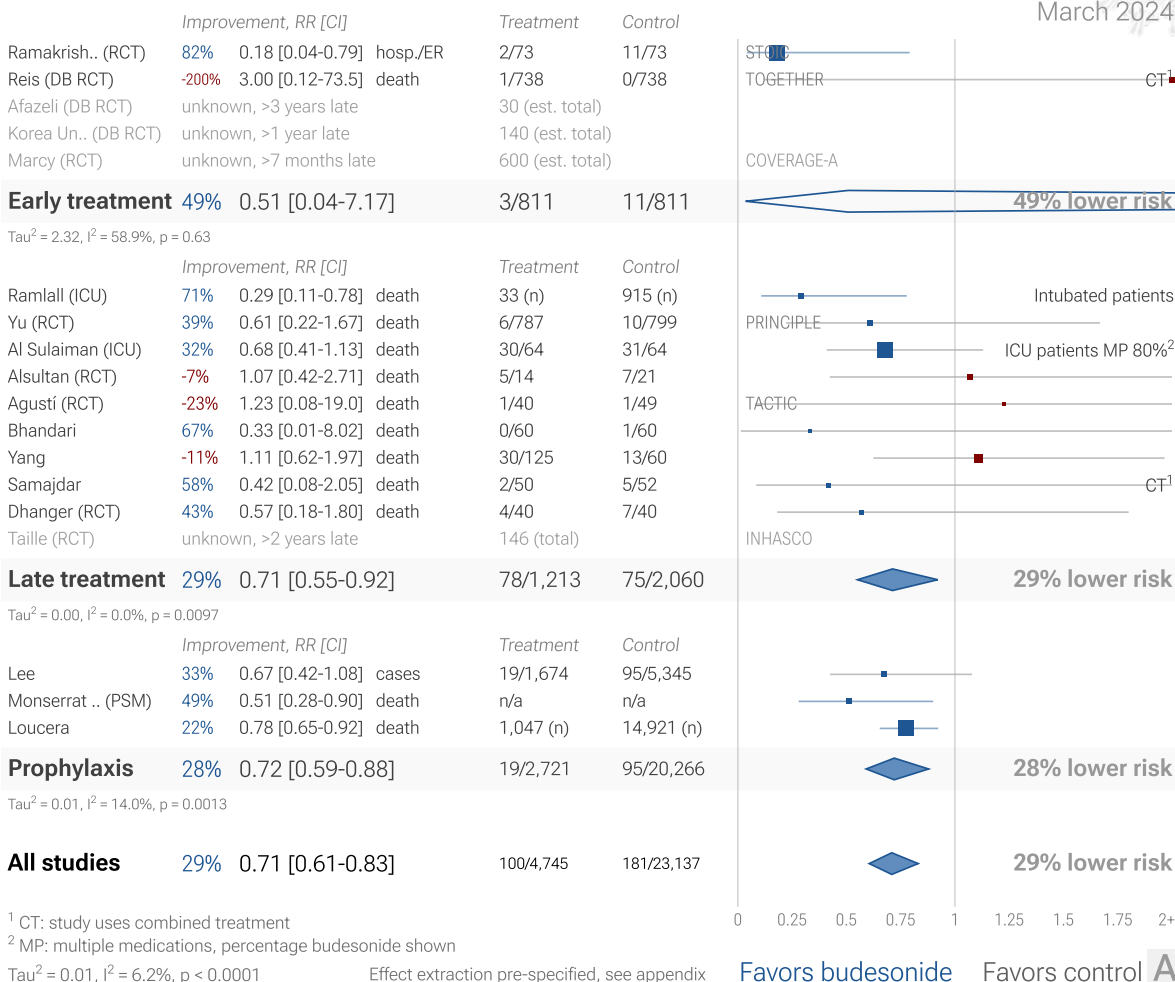
We show traditional outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor in COVID-19 studies.

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

## 14 budesonide COVID-19 studies (+4 unreported RCTs)

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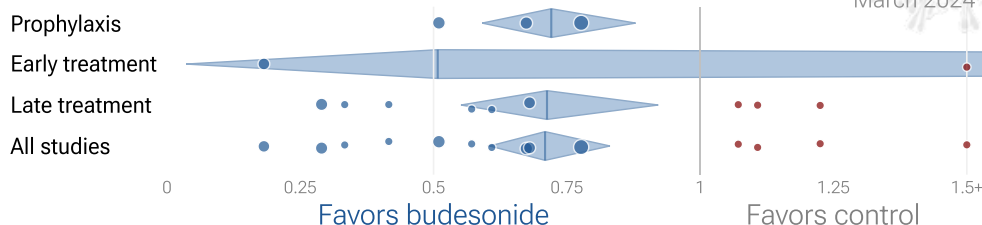
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## Efficacy in COVID-19 budesonide studies (pooled effects)

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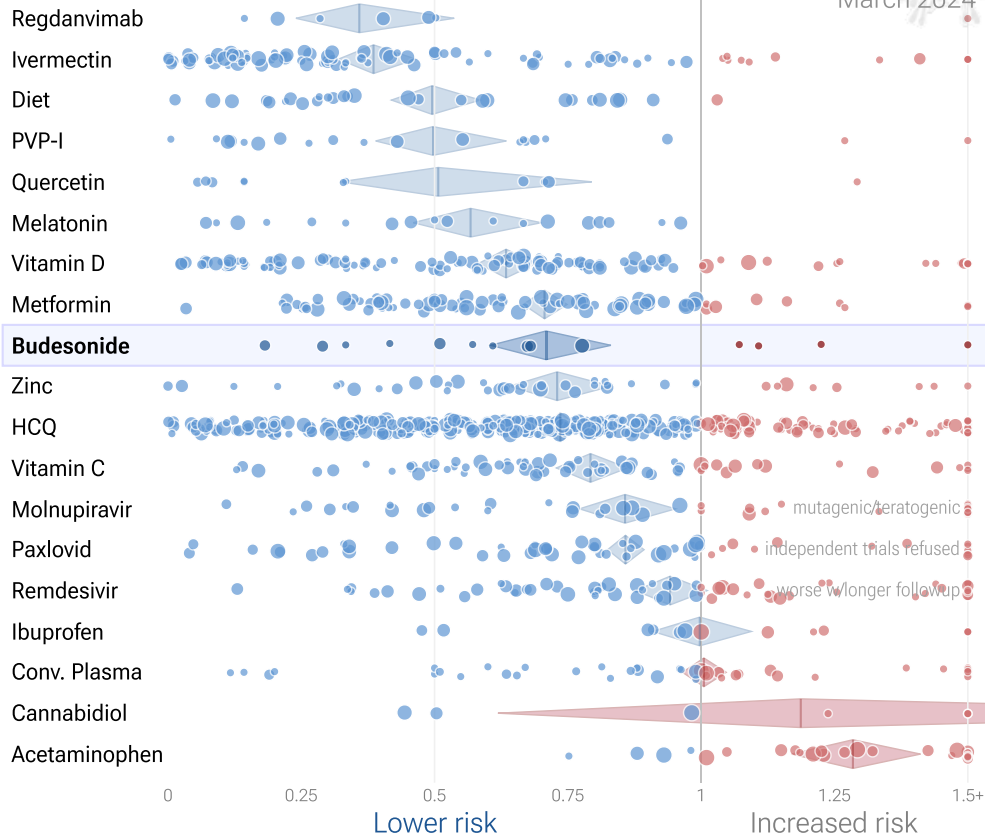
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## Efficacy in COVID-19 studies (pooled effects)

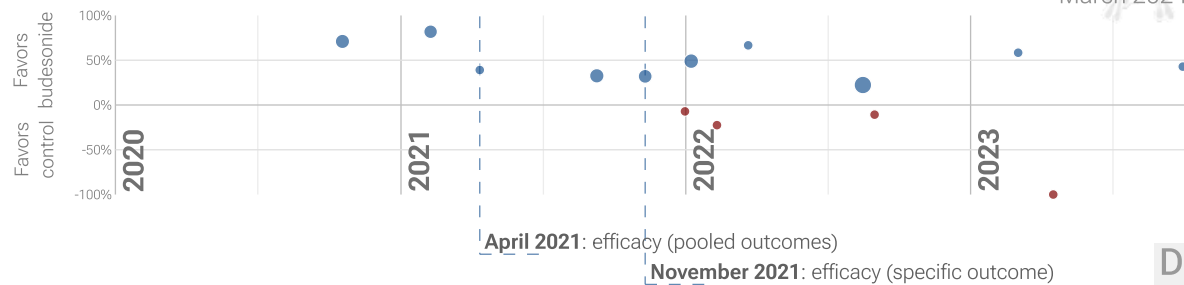
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## Timeline of COVID-19 budesonide studies (pooled effects)

