Lactoferrin for COVID-19: real-time meta analysis of 8 studies

@CovidAnalysis, June 2025, Version 15

https://c19early.org/lfmeta.html

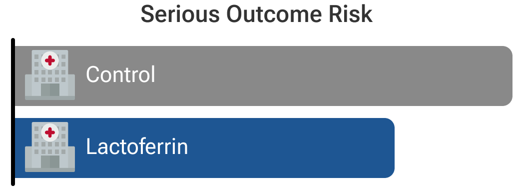
Abstract

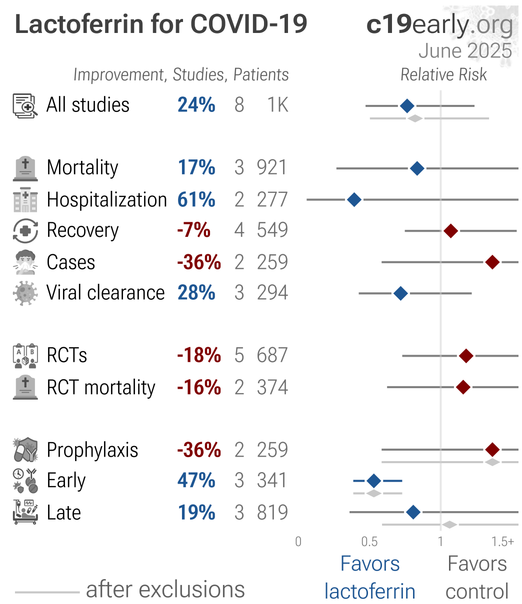
Meta analysis using the most serious outcome reported shows 24% [-24-53%] lower risk, without reaching statistical significance. Results are worse for Randomized Controlled Trials and higher quality studies. Early treatment is more effective than late treatment.

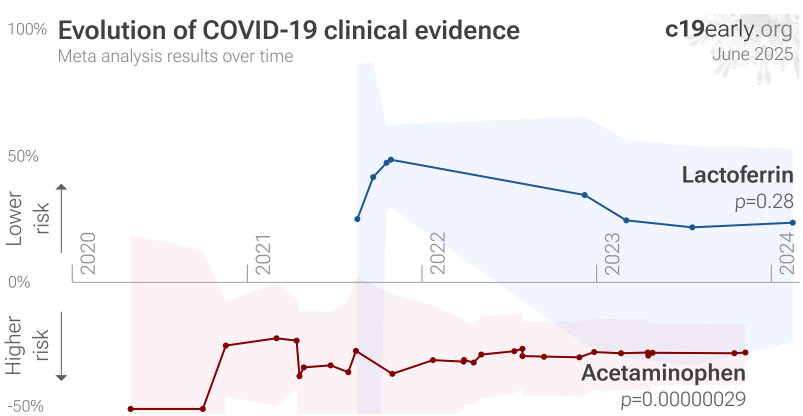
3 studies from 3 independent teams in 2 countries show significant benefit.

1 RCT with 40 patients has not reported results (6 months late) [1].

No treatment is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. Other treatments are more effective. Dietary sources may be preferred. The quality of non-prescription supplements varies widely [2-4]. All data and sources to reproduce this analysis are in the appendix.





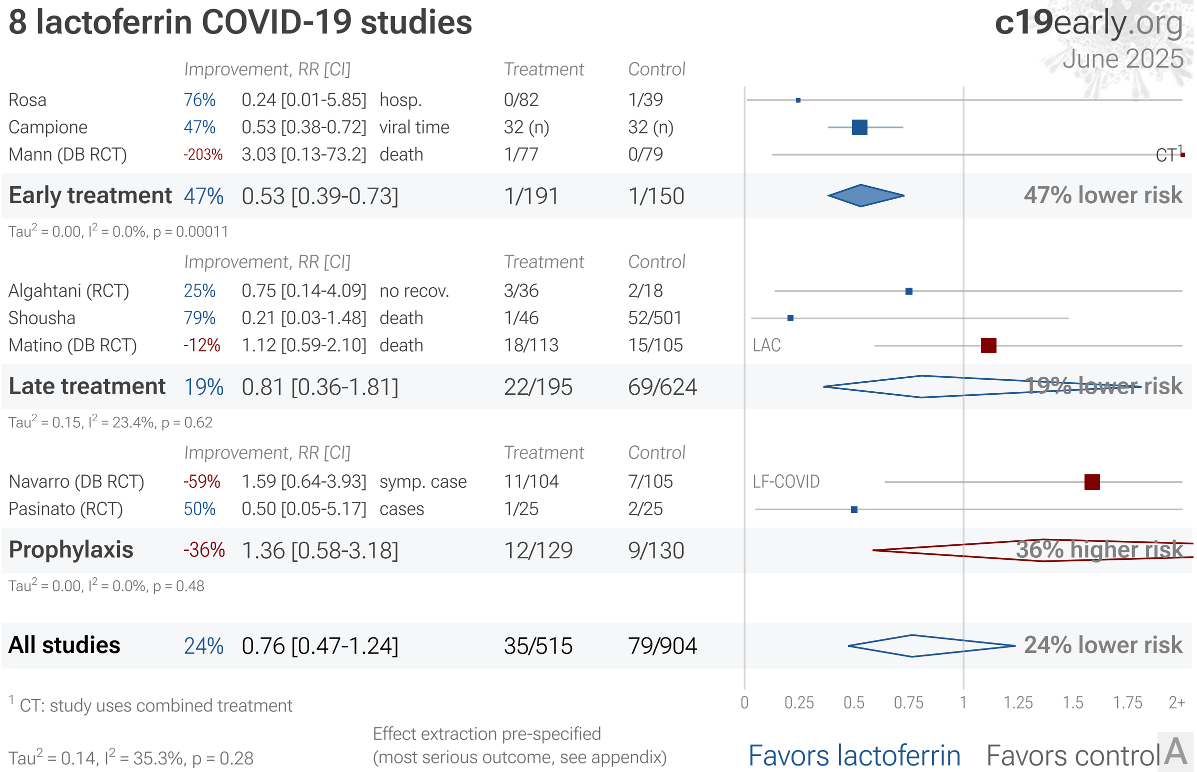


LACTOFERRIN FOR COVID-19 — HIGHLIGHTS

Meta analysis of studies to date shows no significant improvements with lactoferrin.

Early treatment is more effective than late treatment.

Real-time updates and corrections with a consistent protocol for 169 treatments. Outcome specific analysis and combined evidence from all studies including treatment delay, a primary confounding factor.



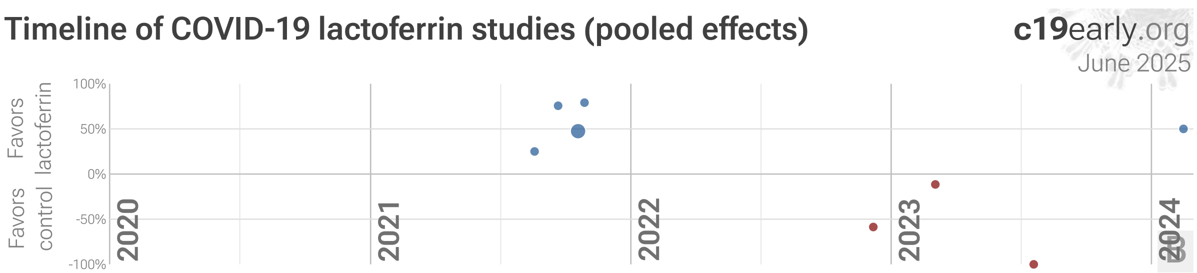


***Figure 1.* A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in lactoferrin studies.**

Introduction

Immediate treatment recommended

SARS-CoV-2 infection primarily begins in the upper respiratory tract and may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems, which may lead to cytokine storm, pneumonia, ARDS, neurological injury[6-18] and cognitive deficits[9,14], cardiovascular complications[19-23], organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits[24]—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Minimizing replication as early as possible is recommended.

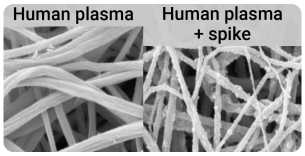


Figure 2. **SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from[5].**

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,25-32], 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[33], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Other infections

Efficacy with lactoferrin has been shown for resipiratory infections [34].

Other infections

Efficacy with lactoferrin has been shown in preclinical research for respiratory infections [34].

Analysis

We analyze all significant controlled studies of lactoferrin 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, 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.

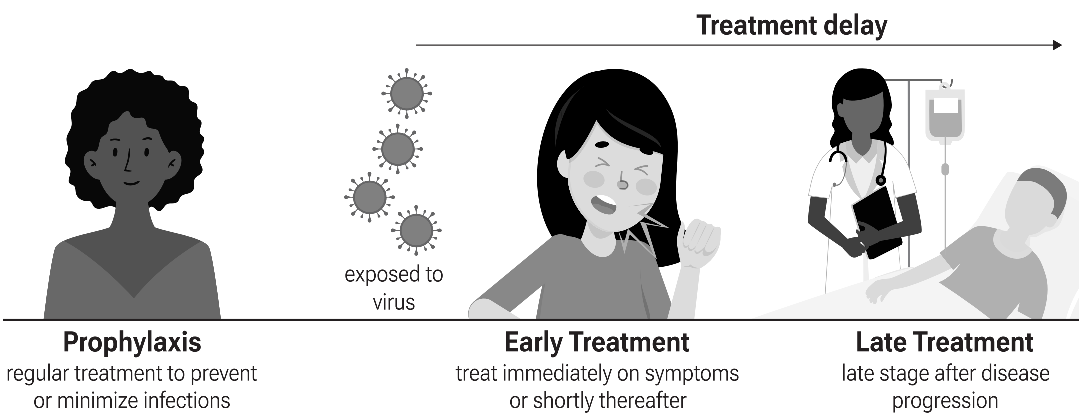


Figure 3. Treatment stages.

