# Probiotics for COVID-19: real-time meta analysis of 26 studies

@CovidAnalysis, April 2024, Version 28
https://c19early.org/kmeta.html

## Abstract

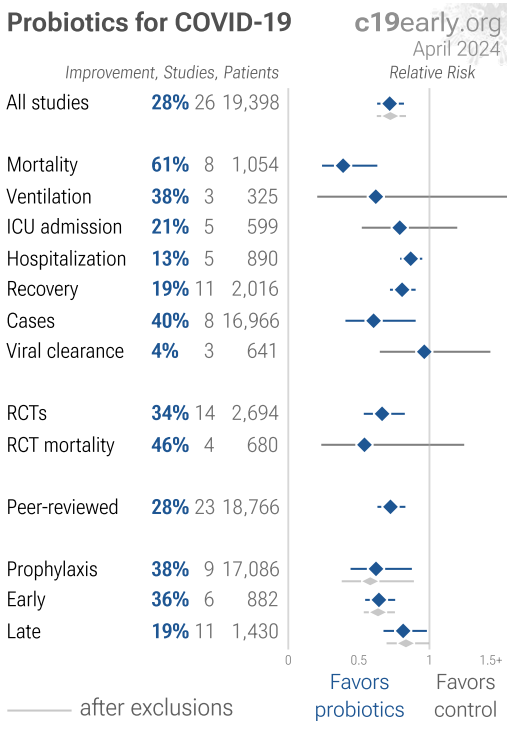
Statistically significant lower risk is seen for mortality, hospitalization, progression, recovery, and cases. 13 studies from 12 independent teams in 9 countries show statistically significant improvements.

Meta analysis using the most serious outcome reported shows 28% [18-37%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies. Better results are seen with early treatment.

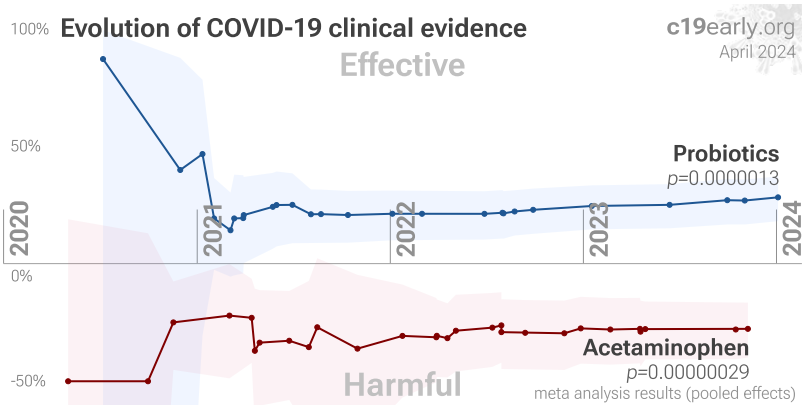
Results are robust — in exclusion sensitivity analysis 24 of 26 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

The immune effects of probiotics are strain-specific and studies use different strains.

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. The quality of non-prescription supplements can vary widely *Crawford, Crighton*. Many probiotic supplements may not include labeled ingredients *Hazan*.




All data to reproduce this paper and sources are in the appendix. Other meta analyses show significant improvements with probiotics for hospitalization *Tian* and recovery *Neris Almeida Viana, Tian*.



## HIGHLIGHTS

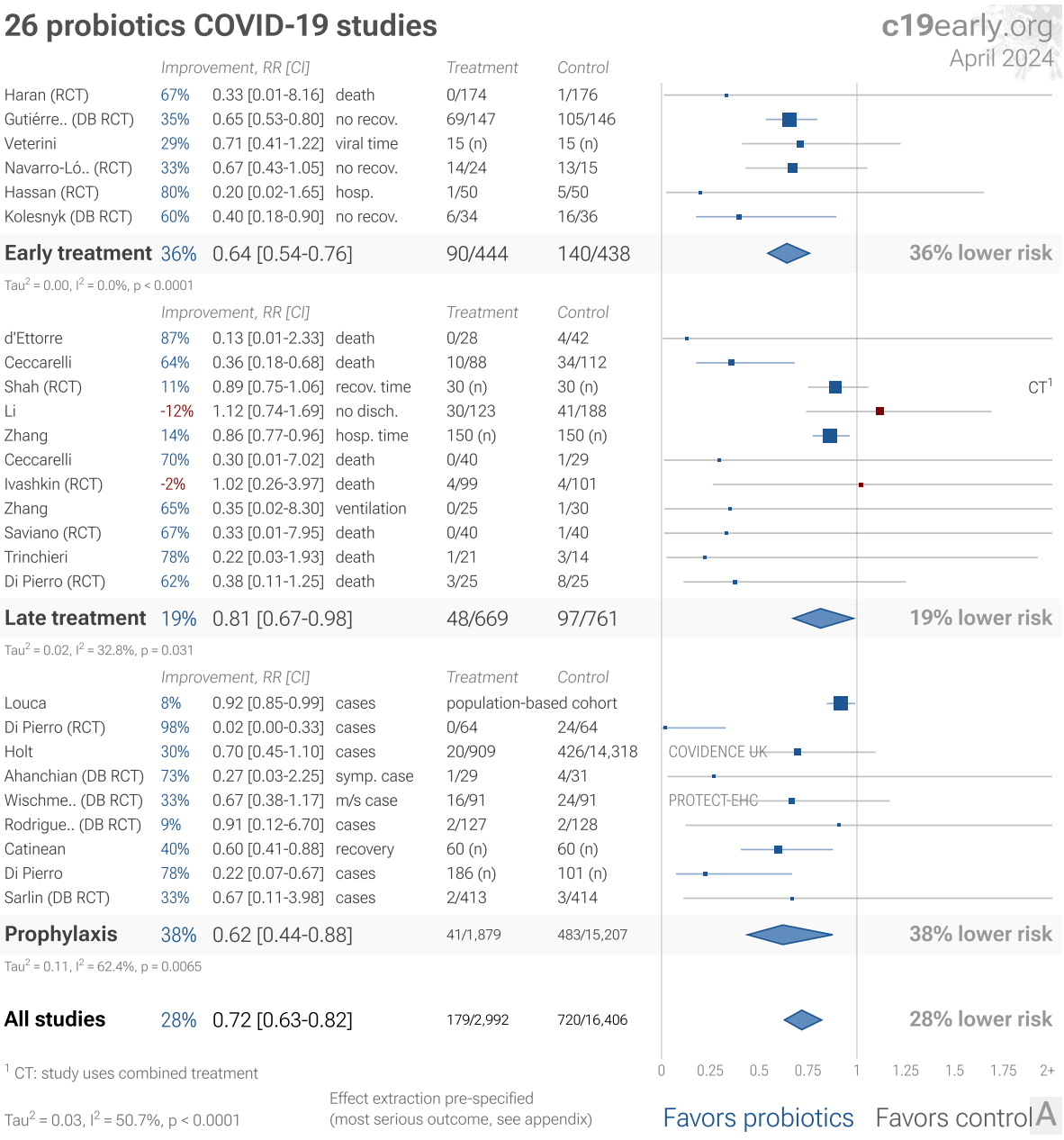
Probiotics reduce risk for COVID-19 with very high confidence for mortality, hospitalization, recovery, and in pooled analysis, high confidence for cases, and low confidence for progression. The immune effects of probiotics are strain-specific.

18th treatment shown effective with ≥3 clinical studies in March 2021, now with $p = 0.0000013$ from 26 studies.

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

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 69 treatments.

## 26 probiotics COVID-19 studies




[1] CT: study uses combined treatment

Tau² = 0.03, I² = 50.7%, p < 0.0001

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

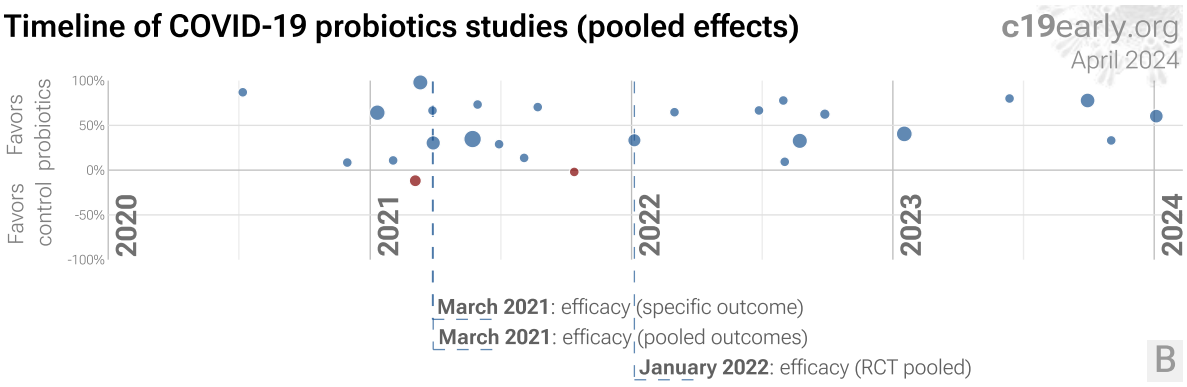



***Figure 1.*** **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in probiotics studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes, one or more specific outcome, and pooled outcomes in RCTs. Efficacy based on RCTs only was delayed by 9.3 months, compared to using all 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 issues *Duloquin, Hampshire, 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, Niarakis*, providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 7,000 compounds may reduce COVID-19 risk *c19early.org*, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

**Other infections.** Efficacy with probiotics has been shown for the common cold *Kobatake*.

**Analysis.** We analyze all significant controlled studies of Probiotics 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.

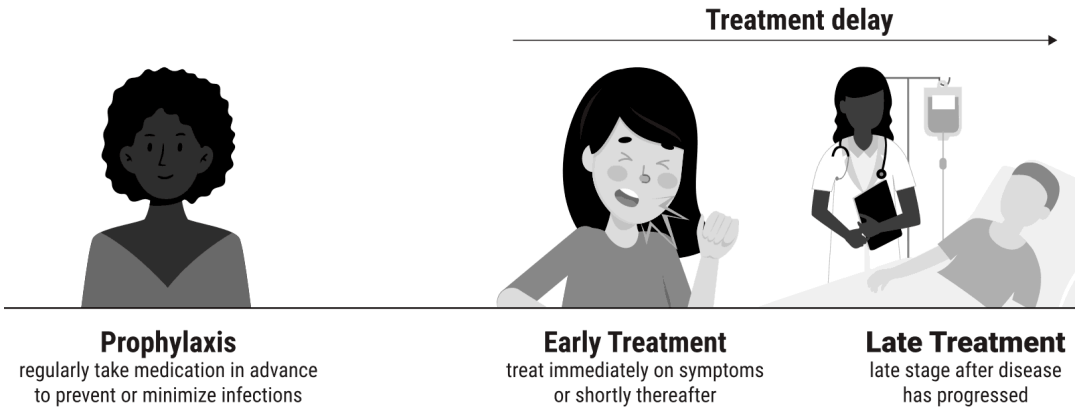



***Figure 2.*** Treatment stages.

## 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 plots individual results by treatment stage. Figure 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, recovery, cases, viral clearance, and peer reviewed studies.

| | *Improvement* | *Studies* | *Patients* | *Authors* |
|---|---|---|---|---|
| All studies | 28% [18-37%] **** | 26 | 19,398 | 289 |
| After exclusions | 28% [17-37%] **** | 23 | 4,091 | 242 |
| Peer-reviewed studies | 28% [17-37%] **** | 23 | 18,766 | 256 |
| Randomized Controlled Trials | 34% [17-47%] *** | 14 | 2,694 | 125 |
| | | | | |
| Mortality | 61% [37-76%] *** | 8 | 1,054 | 84 |
| Ventilation | 38% [-87-79%] | 3 | 325 | 40 |
| ICU admission | 21% [-20-48%] | 5 | 599 | 51 |
| Hospitalization | 13% [5-21%] ** | 5 | 890 | 38 |
| Recovery | 19% [10-28%] *** | 11 | 2,016 | 104 |
| Cases | 40% [10-60%] * | 8 | 16,966 | 121 |
| Viral | 4% [-43-35%] | 3 | 641 | 27 |
| | | | | |
| RCT mortality | 46% [-25-77%] | 4 | 680 | 33 |
| RCT hospitalization | 13% [-2-25%] | 4 | 590 | 24 |

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

| | *Early treatment* | *Late treatment* | *Prophylaxis* |
|---|---|---|---|
| All studies | **36%** [24-46%] **** | **19%** [2-33%] * | **38%** [12-56%] ** |
| After exclusions | **36%** [24-47%] **** | **17%** [0-30%] * | **42%** [11-62%] * |
| Peer-reviewed studies | **35%** [24-45%] **** | **19%** [2-33%] * | **40%** [11-60%] * |
| Randomized Controlled Trials | **36%** [24-47%] **** | **12%** [-4-26%] | **55%** [-13-82%] |
| | | | |
| Mortality | **67%** [-716-99%] | **61%** [36-76%] *** | |
| Ventilation | | **38%** [-87-79%] | |
| ICU admission | | **21%** [-20-48%] | |
| Hospitalization | **69%** [-13-91%] | **13%** [5-20%] ** | |
| Recovery | **30%** [20-39%] **** | **9%** [2-16%] * | **38%** [13-55%] ** |
| Cases | | | **40%** [10-60%] * |
| Viral | **29%** [-22-59%] | **-6%** [-70-34%] | |
| | | | |
| RCT mortality | **67%** [-716-99%] | **44%** [-33-77%] | |
| RCT hospitalization | **69%** [-13-91%] | **11%** [-4-24%] | |

