Vitamin B9 for COVID-19: real-time meta analysis of 18 studies (12 treatment studies and 6 sufficiency studies)

@CovidAnalysis, July 2025, Version 9
https://c19early.org/b9meta.html

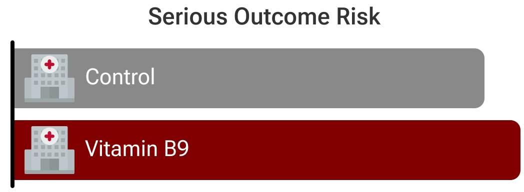
Abstract

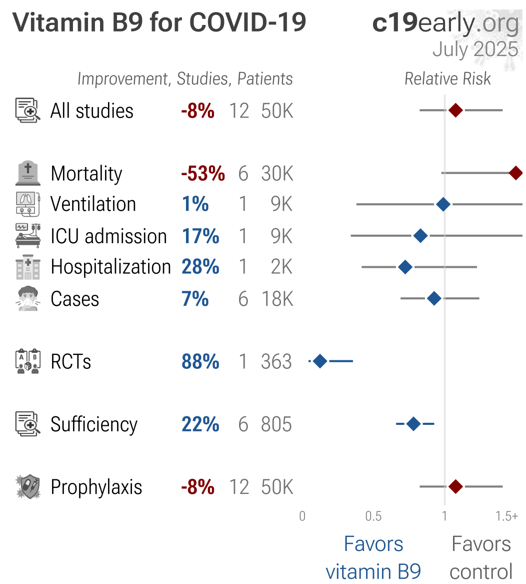
Meta analysis using the most serious outcome reported shows 8% [-18-41%] higher risk, without reaching statistical significance.

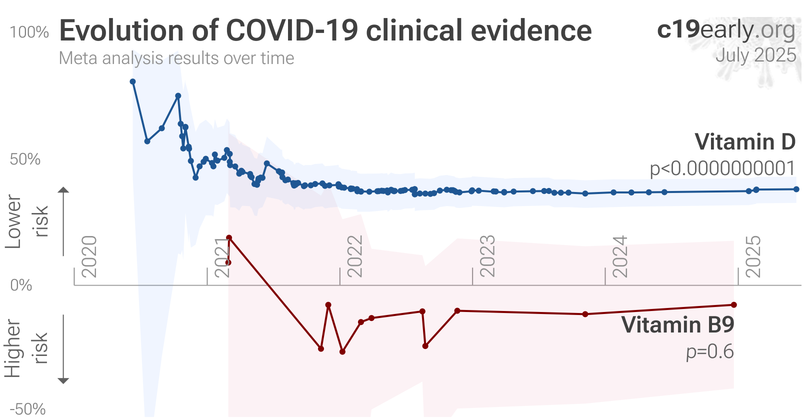
6 sufficiency studies analyze outcomes based on serum levels, showing 22% [7-34%] lower risk for patients with higher vitamin B9 levels.

Results to date are contradictory. Several studies show higher mortality, however counfounding by indication may be significant — patients prescribed folic acid may have significantly higher risk on average. Studies independent of prescriptions based on patient condition show positive results [1,2], as do sufficiency studies. Folic acid may not be the most effective or safest form for supplementation [3]. Studies show that a significant fraction of people have genetic variations limiting the ability to convert folic acid to the active form.

All data and sources to reproduce this analysis are in the appendix.







VITAMIN B9 FOR COVID-19 — HIGHLIGHTS

Meta analysis of studies to date shows no significant improvements with vitamin B9.

Results are contradictory. Several studies show higher mortality, however counfounding by indication may be significant — patients prescribed folic acid may have higher risk on average. Folic acid may not be the best form for treatment.

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

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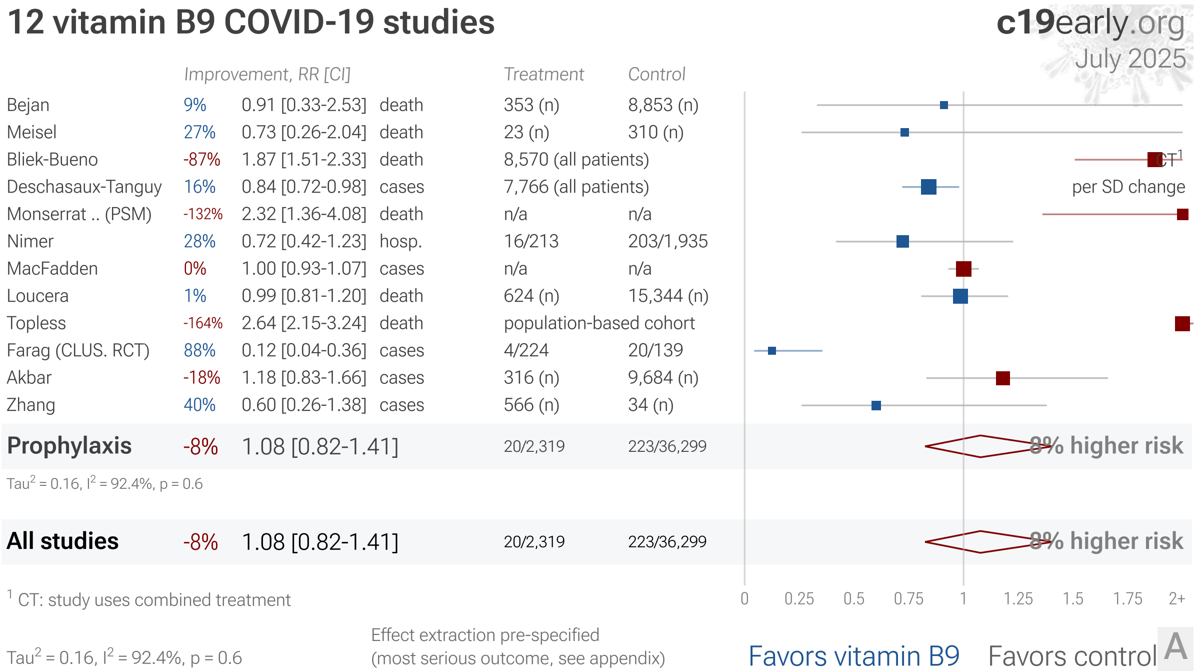


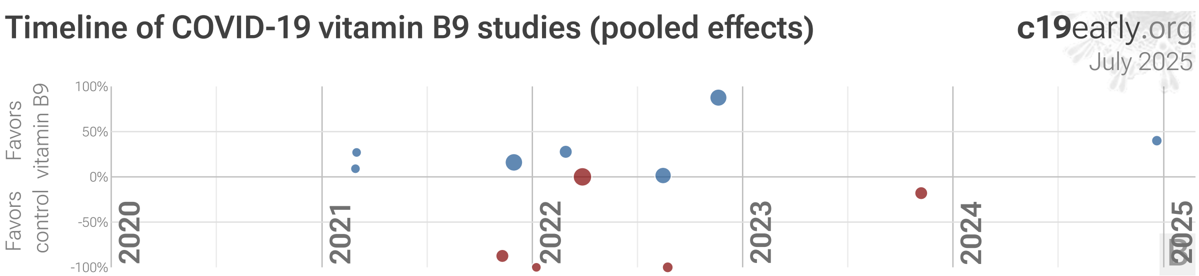


***Figure 1.* A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in vitamin B9 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[5-17] and cognitive deficits[8,13], cardiovascular complications[18-22], organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits[23]—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Minimizing replication as early as possible is recommended.

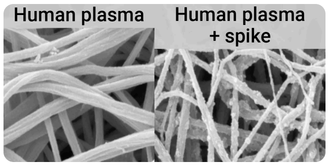


Figure 2. **SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from[4].**

Many treatments are expected to modulate infection

SARS-CoV-2 infection and replication involves the complex interplay of 100+ host and viral proteins and other factors[A,24-31], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 9,000 compounds may reduce COVID-19 risk[32], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Extensive supporting research

Vitamin B9 has been identified by the European Food Safety Authority (EFSA) as having sufficient evidence for a causal relationship between intake and optimal immune system function [33-35]. Vitamin B9 inhibits SARS-CoV-2 In Silico [36-44], reduces spike protein binding ability [36], binds with the spike protein receptor binding domain for alpha and omicron variants [45], inhibits the SARS-CoV-2 nucleocapsid protein [43], inhibits 3CLpro and PLpro in enzymatic assays [45], significantly reduces infection for alpha and omicron SARS-CoV-2 pseudoviruses [45], and inhibits ACE2 expression and SARS-CoV-2 infection in a mouse model [36].

Analysis

We analyze all significant controlled studies of vitamin B9 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, individual outcomes, and Randomized Controlled Trials (RCTs).

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.