Preclinical Research

3 *In Silico* studies support the efficacy of lactoferrin [35-37].

12 *In Vitro* studies support the efficacy of lactoferrin [35,36,38-47].

2 *In Vivo* animal studies support the efficacy of lactoferrin [35,48].

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, 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, and 12 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, hospitalization, recovery, cases, viral clearance, and long COVID.

	Improvement	Studies	Patients	Authors
All studies	24% [-24-53%]	8	1,419	150
After exclusions	18% [-34-50%]	7	872	132
Randomized Controlled Trials	-18% [-90-27%]	5	687	92
Mortality	17% [-161-73%]	3	921	85
Hospitalization	61% [-164-94%]	2	277	22
Recovery	-7% [-53-25%]	4	549	81
Cases	-36% [-218-42%]	2	259	19
Viral	28% [-22-58%]	3	294	54
RCT mortality	-16% [-115-38%]	2	374	67

Table 1. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, after exclusions, and for specific outcomes.** Results show the percentage improvement with treatment and the 95% confidence interval. *** p<0.001.

	Early treatment	Late treatment	Prophylaxis
All studies	47% [27-61%] ***	19% [-81-64%]	-36% [-218-42%]
After exclusions	47% [27-61%] ***	-6% [-92-41%]	-36% [-218-42%]
Randomized Controlled Trials	-203% [-7216-87%]	-6% [-92-41%]	-36% [-218-42%]
Mortality	-203% [-7216-87%]	37% [-198-87%]	
Hospitalization	61% [-164-94%]		
Recovery	11% [-56-49%]	-30% [-86-9%]	
Cases			-36% [-218-42%]
Viral	28% [-22-58%]		
RCT mortality	-203% [-7216-87%]	-12% [-110-41%]	

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<0.001.

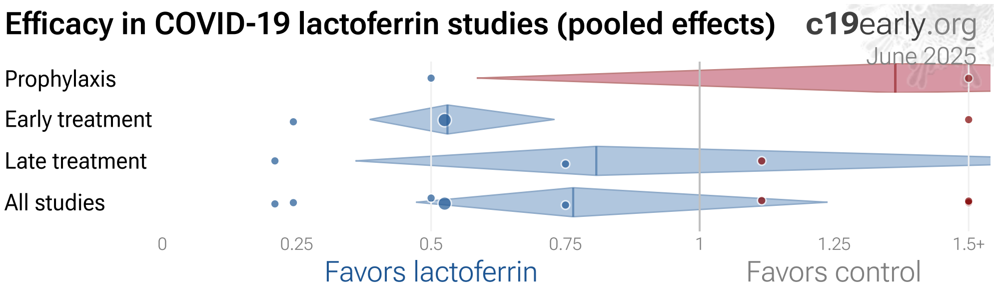


Figure 4. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

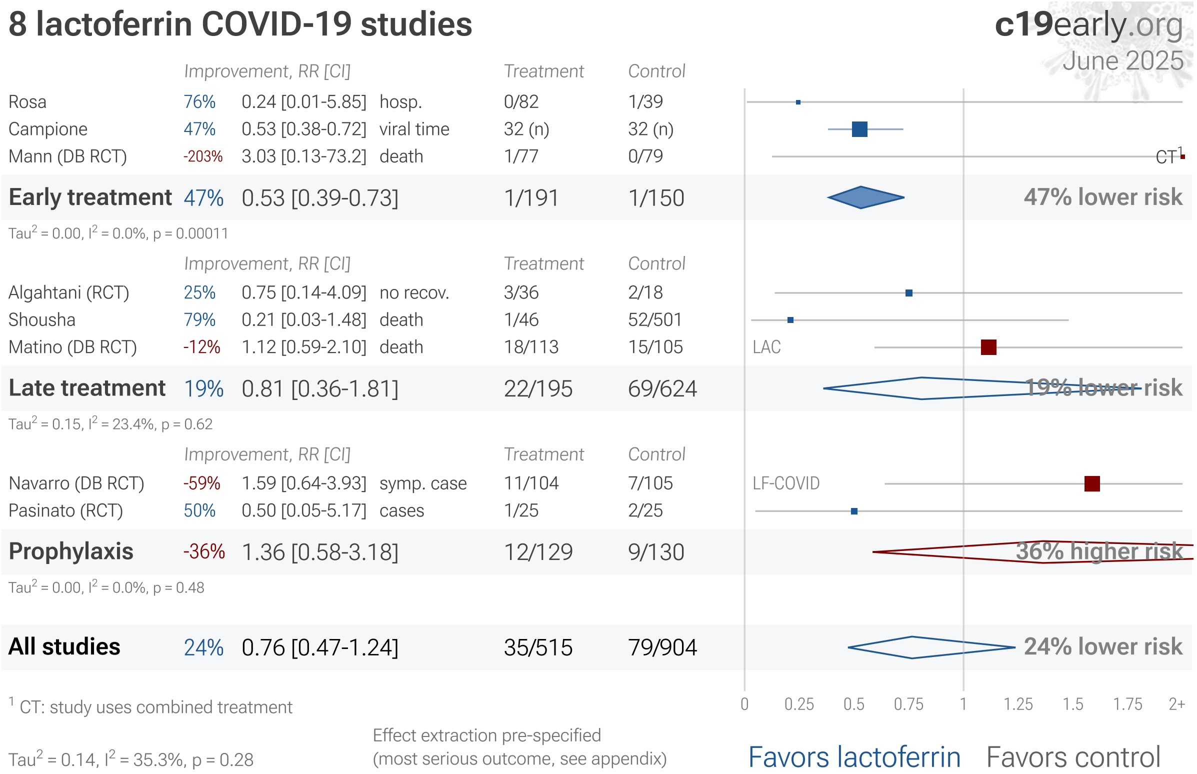


Figure 5. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For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

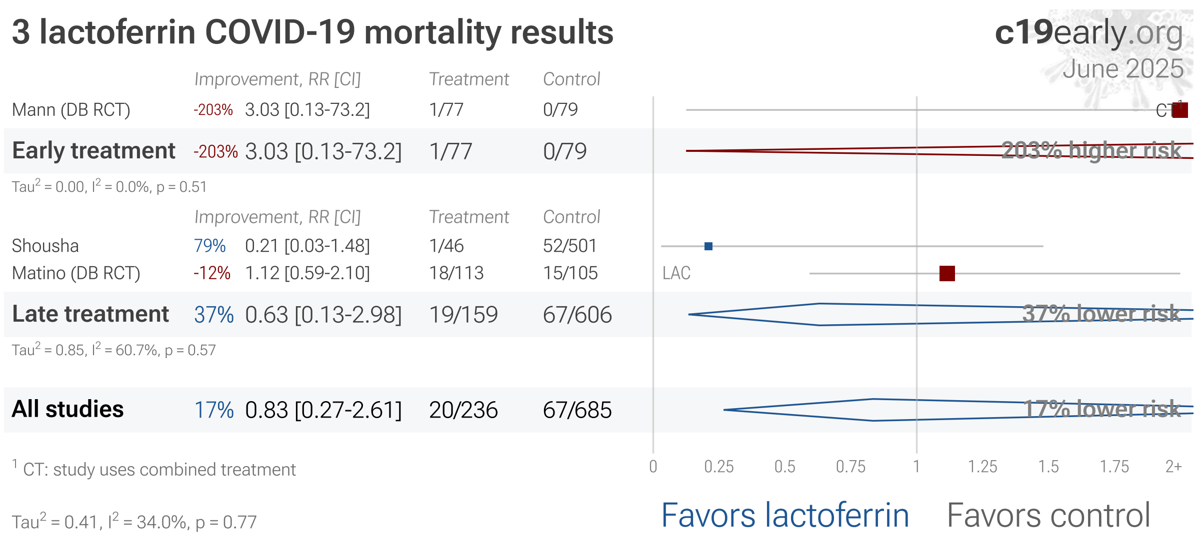


Figure 6. **Random effects meta-analysis for mortality results.**

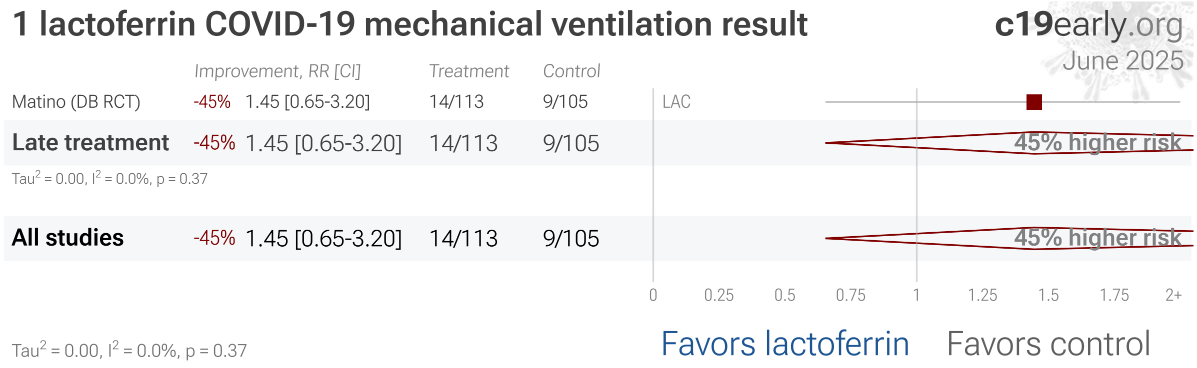


Figure 7. Random effects meta-analysis for ventilation.