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

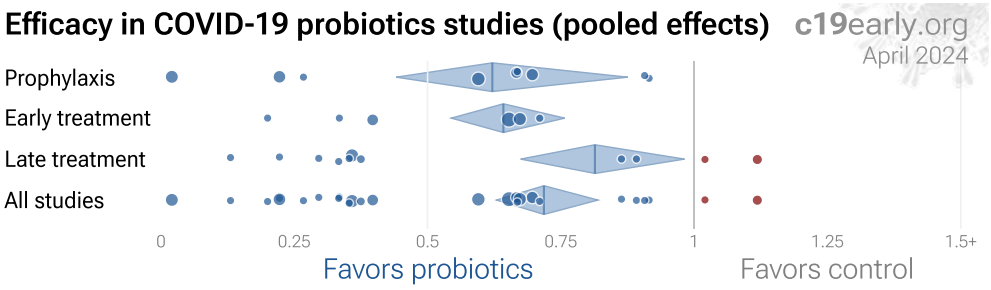



***Figure 3.*** **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

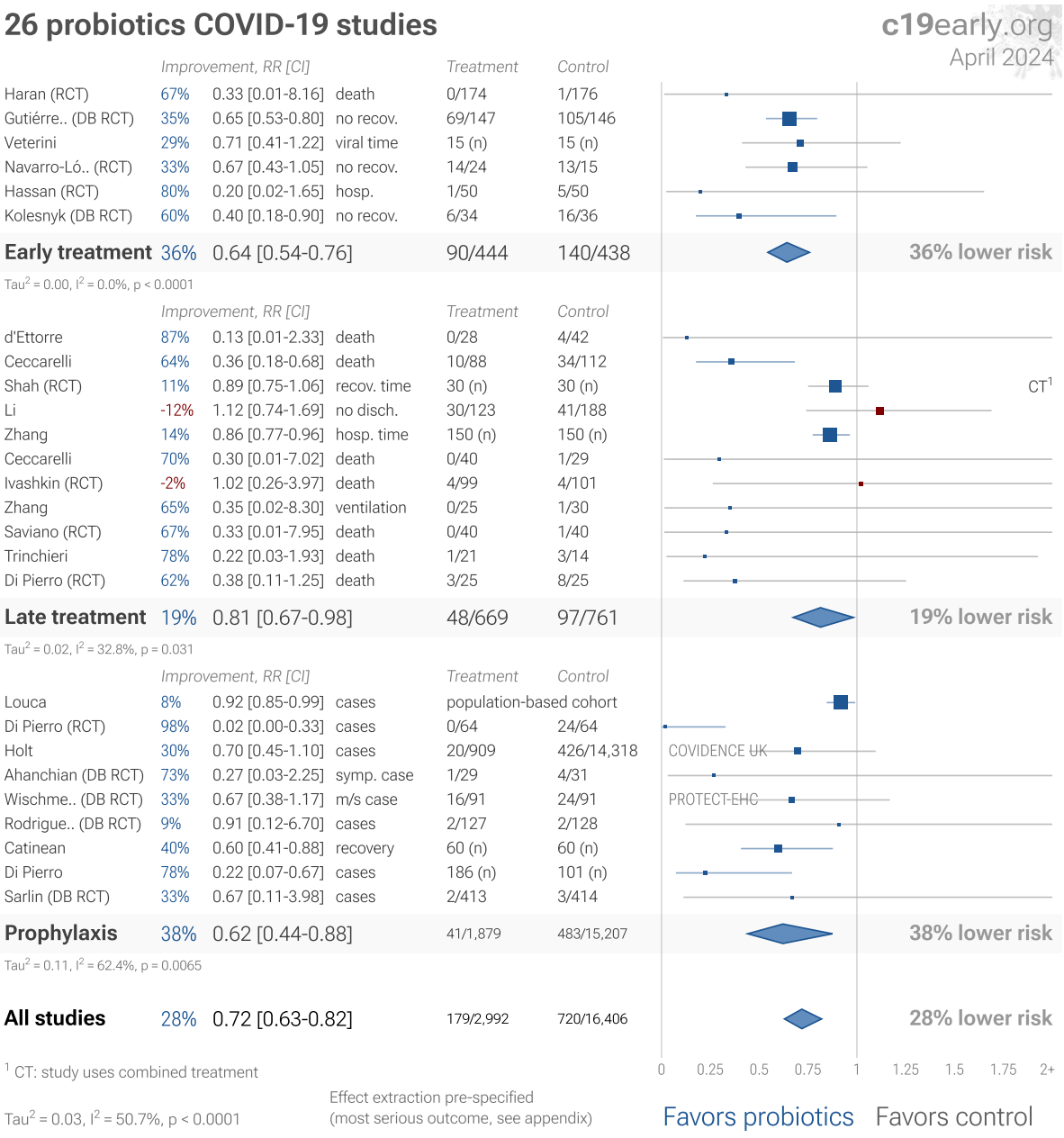



***Figure 4.*** **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

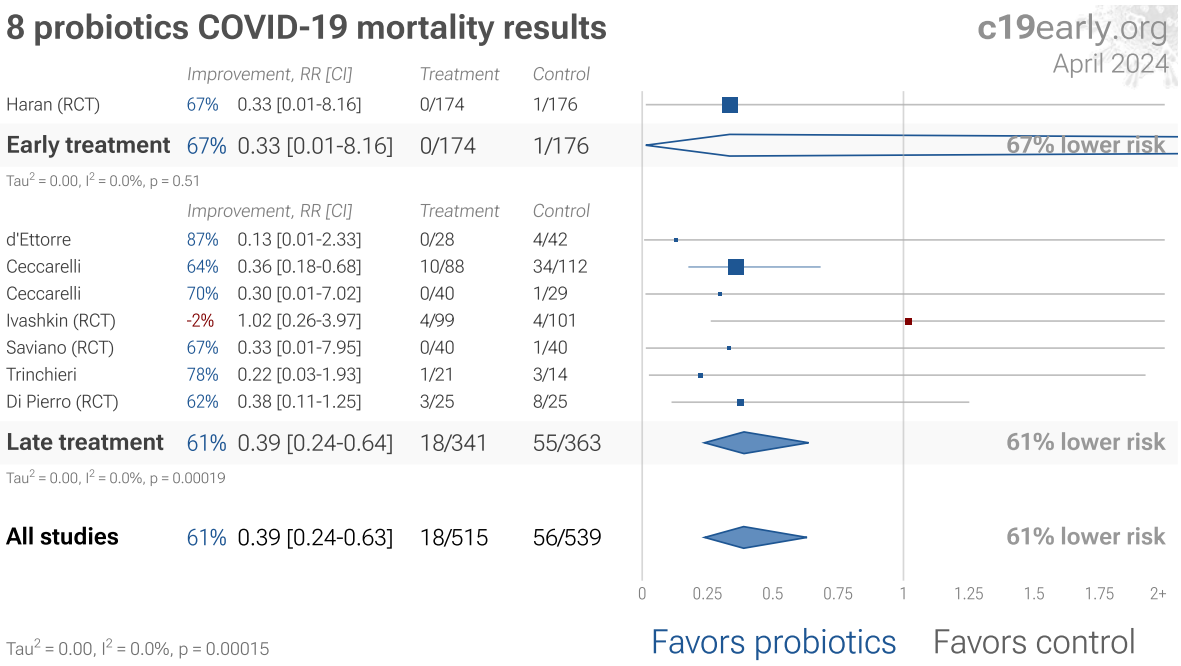



***Figure 5.*** Random effects meta-analysis for mortality results.

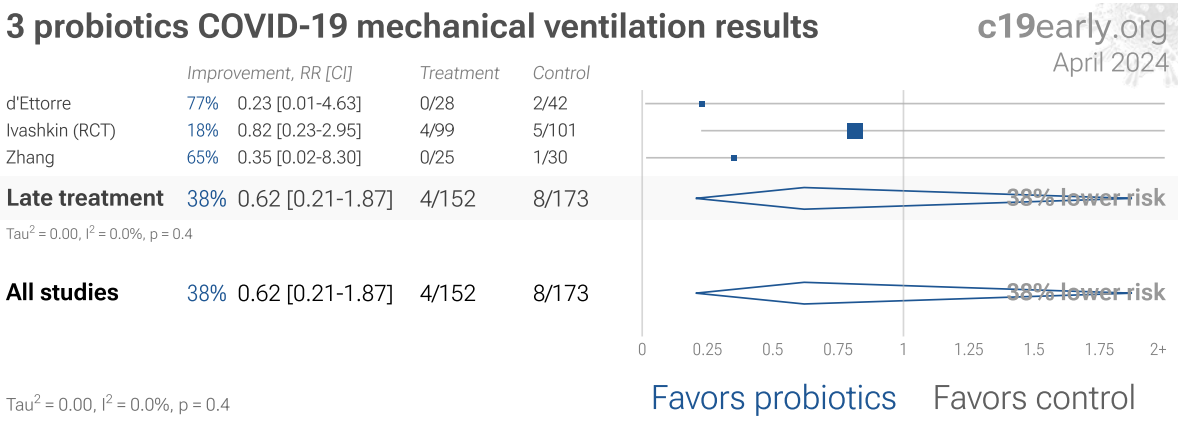



***Figure 6.*** Random effects meta-analysis for ventilation.

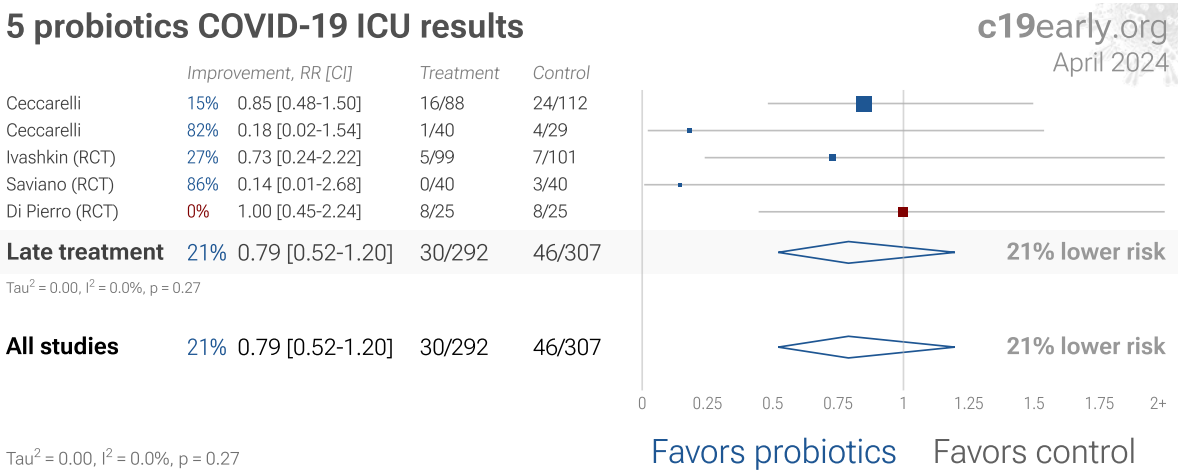



***Figure 7.*** Random effects meta-analysis for ICU admission.

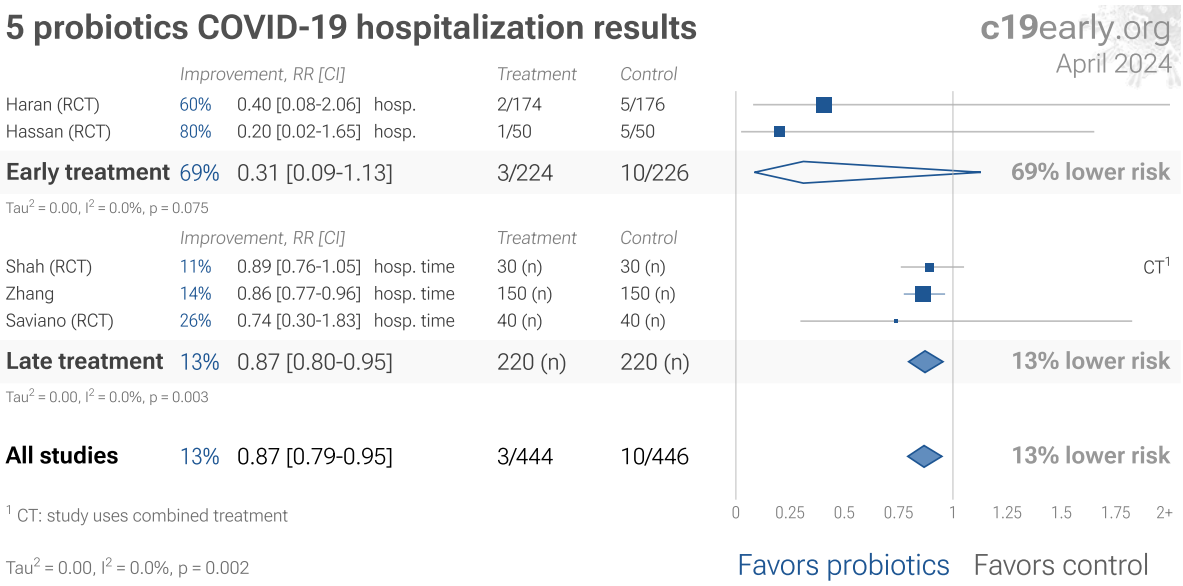



***Figure 8.*** Random effects meta-analysis for hospitalization.

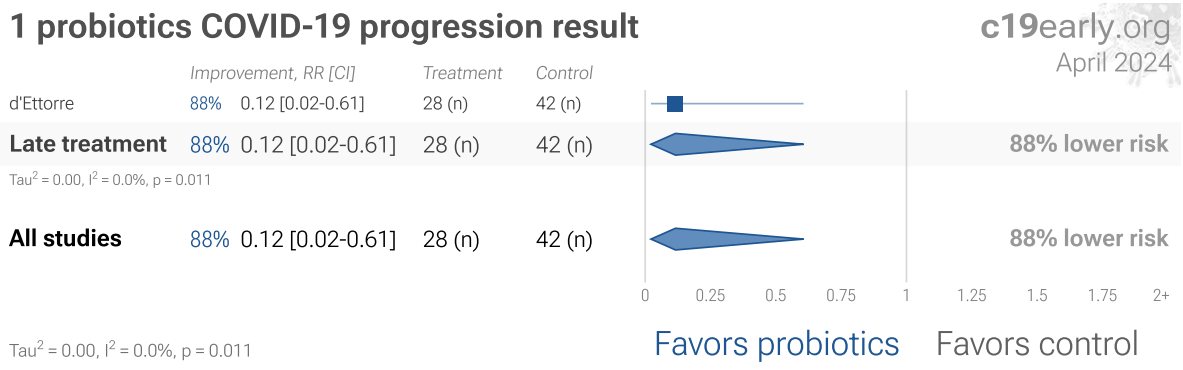



***Figure 9.*** Random effects meta-analysis for progression.

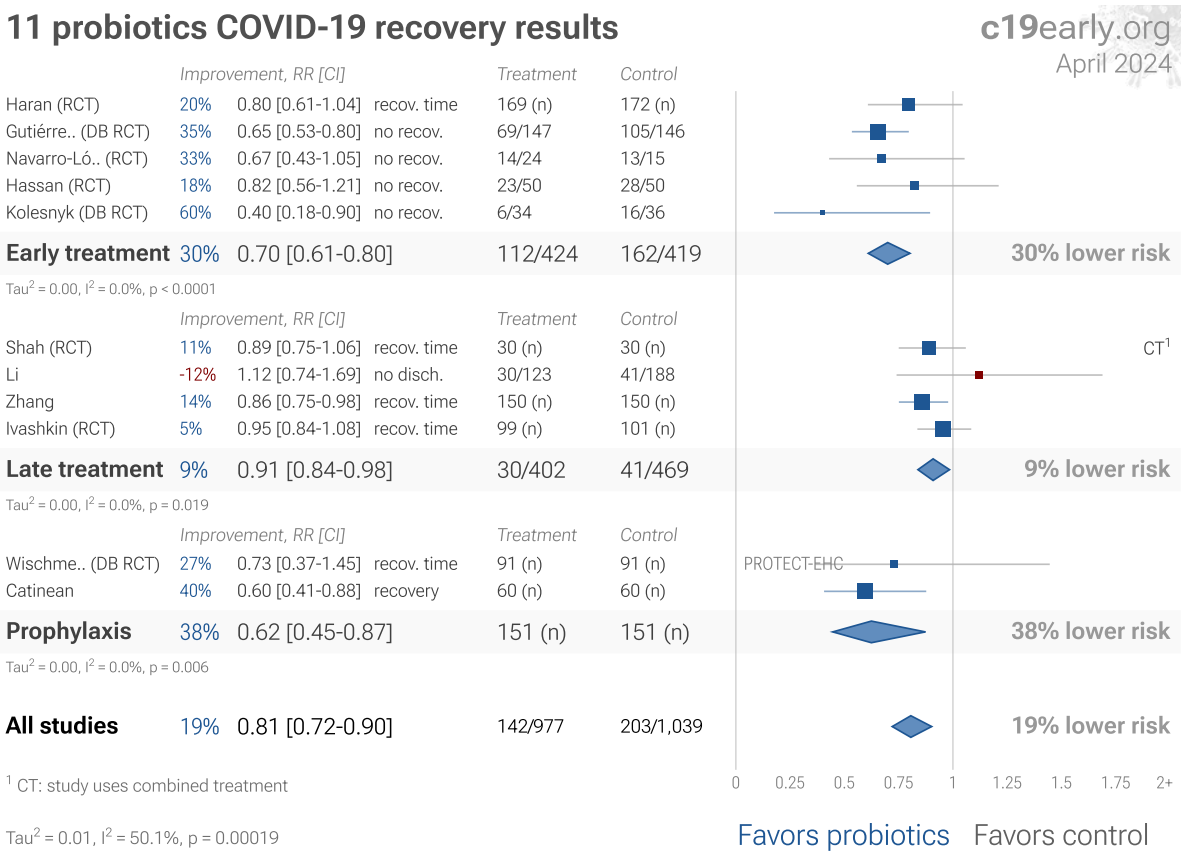



***Figure 10.*** Random effects meta-analysis for recovery.

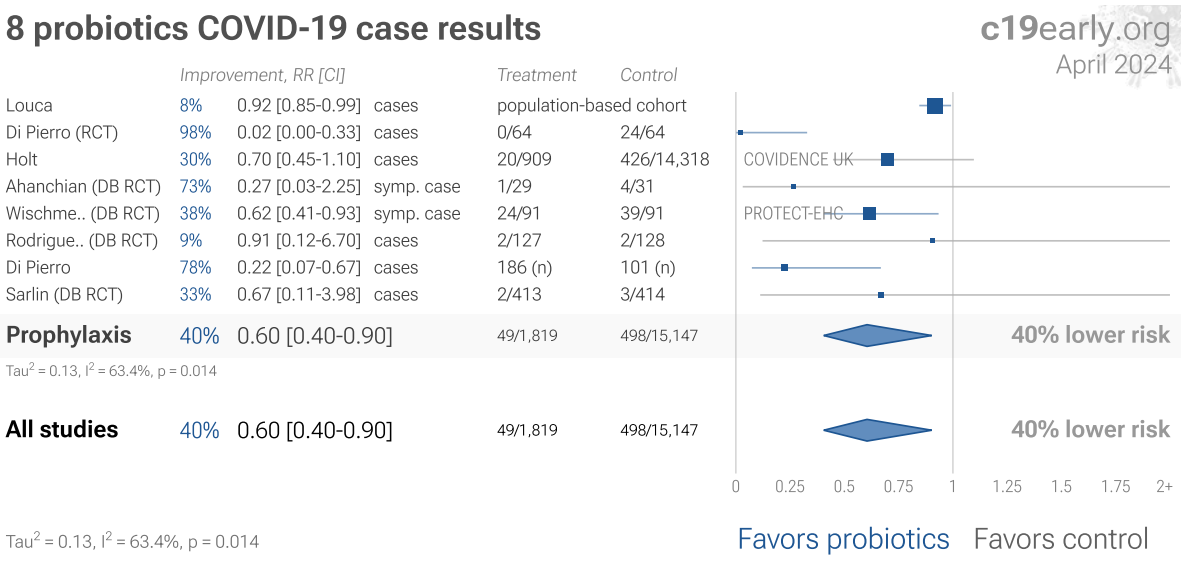