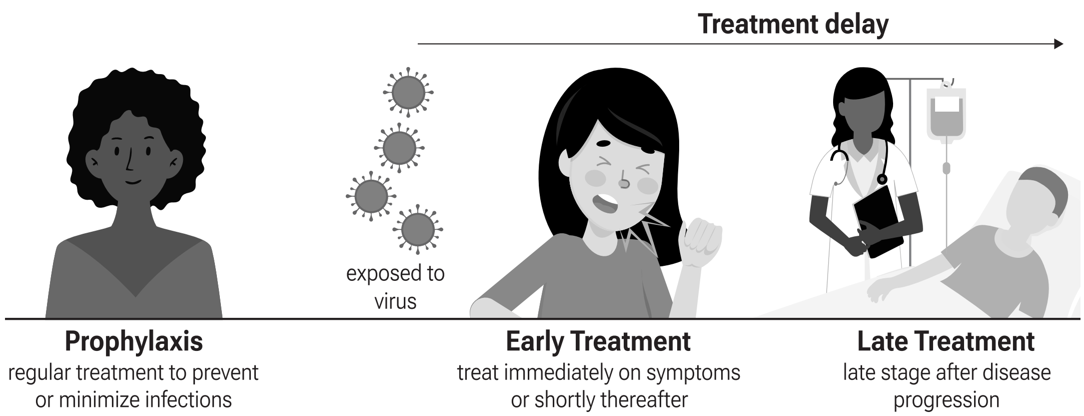


Figure 3. Treatment stages.

Preclinical Research

Vitamin B9 inhibits SARS-CoV-2 In Silico [36-44], reduces spike protein binding ability [36], binds with the spike protein receptor binding domain for alpha and omicron variants [45], inhibits the SARS-CoV-2 nucleocapsid protein [43], inhibits 3CLpro and PLpro in enzymatic assays [45], significantly reduces infection for alpha and omicron SARS-CoV-2 pseudoviruses [45], and inhibits ACE2 expression and SARS-CoV-2 infection in a mouse model [36].

9 *In Silico* studies support the efficacy of vitamin B9 [37-43,45,46].

4 *In Vitro* studies support the efficacy of vitamin B9 [36,43-45].

An *In Vivo* animal study supports the efficacy of vitamin B9 [36].

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 studies, for Randomized Controlled Trials, and for specific outcomes. Figure 4, 5, 6, 7, 8, 9, and 10 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, cases, and sufficiency studies.

	Relative Risk	Studies	Patients
All studies	1.08 [0.82-1.41]	12	50K
RCTs	0.12 [0.04-0.36] ***	1	363
Mortality	1.53 [0.98-2.40]	6	30K
Cases	0.93 [0.69-1.24]	6	10K

***Table 1.* Random effects meta-analysis for all studies, for Randomized Controlled Trials, and for specific outcomes.** Results show the relative risk with treatment and the 95% confidence interval. *** p<0.001.

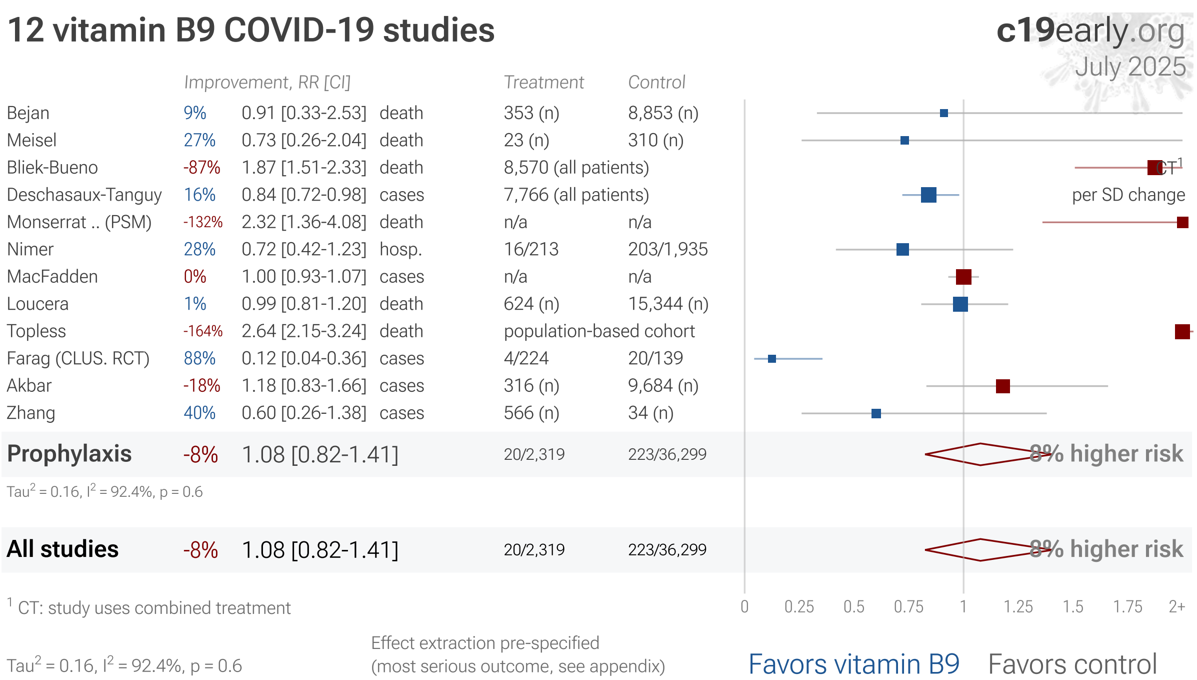


***Figure 4.* Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For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

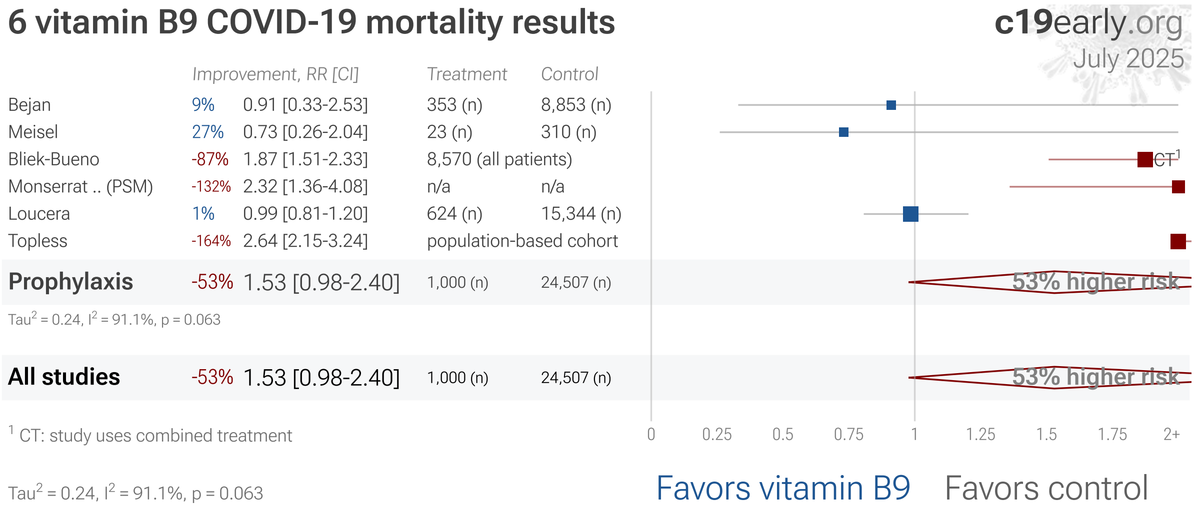


Figure 5. Random effects meta-analysis for mortality results.

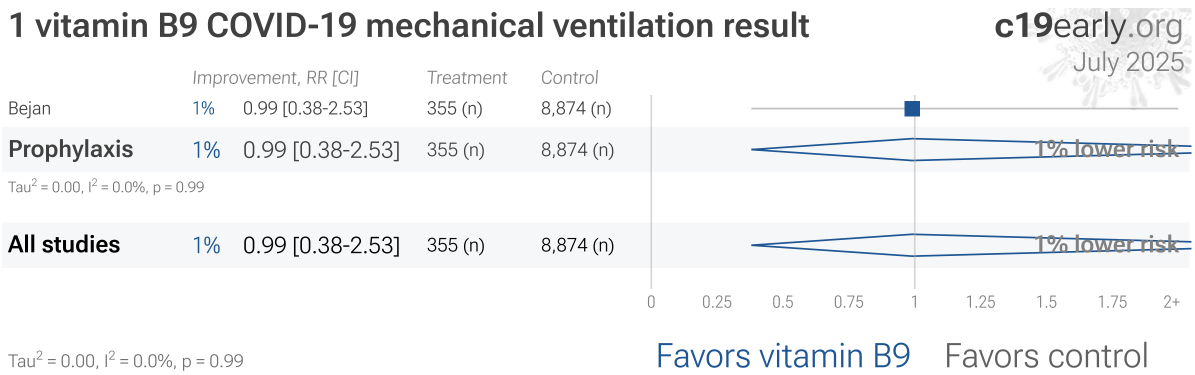


Figure 6. Random effects meta-analysis for ventilation.

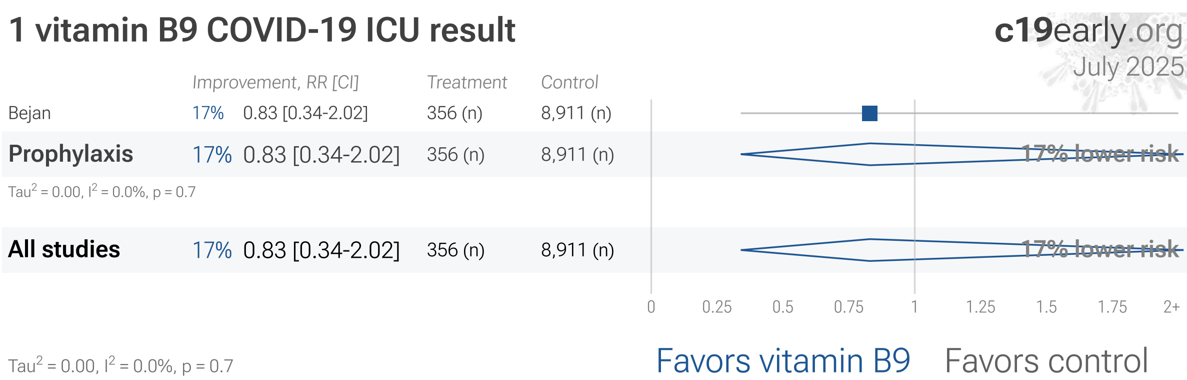


Figure 7. Random effects meta-analysis for ICU admission.