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D

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

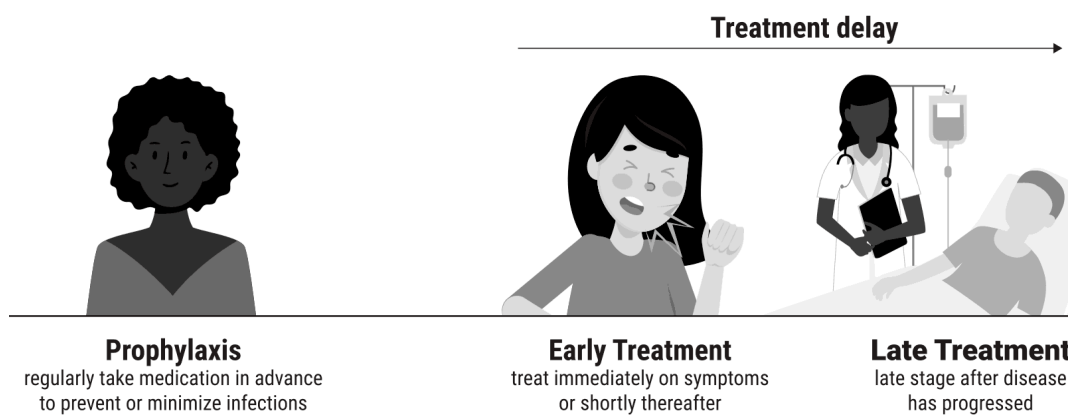
## Introduction

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

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

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



**Figure 2.** Treatment stages.

## Preclinical Research

2 *In Vitro* studies support the efficacy of budesonide *Heinen, Konduri*.

An *In Vivo* animal study supports the efficacy of budesonide *Konduri*.

*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 3, 4, 5, 6, 7, 8, 9, 10, and 11 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, recovery, cases, and peer reviewed studies.

	<i>Improvement</i>	<i>Studies</i>	<i>Patients</i>	<i>Authors</i>
All studies	29% [17-39%] ****	14	27,882	198
After exclusions	29% [19-38%] ****	13	27,697	186
Peer-reviewed studies	26% [15-35%] ****	12	19,915	190
Randomized Controlled Trials	34% [-13-61%]	6	3,412	119
Mortality	26% [15-36%] ****	12	20,717	169
Ventilation	15% [-73-58%]	2	1,662	30
ICU admission	67% [28-85%] **	2	1,630	28
Hospitalization	28% [8-44%] **	3	1,698	44
Recovery	40% [20-55%] ***	5	2,297	61
RCT mortality	20% [-41-54%]	5	3,266	95

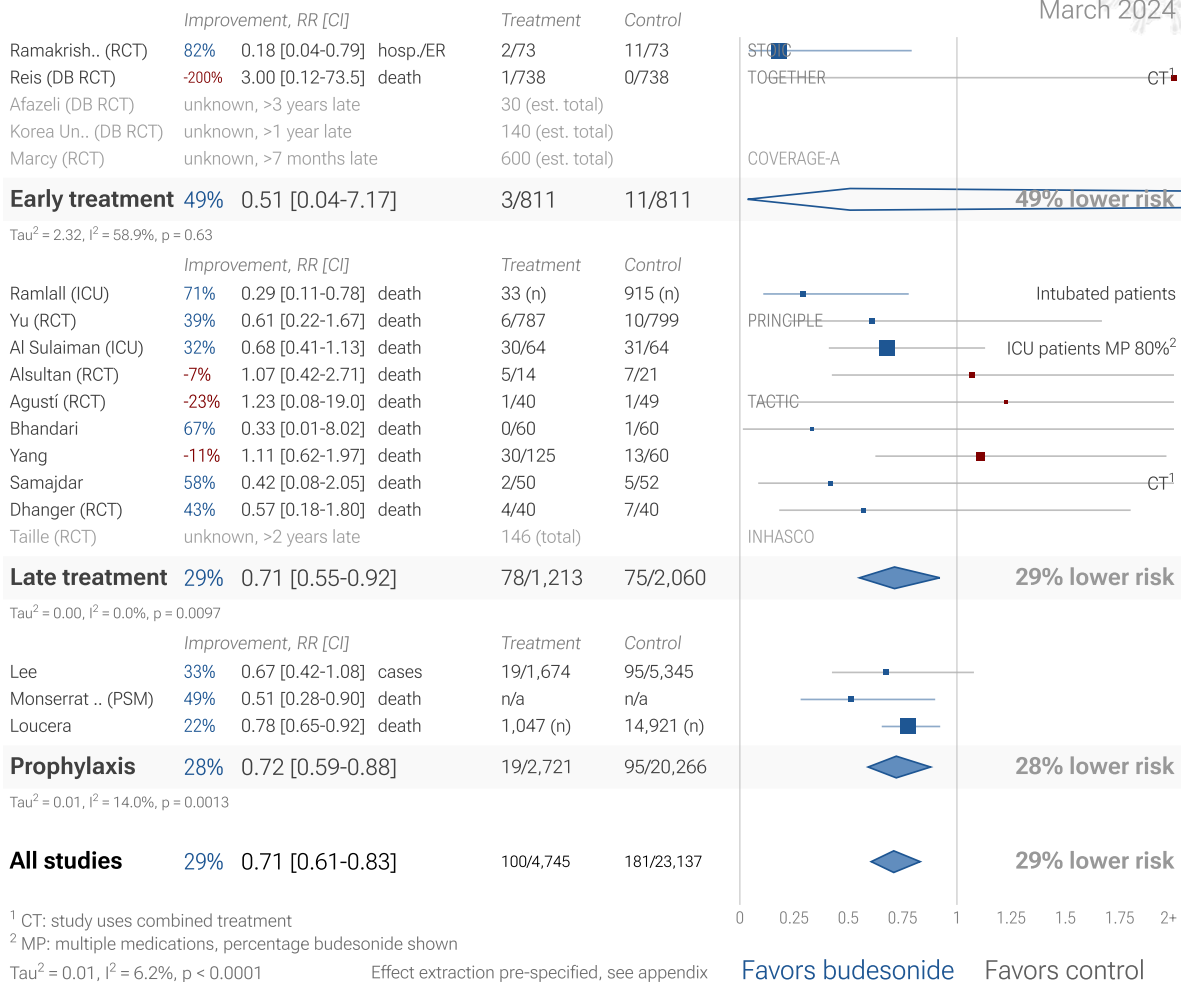
**Table 1.** Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes. Results show the percentage improvement with treatment and the 95% confidence interval. \*  $p < 0.05$  \*\*  $p < 0.01$ .

	<i>Early treatment</i>	<i>Late treatment</i>	<i>Prophylaxis</i>
All studies	49% [-617-96%]	29% [8-45%] **	28% [12-41%] **
After exclusions	49% [-617-96%]	36% [15-52%] **	28% [12-41%] **
Peer-reviewed studies	49% [-617-96%]	24% [1-42%] *	32% [0-54%] *
Randomized Controlled Trials	49% [-617-96%]	23% [-36-57%]	
Mortality	-200% [-7253-88%]	29% [8-45%] **	32% [0-54%] *
Ventilation		15% [-73-58%]	
ICU admission		67% [28-85%] **	
Hospitalization	12% [-140-68%]	40% [-23-71%]	
Recovery	67% [28-85%] **	35% [15-51%] **	
RCT mortality	-200% [-7253-88%]	23% [-36-57%]	

**Table 2.** Random effects meta-analysis results by treatment stage. Results show the percentage improvement with treatment, the 95% confidence interval, and the number of studies for the stage. \*  $p < 0.05$  \*\*  $p < 0.01$ .