***Figure 11.*** Random effects meta-analysis for cases.

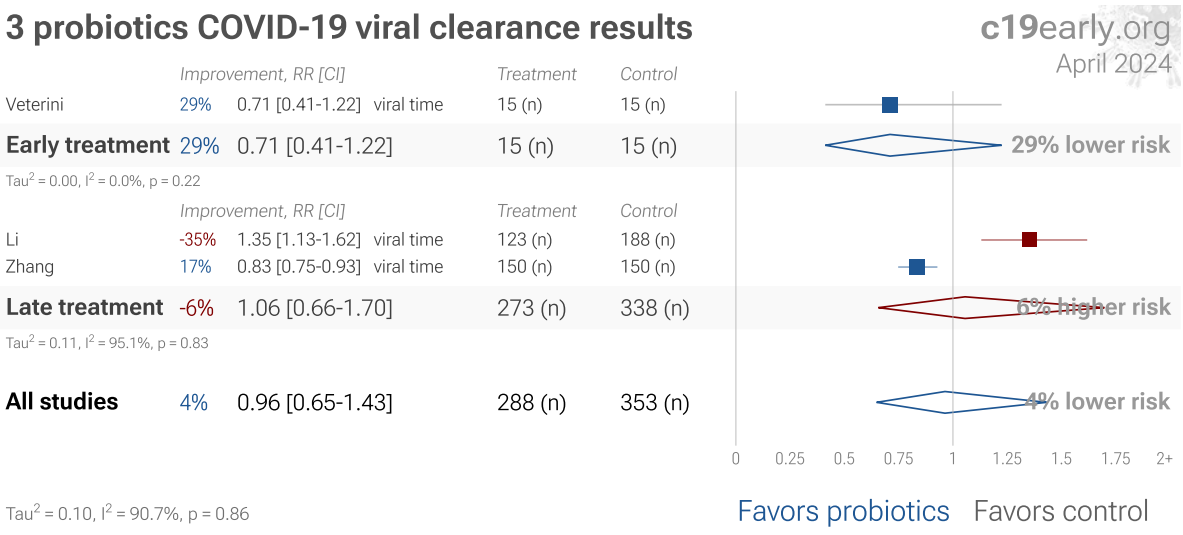



***Figure 12.*** Random effects meta-analysis for viral clearance.

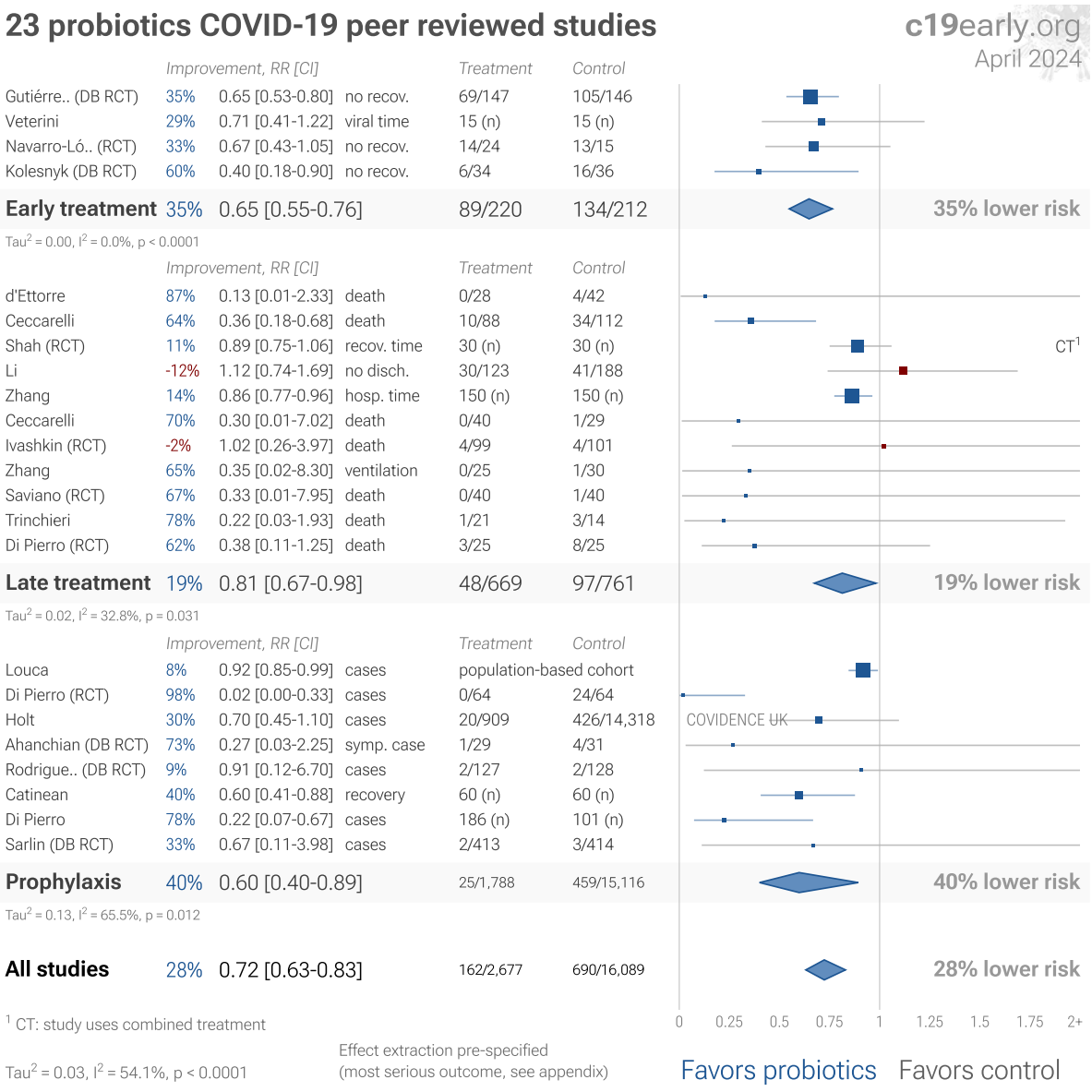



***Figure 13.*** **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. *Davidson et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

## Randomized Controlled Trials (RCTs)

Figure 14 shows a comparison of results for RCTs and non-RCT studies. Random effects meta analysis of RCTs shows 34% improvement, compared to 24% for other studies. Figure 15, 16, and 17 show forest plots for random effects meta-analysis of all Randomized Controlled Trials, RCT mortality results, and RCT hospitalization results. RCT results are included in Table 1 and Table 2.

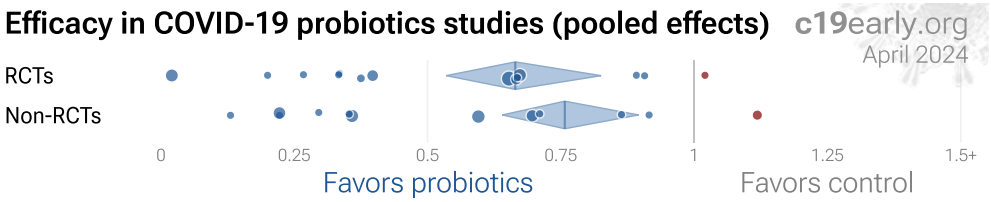



***Figure 14.*** Results for RCTs and non-RCT studies.

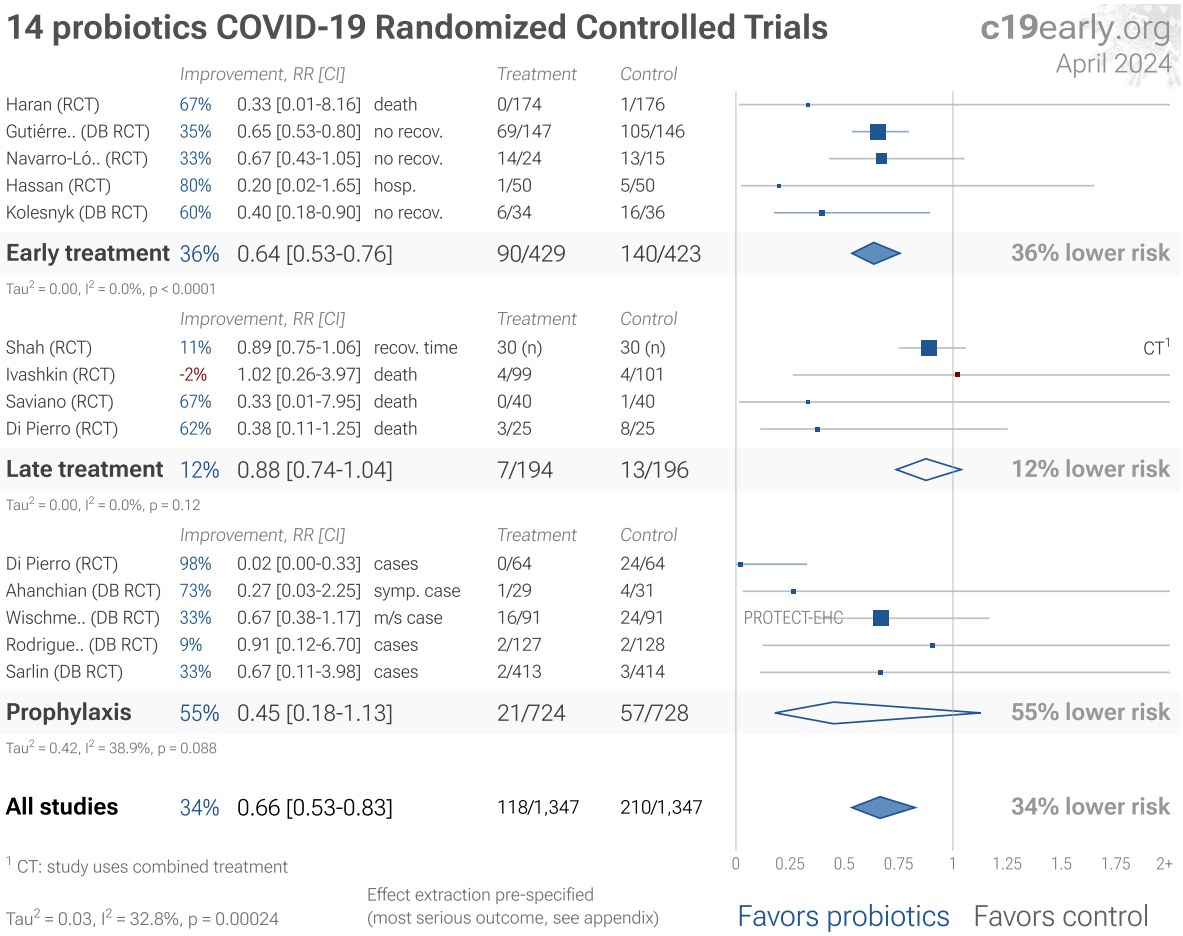



***Figure 15.*** **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious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