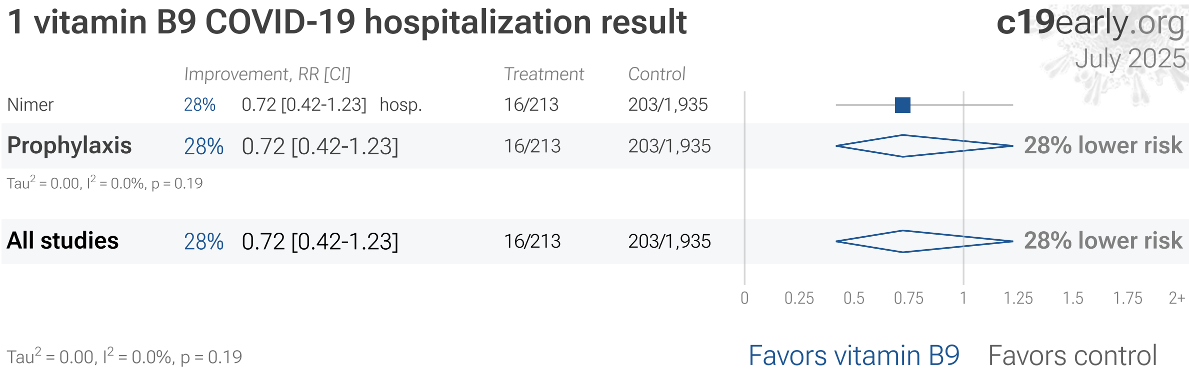


Figure 8. Random effects meta-analysis for hospitalization.

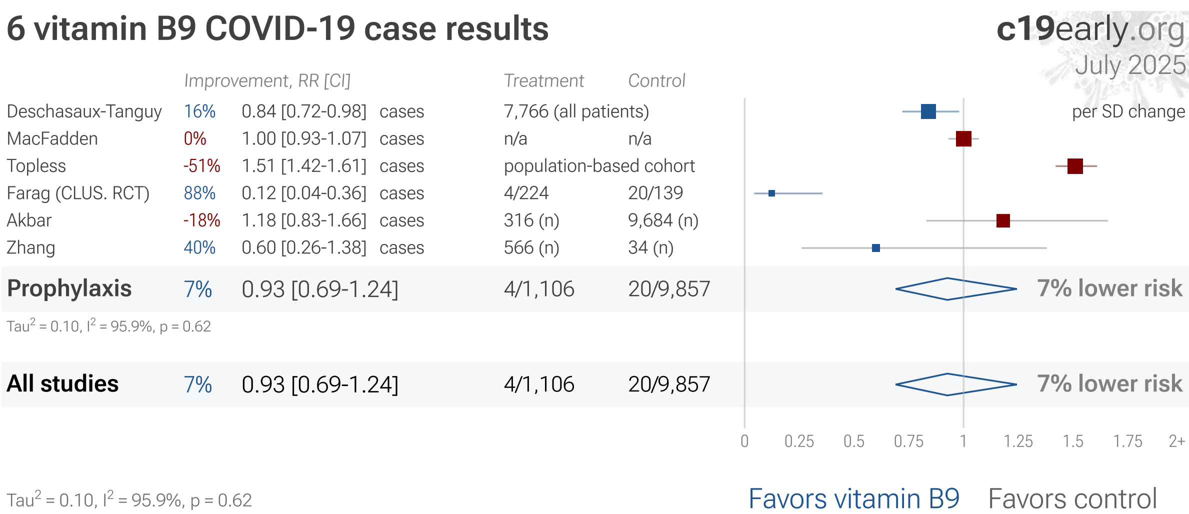


Figure 9. Random effects meta-analysis for cases.

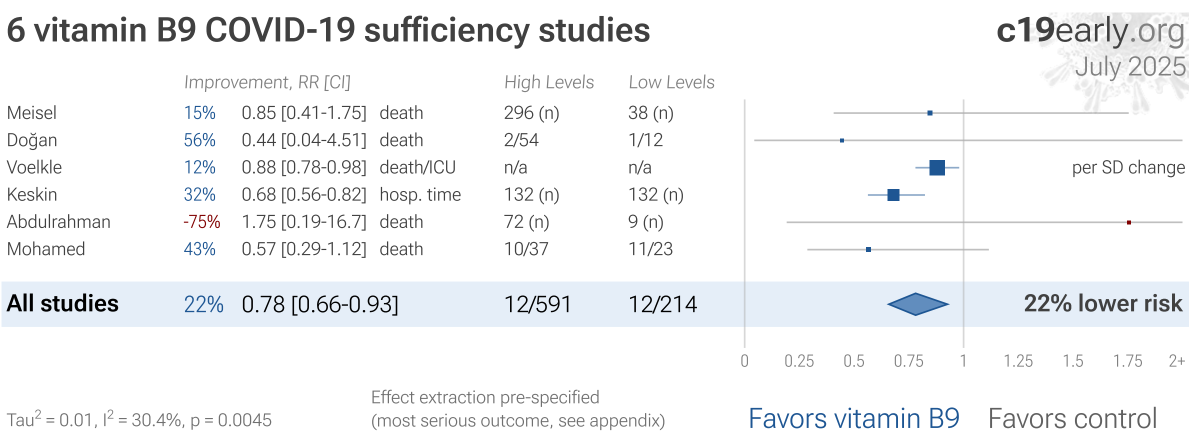


Figure 10. **Random effects meta-analysis for sufficiency studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below.

Randomized Controlled Trials (RCTs)

Figure 11 shows a forest plot for random effects meta-analysis of all Randomized Controlled Trials. RCT results are included in Table 1. Currently there is only one RCT.

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 [47], and analysis of double-blind RCTs has identified extreme levels of bias [48]. For COVID-19, the overhead may delay treatment, dramatically compromising efficacy; they may encourage monotherapy for simplicity at the cost of efficacy which may rely on combined or synergistic effects; the participants that sign up may not reflect real world usage or the population that benefits most in terms of age, comorbidities, severity of illness, or other factors; standard of care may be compromised and unable to evolve quickly based on emerging research for new diseases; errors may be made in randomization and medication delivery; and investigators may have hidden agendas or vested interests influencing design, operation, analysis, reporting, and the potential for fraud. All of these biases have been observed with COVID-19 RCTs. There is no guarantee that a specific RCT provides a higher level of evidence.

Conflicts of interest for COVID-19 RCTs

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

RCTs for novel acute diseases requiring rapid treatment

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

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

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

Summary

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

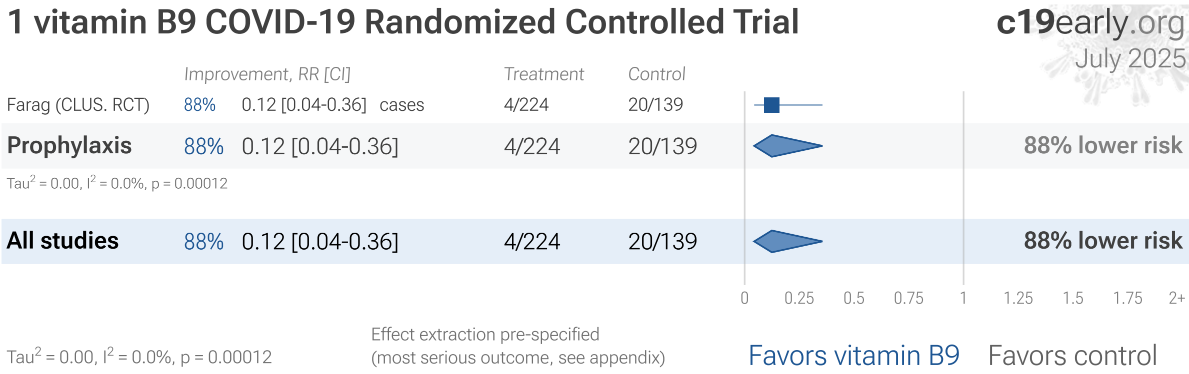


Figure 11. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

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[50,51]. 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 (B) et al.* report only 2.5 hours improvement for inpatient treatment.