# 14 budesonide COVID-19 studies (+4 unreported RCTs)

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

## 12 budesonide COVID-19 mortality results

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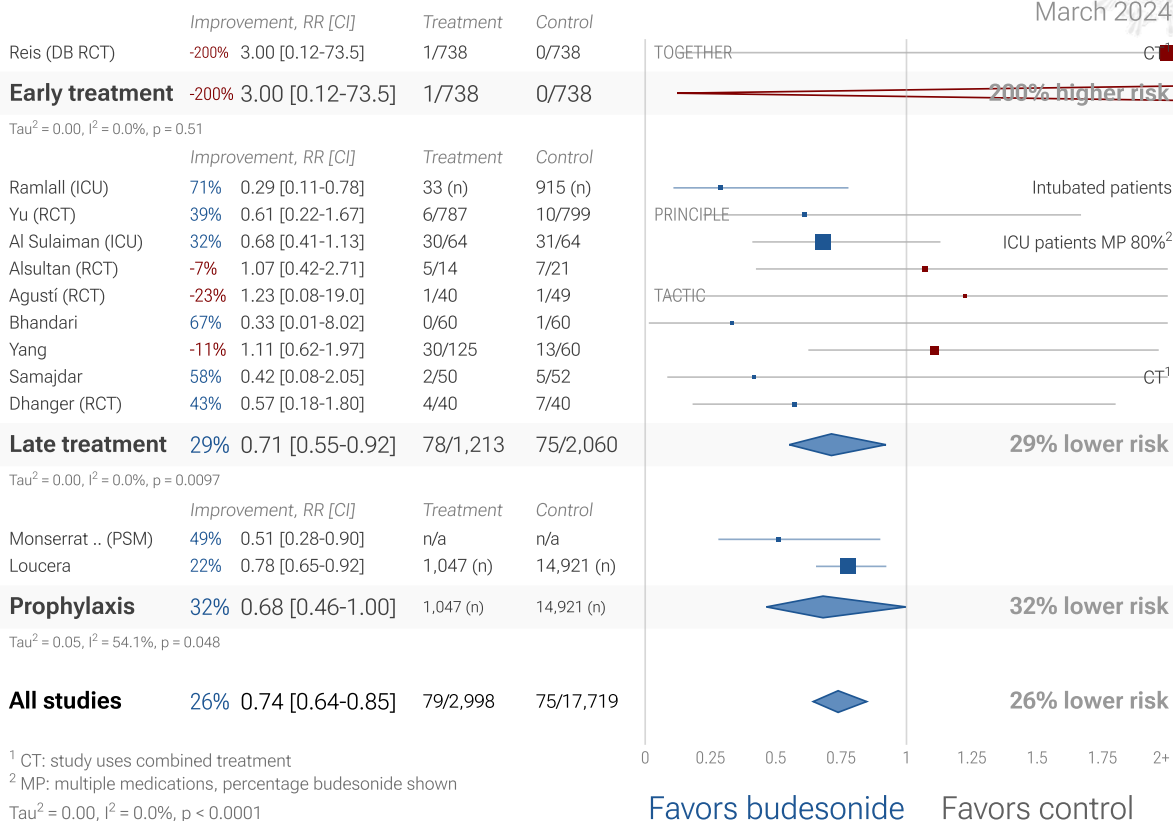


Figure 4. Random effects meta-analysis for mortality results.

## 2 budesonide COVID-19 mechanical ventilation results

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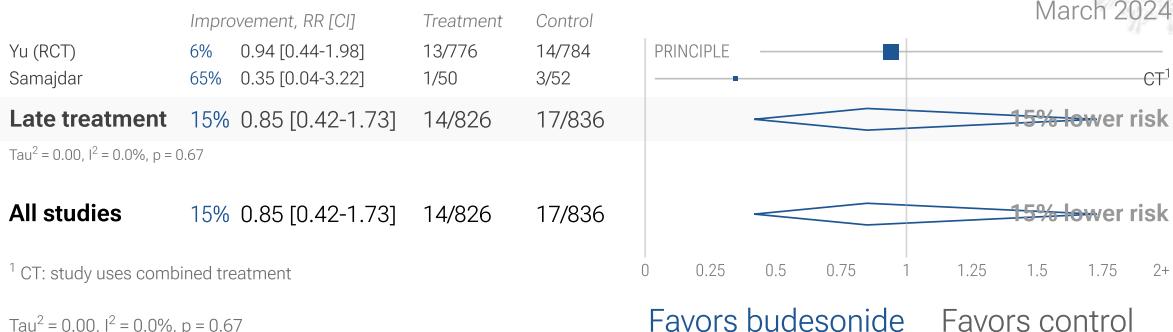


Figure 5. Random effects meta-analysis for ventilation.

## 2 budesonide COVID-19 ICU results

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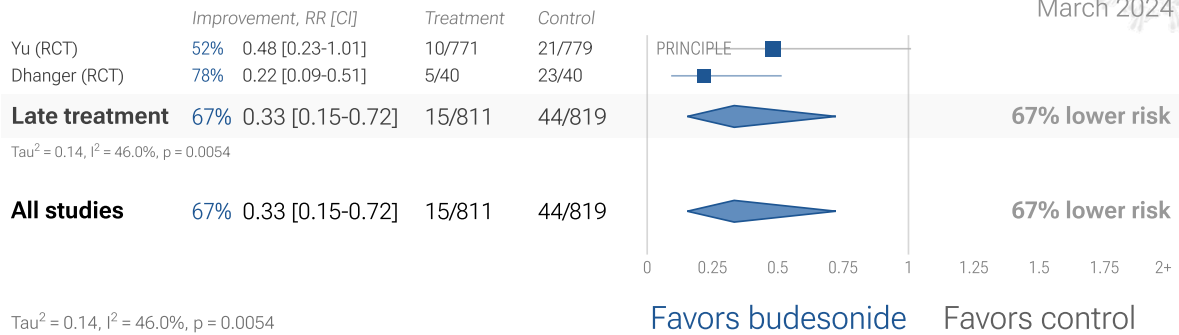


Figure 6. Random effects meta-analysis for ICU admission.

## 3 budesonide COVID-19 hospitalization results

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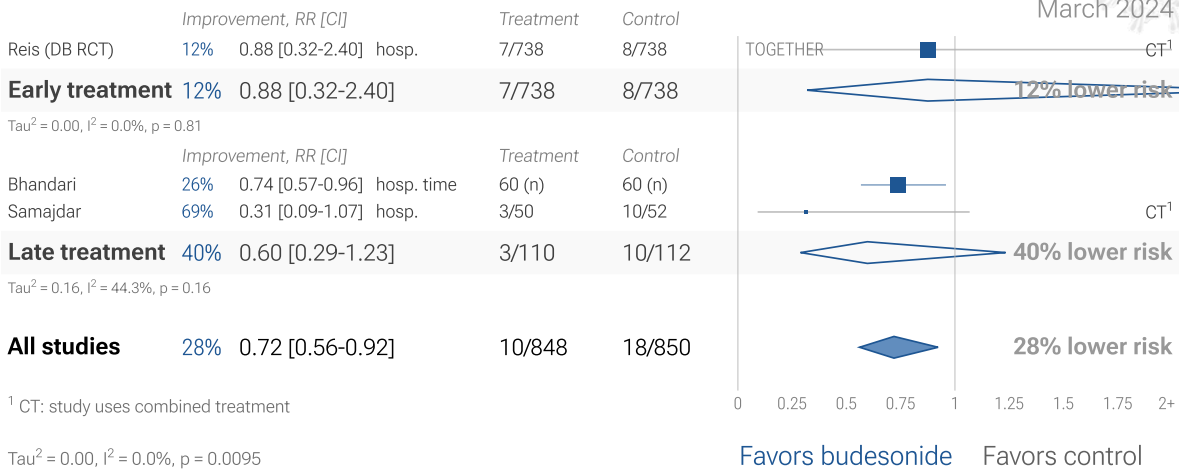


Figure 7. Random effects meta-analysis for hospitalization.

## 2 budesonide COVID-19 progression results

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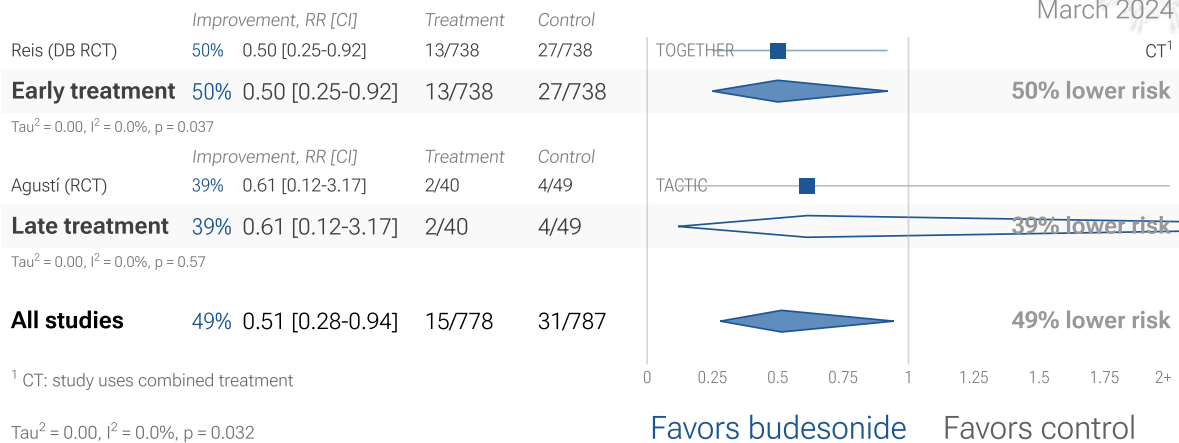
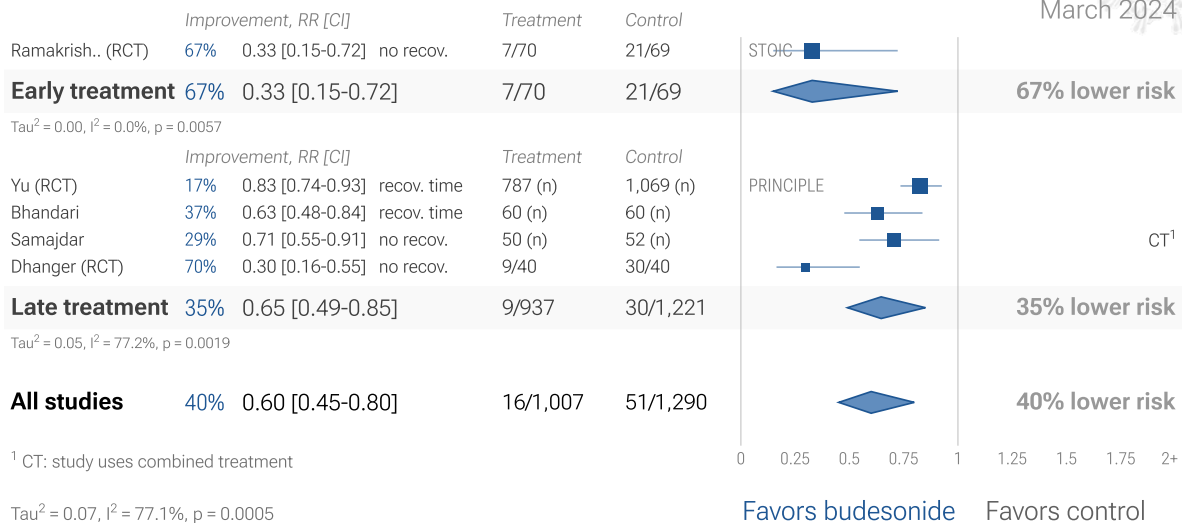