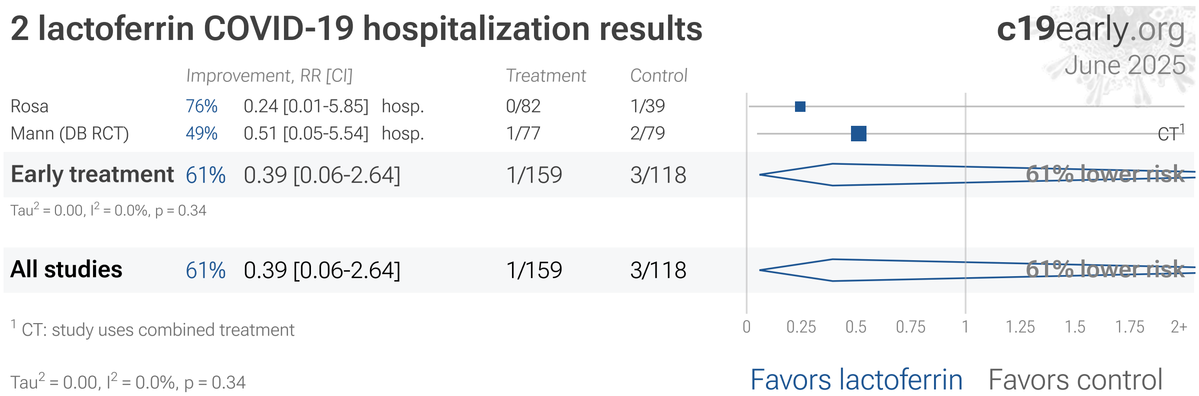


Figure 8. Random effects meta-analysis for hospitalization.

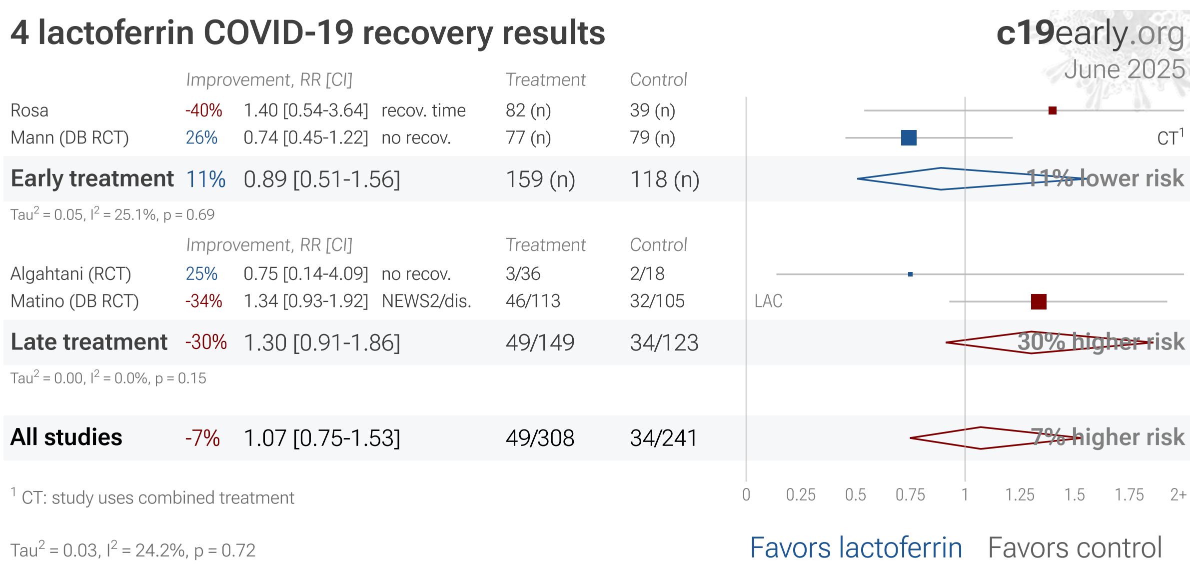


Figure 9. Random effects meta-analysis for recovery.

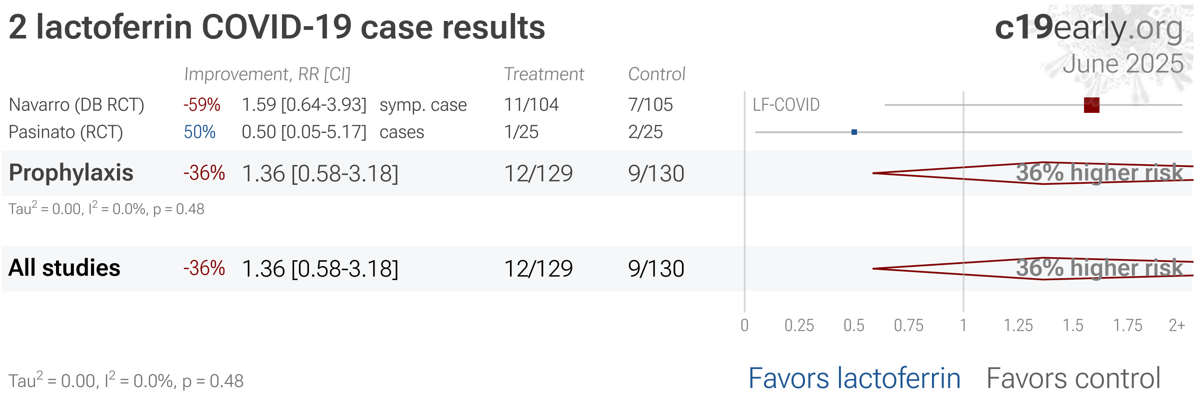


Figure 10. Random effects meta-analysis for cases.

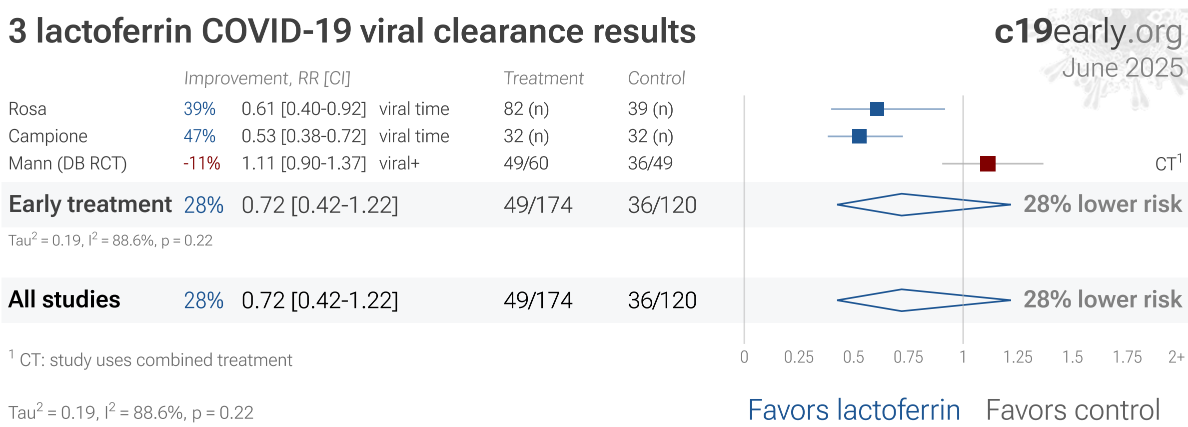


Figure 11. Random effects meta-analysis for viral clearance.

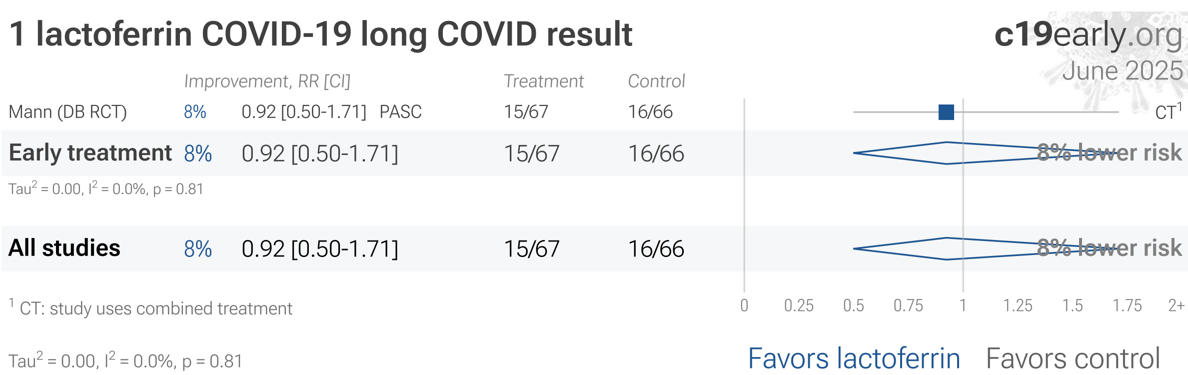


Figure 12. **Random effects meta-analysis for long COVID.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below.

Randomized Controlled Trials (RCTs)

Figure 13 shows a comparison of results for RCTs and non-RCT studies. Figure 14 and 15 show forest plots for random effects meta-analysis of all Randomized Controlled Trials and RCT mortality results. RCT results are included in Table 1 and Table 2.