Treatment delay	*Result*
Post-exposure prophylaxis	86% fewer cases[52]
<24 hours	-33 hours symptoms[53]
24-48 hours	-13 hours symptoms[53]
Inpatients	-2.5 hours to improvement[54]

Table 2. **Studies of baloxavir marboxil for influenza show that early treatment is more effective.**

Figure 12 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 172 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

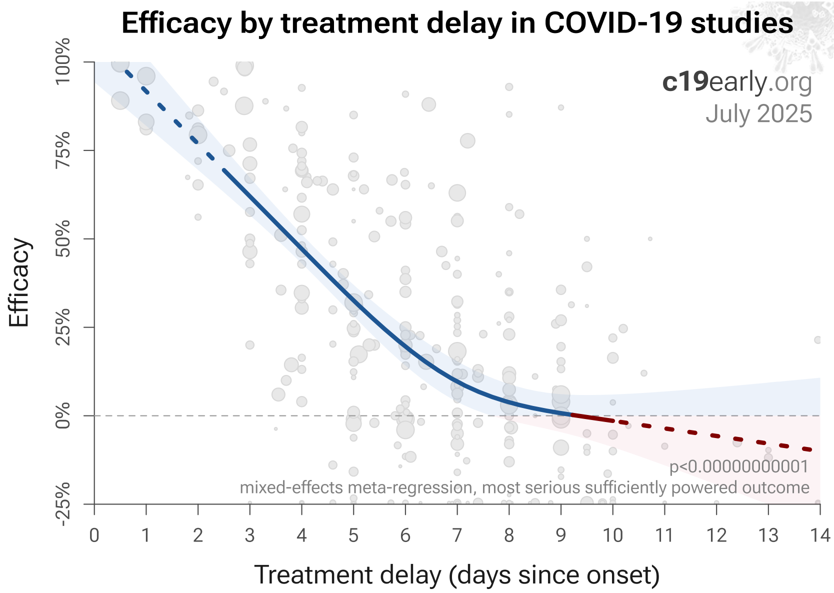


Figure 12. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 172 treatments.

Patient demographics

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

SARS-CoV-2 variants

Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants[56], for example the Gamma variant shows significantly different characteristics[57-60]. 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[61,62].

Treatment regimen

Effectiveness may depend strongly on the dosage and treatment regimen.

Medication quality

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

Other treatments

The use of other treatments may significantly affect outcomes, including supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic[65-81], 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 172 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 13 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 14 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 15 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to Singh et al., with higher confidence due to the larger number of studies. As with Singh et al., the confidence increases when excluding the outlier treatment, from $p = 0.000000082$ to $p = 0.0000000033$.

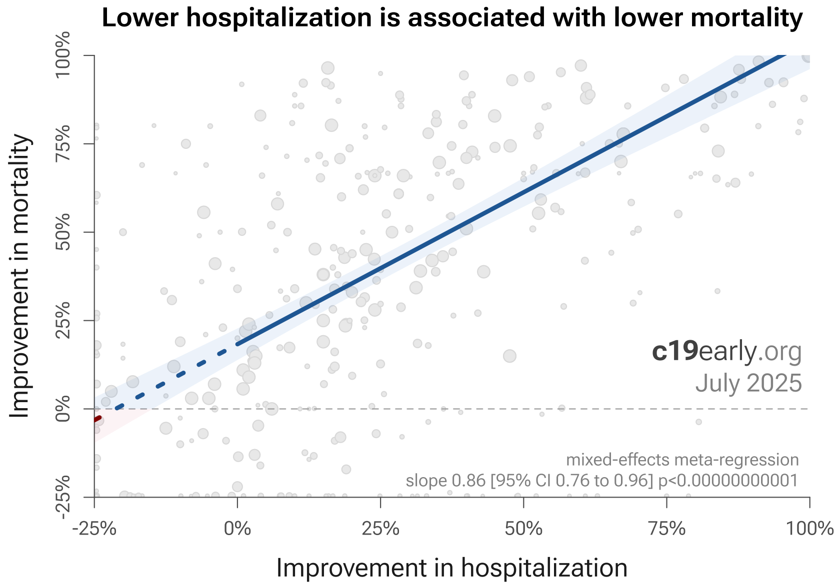


Figure 13. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

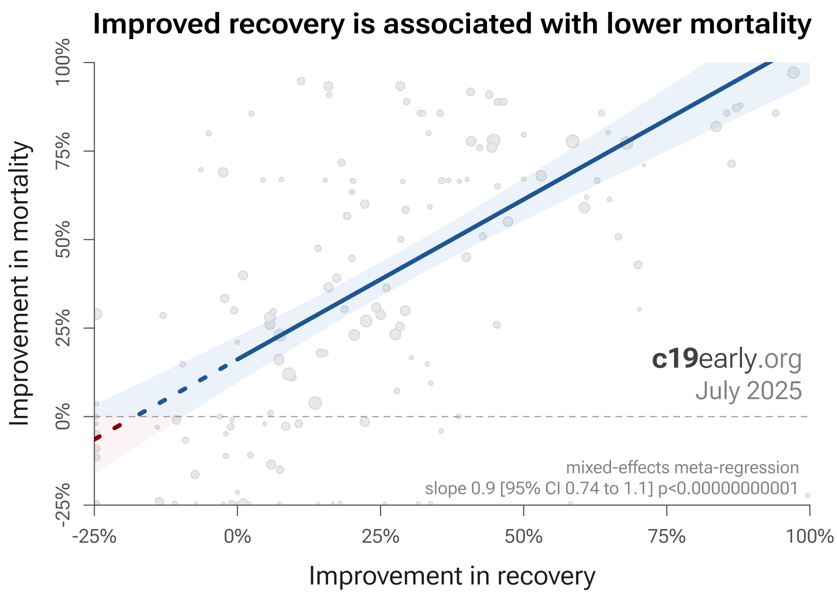


Figure 14. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

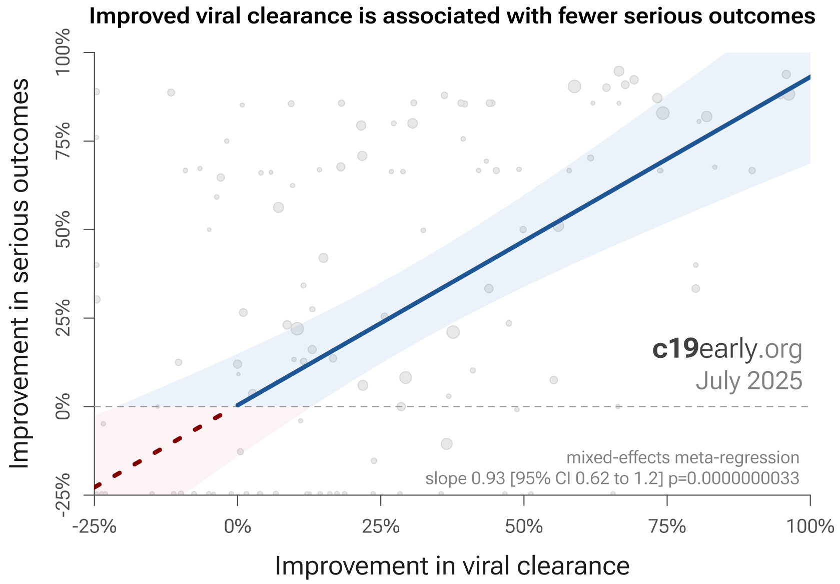


Figure 13. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

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

Currently, 55 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 88% of these have been confirmed with one or more specific outcomes, with a mean delay of 4.9 months. When restricting to RCTs only, 57% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 7.3 months. Figure 16 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