Figure 8. Random effects meta-analysis for progression.



## 5 budesonide COVID-19 recovery results

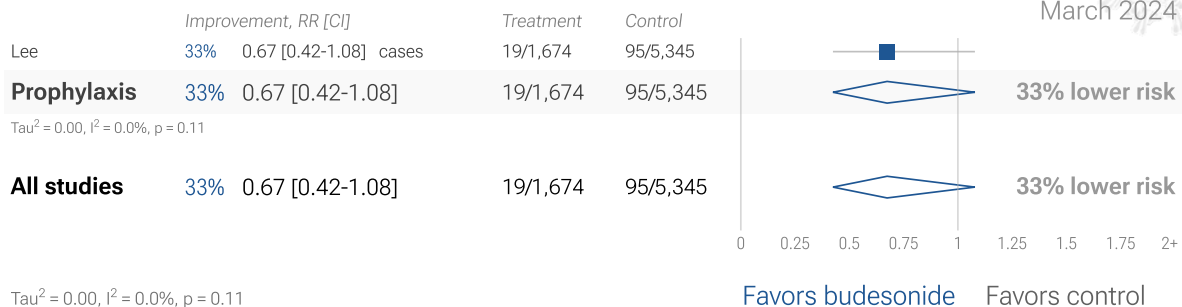
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**Figure 9.** Random effects meta-analysis for recovery.

## 1 budesonide COVID-19 case result

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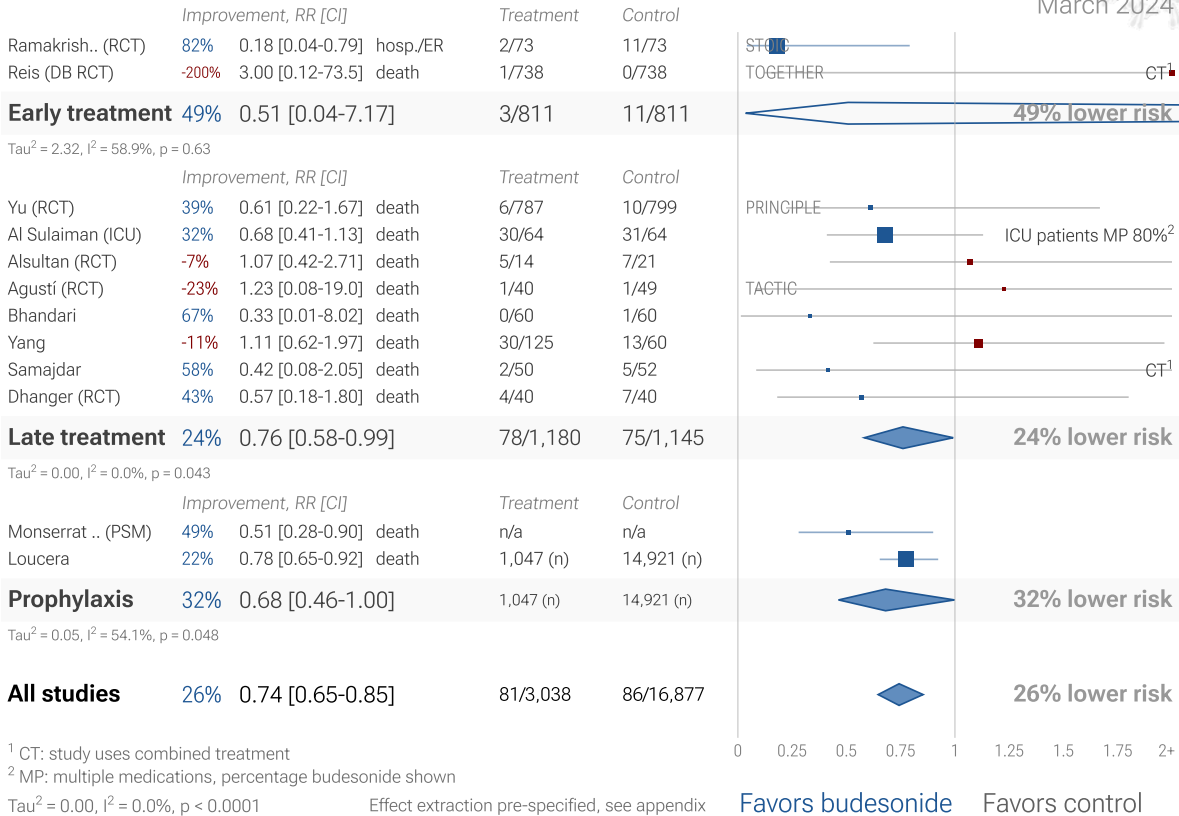


**Figure 10.** Random effects meta-analysis for cases.

## 12 budesonide COVID-19 peer reviewed studies

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

## Randomized Controlled Trials (RCTs)

Figure 12 shows a comparison of results for RCTs and non-RCT studies. Figure 13 and 14 show forest plots for random effects meta-analysis of all Randomized Controlled Trials and RCT mortality results. RCT results are included in Table 1 and Table 2.

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

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

**RCTs for novel acute diseases requiring rapid treatment.** High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way. Every treatment RCT to date involves delayed treatment. Among the 66 treatments we have analyzed, 63% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments (they may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration).

**RCT bias for widely available treatments.** RCTs have a bias against finding an effect for interventions that are widely available — patients that believe they need the intervention are more likely to decline participation and take the intervention. RCTs for budesonide are more likely to enroll low-risk participants that do not need treatment to recover, making the results less applicable to clinical practice. This bias is likely to be greater for widely known treatments, and may be greater when the risk of a serious outcome is overstated. This bias does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable.

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

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

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

## Efficacy in COVID-19 budesonide studies (pooled effects)

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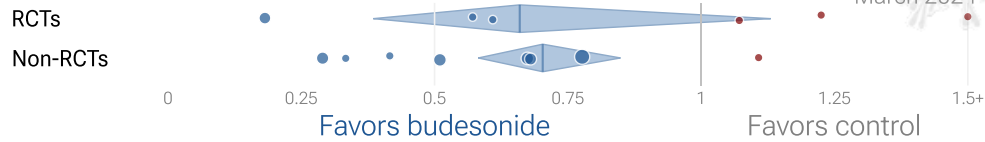


Figure 12. Results for RCTs and non-RCT studies.

## 6 budesonide COVID-19 Randomized Controlled Trials

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

## 5 budesonide COVID-19 RCT mortality results

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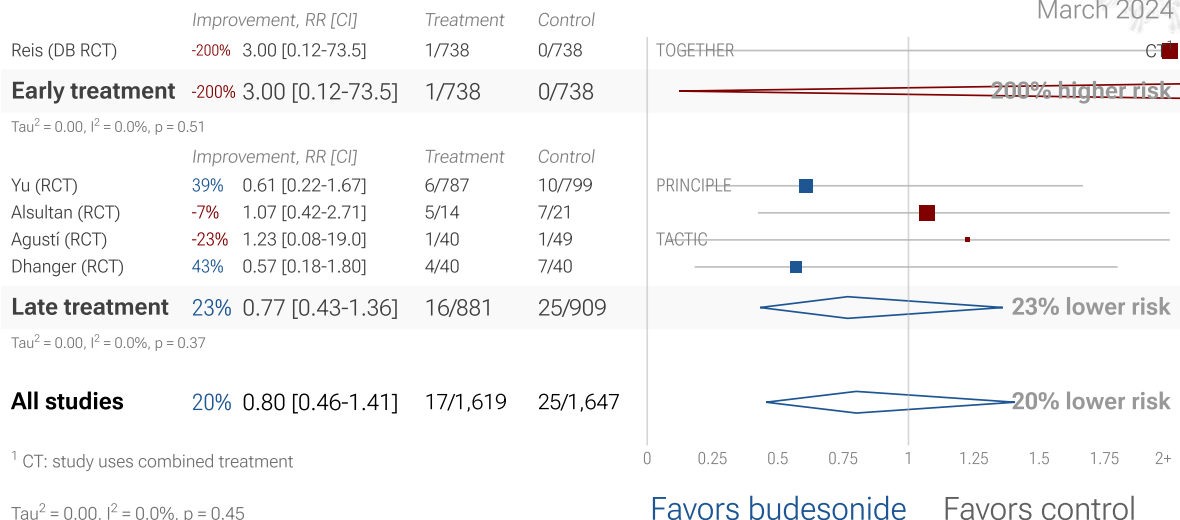


Figure 14. Random effects meta-analysis for RCT mortality results.