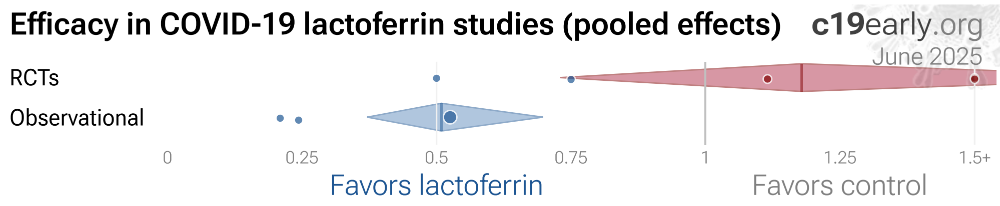


Figure 13. **Results for RCTs and non-RCT studies.**

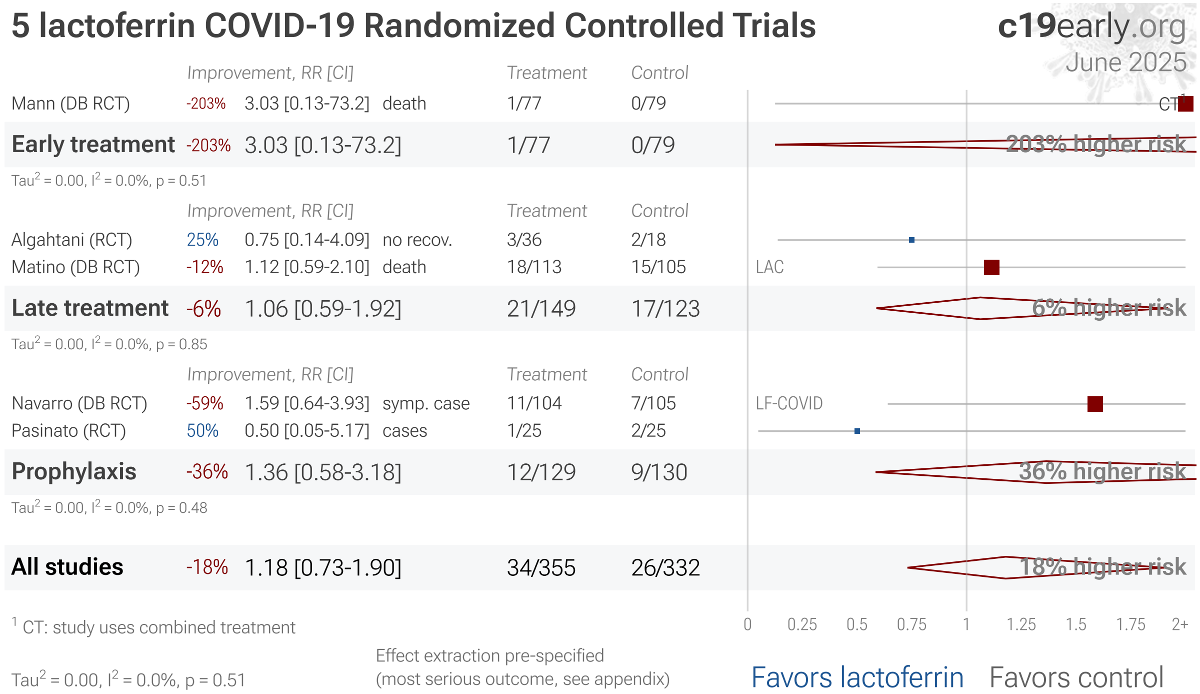


Figure 14. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

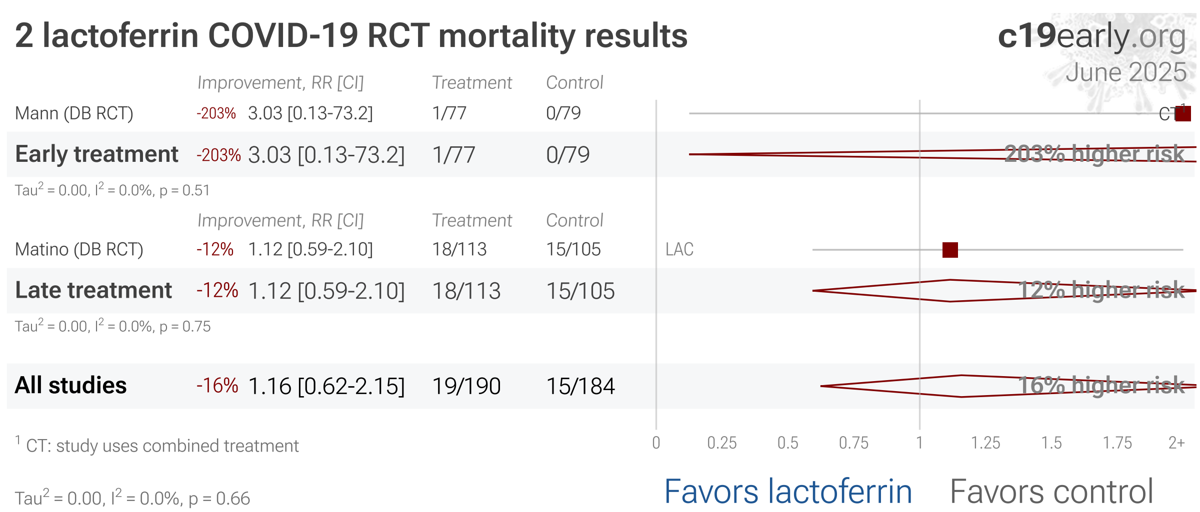


Figure 15. **Random effects meta-analysis for RCT mortality results.**

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 [49], and analysis of double-blind RCTs has identified extreme levels of bias [50]. 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 169 treatments we have analyzed, 66% 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 lactoferrin 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.

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 169 treatments we cover, showing no significant difference in the results of RCTs compared to observational studies, RR 0.99 [0.93-1.06] [55]. Similar results are found for all low-cost treatments, RR 1.01 [0.92-1.11]. High-cost treatments show a non-significant trend towards RCTs showing greater efficacy, RR 0.92 [0.83-1.03]. Details can be found in the supplementary data. *Lee et al.* showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or remote survey bias may have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see [57,58].

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

Currently, 53 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 7.8 months (66% with 8.9 months delay for low-cost treatments). The remaining treatments either have no RCTs, or the point estimate is consistent.

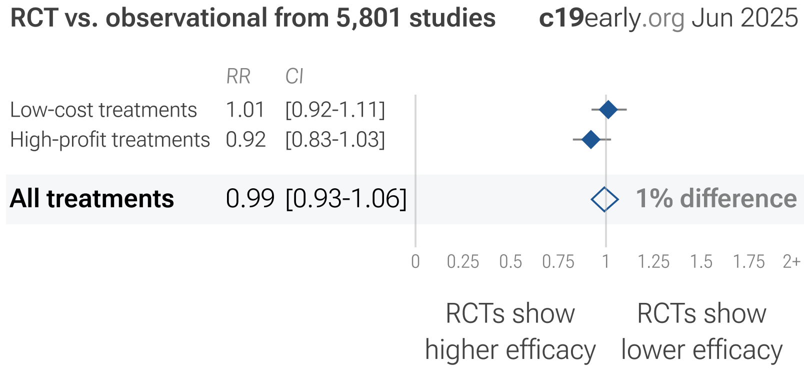


Figure 16. **For COVID-19, observational study results do not systematically differ from RCTs, RR 0.99 [0.93-1.06] across 169 treatments[52].**

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.

Unreported RCTs

1 lactoferrin RCT has not reported results[1]. The trial reports report an estimated total of 40 patients. The result is delayed over 6 months.

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

Rosa, excessive unadjusted differences between groups. Excluded results: no recovery.

Shousha, confounding by indication, unadjusted results and treatment used selectively per official protocol; unadjusted results with no group details.

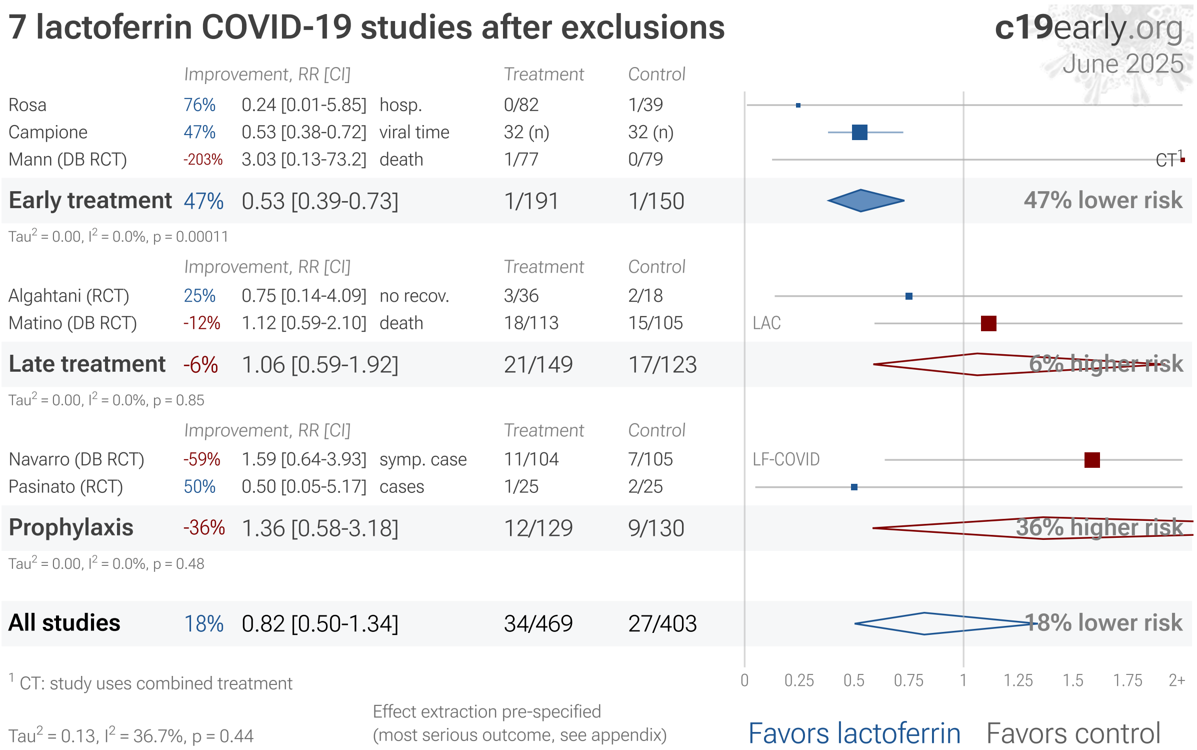


Figure 17. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome 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 [61,62]. 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 [63]
<24 hours	-33 hours symptoms [64]
24-48 hours	-13 hours symptoms [64]
Inpatients	-2.5 hours to improvement [65]

