Vitamin B9 for COVID-19: real-time meta analysis of 15 studies (11 treatment studies and 4 sufficiency studies)
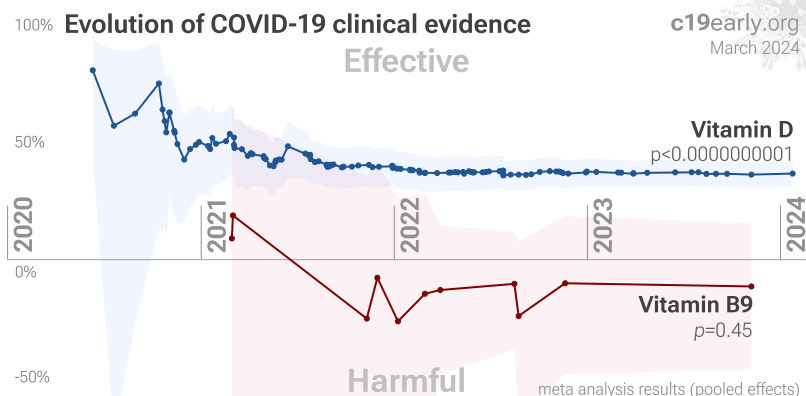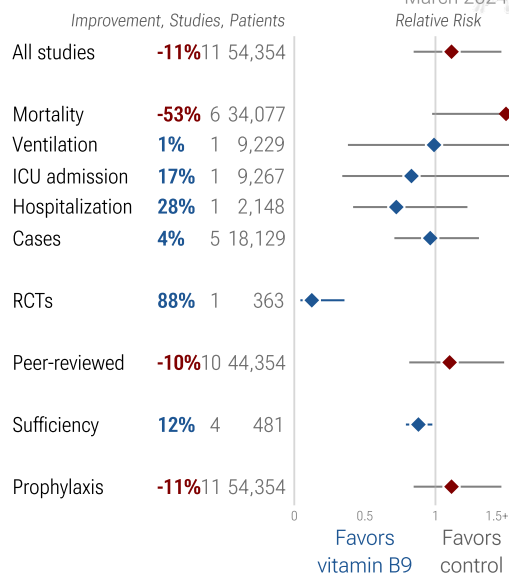
Abstract

Meta analysis using the most serious outcome reported shows 11% [-15-47%] higher risk, without reaching statistical significance.

4 sufficiency studies analyze outcomes based on serum levels, showing 12% [2-21%] 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 *Deschasaux-Tanguy, Farag*, as do sufficiency studies. Folic acid may not be the most effective or safest form for supplementation *Scaglione*. Studies show that a significant fraction of people have genetic variations limiting the ability to convert folic acid to the active form.

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

Vitamin B9 for COVID-19

c19early.org
March 2024
Relative Risk

Improvement, Studies, Patients

	Improvement	Studies	Patients
All studies	**-11%**	11	54,354
Mortality	**-53%**	6	34,077
Ventilation	**1%**	1	9,229
ICU admission	**17%**	1	9,267
Hospitalization	**28%**	1	2,148
Cases	**4%**	5	18,129
RCTs	**88%**	1	363
Peer-reviewed	**-10%**	10	44,354
Sufficiency	**12%**	4	481
Prophylaxis	**-11%**	11	54,354

Favors vitamin B9 — Favors control

Evolution of COVID-19 clinical evidence

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March 2024

Effective

Vitamin D
p<0.0000000001

Harmful

Vitamin B9
p=0.45

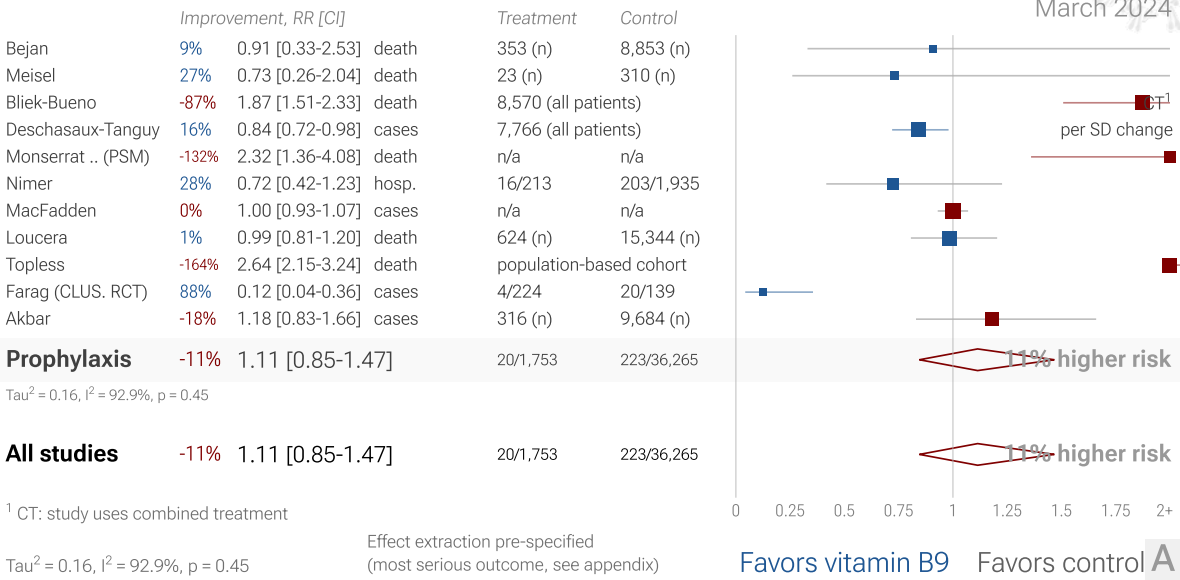meta analysis results (pooled effects)