## Unreported RCTs

4 budesonide RCTs have not reported results *Afazeli, Korea United Pharm., Marcy, Taille*. 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 7 months to over 3 years.

## Exclusions

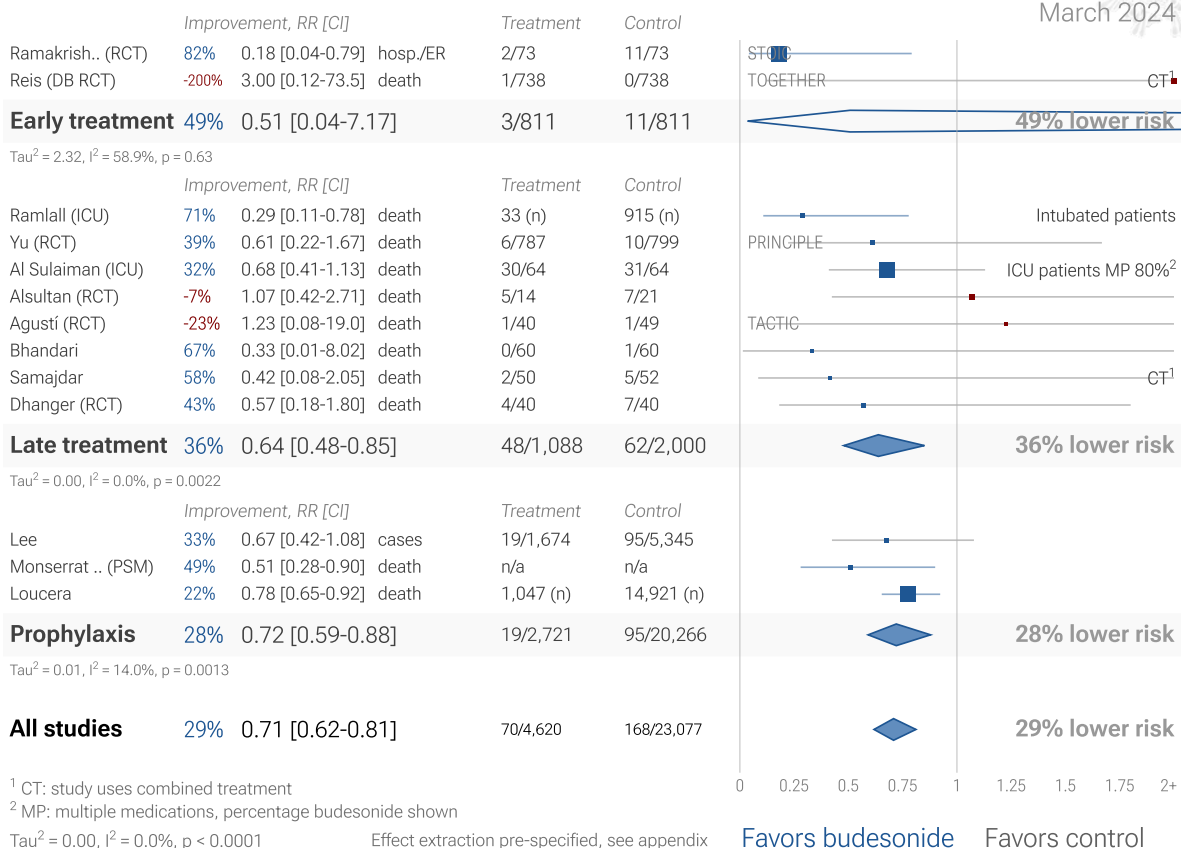
To avoid bias in the selection of studies, we analyze all non-retracted studies. Here we show the results after excluding studies with major issues likely to alter results, non-standard studies, and studies where very minimal detail is currently available. Our bias evaluation is based on analysis of 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 may underemphasize serious issues not captured in the checklists, overemphasize issues unlikely to alter outcomes in specific cases (for example, lack of blinding for an objective mortality outcome, or certain specifics of randomization with a very large effect size), and can be easily influenced by potential bias.

The studies excluded are as below. Figure 15 shows a forest plot for random effects meta-analysis of all studies after exclusions.

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

### 13 budesonide COVID-19 studies after exclusions

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

# Heterogeneity

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

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

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

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

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

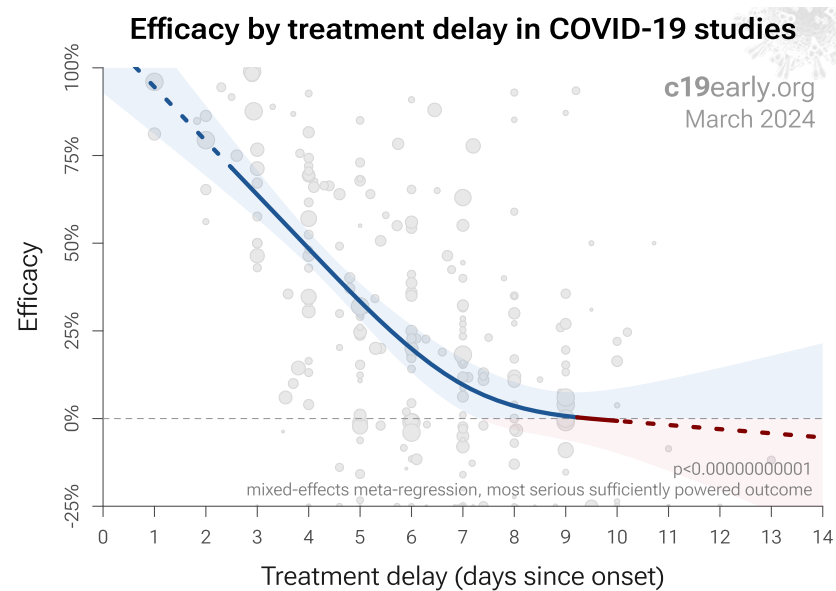


Figure 16. Early treatment is more effective. Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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

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

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

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

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

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

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

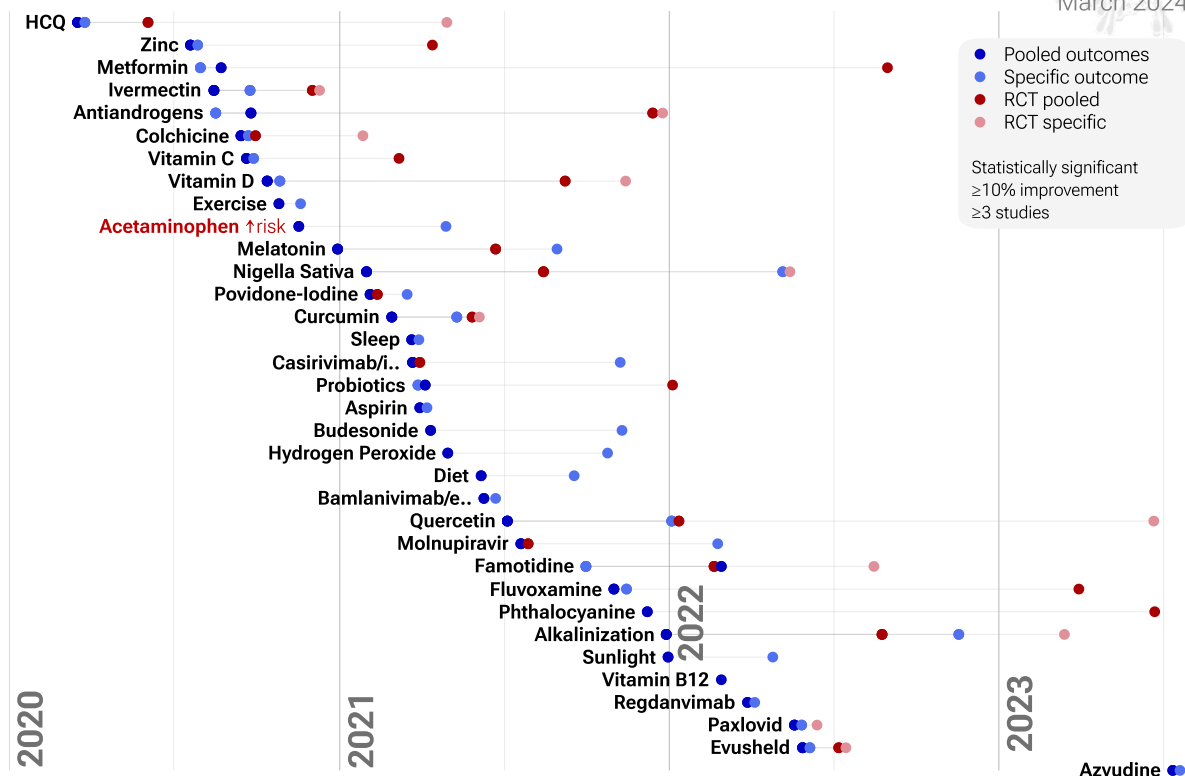
Pooled analysis enables using more of the available information. While there is much more information available, for example dose-response relationships, the advantage of the method used here is simplicity and transparency. Note that pooled analysis could hide efficacy, for example a treatment that is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