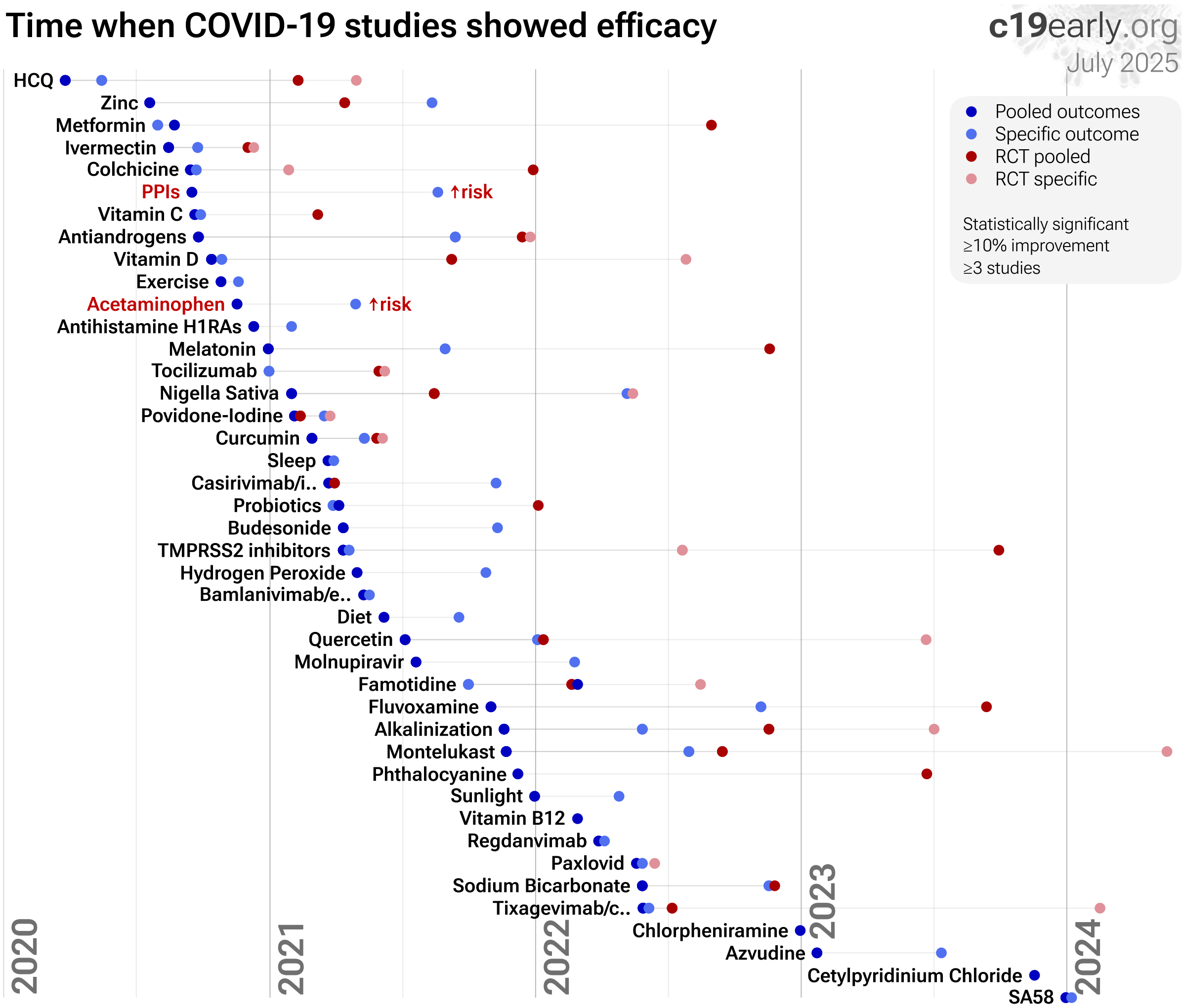


Figure 16. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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

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[83-86]. For vitamin B9, there is currently not enough data to evaluate publication bias with high confidence.

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 17 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 $p < 0.05$[87-94]. 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.

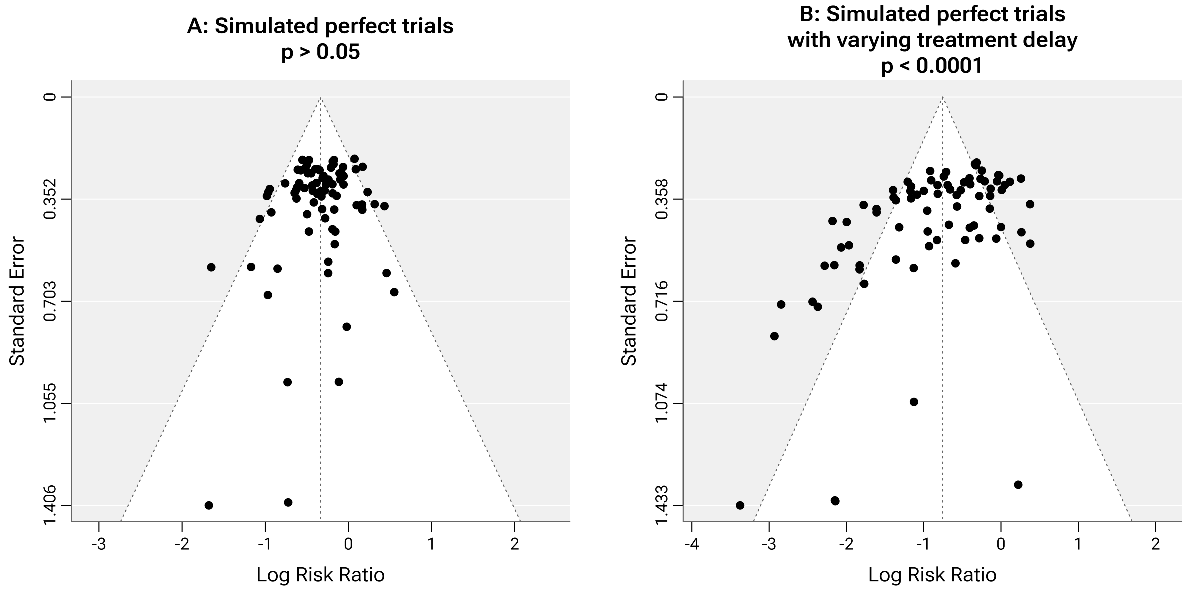


Figure 17. **Example funnel plot analysis for simulated perfect trials.**

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. Vitamin B9 for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 vitamin B9 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 vitamin B9 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 [65-81]. 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 12 studies combine treatments. The results of vitamin B9 alone may differ. None of the RCTs use combined treatment. Currently all studies are peer-reviewed.

Reviews

Multiple reviews cover vitamin B9 for COVID-19, presenting additional background on mechanisms and related results, including [3,95].

Other studies

Srivastava et al. also suggests potential benefits of vitamin B9 for COVID-19. We have not reviewed this paper in detail.

Perspective

Results compared with other treatments

SARS-CoV-2 infection and replication involves a complex interplay of 100+ host and viral proteins and other factors [24-31], providing many therapeutic targets. Over 9,000 compounds have been predicted to reduce COVID-19 risk [32], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 18 shows an overview of the results for vitamin B9 in the context of multiple COVID-19 treatments, and Figure 19 shows a plot of efficacy vs. cost for COVID-19 treatments.

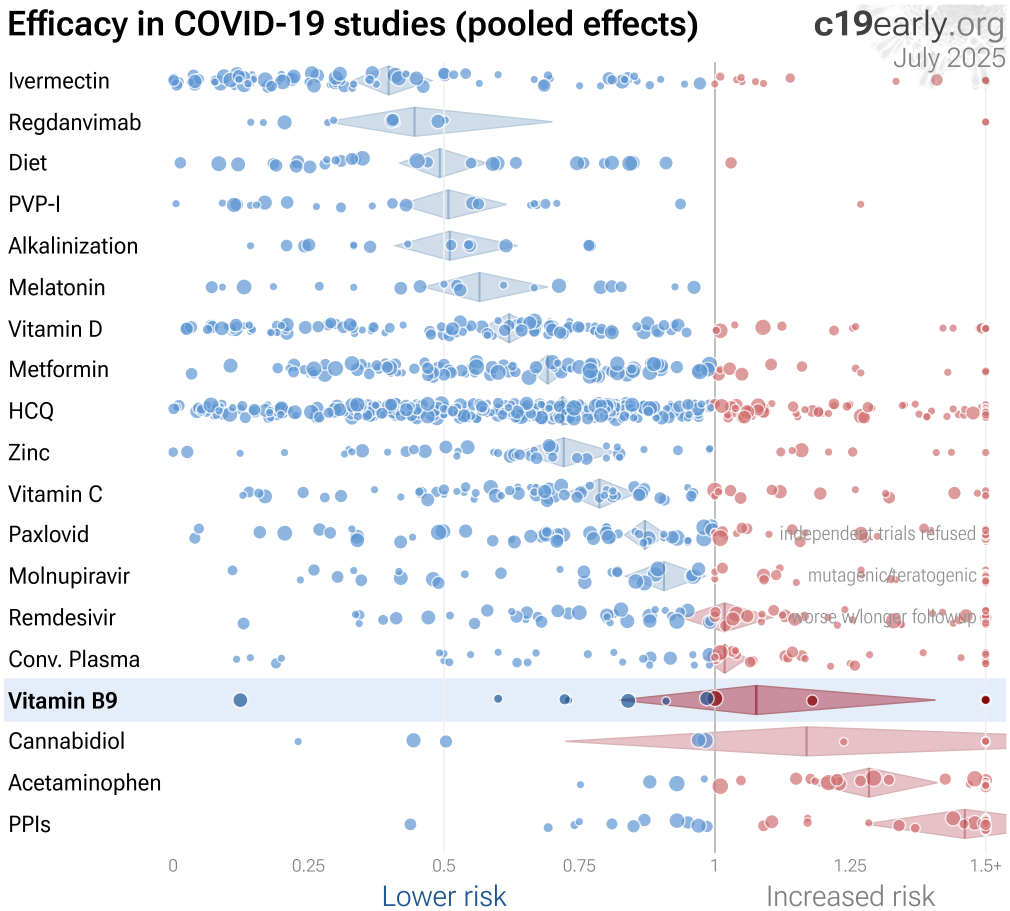


Figure 18. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy [108].