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

Figure 18 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 169 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

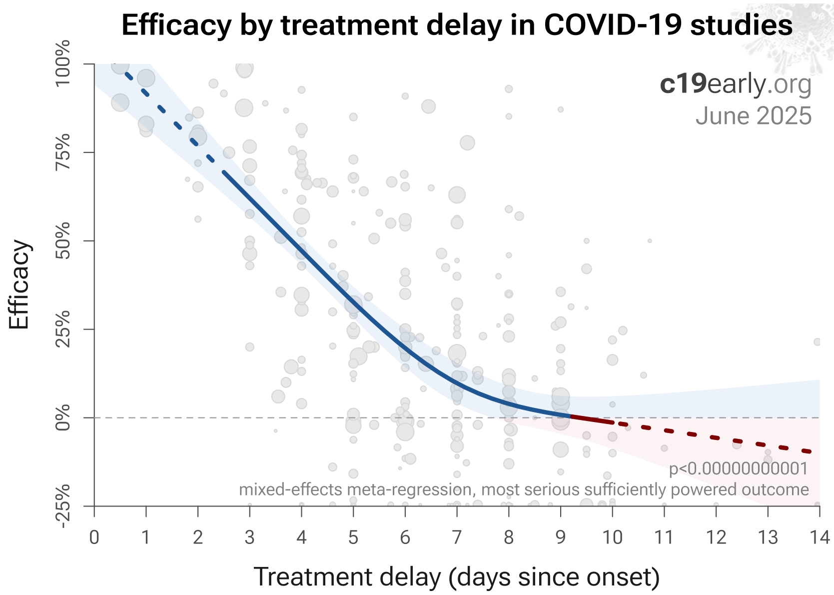


Figure 18. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 169 treatments.

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[67], for example the Gamma variant shows significantly different characteristics[68-71]. 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[72,73].

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. Non-prescription supplements may show very wide variations in quality[2,3].

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[45,76-91], 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

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 169 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 19 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 20 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 21 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 = 0.00000009* to *p = 0.0000000039*.

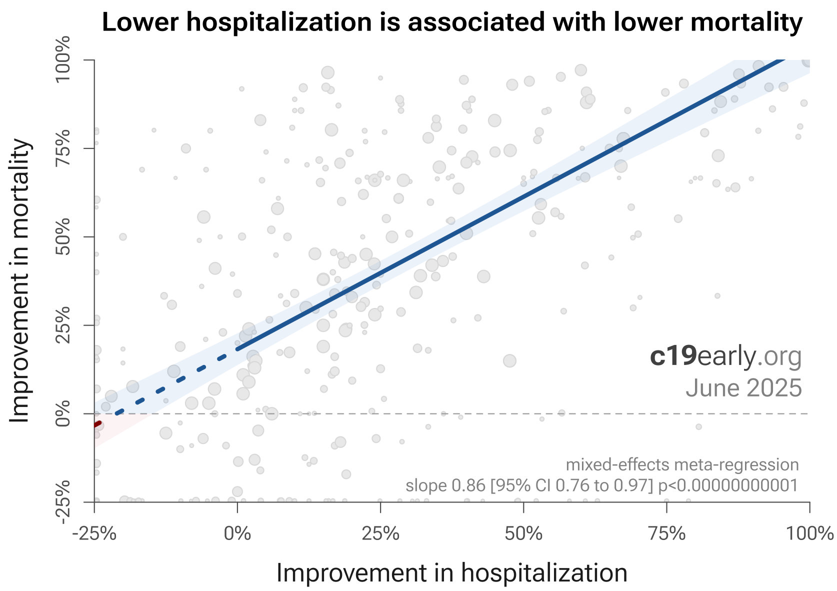


Figure 19. **Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.**

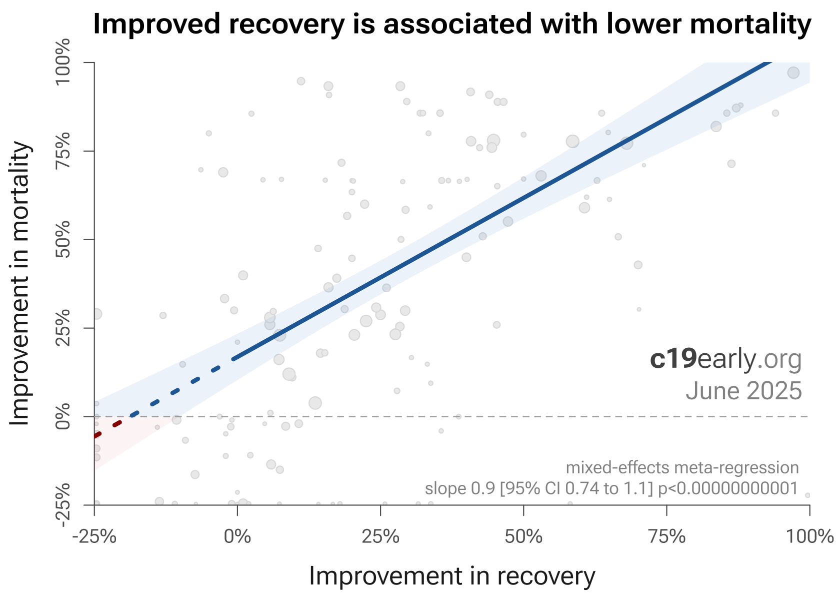


Figure 20. **Improved recovery is associated with lower mortality, supporting pooled outcome analysis.**

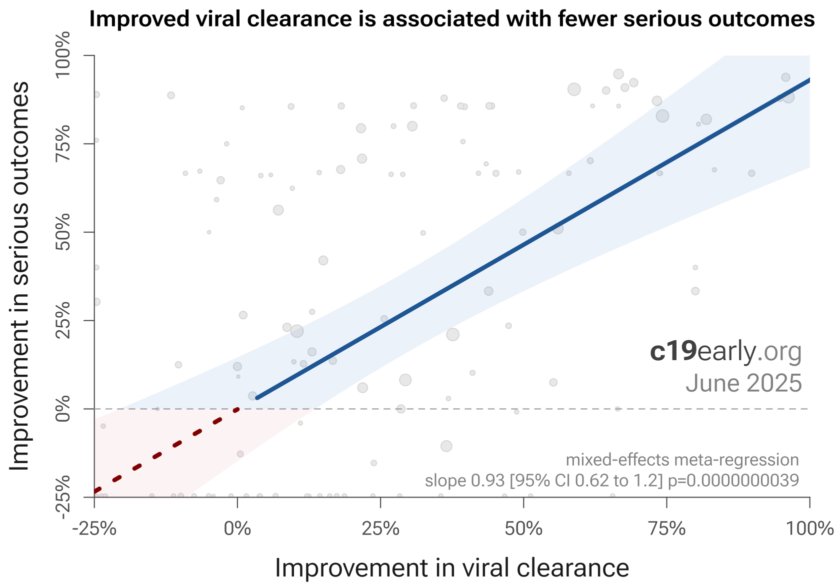


Figure 19. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

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

Currently, 53 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 90% of these have been confirmed with one or more specific outcomes, with a mean delay of 4.9 months. When restricting to RCTs only, 55% 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 22 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

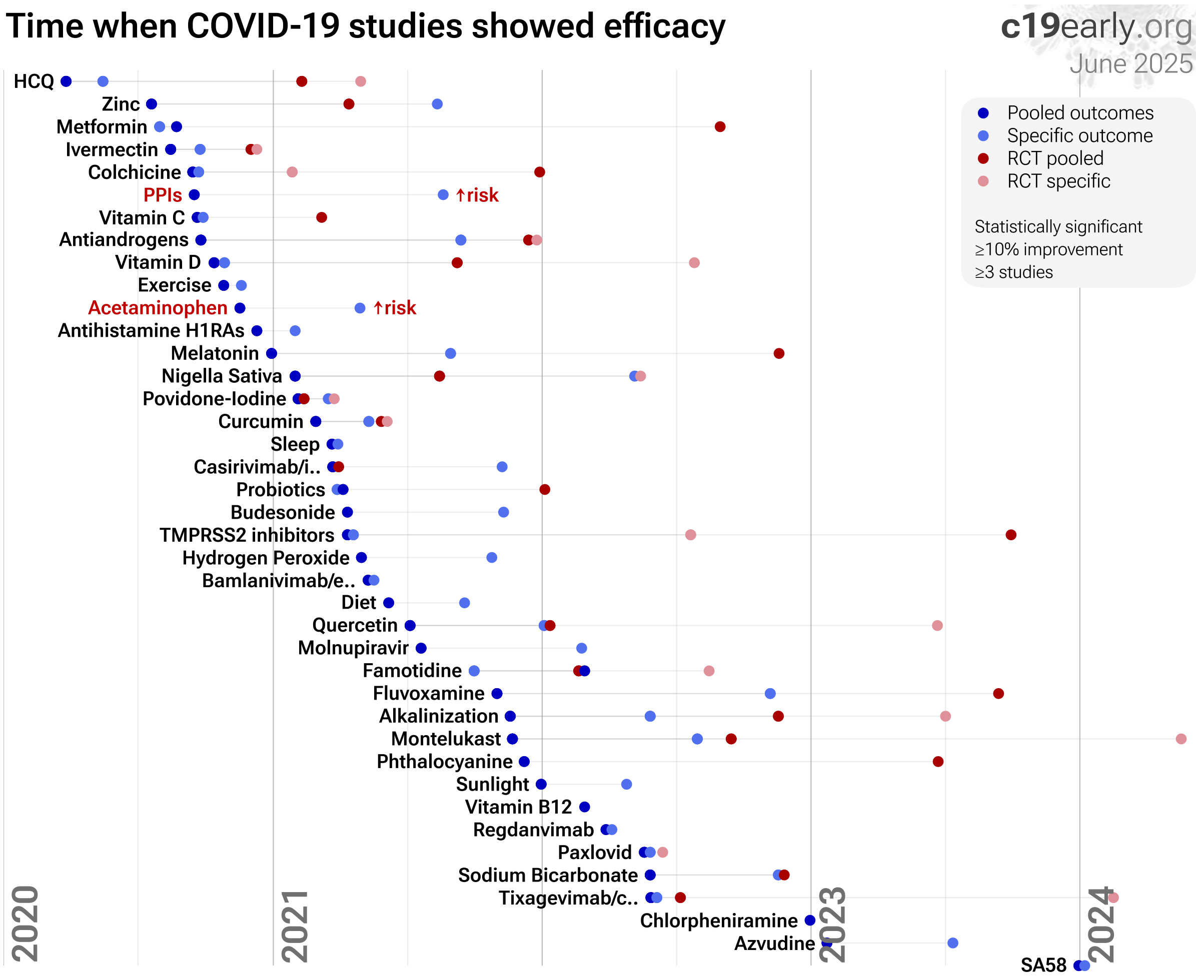


Figure 22. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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

Results for other infections

Efficacy with lactoferrin has also been shown for resipiratory infections [34].Efficacy with lactoferrin has also been shown in preclinical research for respiratory infections [34].