HIGHLIGHTS

Vitamin B9 reduces risk for COVID-19 with very low confidence for hospitalization, however increased risk is seen with low confidence for mortality and very low confidence for pooled analysis. 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. Folic acid may not be the best form for supplementation.

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

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 66 treatments.
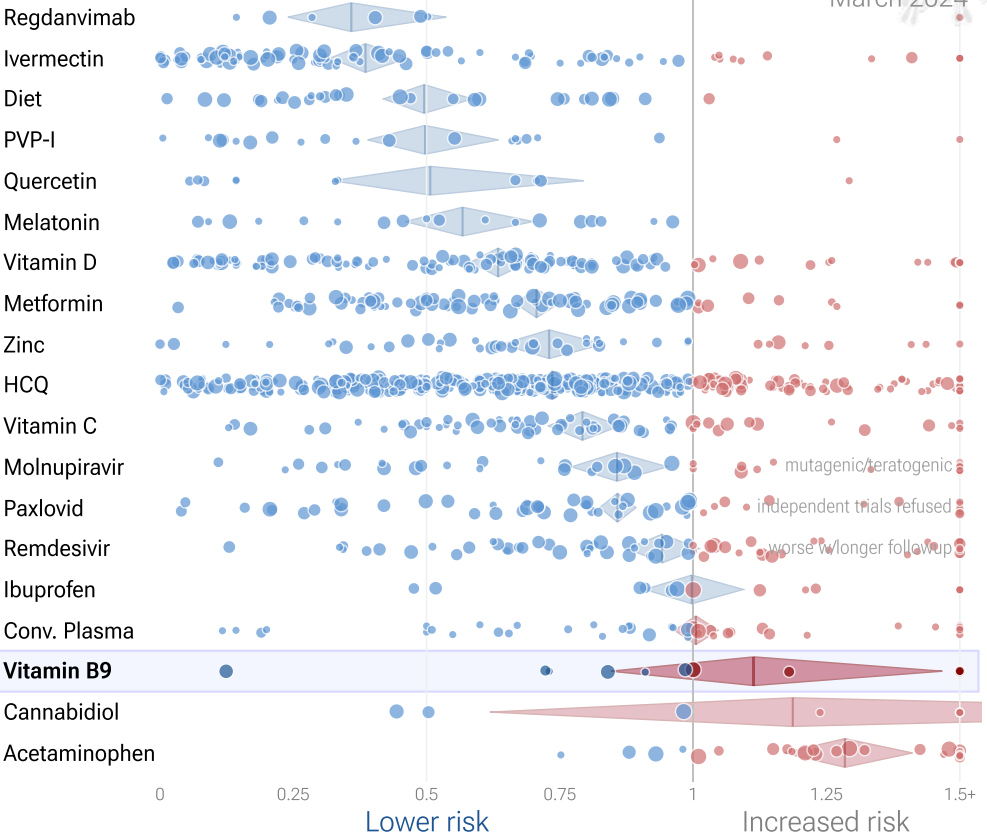
11 vitamin B9 COVID-19 studies