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



## Time when COVID-19 studies showed efficacy

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

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

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

## Discussion

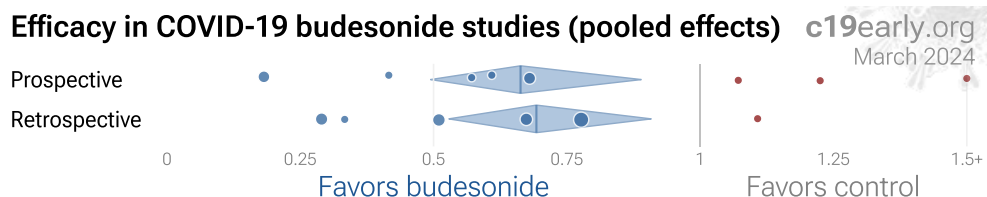
**Publication bias.** Publishing is often biased towards positive results, however evidence suggests that there may be a negative bias for inexpensive treatments for COVID-19. Both negative and positive results are very important for COVID-19, media in many countries prioritizes negative results for inexpensive treatments (inverting the typical



incentive for scientists that value media recognition), and there are many reports of difficulty publishing positive results *Boulware, Meeus, Meneguzzo*. For budesonide, there is currently not enough data to evaluate publication bias with high confidence.

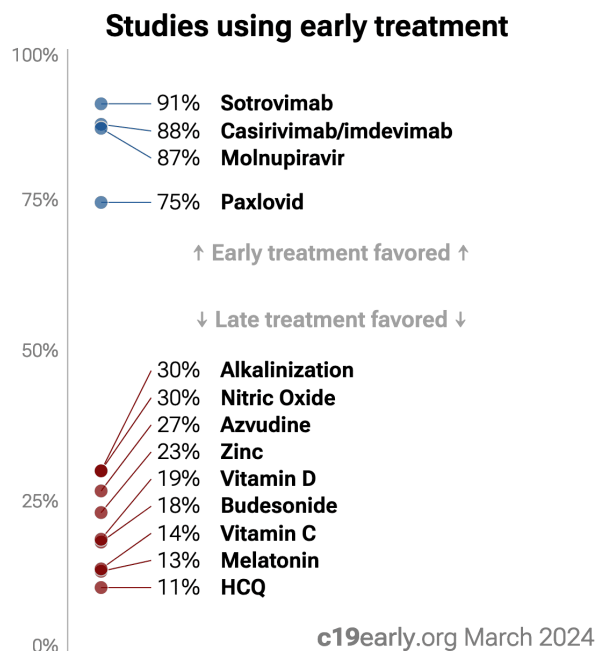
One method to evaluate bias is to compare prospective vs. retrospective studies. Prospective studies are more likely to be published regardless of the result, while retrospective studies are more likely to exhibit bias. For example, researchers may perform preliminary analysis with minimal effort and 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 18 shows a scatter plot of results for prospective and retrospective studies. 67% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 75% of prospective studies, consistent with a bias toward publishing negative results. The median effect size for retrospective studies is 41% improvement, compared to 36% for prospective studies, suggesting a potential bias towards publishing results showing higher efficacy.



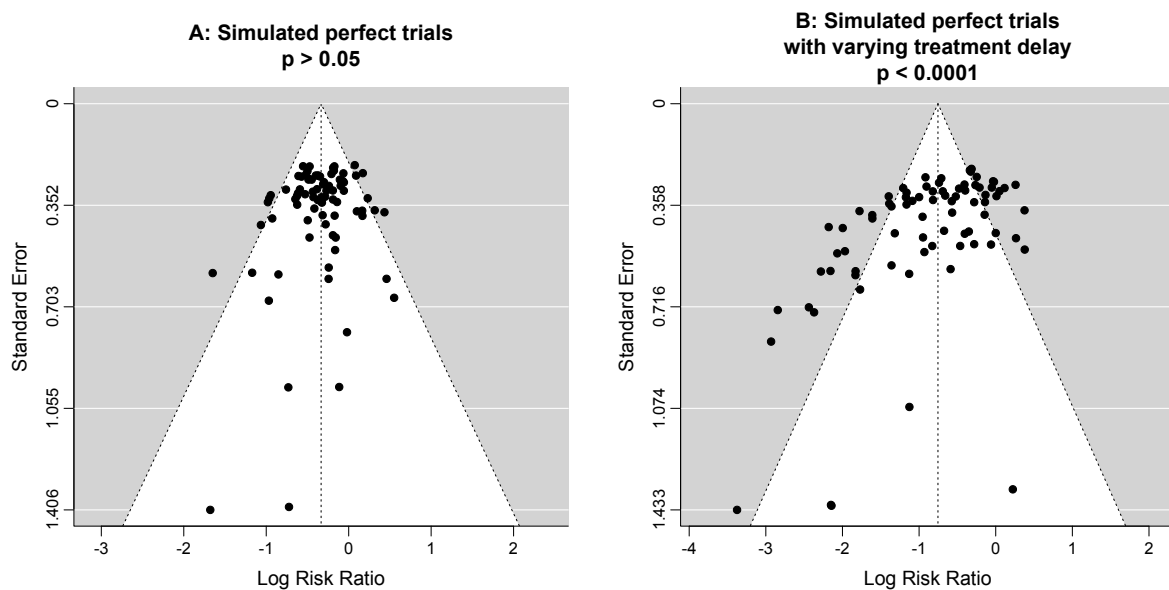
**Figure 18.** Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.

**Late treatment bias.** Studies for budesonide were primarily late treatment studies, in contrast with typical patented treatments that were tested with early treatment as recommended.



**Figure 19.** Patented treatments received mostly early treatment studies, while low cost treatments were typically tested for late treatment.

**Funnel plot analysis.** Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 20 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ( $p > 0.05$ ). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry,  $p < 0.0001$ , with six variants of Egger's test all showing  $p < 0.05$  *Egger, Harbord, Macaskill, Moreno, Peters, Rothstein, Rücker, Stanley*. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.



**Figure 20.** 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 by specific outcomes and by treatment delay, and we aim to identify key characteristics in the forest plots and summaries. Results should be viewed in the context of study characteristics.

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

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

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

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

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

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

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

**Notes.** 2 of 14 studies combine treatments. The results of budesonide alone may differ. 1 of 6 RCTs use combined treatment. *Yu* present another meta analysis for budesonide, showing significant improvement for recovery.

## Conclusion

Studies to date show that budesonide is an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality, ICU admission, hospitalization, progression, and recovery. 10 studies from 10 independent teams in 7 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 29% [17-39%] 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 robust — in exclusion sensitivity analysis 10 of 14 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

Inhaler technique and adherence may significantly affect outcomes *Tichopád*.

*Yu* present another meta analysis for budesonide, showing significant improvement for recovery.

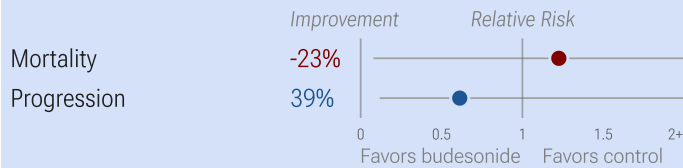
## Study Notes

### Afazeli

*Afazeli*: Estimated 30 patient budesonide early treatment RCT with results not reported over 3 years after estimated completion.

## Agustí

### Budesonide TACTIC LATE TREATMENT RCT



Is **late** treatment with budesonide beneficial for COVID-19?

RCT 89 patients in Spain (April 2020 - March 2021)

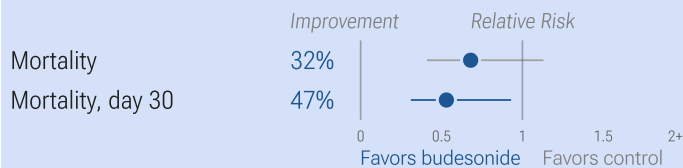
Trial underpowered to detect differences

c19early.org Agustí et al., European Respiratory J., Feb 2022

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

## Al Sulaiman

### Budesonide Al Sulaiman et al. ICU PATIENTS



Is **very late** treatment with budesonide beneficial for COVID-19?