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 [93-96]. For lactoferrin, 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 23 shows a scatter plot of results for prospective and retrospective studies.

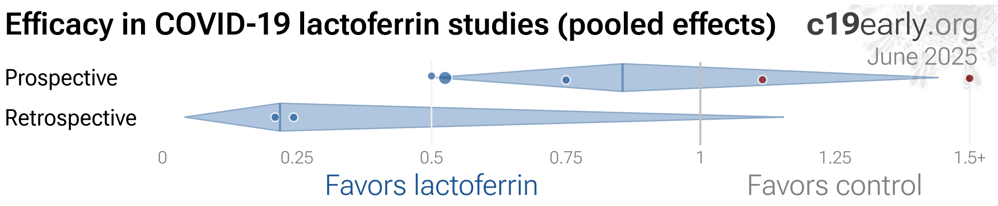


Figure 23. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

Funnel plot analysis

Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 24 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 $p < 0.05$ [97-104]. 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.

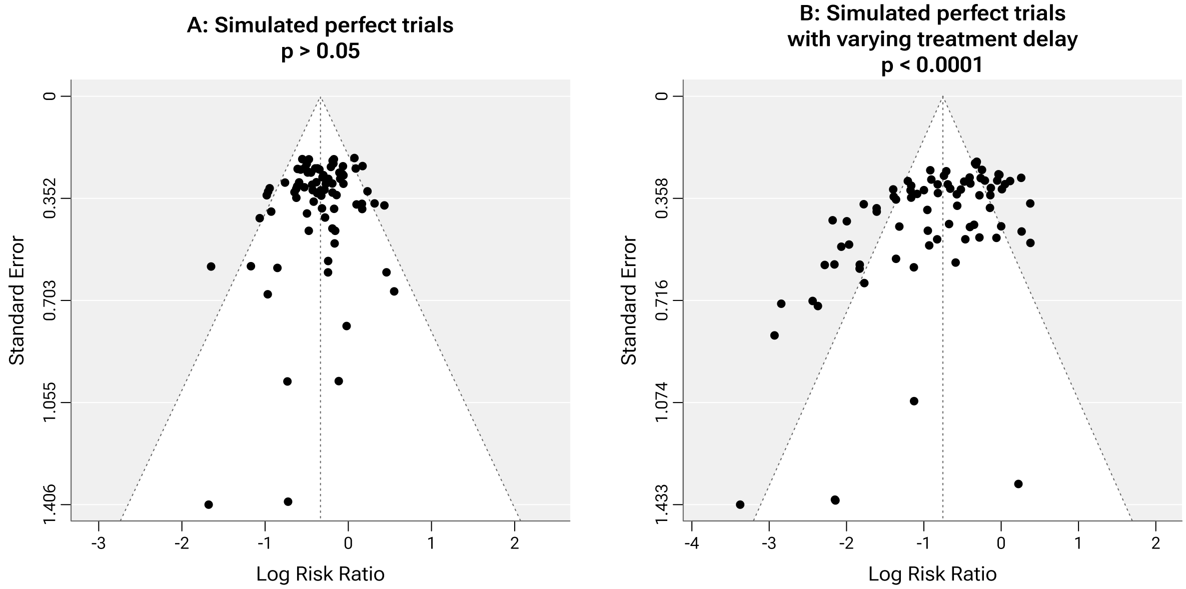


Figure 24. **Example funnel plot analysis for simulated perfect trials.**

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. Lactoferrin for COVID-19 lacks this because it is an inexpensive and widely available supplement. In contrast, most COVID-19 lactoferrin 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 lactoferrin 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 [45,76-91]. 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

1 of 8 studies combine treatments. The results of lactoferrin alone may differ. 1 of 5 RCTs use combined treatment. Currently all studies are peer-reviewed.

Reviews

Many reviews cover lactoferrin for COVID-19, presenting additional background on mechanisms and related results, including [105-110].

Other studies

Additional preclinical or review papers suggesting potential benefits of lactoferrin for COVID-19 include [116-132]. 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 [25-32], providing many therapeutic targets. Over 9,000 compounds have been predicted to reduce COVID-19 risk [33], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 25 shows an overview of the results for lactoferrin in the context of multiple COVID-19 treatments, and Figure 26 shows a plot of efficacy vs. cost for COVID-19 treatments.

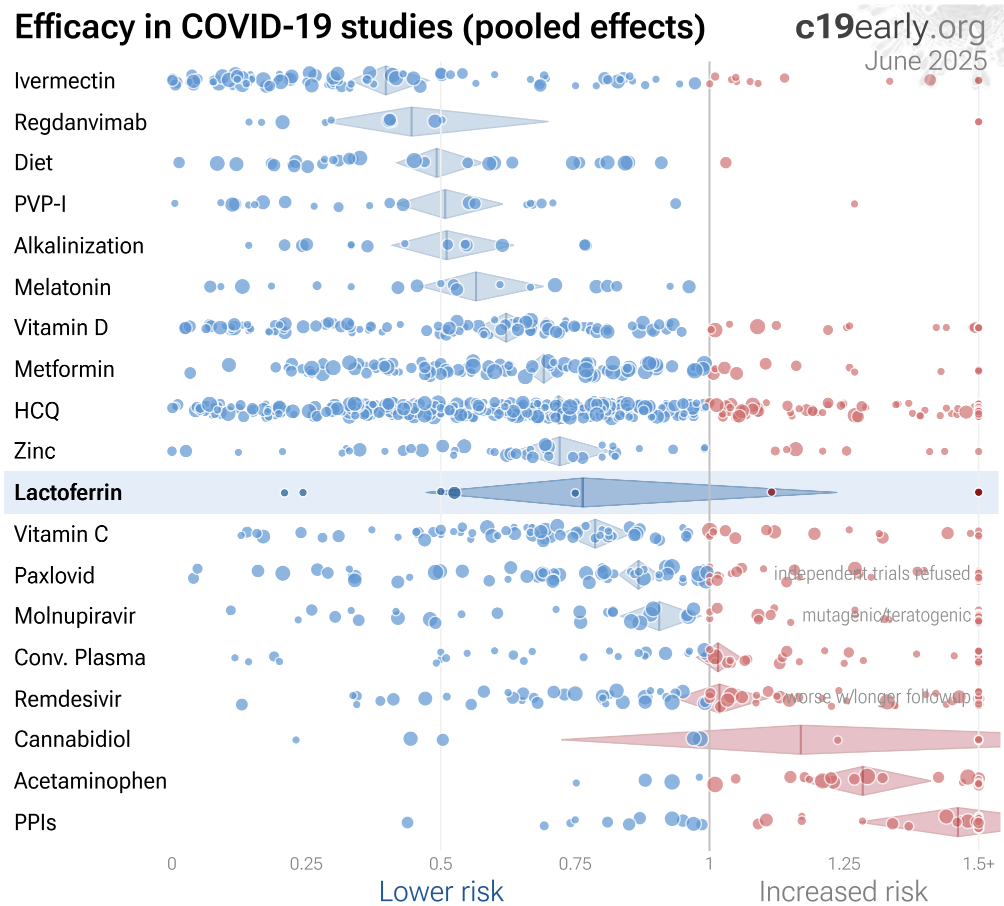


Figure 25. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy [133].

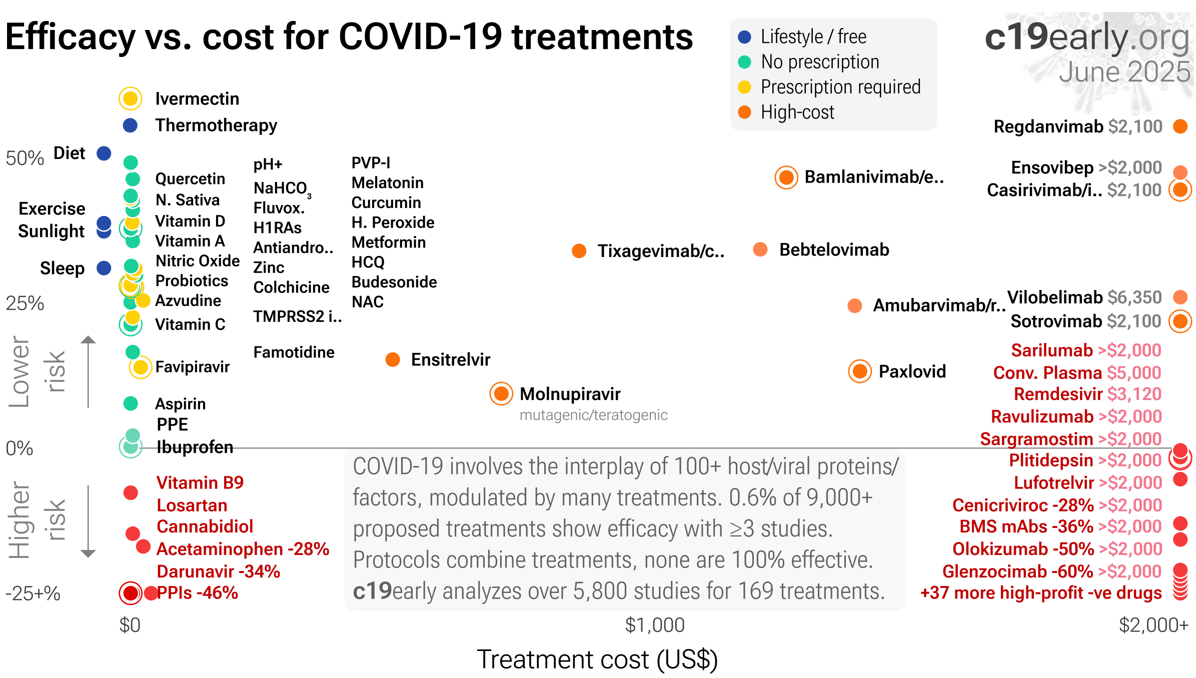


Figure 26. Efficacy vs. cost for COVID-19 treatments.