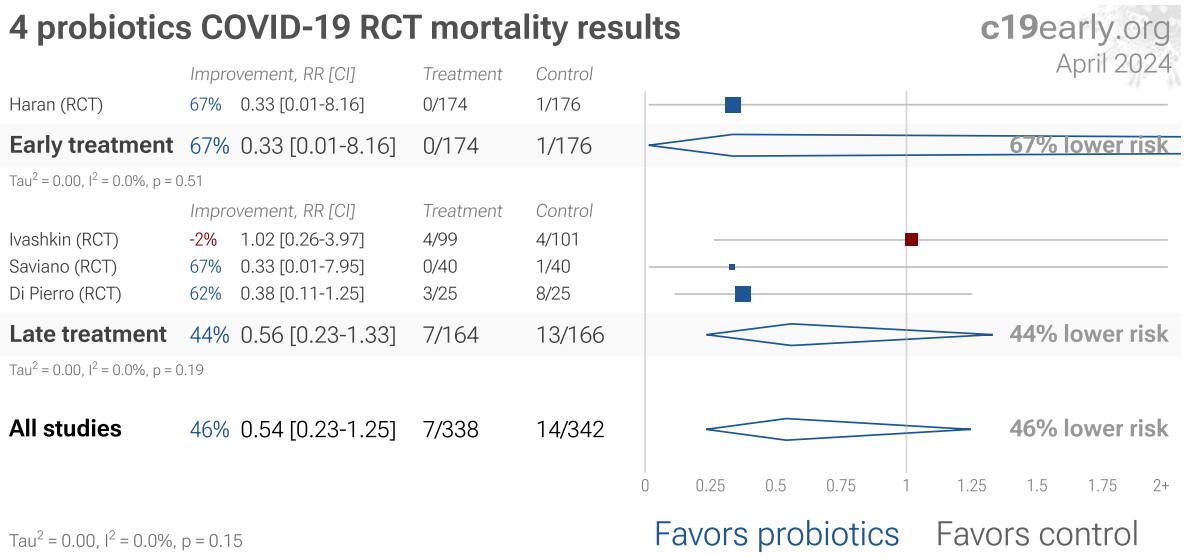



***Figure 16.*** Random effects meta-analysis for RCT mortality results.

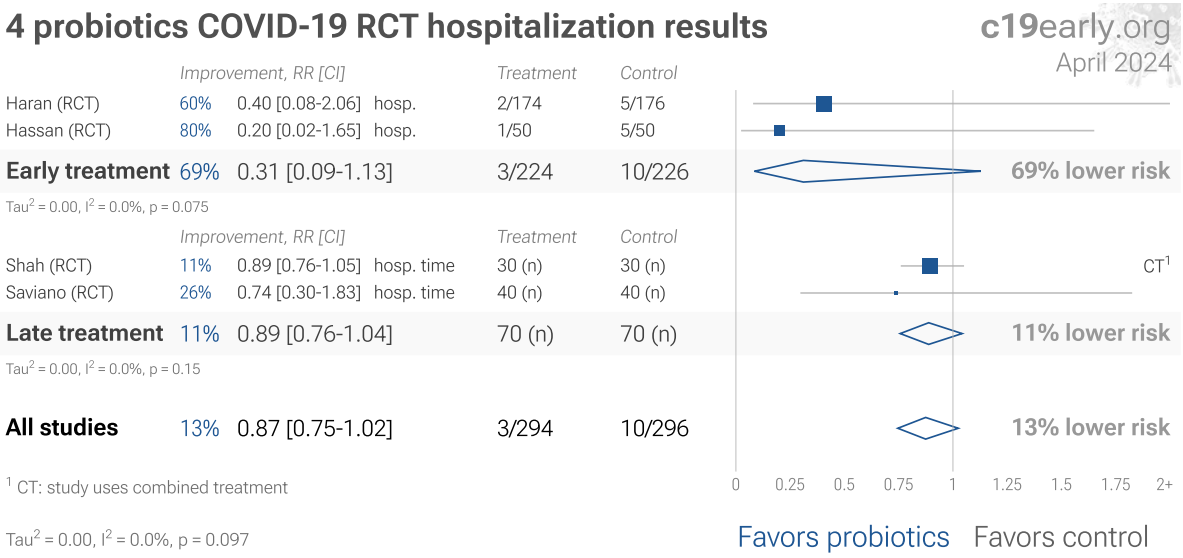



***Figure 17.*** Random effects meta-analysis for RCT hospitalization results.

**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 [Jadad], and analysis of double-blind RCTs has identified extreme levels of bias [Gøtzsche]. For COVID-19, the overhead may delay treatment, dramatically compromising efficacy; they may encourage monotherapy for simplicity at the cost of efficacy which may rely on combined or synergistic effects; the participants that sign up may not reflect real world usage or the population that benefits most in terms of age, comorbidities, severity of illness, or other factors; standard of care may be compromised and unable to evolve quickly based on emerging research for new diseases; errors may be made in randomization and medication delivery; and investigators may have hidden agendas or vested interests influencing design, operation, analysis, 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 69 treatments we have analyzed, 63% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments. They may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration.

**Non-RCT studies have been shown to be reliable.** Evidence shows that non-RCT 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.* 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 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 *Deaton, Nichol*.

**Using all studies identifies efficacy 6+ months faster (7+ months for low-cost treatments).** Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. Of these, 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.

## Exclusions

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

The studies excluded are as below. Figure 18 shows a forest plot for random effects meta-analysis of all studies after exclusions.

*Di Pierro*, unadjusted differences between groups.

*Holt*, significant unadjusted confounding possible.

*Veterini*, the observered difference in duration could be caused by the baseline difference in Ct values.

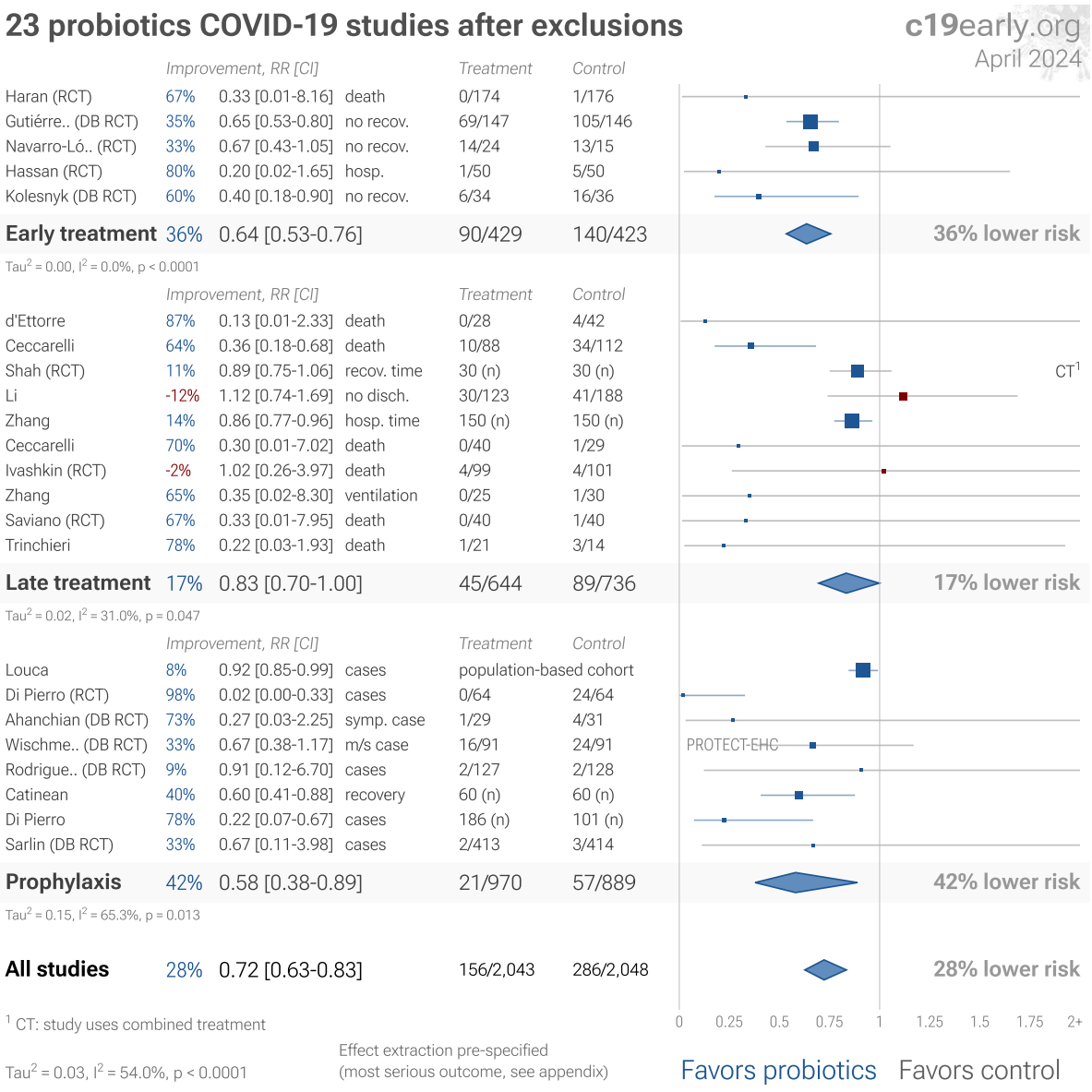



***Figure 18.*** **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

## Heterogeneity

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

**Treatment delay.** The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours *McLean, Treanor*. Baloxavir 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 *Ikematsu* |
| <24 hours | -33 hours symptoms *Hayden* |
| 24-48 hours | -13 hours symptoms *Hayden* |
| Inpatients | -2.5 hours to improvement *Kumar* |

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

Figure 19 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 69 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

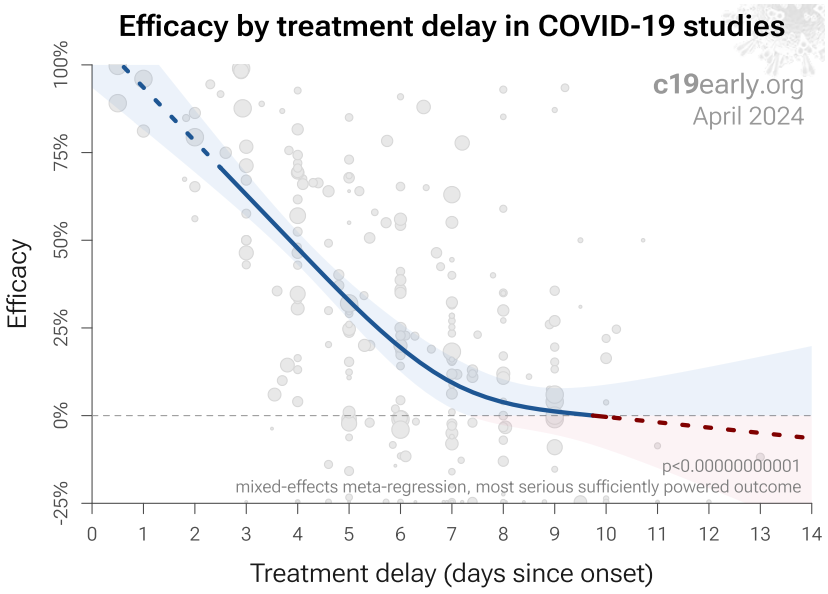



***Figure 19.*** **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 69 treatments.

**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.*

**Variants.** Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants *Korves*, 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 degree to which TMPRSS2 contributes to viral entry can differ across variants *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 supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic *Alsaidi, Andreani, De Forni, Fiaschi, Jeffreys, Jitobaom, Jitobaom (B), Ostrov, Said, Thairu, Wan*, therefore efficacy may depend strongly on combined

treatments.

**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 [Crawford, Crighton].

**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.

**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.

**Using more information.** Another way to view pooled analysis is that we are using more of the available information. Logically we should, and do, use additional information. For example dose-response and treatment delay-response relationships provide significant additional evidence of efficacy that is considered when reviewing the evidence for a treatment.

**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 collection of evidence.

**Improvement across outcomes.** 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.

**Validating pooled outcome analysis for COVID-19.** Analysis of the the association between different outcomes across studies from all 69 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 20 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 21 shows that improved recovery is very strongly associated with lower mortality ($p < 0.000000000001$). Considering the extremes, *Singh et al.* show an association between viral clearance and hospitalization or death, with $p = 0.003$ after excluding one large outlier from a mutagenic treatment, and based on 44 RCTs including 52,384 patients. Figure 22 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to *Singh et al.*, with higher confidence due to the larger number of studies. As with *Singh et al.*, the confidence increases when excluding the outlier treatment, from $p = 0.0000045$ to $p = 0.0000000067$.

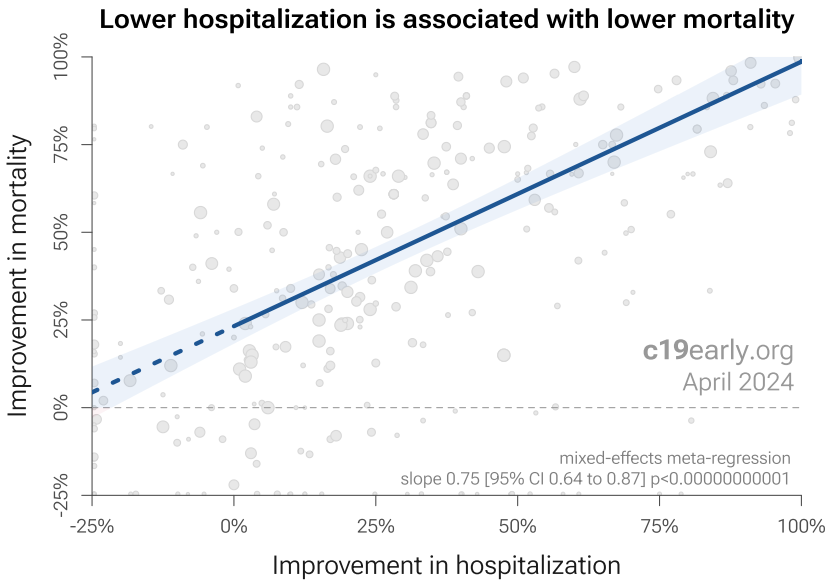



***Figure 20.*** Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

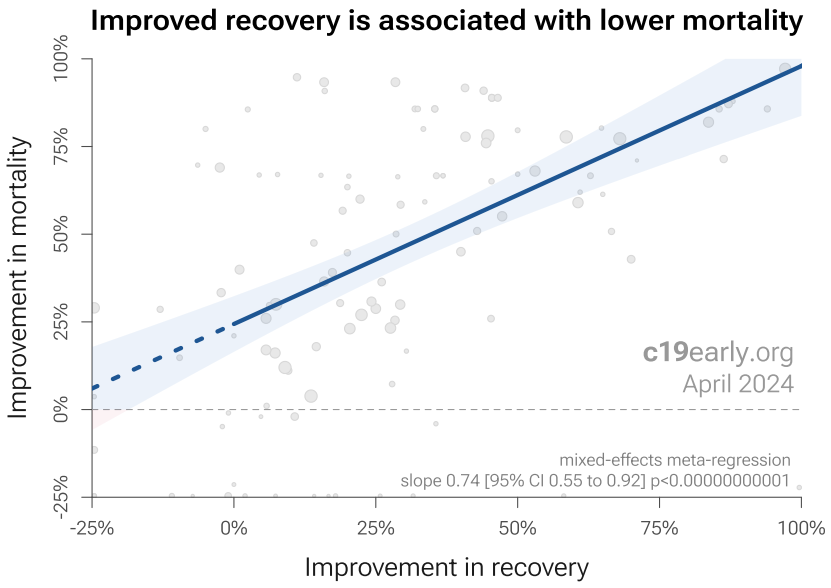



***Figure 21.*** Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

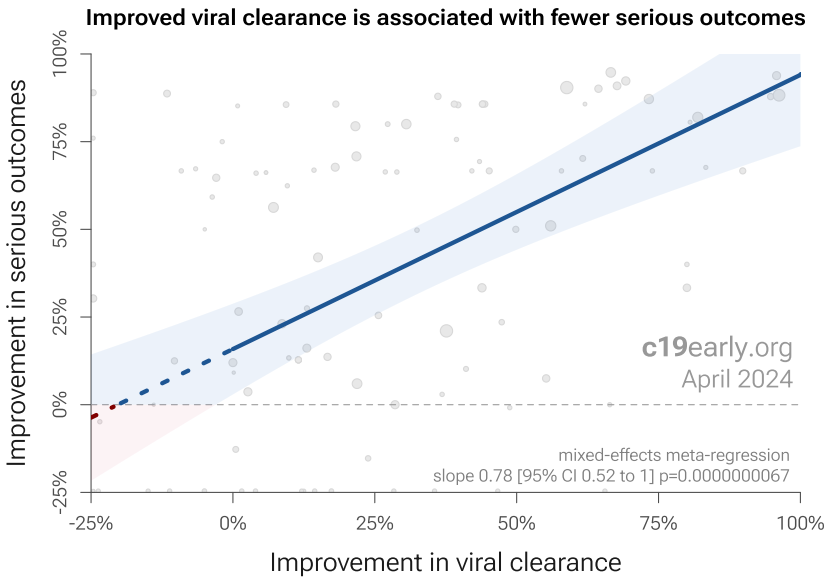



***Figure 20.*** **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

**Pooled outcomes identify efficacy 4 months faster (6 months for RCTs).** Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 85% of these have been confirmed with one or more specific outcomes, with a mean delay of 3.7 months. When restricting to RCTs only, 54% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 5.8 months. Figure 23 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