	Improvement, RR [CI]			Treatment	Control
Bejan	9%	0.91 [0.33-2.53]	death	353 (n)	8,853 (n)
Meisel	27%	0.73 [0.26-2.04]	death	23 (n)	310 (n)
Bliek-Bueno	-87%	1.87 [1.51-2.33]	death	8,570 (all patients)	
Deschasaux-Tanguy	16%	0.84 [0.72-0.98]	cases	7,766 (all patients)	
Monserrat .. (PSM)	-132%	2.32 [1.36-4.08]	death	n/a	n/a
Nimer	28%	0.72 [0.42-1.23]	hosp.	16/213	203/1,935
MacFadden	0%	1.00 [0.93-1.07]	cases	n/a	n/a
Loucera	1%	0.99 [0.81-1.20]	death	624 (n)	15,344 (n)
Topless	-164%	2.64 [2.15-3.24]	death	population-based cohort	
Farag (CLUS. RCT)	88%	0.12 [0.04-0.36]	cases	4/224	20/139
Akbar	-18%	1.18 [0.83-1.66]	cases	316 (n)	9,684 (n)
Prophylaxis	**-11%**	**1.11 [0.85-1.47]**		20/1,753	223/36,265

Tau² = 0.16, I² = 92.9%, p = 0.45

All studies	**-11%**	**1.11 [0.85-1.47]**		20/1,753	223/36,265

¹ CT: study uses combined treatment

Tau² = 0.16, I² = 92.9%, p = 0.45

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

Favors vitamin B9   Favors control

A

Efficacy in COVID-19 vitamin B9 studies (pooled effects)

Prophylaxis
All studies

Favors vitamin B9   Favors control

B

Efficacy in COVID-19 studies (pooled effects)

Regdanvimab
Ivermectin
Diet
PVP-I
Quercetin
Melatonin
Vitamin D
Metformin
Zinc
HCQ
Vitamin C
Molnupiravir — mutagenic/teratogenic
Paxlovid — independent trials refused
Remdesivir — worse w/longer followup
Ibuprofen
Conv. Plasma
Vitamin B9
Cannabidiol
Acetaminophen

Lower risk   Increased risk

C

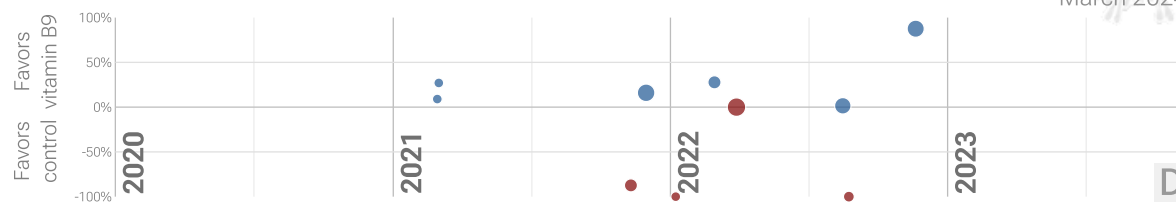**Timeline of COVID-19 vitamin B9 studies (pooled effects)**

Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix. **B. Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis. **C. Results within the context of multiple COVID-19 treatments.** 0.6% of 6,686 proposed treatments show efficacy *c19early.org*. **D. Timeline of results in 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 issues *Scardua-Silva, Yang*, cardiovascular complications *Eberhardt*, organ failure, and death. Minimizing replication as early as possible is recommended.

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

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 *EFSA, Galmés, Galmés (B)*. Vitamin B9 inhibits SARS-CoV-2 In Silico *Chen, Eskandari, Hosseini, Kumar, Moatasim, Pandya, Serseg, Ugurel, Zhang*, reduces spike protein binding ability *Zhang*, binds with the spike protein receptor binding domain for alpha and omicron variants *Pennisi*, inhibits the SARS-CoV-2 nucleocapsid protein *Chen*, inhibits 3CLpro and PLpro in enzymatic assays *Pennisi*, significantly reduces infection for alpha and omicron SARS-CoV-2 pseudoviruses *Pennisi*, and inhibits ACE2 expression and SARS-CoV-2 infection in a mouse model *Zhang*.

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, peer-reviewed studies, and Randomized Controlled Trials (RCTs).

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.

Treatment delay →

Prophylaxis
regularly take medication in advance
to prevent or minimize infections

Early Treatment
treat immediately on symptoms
or shortly thereafter

Late Treatment
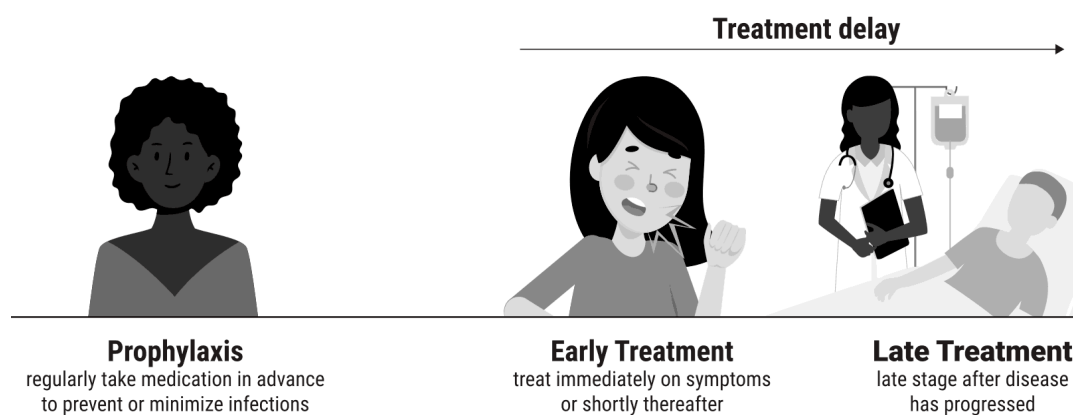late stage after disease
has progressed

Figure 2. Treatment stages.