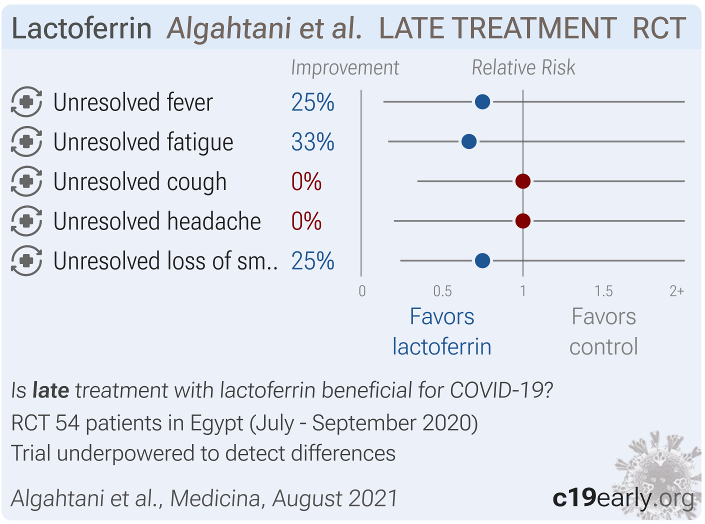
Conclusion

Meta analysis using the most serious outcome reported shows 24% [-24-53%] lower risk, without reaching statistical significance. Results are worse for Randomized Controlled Trials and higher quality studies. Early treatment is more effective than late treatment. 3 studies from 3 independent teams in 2 countries show significant benefit.

Efficacy with lactoferrin has been shown for resipiratory infections[34].

Study Notes

Algahtani

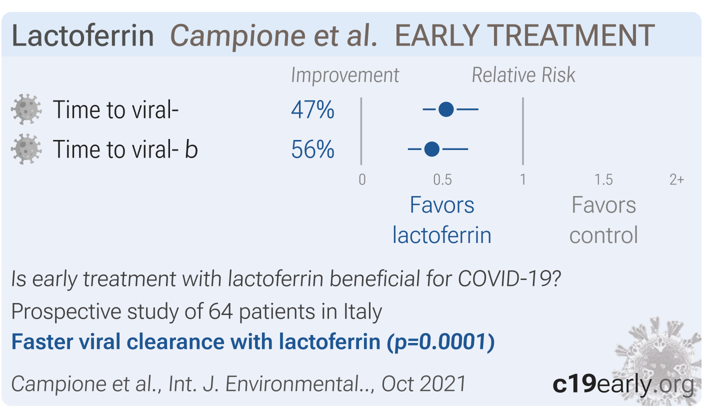


RCT 54 hospitalized patients in Egypt, showing no significant differences in recovery with lactoferrin treatment. 200mg lactoferrin orally once daily (group 1) or 200mg lactoferrin orally twice daily (group 2).

Avella

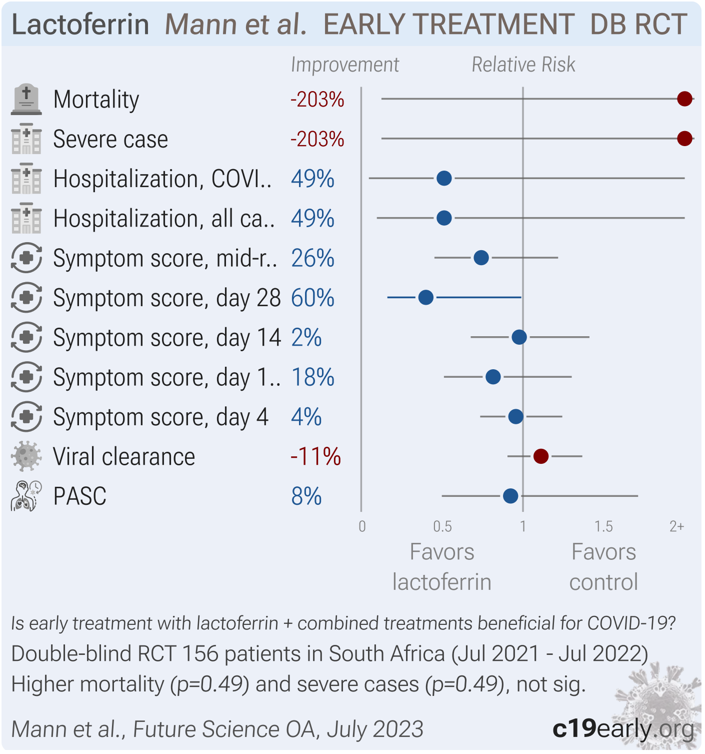
Estimated 40 patient lactoferrin early treatment RCT with results not reported over 6 months after estimated completion.

Campione



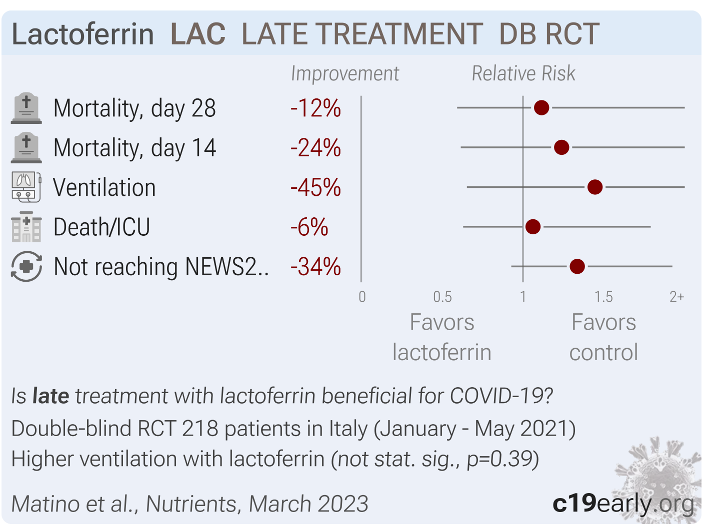
Small prospective study in Italy with 32 lactoferrin patients, 32 SOC, and 28 patients with no treatment, showing significantly faster viral clearance and improved recovery with treatment. Oral and intranasal lactoferrin.

Mann



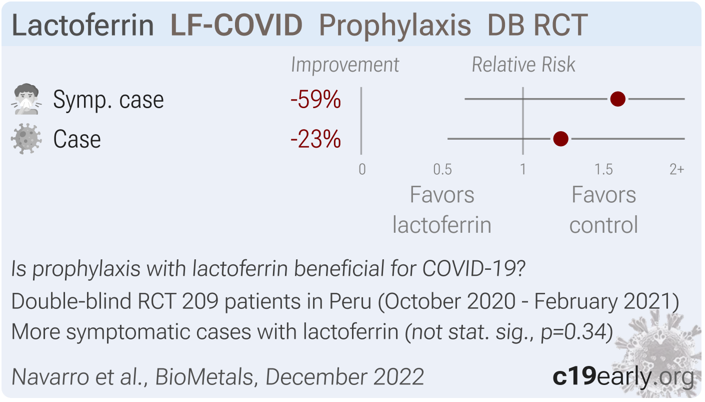
RCT 156 mild/moderate COVID-19 patients, 77 treated with hen egg white and bovine colostrum, showing faster recovery of severe symptoms with treatment. There were no significant differences in overall symptom duration, viral clearance, or post-COVID symptoms. Only one participant progressed to severe COVID-19.

Matino



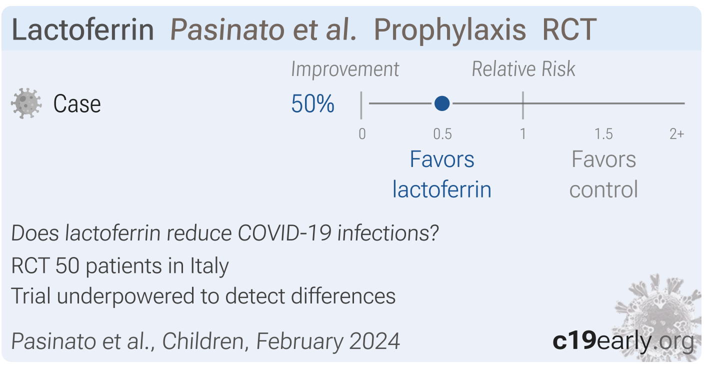
RCT 218 hospitalized patients in Italy, showing no significant differences with lactoferrin treatment. Authors note that in several previous studies showing clinical improvement, lactoferrin was given at an earlier stage of disease. Authors also note that potential benefits with the late treatment in this study could be masked by other SOC medications - corticosteroids may have masked immunomodulatory effects of lactoferrin, and there may be heparin-dependent reduction in lactoferrin antiviral activity. 800mg oral bovine lactoferrin daily.