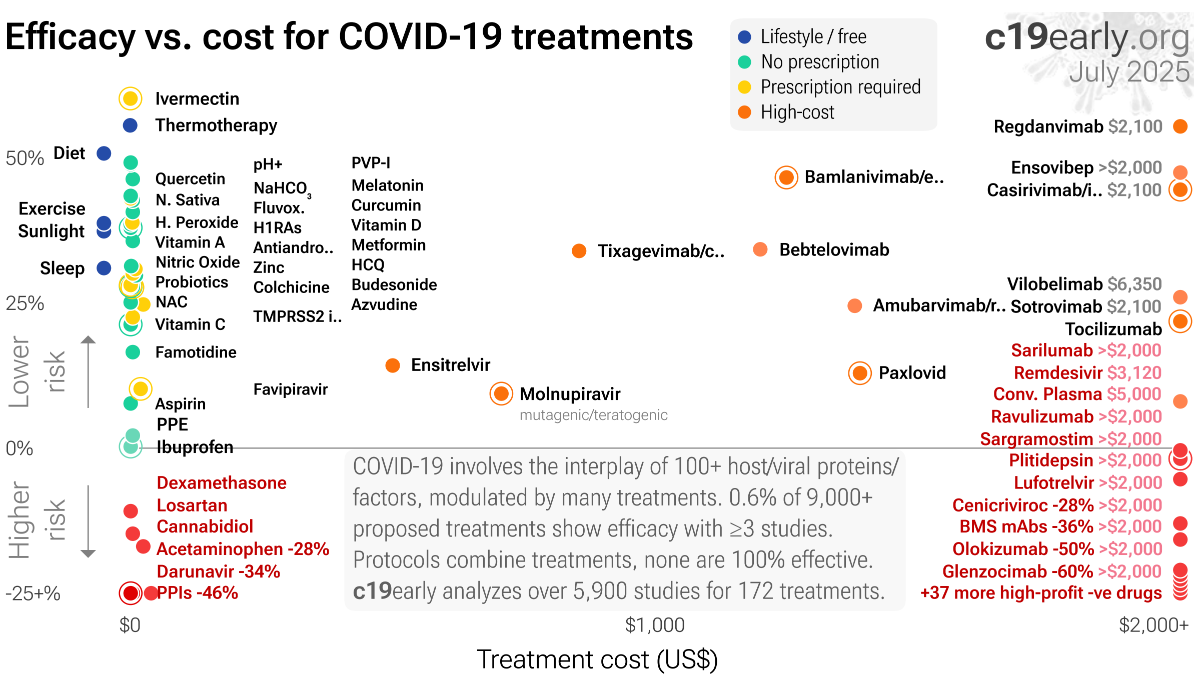


Figure 19. Efficacy vs. cost for COVID-19 treatments.

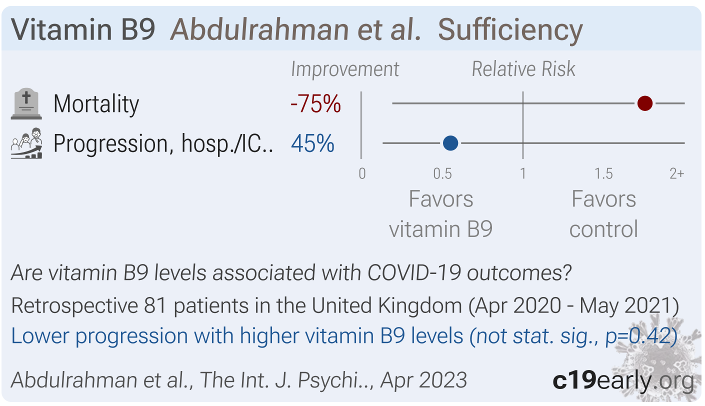
Conclusion

Meta analysis using the most serious outcome reported shows 8% [-18-41%] higher risk, without reaching statistical significance. 6 sufficiency studies analyze outcomes based on serum levels, showing 22% [7-34%] lower risk for patients with higher vitamin B9 levels.

Results to date are contradictory. Several studies show higher mortality, however counfounding by indication may be significant — patients prescribed folic acid may have significantly higher risk on average. Studies independent of prescriptions based on patient condition show positive results[1,2], as do sufficiency studies. Folic acid may not be the most effective or safest form for supplementation[3]. Studies show that a significant fraction of people have genetic variations limiting the ability to convert folic acid to the active form.

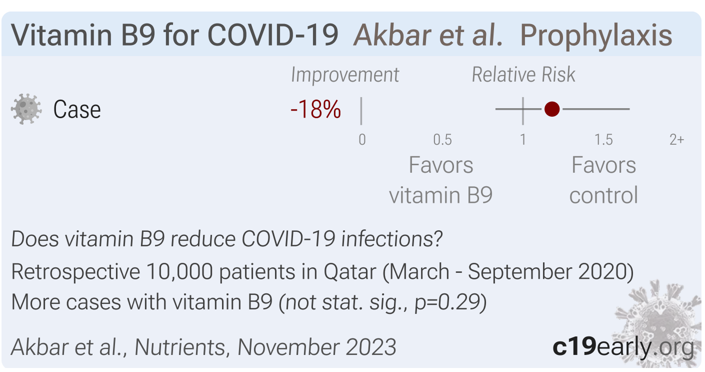
Study Notes

Abdulrahman



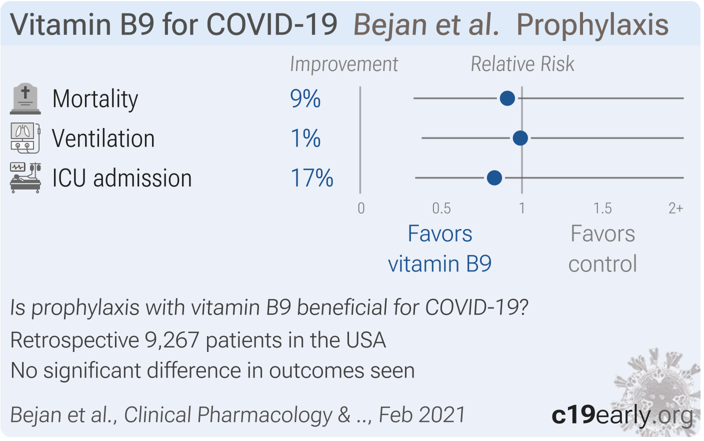
Retrospective 81 pyschiatric inpatients in the UK, mean age 76, showing no significant difference in COVID-19 mortality with folate deficiency.

Akbar



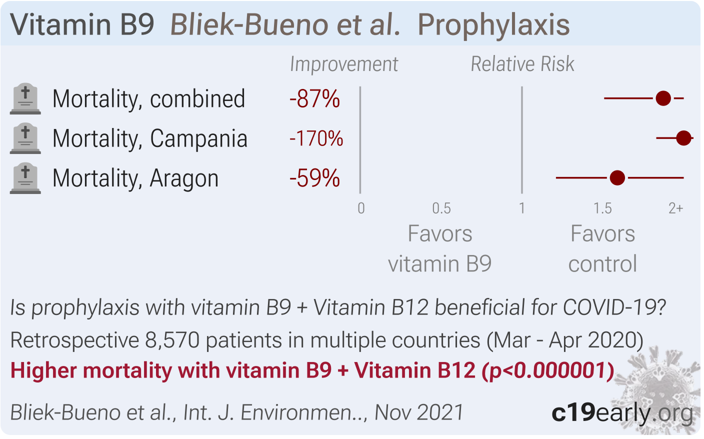
Retrospective 10,000 adults in Qatar, showing higher risk of COVID-19 cases with vitamin B9 supplementation, without statistical significance. Authors do not analyze COVID-19 severity.

Bejan



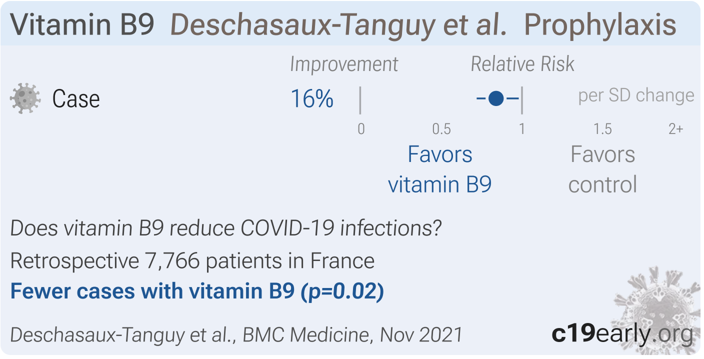
Retrospective 9,748 COVID-19 patients in the USA showing no significant differences with vitamin B9 use, without statistical significance.

Bliek-Bueno



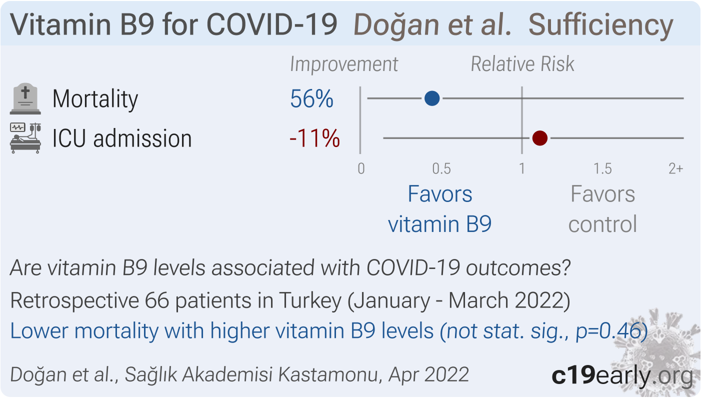
Retrospective 8,570 individuals in Spain and Italy, showing higher mortality with combined vitamin B9 and B12 supplementation. Adjustments only considered age.

Deschasaux-Tanguy



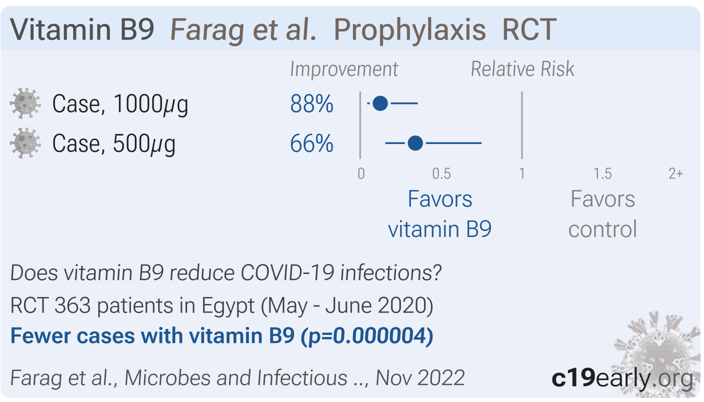
Analysis of 7,766 adults in France, showing higher intakes of vitamin C, folate, vitamin K, dietary fibre, and fruit and vegetables associated with lower seropositivity.