Preclinical Research

Vitamin B9 inhibits SARS-CoV-2 In Silico *Chen, Eskandari, Hosseini, Kumar, Moatasim, Pandya, Serseg, Ugurel, Zhang*, reduces spike protein binding ability *Zhang*, binds with the spike protein receptor binding domain for alpha and omicron variants *Pennisi*, inhibits the SARS-CoV-2 nucleocapsid protein *Chen*, inhibits 3CLpro and PLpro in enzymatic assays *Pennisi*, significantly reduces infection for alpha and omicron SARS-CoV-2 pseudoviruses *Pennisi*, and inhibits ACE2 expression and SARS-CoV-2 infection in a mouse model *Zhang*.

8 *In Silico* studies support the efficacy of vitamin B9 *Chen, Eskandari, Hosseini, Kumar, Pandya, Pennisi, Serseg, Ugurel*.

4 *In Vitro* studies support the efficacy of vitamin B9 *Chen, Moatasim, Pennisi, Zhang*.

An *In Vivo* animal study supports the efficacy of vitamin B9 *Zhang*.

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, for peer-reviewed studies, and for specific outcomes. Figure 3, 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, sufficiency studies, and peer reviewed studies.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	**-11%** [-47-15%]	11	54,354	187
Peer-reviewed studies	**-10%** [-49-19%]	10	44,354	178
Randomized Controlled Trials	**88%** [64-96%] ***	1	363	9
Mortality	**-53%** [-140-2%]	6	34,077	61
Cases	**4%** [-31-29%]	5	18,129	128

Table 1. **Random effects meta-analysis for all studies, for Randomized Controlled Trials, for peer-reviewed studies, and for specific outcomes.** Results show the percentage improvement with treatment and the 95% confidence interval. *** $p<0.001$.
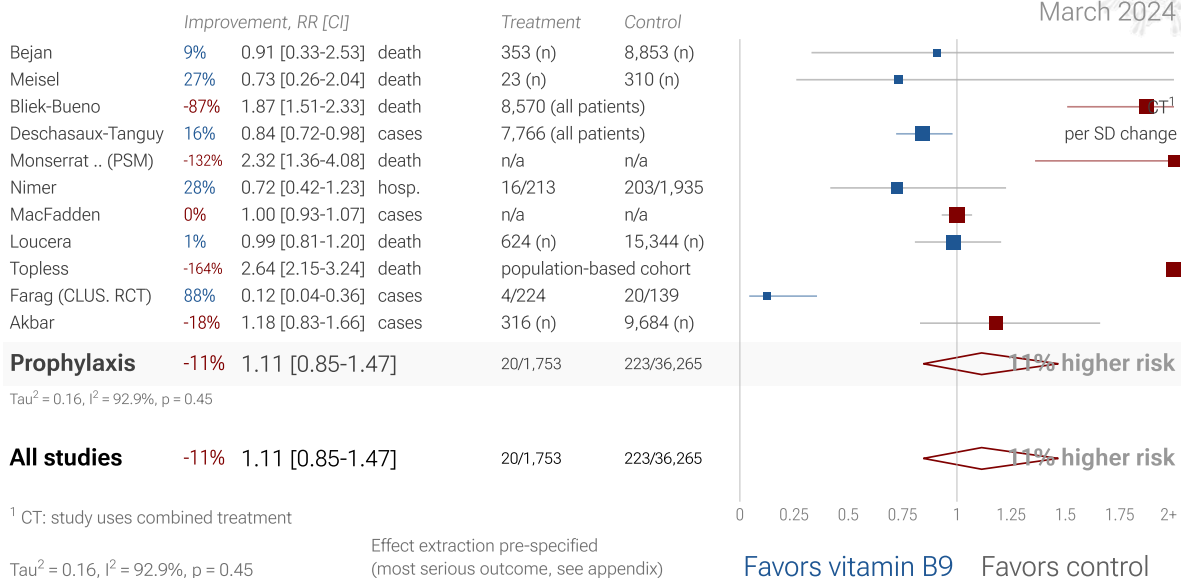
11 vitamin B9 COVID-19 studies