PSM prospective study of 130 patients in Saudi Arabia (Mar 2020 - Mar 2021)

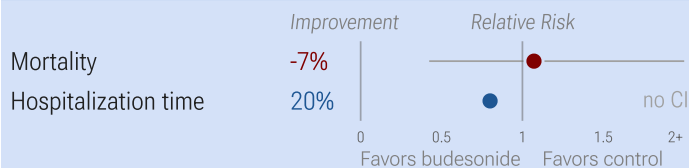
Lower mortality with budesonide (not stat. sig.,  $p=0.13$ )

c19early.org Al Sulaiman et al., J. Intensive Care .., Nov 2021

**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

### Budesonide Alsultan et al. LATE TREATMENT RCT



Is **late** treatment with budesonide beneficial for COVID-19?

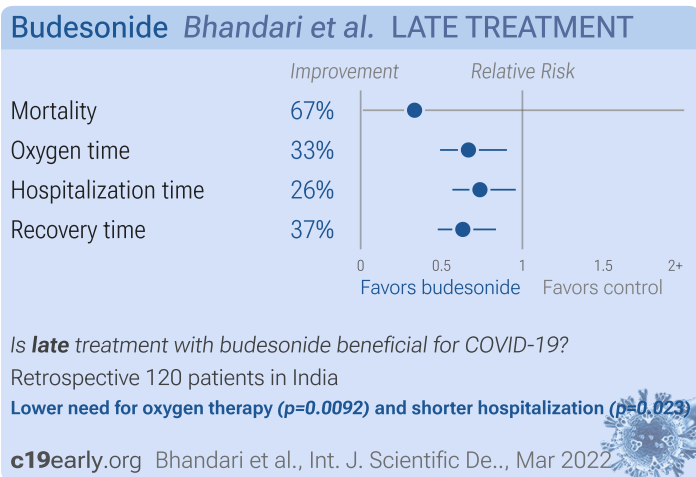
RCT 35 patients in Syria

Trial underpowered to detect differences

c19early.org Alsultan et al., Interdisciplinary Per., Dec 2021

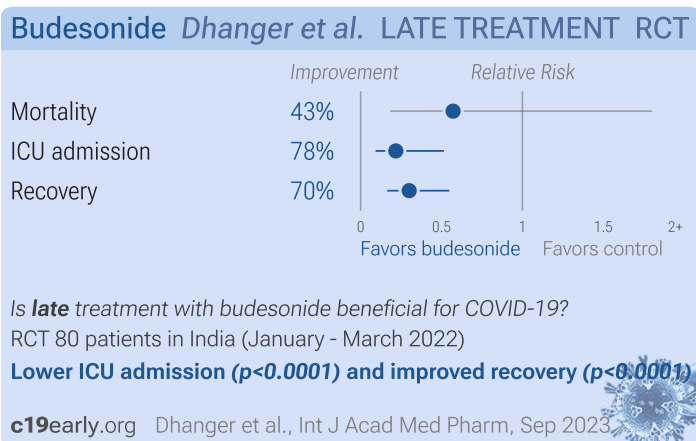
**Alsultan:** Small RCT 49 severe condition hospitalized patients in Syria, showing lower mortality with colchicine and shorter hospitalization time with both colchicine and budesonide (all of these are not statistically significant).

## Bhandari



**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

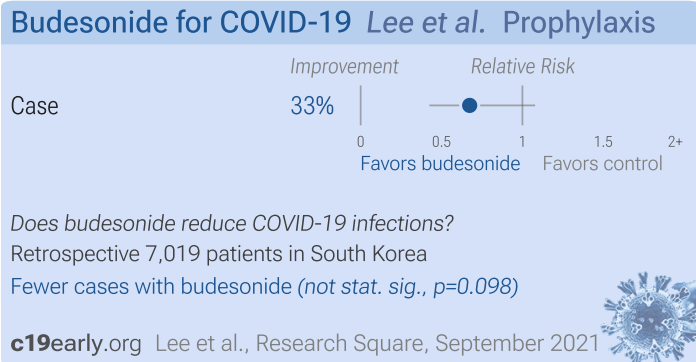


**Dhanger:** RCT inhaled budesonide with 80 moderate COVID-19 pneumonia patients. The budesonide group had significantly faster time to clinical improvement, fewer ICU admissions, shorter oxygen therapy duration, and lower mortality. Inhaled budesonide 400mcg twice daily for 14 days.

## Korea United Pharm.

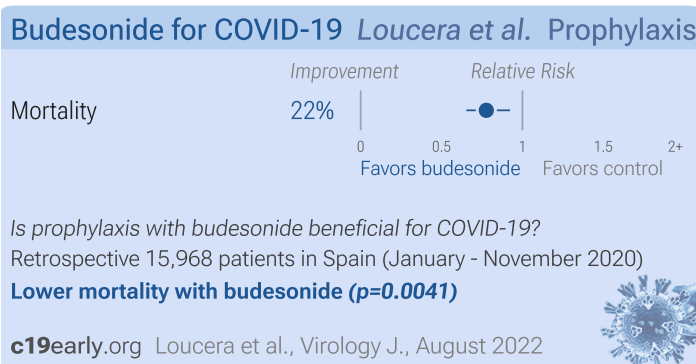
**Korea United Pharm.:** Estimated 140 patient budesonide early treatment RCT with results not reported over 1 year after estimated completion.

## Lee



**Lee (B):** Retrospective 44,968 patients in South Korea, 7,019 on inhaled corticosteroids, showing no statistically significant differences in COVID-19 cases.

## Loucera

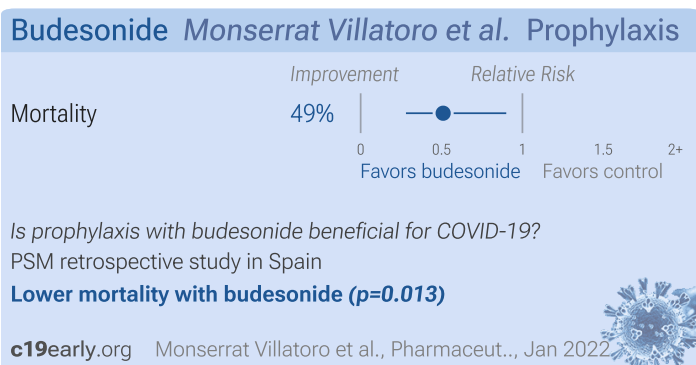


**Loucera:** Retrospective 15,968 COVID-19 hospitalized patients in Spain, showing lower mortality with existing use of several medications including metformin, HCQ, azithromycin, aspirin, vitamin D, vitamin C, and budesonide. Since only hospitalized patients are included, results do not reflect different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

## Marcy

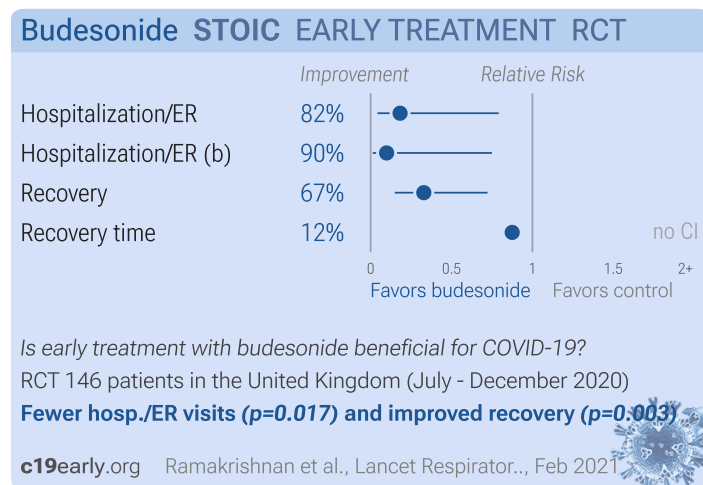
**Marcy:** Estimated 600 patient budesonide early treatment RCT with results not reported over 7 months after estimated completion.