Doğan



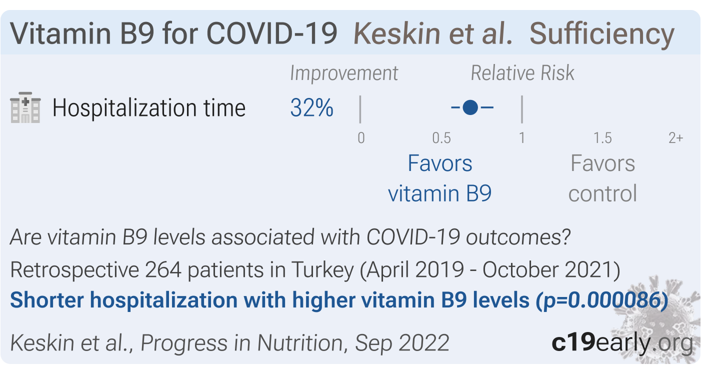
Retrospective 70 COVID-19 cases and 70 non-COVID-19 controls in Turkey, showing no significant differences based on folic acid levels.

Farag



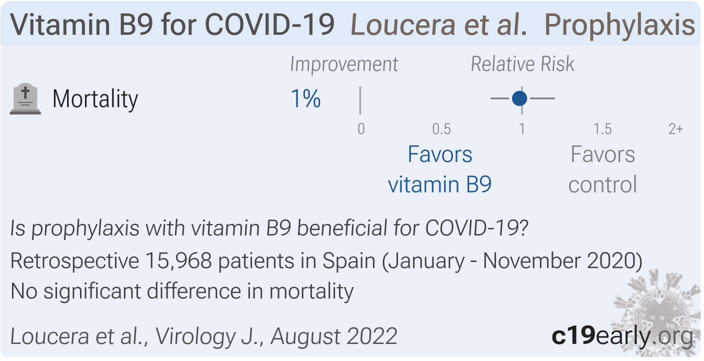
Cluster RCT 526 healthcare workers in Egypt, showing lower COVID-19 cases with folic acid supplementation, and a dose-response relationship. Each wave of health care workers was randomized within 14 day isolation periods, introducing potential confounding by time.

Keskin



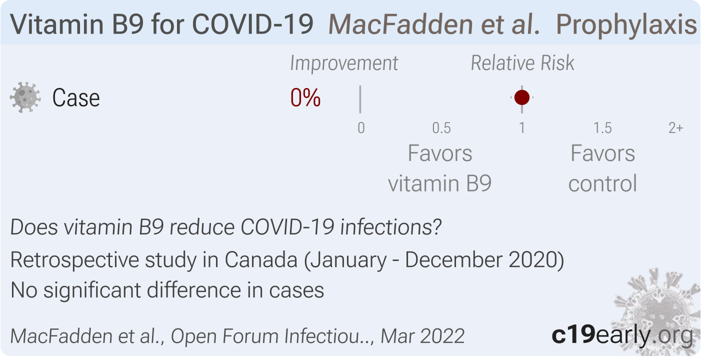
Retrospective 529 hospitalized COVID-19 patients in Turkey showing lower serum folic acid levels associated with longer hospitalization and higher mortality. Folic acid deficiency and insufficiency were common. There was no significant association for vitamin B12 levels and outcomes. Authors hypothesize that folic acid may support the immune response against SARS-CoV-2 and reduce inflammation.

Loucera



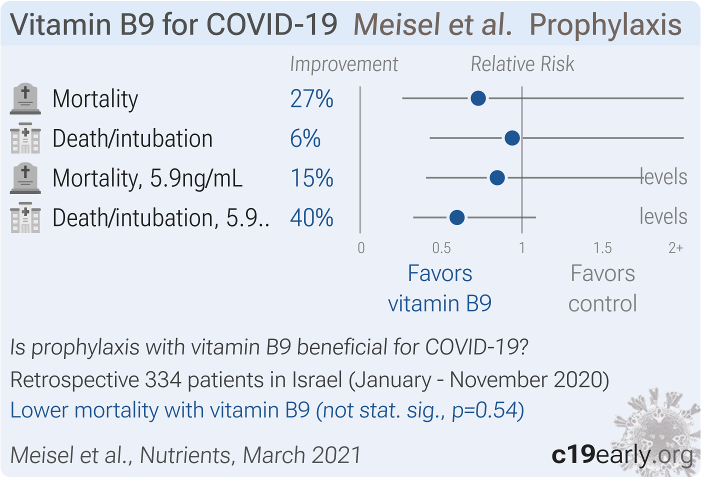
Retrospective 15,968 COVID-19 hospitalized patients in Spain, showing no significant difference in mortality with existing use of folic acid. Since only hospitalized patients are included, results do not reflect different probabilities of hospitalization across treatments.

MacFadden



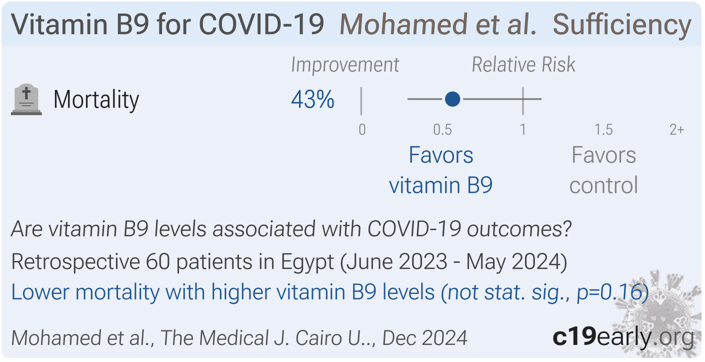
Retrospective 26,121 cases and 2,369,020 controls ≥65yo in Canada, showing no significant difference in cases with chronic use of vitamin B9.

Meisel



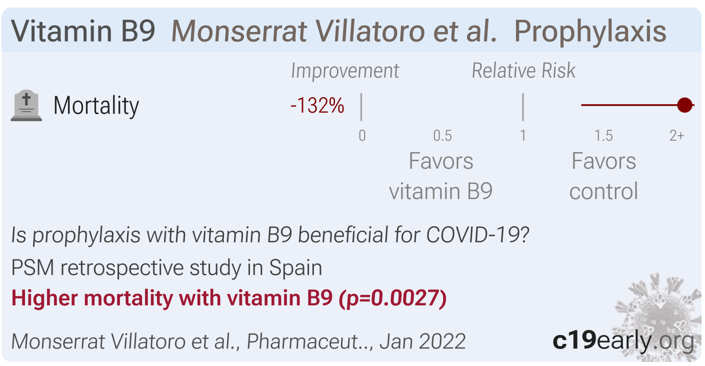
Retrospective 333 hospitalized patients in Israel, showing no significant difference in outcomes with low folate levels or with folic acid supplementation.

Mohamed



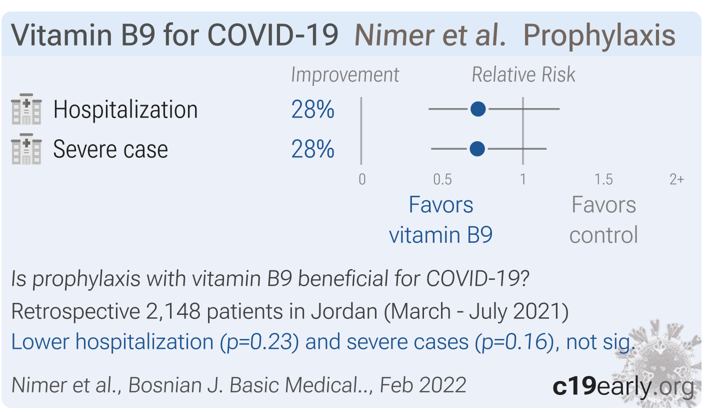
Retrospective 60 hospitalized pediatric COVID-19 patients showing deficiencies in vitamin D, folic acid (B9), zinc, and selenium associated with higher mortality.