	Improvement, RR [CI]			Treatment	Control
Bejan	9%	0.91 [0.33-2.53]	death	353 (n)	8,853 (n)
Meisel	27%	0.73 [0.26-2.04]	death	23 (n)	310 (n)
Bliek-Bueno	-87%	1.87 [1.51-2.33]	death	8,570 (all patients)	CT[1]
Deschasaux-Tanguy	16%	0.84 [0.72-0.98]	cases	7,766 (all patients)	per SD change
Monserrat .. (PSM)	-132%	2.32 [1.36-4.08]	death	n/a	n/a
Nimer	28%	0.72 [0.42-1.23]	hosp.	16/213	203/1,935
MacFadden	0%	1.00 [0.93-1.07]	cases	n/a	n/a
Loucera	1%	0.99 [0.81-1.20]	death	624 (n)	15,344 (n)
Topless	-164%	2.64 [2.15-3.24]	death	population-based cohort	
Farag (CLUS. RCT)	88%	0.12 [0.04-0.36]	cases	4/224	20/139
Akbar	-18%	1.18 [0.83-1.66]	cases	316 (n)	9,684 (n)
Prophylaxis	**-11%**	**1.11 [0.85-1.47]**		20/1,753	223/36,265	11% higher risk

Tau² = 0.16, I² = 92.9%, p = 0.45

| **All studies** | **-11%** | **1.11 [0.85-1.47]** | | 20/1,753 | 223/36,265 | 11% higher risk |

[1] CT: study uses combined treatment

Tau² = 0.16, I² = 92.9%, p = 0.45

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

Favors vitamin B9   Favors control

Figure 3. Random effects meta-analysis for all studies with pooled effects. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.
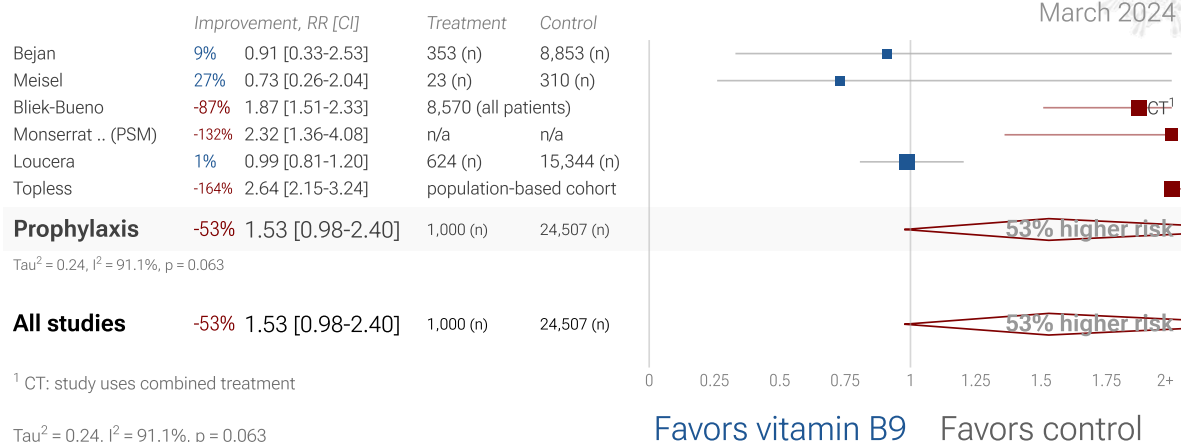
6 vitamin B9 COVID-19 mortality results

	Improvement, RR [CI]		Treatment	Control
Bejan	9%	0.91 [0.33-2.53]	353 (n)	8,853 (n)
Meisel	27%	0.73 [0.26-2.04]	23 (n)	310 (n)
Bliek-Bueno	-87%	1.87 [1.51-2.33]	8,570 (all patients)	CT[1]
Monserrat .. (PSM)	-132%	2.32 [1.36-4.08]	n/a	n/a
Loucera	1%	0.99 [0.81-1.20]	624 (n)	15,344 (n)
Topless	-164%	2.64 [2.15-3.24]	population-based cohort	
Prophylaxis	**-53%**	**1.53 [0.98-2.40]**	1,000 (n)	24,507 (n)	53% higher risk

Tau² = 0.24, I² = 91.1%, p = 0.063

| **All studies** | **-53%** | **1.53 [0.98-2.40]** | 1,000 (n) | 24,507 (n) | 53% higher risk |