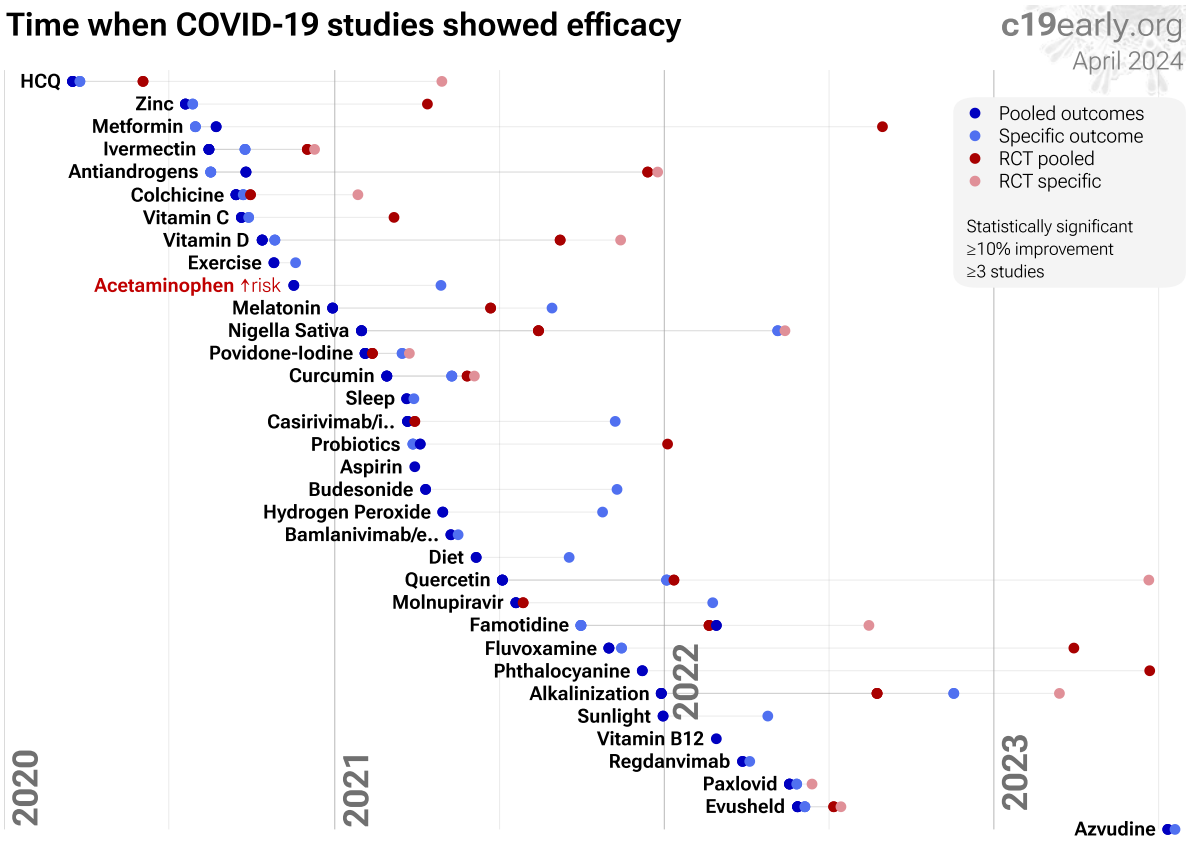



***Figure 23.*** **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

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

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

## Discussion

**Results for other viruses.** Efficacy with probiotics has also been shown for the common cold *Kobatake*.

**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, Meneguesso, twitter.com*.

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

continue. Retrospective studies also provide more opportunities for the specifics of data extraction and adjustments to influence results.

Figure 24 shows a scatter plot of results for prospective and retrospective studies. 70% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 38% of prospective studies, consistent with a bias toward publishing positive results. The median effect size for retrospective studies is 52% improvement, compared to 48% for prospective studies, showing similar results.

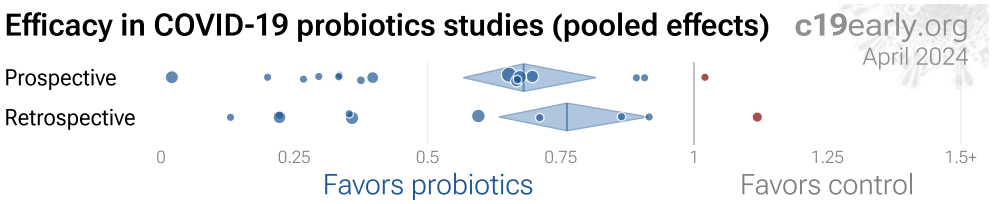



***Figure 24.*** **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

**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 25 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.

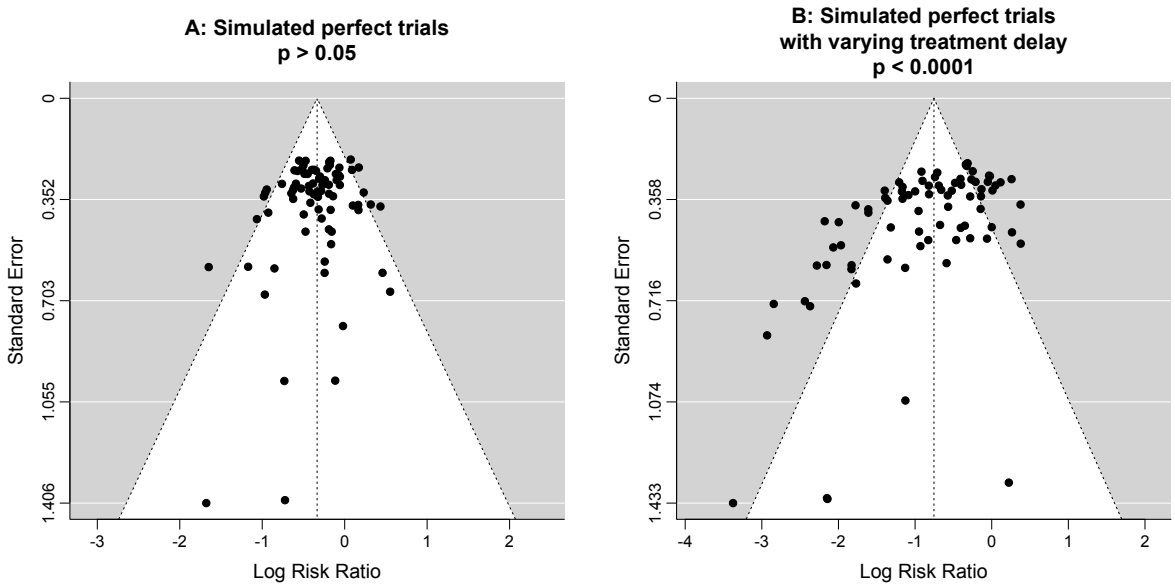



***Figure 25.*** **Example funnel plot analysis for simulated perfect trials.**

**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. Probiotics for COVID-19 lack this because they are generally inexpensive and widely available. In contrast, most COVID-19 probiotics 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 probiotics 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 *Alsaidi, Andreani, De Forni, Fiaschi, Jeffreys, Jitobaom, Jitobaom (B), Ostrov, Said, Thairu, Wan*. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

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

No treatment 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 26 studies combine treatments. The results of probiotics alone may differ. 1 of 14 RCTs use combined treatment. Other meta analyses show significant improvements with probiotics for hospitalization *Tian* and recovery *Neris Almeida Viana, Tian*.

**Reviews.** Many reviews cover probiotics for COVID-19, presenting additional background on mechanisms and related results, including *Baud, Di Pierro (B), Kurian, Olaimat, Petrariu, Righi, Singh (B), Stavropoulou, Taufer, Taufer (B)*.

## Perspective

**Results compared with other treatments.** SARS-CoV-2 infection and replication involves a complex interplay of 50+ host and viral proteins and other factors *Lui, Lv, Malone, Murigneux, Niarakis*, providing many therapeutic targets. Over 7,000 compounds have been predicted to reduce COVID-19 risk *c19early.org*, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 26 shows an overview of the results for probiotics in the context of multiple COVID-19 treatments, and Figure 27 shows a plot of efficacy vs. cost for COVID-19 treatments.

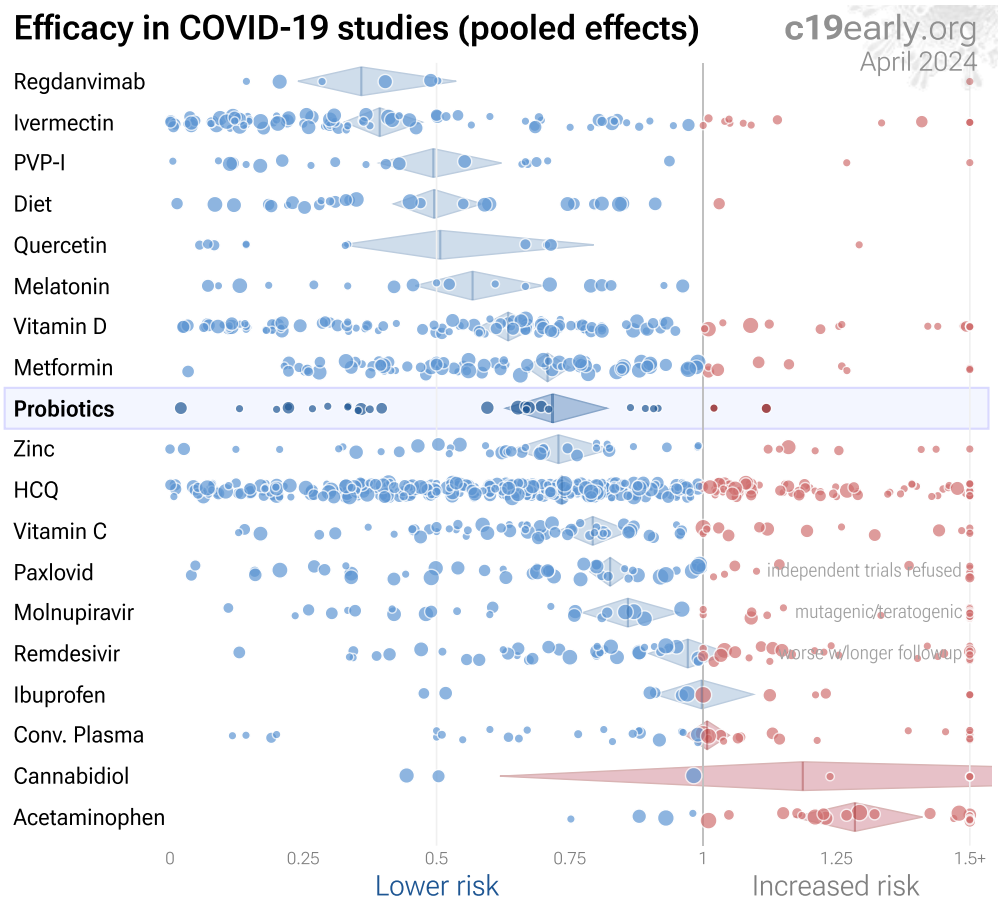



***Figure 26.*** **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 7,400 proposed treatments show efficacy *c19early.org (B)*.

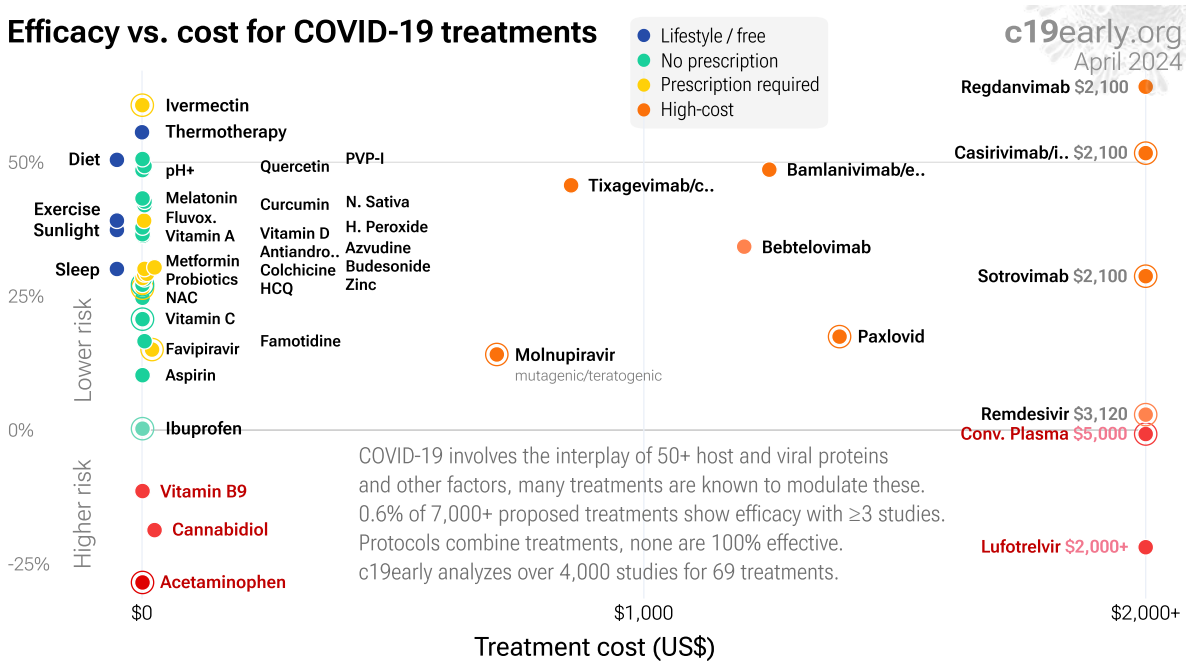



***Figure 27.*** Efficacy vs. cost for COVID-19 treatments.

## Conclusion

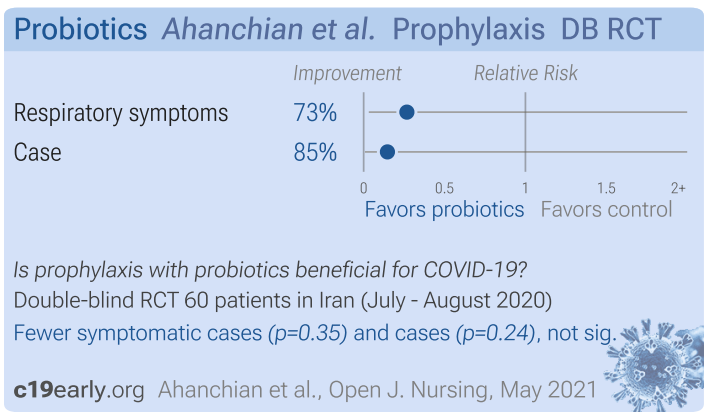
Statistically significant lower risk is seen for mortality, hospitalization, progression, recovery, and cases. 13 studies from 12 independent teams in 9 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 28% [18-37%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies. Better results are seen with early treatment. Results are robust — in exclusion sensitivity analysis 24 of 26 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

The immune effects of probiotics are strain-specific and studies use different strains.

Other meta analyses show significant improvements with probiotics for hospitalization *Tian* and recovery *Neris Almeida Viana, Tian*.