## Montserrat Villatoro



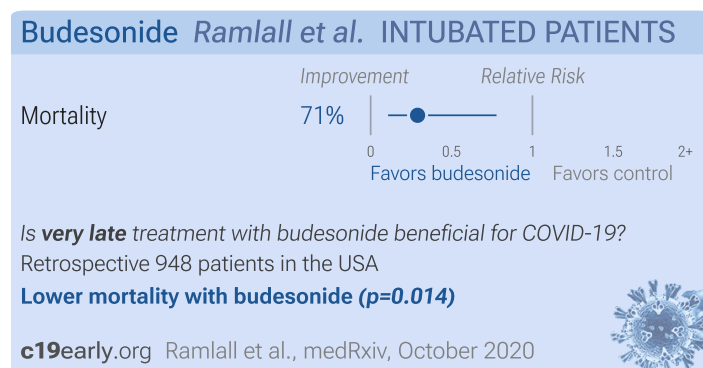
*Montserrat Villatoro*: PSM retrospective 3,712 hospitalized patients in Spain, showing lower mortality with existing use of azithromycin, bemiparine, budesonide-formoterol fumarate, cefuroxime, colchicine, enoxaparin, ipratropium bromide, loratadine, mepyramine theophylline acetate, oral rehydration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

## Ramakrishnan



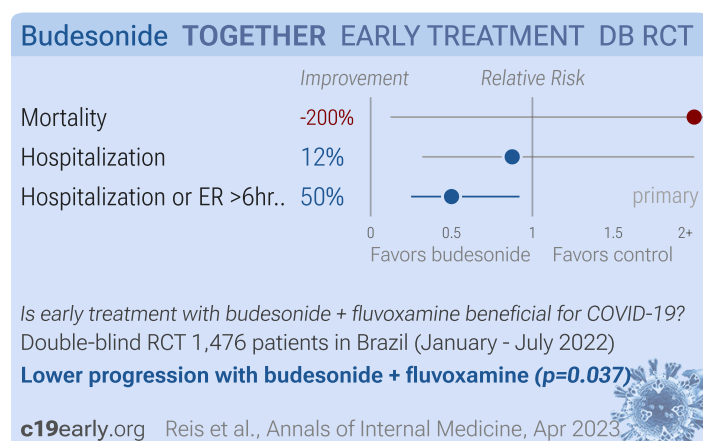
*Ramakrishnan*: RCT with 73 budesonide patients and 73 control patients, showing significantly lower combined risk of an ER visit or hospitalization, and lower risk of no recovery at day 14.

## Ramlall



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

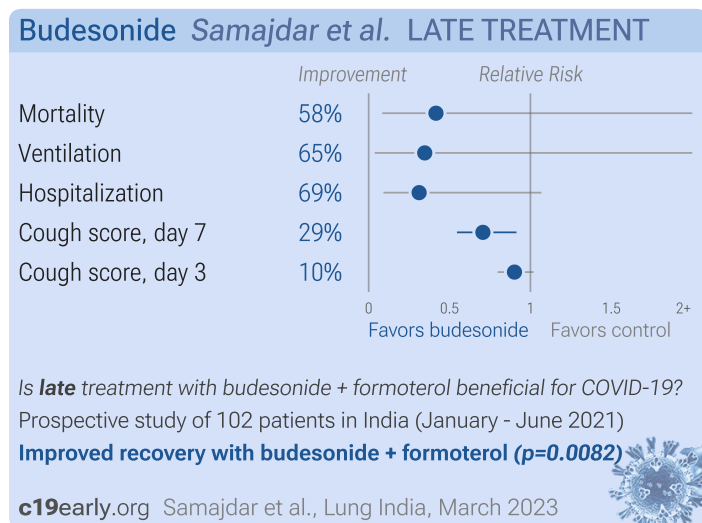
## Reis



*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 *Reis (B)*, *Reis (C)*, *Reis (D)*, *Reis (E)*, *Reis (F)*, *Reis (G)*.

## Samajdar

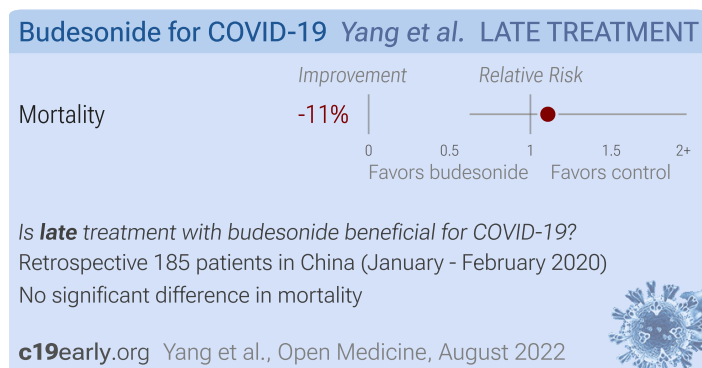


*Samajdar*: Prospective study of 102 patients in India, showing improved recovery of cough with budesonide+formoterol. Authors note better results with earlier treatment. Budesonide 800mcg + formoterol 12mcg bid for 7 days.

## Taille

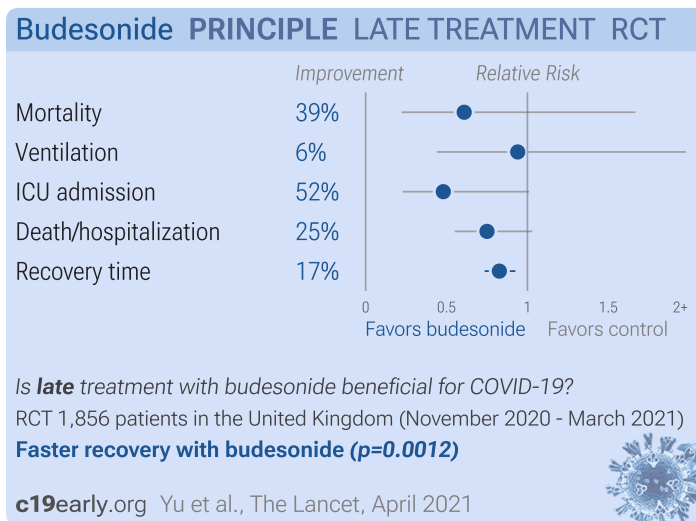
*Taille*: 146 patient budesonide late treatment RCT with results not reported over 2 years after completion.

## Yang



*Yang (B)*: Retrospective 185 hospitalized COVID-19 patients in China, showing no significant difference in mortality with budesonide use in unadjusted results.





Yu (B): 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. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral test status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO<sub>2</sub> is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to *Zhang*. Reported confidence intervals and  $p$ -values were used when available, using adjusted values when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported  $p$ -values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate  $p$ -values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 *Sweeting*. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only

report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.12.2) with scipy (1.12.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.1), and plotly (5.19.0).

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

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

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.

<i>Afazeli</i> , 5/20/2020, Double Blind Randomized Controlled Trial, Iran, trial NCT04331470 (history).	Estimated 30 patient RCT with results unknown and over 3 years late.
<i>Korea United Pharm.</i> , 11/1/2022, Double Blind Randomized Controlled Trial, placebo-controlled, South Korea, trial NCT05055414 (history).	Estimated 140 patient RCT with results unknown and over 1 year late.
<i>Marcy</i> , 8/1/2023, Randomized Controlled Trial, multiple countries, trial NCT04920838 (history) (COVERAGE-A).	Estimated 600 patient RCT with results unknown and over 7 months late.
<i>Ramakrishnan</i> , 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.
<i>Reis</i> , 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	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

treatment arm (combined with fluvoxamine) - results of individual treatments may vary, trial NCT04727424 (history) (TOGETHER).	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.

<i>Agustí</i> , 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.
<i>Al Sulaiman</i> , 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.
<i>Alsultan</i> , 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%).
<i>Bhandari</i> , 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 ( $\pm 4.23$ ) $n=60$ , control mean 7.82 ( $\pm 6.35$ ) $n=60$ .
	hospitalization time, 26.3% lower, relative time 0.74, $p = 0.02$ , treatment mean 6.54 ( $\pm 4.87$ ) $n=60$ , control mean 8.87 ( $\pm 6.12$ ) $n=60$ .
	recovery time, 36.8% lower, relative time 0.63, $p = 0.001$ , treatment mean 4.85 ( $\pm 3.94$ ) $n=60$ , control mean 7.68 ( $\pm 5.43$ ) $n=60$ , cough.
<i>Dhanger</i> , 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.
<i>Ramlall</i> , 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.
<i>Samajdar</i> , 3/3/2023, prospective, India, peer-reviewed, mean age 47.2, 6 authors, study period January 2021 - June 2021, 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 ( $\pm 1.24$ ) $n=50$ , control mean 3.03 ( $\pm 1.99$ ) $n=52$ , day 7.
	cough score, 9.9% lower, RR 0.90, $p = 0.10$ , treatment mean 4.66 ( $\pm 1.42$ ) $n=50$ , control mean 5.17 ( $\pm 1.65$ ) $n=52$ , day 3.
<i>Taille</i> , 5/28/2021, Randomized Controlled Trial, France, trial NCT04331054 (history) (INHASCO).	146 patient RCT with results unknown and over 2 years late.
<i>Yang (B)</i> , 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%).
<i>Yu (B)</i> , 4/12/2021, Randomized Controlled Trial, United Kingdom, peer-reviewed, 24 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.

<i>Lee (B)</i> , 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.
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<i>Loucera</i> , 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.
<i>Montserrat Villatoro</i> , 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.

## References

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