[1] CT: study uses combined treatment

Tau² = 0.24, I² = 91.1%, p = 0.063

Favors vitamin B9   Favors control

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

1 vitamin B9 COVID-19 mechanical ventilation result
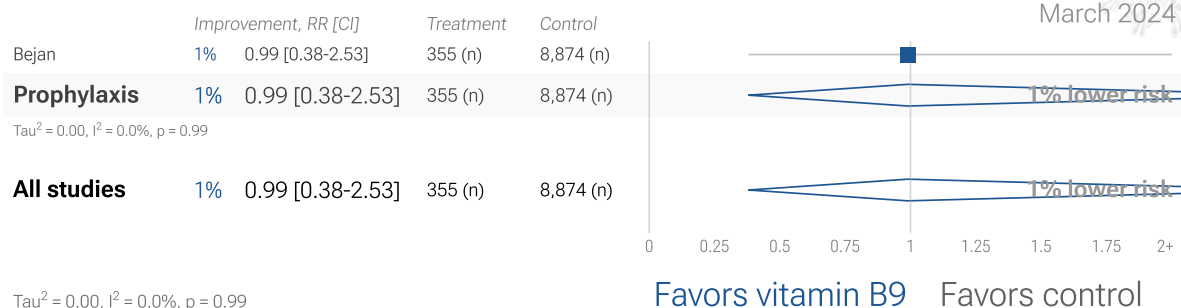
	Improvement, RR [CI]		Treatment	Control
Bejan	1%	0.99 [0.38-2.53]	355 (n)	8,874 (n)
Prophylaxis	**1%**	**0.99 [0.38-2.53]**	355 (n)	8,874 (n)	1% lower risk

Tau² = 0.00, I² = 0.0%, p = 0.99

| **All studies** | **1%** | **0.99 [0.38-2.53]** | 355 (n) | 8,874 (n) | 1% lower risk |

Tau² = 0.00, I² = 0.0%, p = 0.99

Favors vitamin B9   Favors control

Figure 5. Random effects meta-analysis for ventilation.

1 vitamin B9 COVID-19 ICU result

	Improvement, RR [CI]		Treatment	Control
Bejan	17%	0.83 [0.34-2.02]	356 (n)	8,911 (n)
Prophylaxis	17%	0.83 [0.34-2.02]	356 (n)	8,911 (n)
Tau² = 0.00, I² = 0.0%, p = 0.7				
All studies	17%	0.83 [0.34-2.02]	356 (n)	8,911 (n)

17% lower risk

17% lower risk

0   0.25   0.5   0.75   1   1.25   1.5   1.75   2+

Tau² = 0.00, I² = 0.0%, p = 0.7

Favors vitamin B9   Favors control
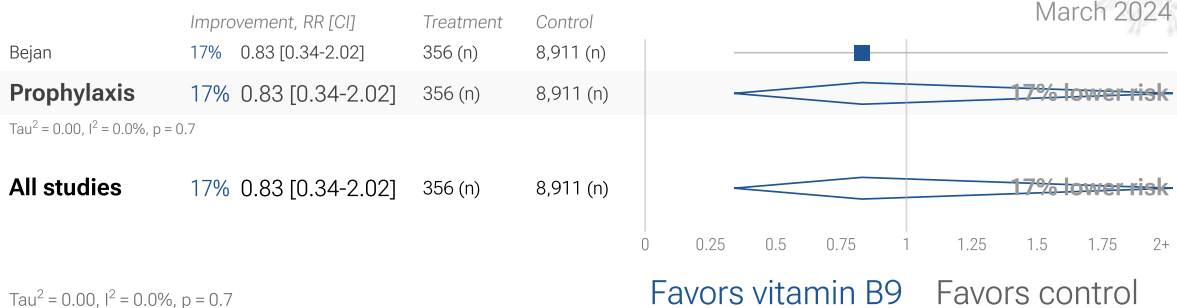
Figure 6. Random effects meta-analysis for ICU admission.

1 vitamin B9 COVID-19 hospitalization result

	Improvement, RR [CI]			Treatment	Control
Nimer	28%	0.72 [0.42-1.23]	hosp.	16/213	203/1,935
Prophylaxis	28%	0.72 [0.42-1.23]		16/213	203/1,935
Tau² = 0.00, I² = 0.0%, p = 0.19					
All studies	28%	0.72 [0.42-1.23]		16/213	203/1,935