Navarro



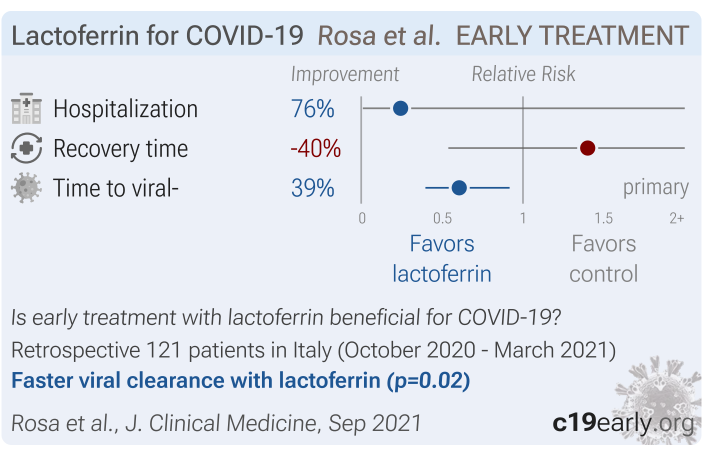
Early terminated low-risk patient prophylaxis RCT in Peru, showing no significant difference in cases with lactoferrin. There were no moderate or severe cases.

Pasinato



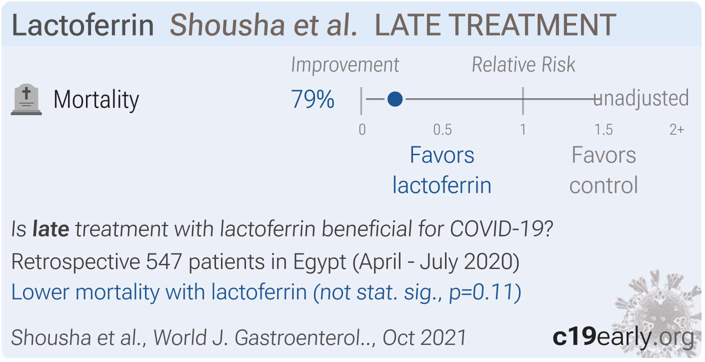
RCT 50 preschool children, 25 treated with bovine lactoferrin (bLf) prophylaxis, showing significantly lower frequency and duration of respiratory infections during the active phase with treatment. The only COVID-19 specific results reported are the number as patients with COVID, 1 vs. 2 for treatment vs. control. bLf 400mg bid for 4 months.

Rosa



Retrospective survey based study in Italy with 82 patients treated with lactoferrin, and 39 control patients, showing significantly faster viral clearance with treatment. There was no significant difference in recovery time overall, however the treatment group had significantly more moderate condition patients (39% versus 8%), and improved recovery was seen with treatment as age increased. Median dose for asymptomatic patients was 400mg/day, for paucisymptomatic patients 600mg/day, and for moderate condition patients 1000mg three times a day.

Shousha



Retrospective 547 hospitalized COVID+ patients in Egypt, showing lower mortality with lactoferrin treatment (without statistical significance).

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 lactoferrin 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 lactoferrin 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 both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral test status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO_2 is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to [134]. 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 [137]. 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 (3.13.3) with scipy (1.15.3), pythonmeta (1.26), numpy (2.2.6), statsmodels (0.14.4), and plotly (6.0.1).

Forest plots are computed using PythonMeta[138] 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[61,62].

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/lfmeta.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.

Avella, 11/1/2024, Double Blind Randomized Controlled Trial, placebo-controlled, USA, trial NCT05783180 (history).	Estimated 40 patient RCT with results unknown and over 6 months late.
Campione (B), 10/19/2021, prospective, Italy, peer-reviewed, 32 authors.	time to viral-, 47.5% lower, relative time 0.53, *p* < 0.001, treatment 32, control 32, vs. SOC.
	time to viral-, 56.3% lower, relative time 0.44, *p* < 0.001, treatment 32, control 28, vs. untreated.
Mann, 7/20/2023, Double Blind Randomized Controlled Trial, placebo-controlled, South Africa, peer-reviewed, 14 authors, study period 28 July, 2021 - 5 July, 2022, this trial uses multiple treatments in the treatment arm (combined with bovine colostrum and egg white) - results of individual treatments may vary, trial DOH-27-062021-9191.	risk of death, 202.6% higher, RR 3.03, *p* = 0.49, treatment 1 of 77 (1.3%), control 0 of 79 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of severe case, 202.6% higher, RR 3.03, *p* = 0.49, treatment 1 of 77 (1.3%), control 0 of 79 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of hospitalization, 48.7% lower, RR 0.51, *p* = 1.00, treatment 1 of 77 (1.3%), control 2 of 79 (2.5%), NNT 81, COVID-19.
	risk of hospitalization, 48.7% lower, RR 0.51, *p* = 0.68, treatment 2 of 77 (2.6%), control 4 of 79 (5.1%), NNT 41, all cause.
	relative symptom score, 25.8% better, RR 0.74, *p* = 0.24, treatment 77, control 79, mid-recovery, day 7.
	relative symptom score, 60.0% better, RR 0.40, *p* = 0.047, treatment 77, control 79, day 28.
	relative symptom score, 2.3% better, RR 0.98, *p* = 0.91, treatment 77, control 79, day 14.

	relative symptom score, 18.4% better, RR 0.82, *p* = 0.40, treatment 77, control 79, day 11-13.
	relative symptom score, 4.4% better, RR 0.96, *p* = 0.75, treatment 77, control 79, day 4.
	risk of no viral clearance, 11.2% higher, RR 1.11, *p* = 0.36, treatment 49 of 60 (81.7%), control 36 of 49 (73.5%), day 11-3.
	risk of PASC, 7.6% lower, RR 0.92, *p* = 0.84, treatment 15 of 67 (22.4%), control 16 of 66 (24.2%), NNT 54, day 42.
Rosa, 9/21/2021, retrospective, Italy, peer-reviewed, 8 authors, study period October 2020 - March 2021.	**risk of hospitalization, 75.6% lower, RR 0.24, *p* = 0.32**, treatment 0 of 82 (0.0%), control 1 of 39 (2.6%), NNT 39, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	recovery time, 40.0% higher, relative time 1.40, *p* = 0.50, treatment 82, control 39, excluded in exclusion analyses: excessive unadjusted differences between groups.
	time to viral-, 39.4% lower, relative time 0.61, *p* = 0.02, treatment 82, control 39, inverted to make RR<1 favor treatment, Cox regression, 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.

Algahtani, 8/19/2021, Randomized Controlled Trial, Egypt, peer-reviewed, 6 authors, study period 8 July, 2020 - 18 September, 2020.	**risk of unresolved fever, 25.0% lower, RR 0.75, *p* = 1.00**, treatment 3 of 36 (8.3%), control 2 of 18 (11.1%), NNT 36, day 7.
	risk of unresolved fatigue, 33.3% lower, RR 0.67, *p* = 0.67, treatment 4 of 36 (11.1%), control 3 of 18 (16.7%), NNT 18, day 7.
	risk of unresolved cough, no change, RR 1.00, *p* = 1.00, treatment 8 of 36 (22.2%), control 4 of 18 (22.2%), day 7.
	risk of unresolved headache, no change, RR 1.00, *p* = 1.00, treatment 4 of 36 (11.1%), control 2 of 18 (11.1%), day 7.
	risk of unresolved loss of smell/taste, 25.0% lower, RR 0.75, *p* = 0.72, treatment 6 of 36 (16.7%), control 4 of 18 (22.2%), NNT 18, day 7.
Matino, 3/4/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Italy, peer-reviewed, 53 authors, study period January 2021 - May 2021, average treatment delay 6.0 days, trial NCT04847791 (history) (LAC).	**risk of death, 11.5% higher, RR 1.12, *p* = 0.85**, treatment 18 of 113 (15.9%), control 15 of 105 (14.3%), day 28.
	risk of death, 23.9% higher, RR 1.24, *p* = 0.69, treatment 16 of 113 (14.2%), control 12 of 105 (11.4%), day 14.
	risk of mechanical ventilation, 44.5% higher, RR 1.45, *p* = 0.39, treatment 14 of 113 (12.4%), control 9 of 105 (8.6%).
	risk of death/ICU, 6.2% higher, RR 1.06, *p* = 0.87, treatment 24 of 113 (21.2%), control 21 of 105 (20.0%).

	not reaching NEWS2 ≤2 or discharge within 14 days, 33.6% higher, RR 1.34, $p = 0.12$, treatment 46 of 113 (40.7%), control 32 of 105 (30.5%).
Shousha, 10/28/2021, retrospective, Egypt, peer-reviewed, 18 authors, study period 15 April, 2020 - 29 July, 2020, excluded in exclusion analyses: confounding by indication, unadjusted results and treatment used selectively per official protocol; unadjusted results with no group details.	risk of death, 79.1% lower, RR 0.21, $p = 0.11$, treatment 1 of 46 (2.2%), control 52 of 501 (10.4%), NNT 12, unadjusted.

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.

Navarro, 12/7/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Peru, peer-reviewed, median age 37.0, 14 authors, study period October 2020 - February 2021, trial NCT04526821 (history) (LF-COVID).	risk of symptomatic case, 58.7% higher, RR 1.59, $p = 0.34$, treatment 11 of 104 (10.6%), control 7 of 105 (6.7%).
	risk of case, 23.4% higher, RR 1.23, $p = 0.65$, treatment 11 of 104 (10.6%), control 9 of 105 (8.6%).
Pasinato, 2/15/2024, Randomized Controlled Trial, Italy, peer-reviewed, mean age 4.2, 5 authors.	risk of case, 50.0% lower, RR 0.50, $p = 1.00$, treatment 1 of 25 (4.0%), control 2 of 25 (8.0%), NNT 25.

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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