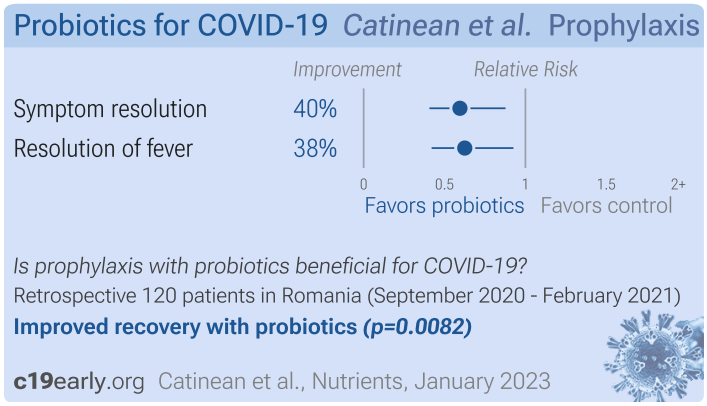
## Study Notes

### Ahanchian



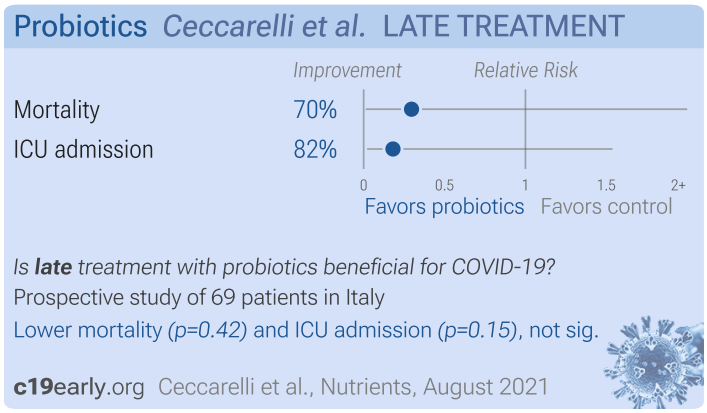
*Ahanchian*: Small RCT 60 healthcare workers in Iran, showing lower cases with treatment but without statistical significance. Once daily oral synbiotic capsule (Lactocare®) containing 1 billion CFU L. (Lactobacillus) casei, L. rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, L. acidophilus, Bifidobacterium infantis, L. bulgaricus, and Fructooligosaccharide.

### Catinean



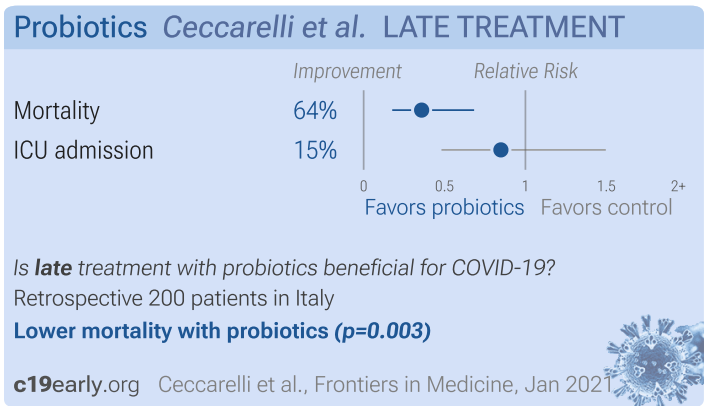

*Catinean*: Retrospective 60 patients in Romania taking probiotics and 60 matched controls, showing faster symptom resolution with the use of probiotics. Spore-based probiotic containing five strains of *Bacillus*.

### Ceccarelli



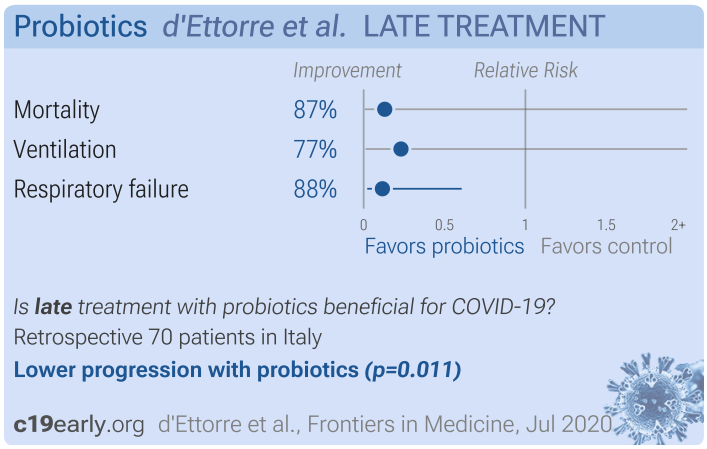

*Ceccarelli*: Prospective analysis of 69 severe COVID-19 patients requiring non-invasive oxygen therapy, 40 treated with probiotic formulation SLAB51, showing lower oxygen requirements and higher blood levels of pO2, O2Hb and SaO2 with treatment. Authors suggest that enzymes in SLAB51 could reduce oxygen requirements in intestinal cells, resulting in more oxygen available for other organs.

### Ceccarelli



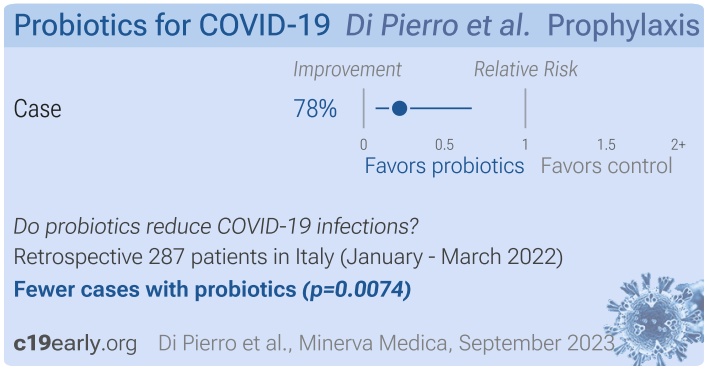
*Ceccarelli (B)*: Retrospective 200 severe condition hospitalized patients in Italy, 88 treated with probiotic Sivomixx, showing lower mortality with treatment.

### d'Ettorre



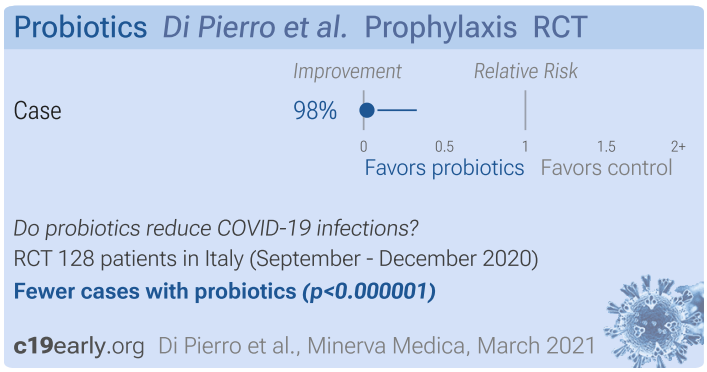

*d'Ettorre*: Retrospective 70 hospitalized patients in Italy, 28 treated with probiotic Sivomixx, showing lower risk of respiratory failure and faster recovery with treatment.

### Di Pierro



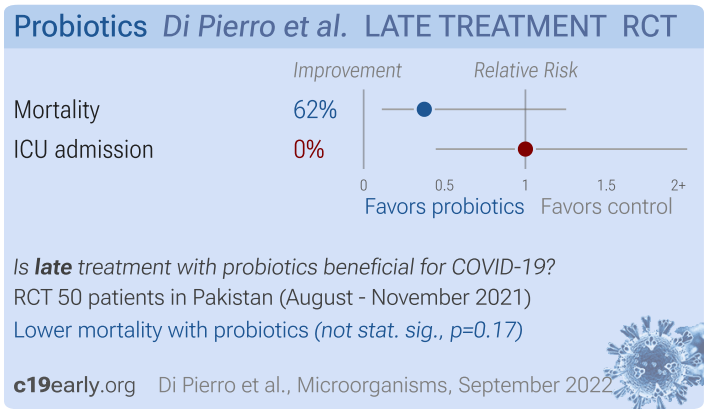

*Di Pierro (C)*: Retrospective study of 287 nursery school children in Italy, 186 treated with S. salivarius K12 probiotic. The probiotic group had significantly lower rates of COVID-19, bronchitis, sinusitis, and laryngitis as well as lower antibiotic use. The study was registered retrospectively and details of COVID-19 diagnosis are not provided. Parents that administer the treatment may also use other treatments or take other actions that reduce risk for their children.

### Di Pierro



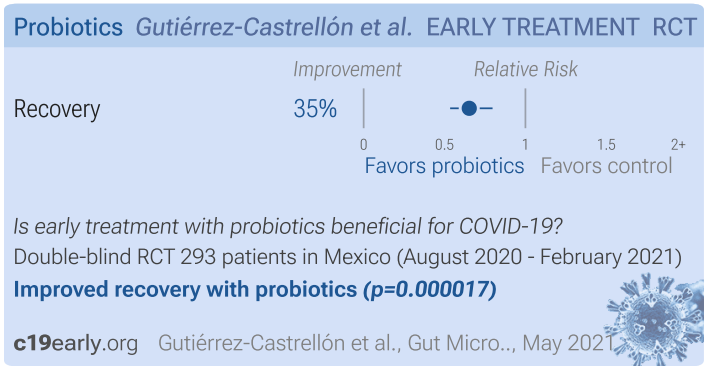
*Di Pierro (D)*: Interim report on an RCT for prophylactic treatment with S. salivarius K12, showing significantly lower cases with treatment. Only patients with symptoms or known positive contacts were tested. Trial identification/registration details are not provided.

### Di Pierro



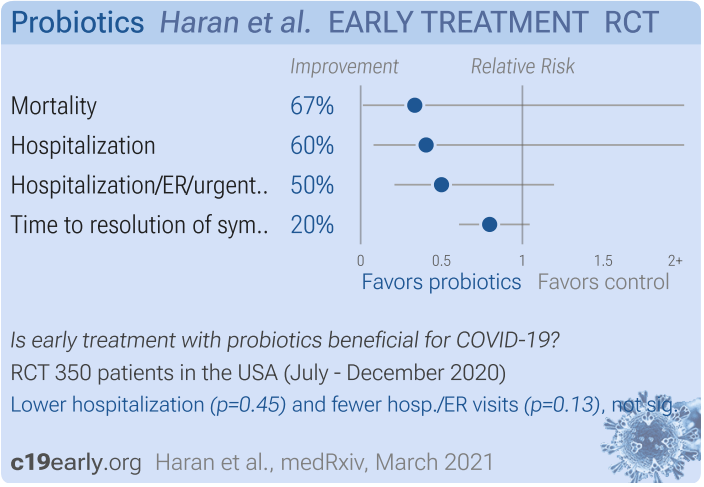

*Di Pierro*: RCT 50 hospitalized patients in Pakistan, 25 treated with S. salivarius K12, showing lower mortality with treatment, without statistical significance. There were more patients with higher oxygen requirements at baseline in the control group - 18 vs. 6 with O2 ≥ 8 L/min.

### Gutiérrez-Castrellón



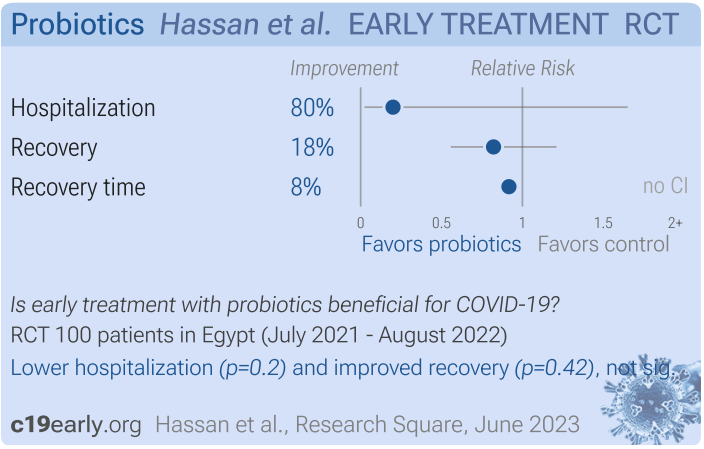

*Gutiérrez-Castrellón*: RCT 293 outpatients in Mexico, 147 treated with a probiotic composed of three L. plantarum strains (KABP022, KABP023 and KABP033) and one P. acidilacti strain (KABP021), showing improved recovery with treatment. There were no hospitalizations or deaths.

### Haran



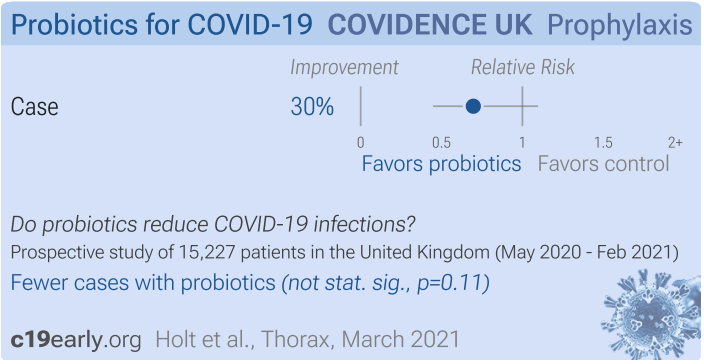

*Haran*: RCT 350 COVID+ outpatients in the USA, 174 treated with prebiotic KB109 (a microbiome metabolic therapy candidate), showing lower combined hospitalization, ER, and urgent care visits with treatment. NCT04414124.

### Hassan




*Hassan*: RCT 150 patients in Egypt showing no significant difference in outcomes with probiotic lactobacillus acidophilus, although hospitalization was 2% versus 10% for control. SOC included vitamin C, D, and zinc.

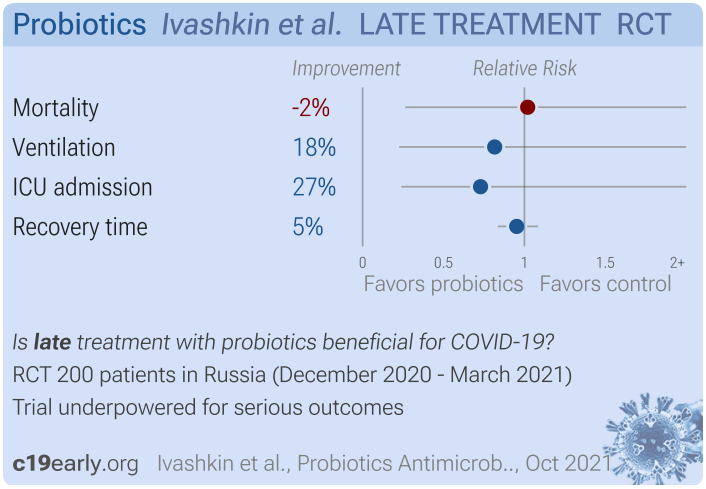
### Holt




*Holt*: Prospective survey-based study with 15,227 people in the UK, showing lower risk of COVID-19 cases with vitamin A, vitamin D, zinc, selenium, probiotics, and inhaled corticosteroids; and higher risk with metformin and vitamin C. Statistical significance was not reached for any of these. Except for vitamin D, the results for treatments we

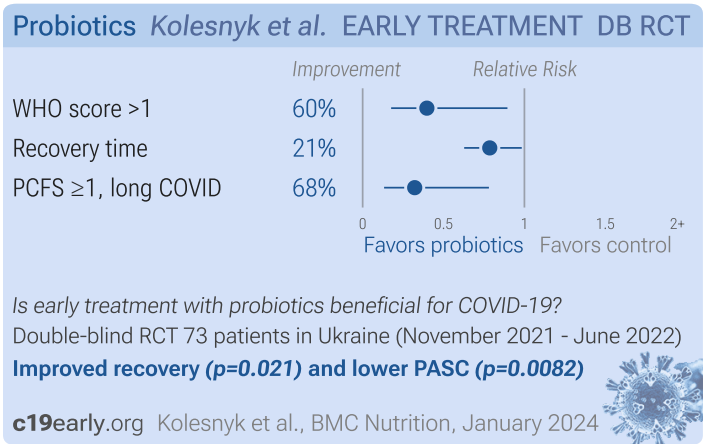
follow were only adjusted for age, sex, duration of participation, and test frequency. NCT04330599. COVIDENCE UK.