28% lower risk

28% lower risk

0   0.25   0.5   0.75   1   1.25   1.5   1.75   2+

Tau² = 0.00, I² = 0.0%, p = 0.19

Favors vitamin B9   Favors control
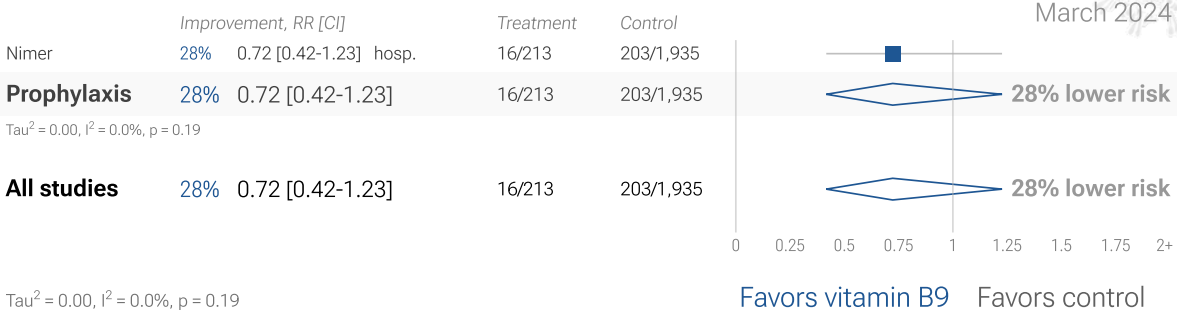
Figure 7. Random effects meta-analysis for hospitalization.

5 vitamin B9 COVID-19 case results

	Improvement, RR [CI]			Treatment	Control
Deschasaux-Tanguy	16%	0.84 [0.72-0.98]	cases	7,766 (all patients)	
MacFadden	0%	1.00 [0.93-1.07]	cases	n/a	n/a
Topless	-51%	1.51 [1.42-1.61]	cases	population-based cohort	
Farag (CLUS. RCT)	88%	0.12 [0.04-0.36]	cases	4/224	20/139
Akbar	-18%	1.18 [0.83-1.66]	cases	316 (n)	9,684 (n)
Prophylaxis	4%	0.96 [0.71-1.31]		4/540	20/9,823
Tau² = 0.10, I² = 96.6%, p = 0.82					
All studies	4%	0.96 [0.71-1.31]		4/540	20/9,823

per SD change

4% lower risk

4% lower risk

0   0.25   0.5   0.75   1   1.25   1.5   1.75   2+

Tau² = 0.10, I² = 96.6%, p = 0.82

Favors vitamin B9   Favors control

Figure 8. Random effects meta-analysis for cases.

4 vitamin B9 COVID-19 sufficiency studies

	Improvement, RR [CI]			High Levels	Low Levels
Meisel	15%	0.85 [0.41-1.75]	death	296 (n)	38 (n)
Doğan	56%	0.44 [0.04-4.51]	death	2/54	1/12
Voelkle	12%	0.88 [0.78-0.98]	death/ICU	n/a	n/a
Abdulrahman	-75%	1.75 [0.19-16.7]	death	72 (n)	9 (n)
All studies	**12%**	**0.88 [0.79-0.98]**		**2/422**	**1/59**

per SD change

12% lower risk

Tau^2 = 0.00, I^2 = 0.0%, p = 0.018

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

Favors vitamin B9   Favors control
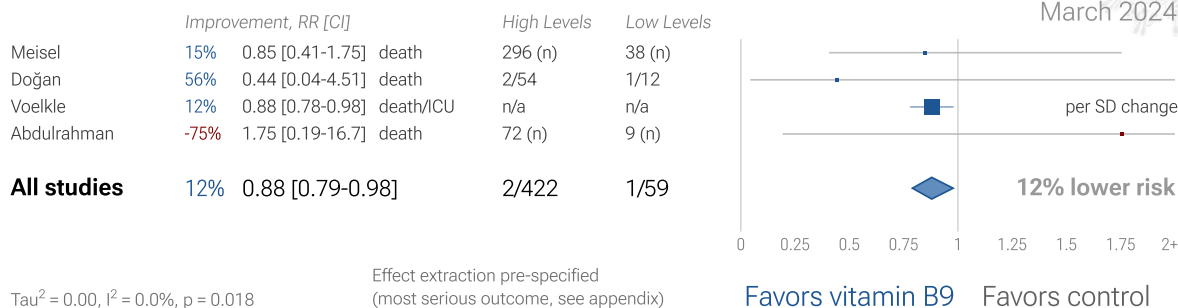
Figure 9. Random effects meta-analysis for sufficiency studies. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.