Monserrat Villatoro



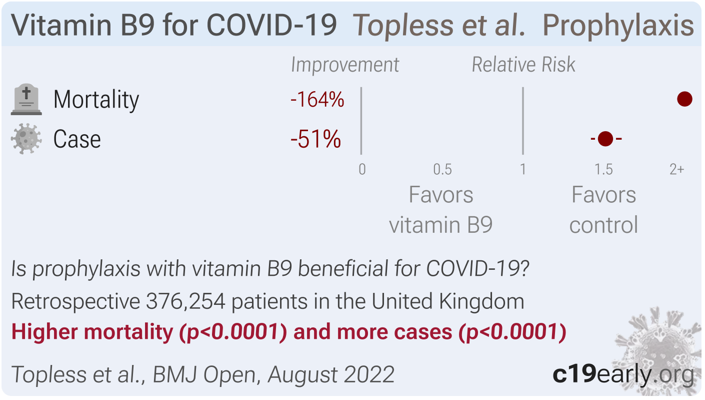
PSM retrospective 3,712 hospitalized patients in Spain, showing lower mortality with existing use of azithromycin, bemiparine, budesonide-formoterol fumarate, cefuroxime, colchicine, enoxaparin, ipratropium bromide, loratadine, mepyramine theophylline acetate, oral rehydration salts, and salbutamol sulphate,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

Nimer



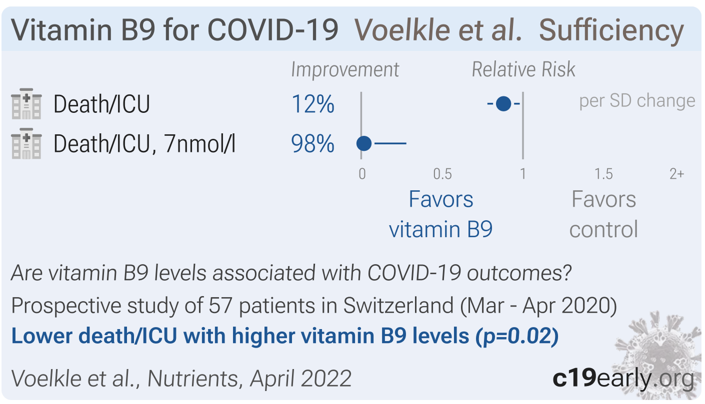
Retrospective 2,148 COVID-19 recovered patients in Jordan, showing lower risk of severity and hospitalization with vitamin B9 prophylaxis, without statistical significance.

Topless



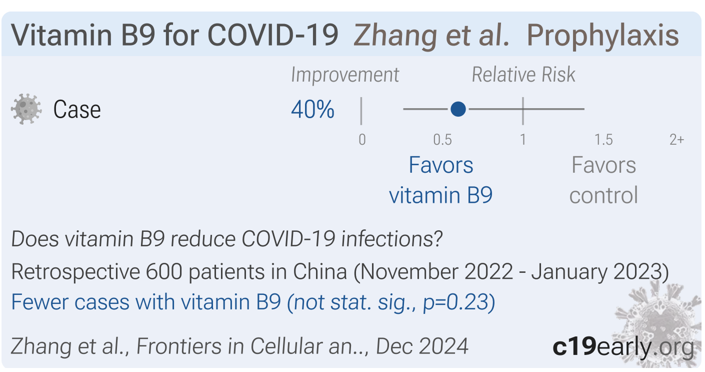
UK Biobank retrospective showing higher cases and mortality with folic acid supplementation.

Voelkle



Prospective study of 57 consecutive hospitalized COVID-19 patients in Switzerland, showing lower risk of mortality/ICU admission with vitamin B9. Adjustments only considered age.

Zhang



Retrospective 600 pregnant women in an urban area of China showing a significantly lower risk of SARS-CoV-2 infection in late pregnancy with higher gestational ozone exposure levels. Ozone exposure, driven by photochemical reactions, is strongly correlated with sunlight in this urban population. There was a non-significant trend towards lower risk of COVID-19 with folic acid supplementation.

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 vitamin B9 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 vitamin B9 for COVID-19 that report a comparison with a control group are included in the main analysis. 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.

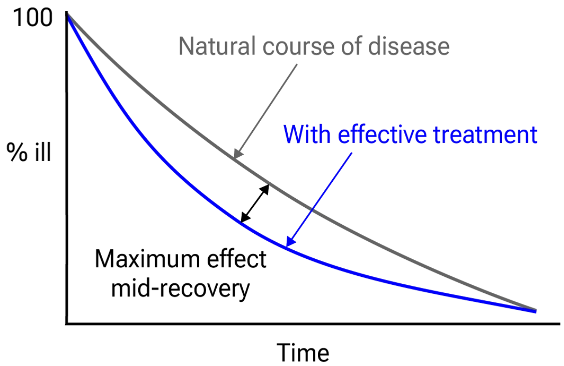


Figure 20. **Mid-recovery results can more accurately reflect efficacy when almost all patients recover.** *Mateja et al.* **confirm that intermediate viral load results more accurately reflect hospitalization/death.**

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are reported then they are both used in specific outcome analyses, while mortality is used for pooled analysis. If symptomatic results are reported at multiple times, we use the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral outcomes. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. An IPD meta-analysis confirms that intermediate viral load reduction is more closely associated with hospitalization/death than later viral load reduction [109]. 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 (C) et al.* Reported confidence intervals and *p*-values are used when available, and adjusted values are used when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 [113]. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.13.5) with scipy (1.16.0), pythonmeta (1.26), numpy (2.3.1), statsmodels (0.14.4), and plotly (6.2.0).

Forest plots are computed using PythonMeta [114] 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 [50,51].

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/b9meta.html.

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.

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.

Akbar, 11/7/2023, retrospective, Qatar, peer-reviewed, mean age 40.3, 9 authors, study period March 2020 - September 2020.	risk of case, 18.0% higher, OR 1.18, $p = 0.29$, treatment 316, control 9,684, adjusted per study, multivariable, model 2, RR approximated with OR.
Bejan, 2/28/2021, retrospective, USA, peer-reviewed, mean age 42.0, 6 authors.	risk of death, 9.0% lower, OR 0.91, $p = 0.87$, treatment 353, control 8,853, adjusted per study, RR approximated with OR.
	risk of mechanical ventilation, 1.0% lower, OR 0.99, $p = 0.99$, treatment 355, control 8,874, adjusted per study, RR approximated with OR.
	risk of ICU admission, 17.0% lower, OR 0.83, $p = 0.70$, treatment 356, control 8,911, adjusted per study, RR approximated with OR.
Bliek-Bueno, 11/10/2021, retrospective, multiple countries, peer-reviewed, mean age 67.7, 15 authors, study period 4 March, 2020 - 17 April, 2020, this trial uses multiple treatments in the treatment arm (combined with Vitamin B12) - results of individual treatments may vary.	risk of death, 87.4% higher, OR 1.87, $p < 0.001$, combined, RR approximated with OR.
	risk of death, 170.0% higher, OR 2.70, $p < 0.001$, Campania, RR approximated with OR.
	risk of death, 59.0% higher, OR 1.59, $p < 0.001$, Aragon, RR approximated with OR.
Deschasaux-Tanguy, 11/30/2021, retrospective, France, peer-reviewed, 95 authors.	risk of case, 16.0% lower, OR 0.84, $p = 0.02$, RR approximated with OR, per standard deviation change.
Farag, 11/20/2022, Cluster Randomized Controlled Trial, Egypt, peer-reviewed, mean age 37.5, 9 authors, study period 17 May, 2020 - 30 June, 2020, trial PACTR202005599385499.	risk of case, 87.6% lower, RR 0.12, $p < 0.001$, treatment 4 of 224 (1.8%), control 20 of 139 (14.4%), NNT 7.9, 1000μg.
	risk of case, 65.9% lower, RR 0.34, $p = 0.005$, treatment 8 of 163 (4.9%), control 20 of 139 (14.4%), NNT 11, 500μg.
Loucera, 8/16/2022, retrospective, Spain, peer-reviewed, 8 authors, study period January 2020 - November 2020.	risk of death, 1.5% lower, HR 0.99, $p = 0.88$, treatment 624, control 15,344, Cox proportional hazards, day 30.

MacFadden, 3/29/2022, retrospective, Canada, peer-reviewed, 9 authors, study period 15 January, 2020 - 31 December, 2020.	risk of case, no change, OR 1.00, *p* = 1.00, RR approximated with OR.
Meisel, 3/2/2021, retrospective, Israel, peer-reviewed, 8 authors, study period 27 January, 2020 - 23 November, 2020.	risk of death, 27.0% lower, OR 0.73, *p* = 0.54, treatment 23, control 310, RR approximated with OR.
	risk of death/intubation, 6.0% lower, OR 0.94, *p* = 0.88, treatment 23, control 310, RR approximated with OR.
Monserrat Villatoro, 1/8/2022, retrospective, propensity score matching, Spain, peer-reviewed, 18 authors.	risk of death, 132.0% higher, OR 2.32, *p* = 0.003, RR approximated with OR.
Nimer, 2/28/2022, retrospective, Jordan, peer-reviewed, survey, 4 authors, study period March 2021 - July 2021.	risk of hospitalization, 27.7% lower, RR 0.72, *p* = 0.23, treatment 16 of 213 (7.5%), control 203 of 1,935 (10.5%), NNT 34, adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of severe case, 28.2% lower, RR 0.72, *p* = 0.16, treatment 19 of 213 (8.9%), control 241 of 1,935 (12.5%), NNT 28, adjusted per study, odds ratio converted to relative risk, multivariable.
Topless, 8/24/2022, retrospective, United Kingdom, peer-reviewed, 6 authors.	risk of death, 164.0% higher, OR 2.64, *p* < 0.001, adjusted per study, multivariable, model 2, RR approximated with OR.
	risk of case, 51.0% higher, OR 1.51, *p* < 0.001, adjusted per study, multivariable, model 2, RR approximated with OR.
Zhang (B), 12/20/2024, retrospective, China, peer-reviewed, 3 authors, study period 3 November, 2022 - 6 January, 2023.	risk of case, 40.0% lower, OR 0.60, *p* = 0.23, treatment 566, control 34, RR approximated with OR.

Supplementary Data

Supplementary Data

Footnotes

a. Viral infection and replication involves attachment, entry, uncoating and release, genome replication and transcription, translation and protein processing, assembly and budding, and release. Each step can be disrupted by therapeutics.

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