### Ivashkin



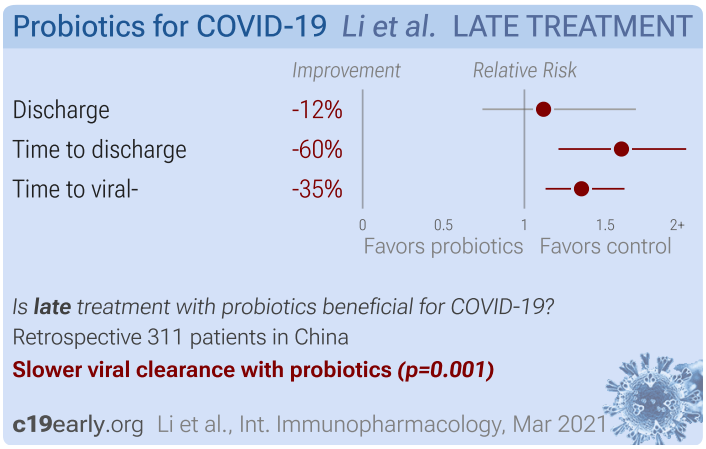

*Ivashkin*: RCT 200 patients, 99 treated with a probiotic (Lacticaseibacillus rhamnosus PDV 1705, Bifidobacterium bifidum PDV 0903, Bifidobacterium longum subsp. infantis PDV 1911, and Bifidobacterium longum subsp. longum PDV 2301). There was no significant difference in mortality or recovery time, however benefits were seen for diarrhea. NCT04854941.

### Kolesnyk



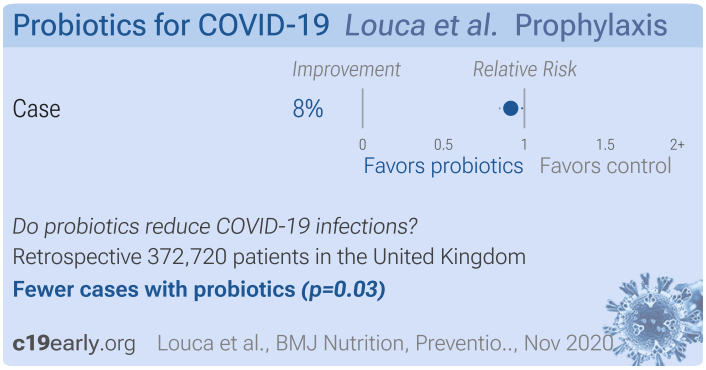

*Kolesnyk*: RCT 73 outpatients with mild COVID-19 showing improved recovery and increased RBD/spike antibody response with 28 days of a multi-strain probiotic (Bifidobacterium (B.) lactis BI040, B. longum BL020, Lactobacillus (L) rhamnosus LR110, L. casei LC130, L. acidophilus LA120, 5 billion CFU total).

### Li



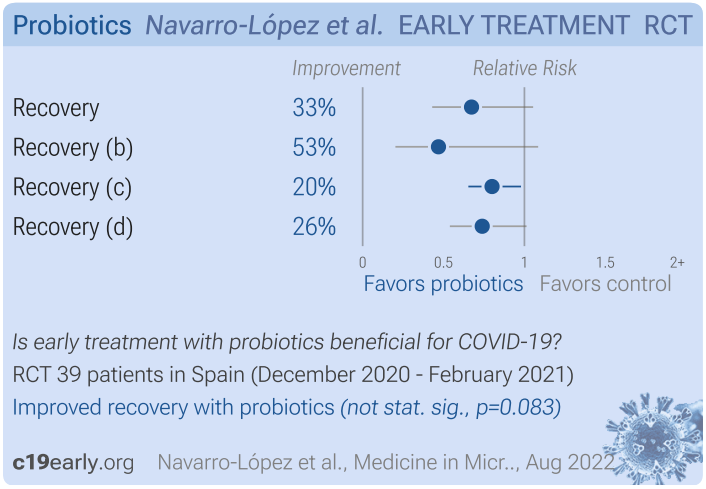

*Li*: Retrospective 311 severe condition hospitalized patients in China, 123 treated with probiotics, showing slower viral clearance and recovery with treatment. Authors note that probiotics were able to moderate immunity and decrease the incidence of secondary infections.

### Louca



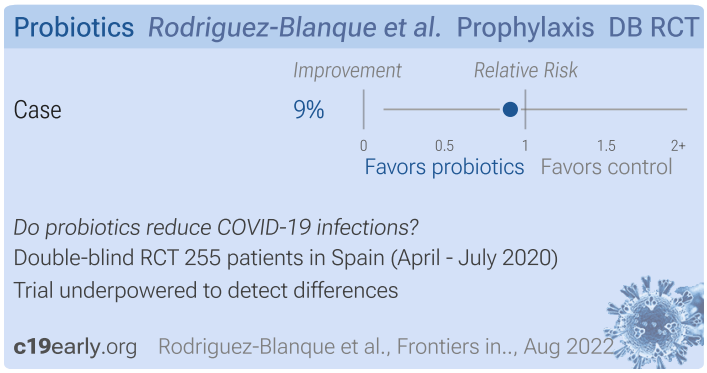

*Louca*: Survey analysis of dietary supplements showing probiotic usage associated with lower incidence of COVID-19. These results are for PCR+ cases only, they do not reflect potential benefits for reducing the severity of cases. A number of biases could affect the results, for example users of the app may not be representative of the general population, and people experiencing symptoms may be more likely to install and use the app.

### Navarro-López



*Navarro-López*: RCT with 24 probiotics and 15 control patients in Spain, showing lower overall symptoms and lower digestive symptoms with treatment. Kluyveromyces marxianus B0399 plus lactobacillus rhamnosus CECT 30579.

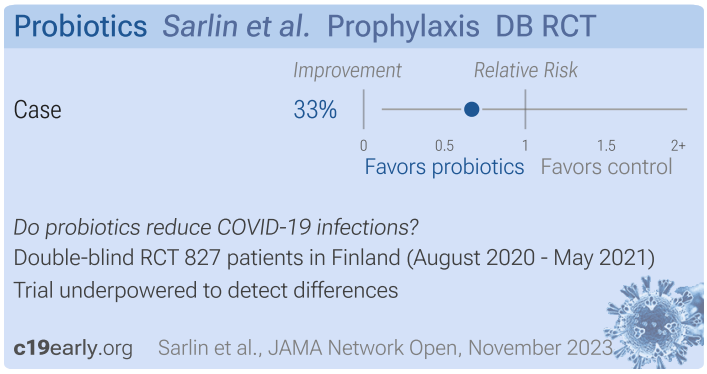
### Rodriguez-Blanque




*Rodriguez-Blanque*: Prophylaxis RCT with 127 probiotics and 128 control healthcare workers in Spain, showing no significant difference in cases. There were only 4 cases. Severity information by arm is not provided. L. coryniformis K8 CECT 5711.

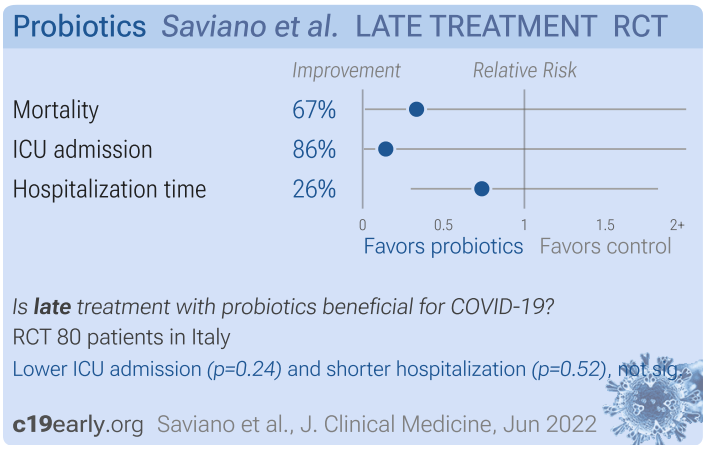
Treatment may help sustain the immune response to vaccination - in the subgroup of subjects for whom more than 81 days had passed since they received the first dose, IgG levels were significantly higher in the treatment group. Patients that started probiotic consumption before the first vaccine dose also reported significantly fewer side effects.

### Sarlin



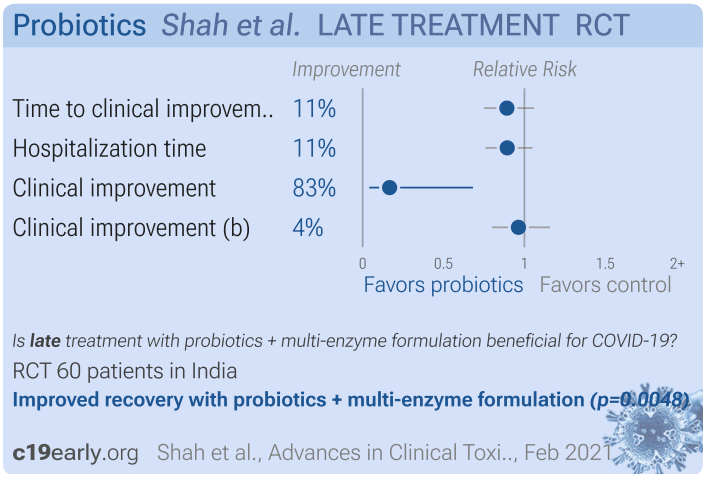

*Sarlin*: RCT 827 children aged 1-6 years in daycare in Finland analyzing the effectiveness of daily Streptococcus salivarius K12 oral probiotic use for 6 months in preventing acute otitis media (AOM). The probiotic group did not have a significantly lower rate of AOM requiring antibiotics compared to placebo. A secondary outcome shows no significant difference in COVID-19, with only 2 and 3 cases in the treatment and placebo groups.

### Saviano



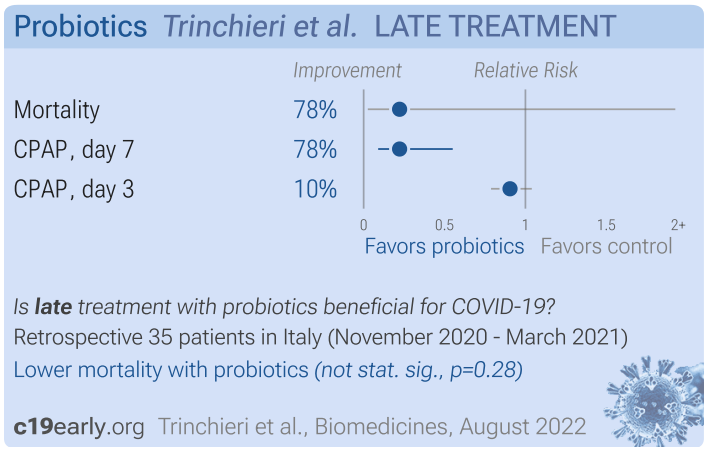

*Saviano*: RCT 80 COVID-19 interstitial pneumonia patients in Italy, 40 treated with probiotics, showing significantly reduced gut inflammatory markers with treatment, and lower ICU admission and mortality, without statistical significance. Bifidobacterium lactis LA 304, lactobacillus salivarius LA 302, and lactobacillus acidophilus LA 201 bid for 10 days.

### Shah



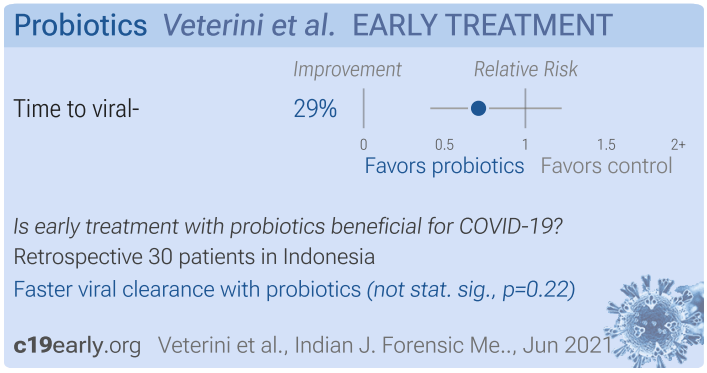

*Shah*: Small RCT 60 patients in India, 30 treated with ImmunoSEB and ProbioSEB CSC3, showing faster recovery with treatment. CTRI/2020/09/027685, CTRI/2020/08/027168.

### Trinchieri



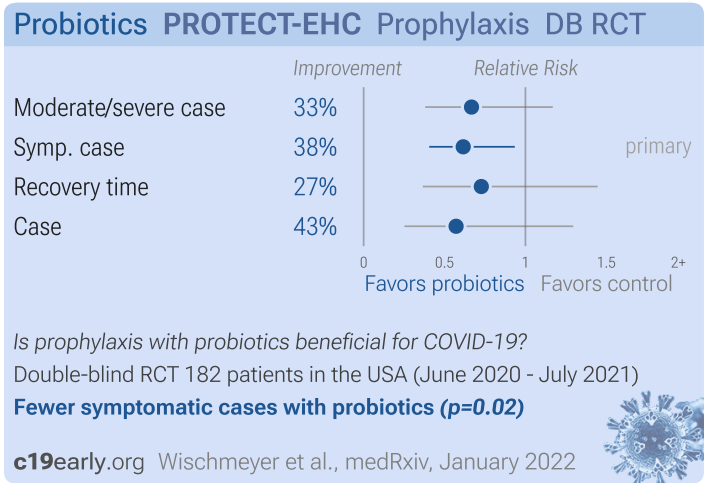

*Trinchieri*: Retrospective COVID-19 patients requiring CPAP, 21 treated with SLAB51 probiotics and 15 control patients, showing improved outcomes with treatment, despite significantly lower blood oxygenation at baseline in the treatment group.

### Veterini



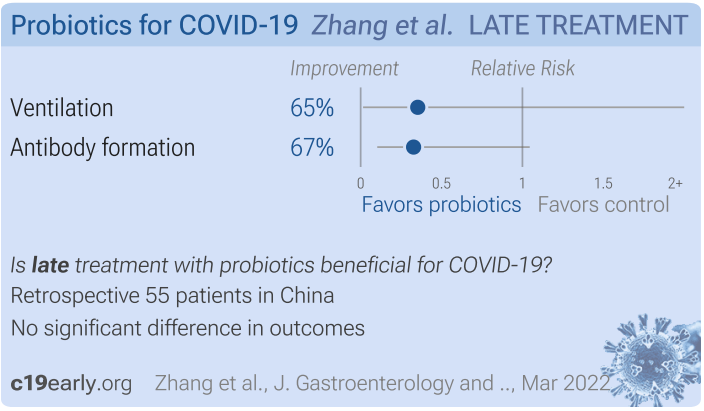

*Veterini*: Small case control analysis with 15 probiotics patients and 15 contol patients, showing no significant differences. PCR tests were only done weekly. Dosage is unknown. 115/LOE/301.4.2/IX/2020.

### Wischmeyer



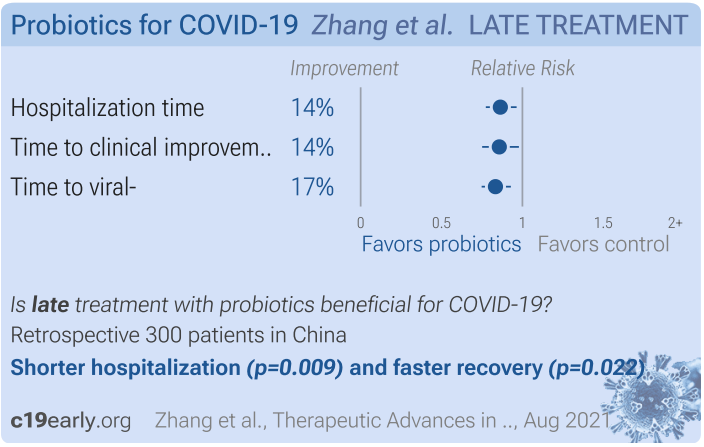
*Wischmeyer*: RCT 182 COVID-19 exposed patients, 91 treated with daily probiotic Lactobacillus rhamnosus GG starting a median of 3 days from exposure, showing lower symptomatic COVID-19 with treatment. There were no hospitalizations or deaths.

### Zhang




*Zhang (B)*: Pilot study of probiotic SIM01 with 25 consecutive COVID-19 patients in Hong Kong and 30 control patients treated by a different team during the same time period, showing improved antibody formation, reduced viral load and pro-inflammatory responses, and improvements for gut dysbiosis. SIM01 contains bifidobacteria strains, galactooligosaccharides, xylooligosaccharide, and resistant dextrin (derived from metagenomic databases of COVID-19 patients and healthy patients).

### Zhang




*Zhang (C)*: Retrospective 375 patients in China, 179 treated with probiotics (Bifidobacterium, Lactobacillus, and Enterococcus), showing improved clinical outcomes 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 probiotics 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 probiotics for COVID-19 that report a comparison with a control group are included in the main analysis. Sensitivity analysis is performed, excluding studies with major issues, epidemiological studies, and studies with minimal available information. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral test status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low $SpO_2$ is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to *Zhang*. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 *Sweeting*. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.12.2) with scipy (1.12.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.1), and plotly (5.20.0).

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

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

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

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

| | |
|---|---|
| *Gutiérrez-Castrellón*, 5/24/2021, Double Blind Randomized Controlled Trial, placebo-controlled, Mexico, peer-reviewed, 9 authors, study period 19 | risk of no recovery, 34.7% lower, RR 0.65, $p < 0.001$, treatment 69 of 147 (46.9%), control 105 of 146 (71.9%), NNT 4.0. |

| | |
|---|---|
| August, 2020 - 2 February, 2021, average treatment delay 4.0 days, trial NCT04517422 (history). | |
| *Haran*, 3/29/2021, Randomized Controlled Trial, USA, preprint, 6 authors, study period 2 July, 2020 - 23 December, 2020, trial NCT04414124 (history). | risk of death, 66.5% lower, RR 0.33, $p = 1.00$, treatment 0 of 174 (0.0%), control 1 of 176 (0.6%), NNT 176, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), death two weeks after study withdrawal. |
| | risk of hospitalization, 59.5% lower, RR 0.40, $p = 0.45$, treatment 2 of 174 (1.1%), control 5 of 176 (2.8%), NNT 59, including treatment period. |
| | risk of hospitalization/ER/urgent care, 50.0% lower, RR 0.50, $p = 0.13$, treatment 7 of 169 (4.1%), control 15 of 181 (8.3%), NNT 24. |
| | time to resolution of symptoms, 20.3% lower, relative time 0.80, $p = 0.10$, treatment 169, control 172, inverted to make RR<1 favor treatment. |
| *Hassan*, 6/13/2023, Randomized Controlled Trial, Egypt, preprint, 6 authors, study period July 2021 - August 2022. | risk of hospitalization, 80.0% lower, RR 0.20, $p = 0.20$, treatment 1 of 50 (2.0%), control 5 of 50 (10.0%), NNT 12. |
| | risk of no recovery, 17.9% lower, RR 0.82, $p = 0.42$, treatment 23 of 50 (46.0%), control 28 of 50 (56.0%), NNT 10.0. |
| *Kolesnyk*, 1/4/2024, Double Blind Randomized Controlled Trial, placebo-controlled, Ukraine, peer-reviewed, 10 authors, study period November 2021 - June 2022, trial NCT04907877 (history). | WHO score >1, 60.3% lower, RR 0.40, $p = 0.02$, treatment 6 of 34 (17.6%), control 16 of 36 (44.4%), NNT 3.7. |
| | recovery time, 21.4% lower, relative time 0.79, $p = 0.04$, treatment 34, control 36. |
| | PCFS ≥1, 67.8% lower, RR 0.32, $p = 0.008$, treatment 5 of 34 (14.7%), control 16 of 35 (45.7%), NNT 3.2, long COVID, Supplementary Table 1. |
| *Navarro-López*, 8/24/2022, Randomized Controlled Trial, Spain, peer-reviewed, 13 authors, study period December 2020 - February 2021, trial NCT04390477 (history). | risk of no recovery, 32.7% lower, RR 0.67, $p = 0.08$, treatment 14 of 24 (58.3%), control 13 of 15 (86.7%), NNT 3.5, day 30. |
| | risk of no recovery, 53.1% lower, RR 0.47, $p = 0.10$, treatment 6 of 24 (25.0%), control 8 of 15 (53.3%), NNT 3.5, digestive symptoms, day 30. |
| | relative recovery, 20.0% better, RR 0.80, $p = 0.03$, treatment 24, control 15, relative symptom improvement, day 30. |
| | relative recovery, 26.1% better, RR 0.74, $p = 0.06$, treatment 24, control 15, relative improvement for digestive symptoms, day 30. |
| *Veterini*, 6/30/2021, retrospective, Indonesia, peer-reviewed, 6 authors, excluded in exclusion analyses: the observered difference in duration could be caused by the baseline difference in Ct values. | time to viral-, 29.0% lower, relative time 0.71, $p = 0.22$, treatment 15, control 15. |

### 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.

| | |
|---|---|
| *Ceccarelli*, 8/23/2021, prospective, Italy, peer-reviewed, 10 authors. | risk of death, 70.4% lower, RR 0.30, $p = 0.42$, treatment 0 of 40 (0.0%), control 1 of 29 (3.4%), NNT 29, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm). |
| | risk of ICU admission, 81.9% lower, RR 0.18, $p = 0.15$, treatment 1 of 40 (2.5%), control 4 of 29 (13.8%), NNT 8.9. |
| *Ceccarelli (B)*, 1/11/2021, retrospective, Italy, peer-reviewed, 14 authors. | risk of death, 64.2% lower, RR 0.36, $p = 0.003$, treatment 10 of 88 (11.4%), control 34 of 112 (30.4%), NNT 5.3, adjusted per study, odds ratio converted to relative risk. |
| | risk of ICU admission, 15.2% lower, RR 0.85, $p = 0.60$, treatment 16 of 88 (18.2%), control 24 of 112 (21.4%), NNT 31. |
| *d'Ettorre*, 7/7/2020, retrospective, Italy, peer-reviewed, 17 authors. | risk of death, 87.0% lower, RR 0.13, $p = 0.14$, treatment 0 of 28 (0.0%), control 4 of 42 (9.5%), NNT 10, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm). |
| | risk of mechanical ventilation, 76.9% lower, RR 0.23, $p = 0.51$, treatment 0 of 28 (0.0%), control 2 of 42 (4.8%), NNT 21, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm). |
| | respiratory failure, 88.4% lower, OR 0.12, $p = 0.01$, treatment 28, control 42, inverted to make OR<1 favor treatment, RR approximated with OR. |
| *Di Pierro*, 9/28/2022, Randomized Controlled Trial, Pakistan, peer-reviewed, mean age 48.5, 7 authors, study period 11 August, 2021 - 18 November, 2021, trial NCT05043376 (history), excluded in exclusion analyses: unadjusted differences between groups. | risk of death, 62.5% lower, RR 0.38, $p = 0.17$, treatment 3 of 25 (12.0%), control 8 of 25 (32.0%), NNT 5.0. |
| | risk of ICU admission, no change, RR 1.00, $p = 1.00$, treatment 8 of 25 (32.0%), control 8 of 25 (32.0%). |
| *Ivashkin*, 10/13/2021, Randomized Controlled Trial, Russia, peer-reviewed, 11 authors, study period December 2020 - March 2021, average treatment delay 8.0 days, trial NCT04854941 (history). | risk of death, 2.0% higher, RR 1.02, $p = 1.00$, treatment 4 of 99 (4.0%), control 4 of 101 (4.0%). |
| | risk of mechanical ventilation, 18.4% lower, RR 0.82, $p = 1.00$, treatment 4 of 99 (4.0%), control 5 of 101 (5.0%), NNT 110. |
| | risk of ICU admission, 27.1% lower, RR 0.73, $p = 0.77$, treatment 5 of 99 (5.1%), control 7 of 101 (6.9%), NNT 53. |
| | recovery time, 4.8% lower, relative time 0.95, $p = 0.47$, treatment 99, control 101. |
| *Li*, 3/5/2021, retrospective, China, peer-reviewed, 7 authors, average treatment delay 13.0 days. | risk of no hospital discharge, 11.8% higher, RR 1.12, $p = 0.68$, treatment 30 of 123 (24.4%), control 41 of 188 (21.8%). |

| | |
|---|---|
| | time to discharge, 60.0% higher, relative time 1.60, $p < 0.001$, treatment 123, control 188. |
| | time to viral-, 35.3% higher, relative time 1.35, $p < 0.001$, treatment 123, control 188. |
| *Saviano*, 6/28/2022, Randomized Controlled Trial, Italy, peer-reviewed, mean age 59.8, 9 authors. | risk of death, 66.7% lower, RR 0.33, $p = 1.00$, treatment 0 of 40 (0.0%), control 1 of 40 (2.5%), NNT 40, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm). |
| | risk of ICU admission, 85.7% lower, RR 0.14, $p = 0.24$, treatment 0 of 40 (0.0%), control 3 of 40 (7.5%), NNT 13, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm). |
| | hospitalization time, 26.3% lower, relative time 0.74, $p = 0.52$, treatment mean 14.0 (±6.0) n=40, control mean 19.0 (±10.0) n=40. |
| *Shah*, 2/2/2021, Randomized Controlled Trial, India, peer-reviewed, 3 authors, this trial uses multiple treatments in the treatment arm (combined with multi-enzyme formulation) - results of individual treatments may vary. | time to clinical improvement, 10.8% lower, relative time 0.89, $p = 0.19$, treatment 30, control 30. |
| | hospitalization time, 10.6% lower, relative time 0.89, $p = 0.18$, treatment 30, control 30. |
| | risk of no clinical improvement, 83.3% lower, RR 0.17, $p = 0.005$, treatment 2 of 30 (6.7%), control 12 of 30 (40.0%), NNT 3.0, day 10 mid-recovery. |
| | risk of no clinical improvement, 3.7% lower, RR 0.96, $p = 1.00$, treatment 26 of 30 (86.7%), control 27 of 30 (90.0%), NNT 30, day 7. |
| *Trinchieri*, 8/1/2022, retrospective, Italy, peer-reviewed, 10 authors, study period November 2020 - March 2021. | risk of death, 77.8% lower, RR 0.22, $p = 0.28$, treatment 1 of 21 (4.8%), control 3 of 14 (21.4%), NNT 6.0. |
| | risk of miscellaneous, 77.8% lower, RR 0.22, $p < 0.001$, treatment 4 of 21 (19.0%), control 12 of 14 (85.7%), NNT 1.5, CPAP, day 7. |
| | risk of miscellaneous, 9.5% lower, RR 0.90, $p = 0.51$, treatment 19 of 21 (90.5%), control 14 of 14 (100.0%), NNT 10, CPAP, day 3. |
| *Zhang (B)*, 3/2/2022, retrospective, China, peer-reviewed, 12 authors, trial NCT04581018 (history). | risk of mechanical ventilation, 64.7% lower, RR 0.35, $p = 1.00$, treatment 0 of 25 (0.0%), control 1 of 30 (3.3%), NNT 30, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm). |
| | risk of no antibody formation, 67.3% lower, RR 0.33, $p = 0.06$, treatment 3 of 25 (12.0%), control 11 of 30 (36.7%), NNT 4.1. |
| *Zhang (C)*, 8/4/2021, retrospective, China, peer-reviewed, 14 authors. | hospitalization time, 13.6% lower, relative time 0.86, $p = 0.009$, treatment 150, control 150, PSM. |

| | |
|---|---|
| | time to clinical improvement, 14.3% lower, relative time 0.86, $p$ = 0.02, treatment 150, control 150, PSM. |
| | time to viral-, 16.7% lower, relative time 0.83, $p$ < 0.001, treatment 150, control 150, PSM. |

## 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.

| | |
|---|---|
| *Ahanchian*, 5/31/2021, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, peer-reviewed, 14 authors, study period July 2020 - August 2020, trial IRCT20101020004976N6. | respiratory symptoms, 73.3% lower, RR 0.27, $p$ = 0.35, treatment 1 of 29 (3.4%), control 4 of 31 (12.9%), NNT 11. |
| | risk of case, 85.3% lower, RR 0.15, $p$ = 0.24, treatment 0 of 29 (0.0%), control 3 of 31 (9.7%), NNT 10, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm). |
| *Catinean*, 1/17/2023, retrospective, Romania, peer-reviewed, 4 authors, study period 15 September, 2020 - 15 February, 2021. | symptom resolution, 40.5% lower, HR 0.60, $p$ = 0.008, treatment 60, control 60, inverted to make HR<1 favor treatment. |
| | resolution of fever, 37.5% lower, HR 0.62, $p$ = 0.02, treatment 60, control 60, inverted to make HR<1 favor treatment, fever. |
| *Di Pierro (C)*, 9/30/2023, retrospective, Italy, peer-reviewed, 10 authors, study period January 2022 - March 2022, trial NCT05840926 (history). | risk of case, 77.8% lower, RR 0.22, $p$ = 0.007, treatment mean 0.02 (±0.15) n=186, control mean 0.09 (±0.29) n=101. |
| *Di Pierro (D)*, 3/12/2021, Randomized Controlled Trial, Italy, peer-reviewed, 2 authors, study period September 2020 - December 2020. | risk of case, 98.0% lower, RR 0.02, $p$ < 0.001, treatment 0 of 64 (0.0%), control 24 of 64 (37.5%), NNT 2.7, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm). |
| *Holt*, 3/30/2021, prospective, United Kingdom, peer-reviewed, 34 authors, study period 1 May, 2020 - 5 February, 2021, trial NCT04330599 (history) (COVIDENCE UK), excluded in exclusion analyses: significant unadjusted confounding possible. | risk of case, 30.4% lower, RR 0.70, $p$ = 0.11, treatment 20 of 909 (2.2%), control 426 of 14,318 (3.0%), NNT 129, adjusted per study, odds ratio converted to relative risk, minimally adjusted, group sizes approximated. |
| *Louca*, 11/30/2020, retrospective, United Kingdom, peer-reviewed, 26 authors. | risk of case, 8.5% lower, RR 0.92, $p$ = 0.03, odds ratio converted to relative risk, United Kingdom, all adjustment model. |
| *Rodriguez-Blanque*, 8/3/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Spain, peer-reviewed, 7 authors, study period 24 April, 2020 - 20 July, 2020, trial NCT04366180 (history). | risk of case, 9.3% lower, RR 0.91, $p$ = 0.92, treatment 2 of 127 (1.6%), control 2 of 128 (1.6%), adjusted per study, multivariable. |
| *Sarlin*, 11/2/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Finland, peer-reviewed, 7 authors, study period 1 August, 2020 - | risk of case, 33.2% lower, RR 0.67, $p$ = 1.00, treatment 2 of 413 (0.5%), control 3 of 414 (0.7%), NNT 416. |

| | |
|---|---|
| 31 May, 2021. | |
| *Wischmeyer*, 1/5/2022, Double Blind Randomized Controlled Trial, USA, preprint, 21 authors, study period 24 June, 2020 - 8 July, 2021, trial NCT04399252 (history) (PROTECT-EHC). | risk of moderate/severe case, 33.3% lower, RR 0.67, $p$ = 0.15, treatment 16 of 91 (17.6%), control 24 of 91 (26.4%), NNT 11. |
| | risk of symptomatic case, 38.5% lower, RR 0.62, $p$ = 0.02, treatment 24 of 91 (26.4%), control 39 of 91 (42.9%), NNT 6.1, primary outcome. |
| | recovery time, 27.3% lower, relative time 0.73, $p$ = 0.37, treatment 91, control 91. |
| | risk of case, 42.9% lower, RR 0.57, $p$ = 0.17, treatment 8 of 91 (8.8%), control 14 of 91 (15.4%), NNT 15. |

## 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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