10 vitamin B9 COVID-19 peer reviewed studies

	Improvement, RR [CI]			Treatment	Control
Bejan	9%	0.91 [0.33-2.53]	death	353 (n)	8,853 (n)
Meisel	27%	0.73 [0.26-2.04]	death	23 (n)	310 (n)
Bliek-Bueno	-87%	1.87 [1.51-2.33]	death	8,570 (all patients)	
Deschasaux-Tanguy	16%	0.84 [0.72-0.98]	cases	7,766 (all patients)	
Monserrat .. (PSM)	-132%	2.32 [1.36-4.08]	death	n/a	n/a
Nimer	28%	0.72 [0.42-1.23]	hosp.	16/213	203/1,935
MacFadden	0%	1.00 [0.93-1.07]	cases	n/a	n/a
Loucera	1%	0.99 [0.81-1.20]	death	624 (n)	15,344 (n)
Topless	-164%	2.64 [2.15-3.24]	death	population-based cohort	
Farag (CLUS. RCT)	88%	0.12 [0.04-0.36]	cases	4/224	20/139
Prophylaxis	**-10%**	**1.10 [0.81-1.49]**		**20/1,437**	**223/26,581**

CT[1]

per SD change

10% higher risk

Tau^2 = 0.17, I^2 = 93.6%, p = 0.54

All studies	**-10%**	**1.10 [0.81-1.49]**		**20/1,437**	**223/26,581**

10% higher risk

[1] CT: study uses combined treatment

Tau^2 = 0.17, I^2 = 93.6%, p = 0.54

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

Favors vitamin B9   Favors control

Figure 10. Random effects meta-analysis for peer reviewed studies. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. *Davidson et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

Randomized Controlled Trials (RCTs)

Figure 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. Bias in clinical research may be defined as something that tends to make conclusions differ systematically from the truth. RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases *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, and the potential for fraud. All of these biases have been observed with COVID-19 RCTs. There is no guarantee that a specific RCT provides a higher level of evidence.

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

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

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

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

1 vitamin B9 COVID-19 Randomized Controlled Trials

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March 2024

	Improvement, RR [CI]		Treatment	Control			
Farag (CLUS. RCT)	88%	0.12 [0.04-0.36] cases	4/224	20/139			
Prophylaxis	**88%**	**0.12 [0.04-0.36]**	**4/224**	**20/139**			**88% lower risk**

Tau² = 0.00, I² = 0.0%, p = 0.00012

| **All studies** | **88%** | **0.12 [0.04-0.36]** | **4/224** | **20/139** | | | **88% lower risk** |

0   0.25   0.5   0.75   1   1.25   1.5   1.75   2+

Tau² = 0.00, I² = 0.0%, p = 0.00012

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

Favors vitamin B9   Favors control

Figure 11. Random effects meta-analysis for all Randomized Controlled Trials. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

Heterogeneity

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

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

Table 2. Studies of baloxavir 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 66 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.
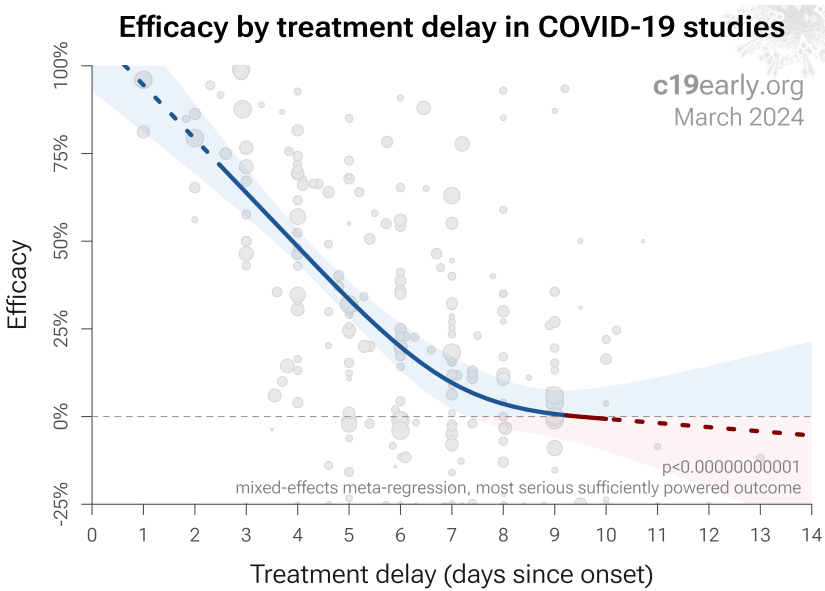
Figure 12. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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

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

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

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

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

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

Pooled outcome analysis. We present both pooled analyses and specific outcome analyses. Notably, pooled analysis often results in earlier detection of efficacy as shown in Figure 13. For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, etc. An antiviral tested with a low-risk population may report zero mortality in both arms, however a reduction in severity and improved viral clearance may translate into lower mortality among a high-risk population, and including these results in pooled analysis allows faster detection of efficacy. Trials with high-risk patients may also be restricted due to ethical concerns for treatments that are known or expected to be effective.

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

Pooled outcomes identify efficacy faster. Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 88% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 3.6 months. When restricting to RCTs only, 50% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.1 months.
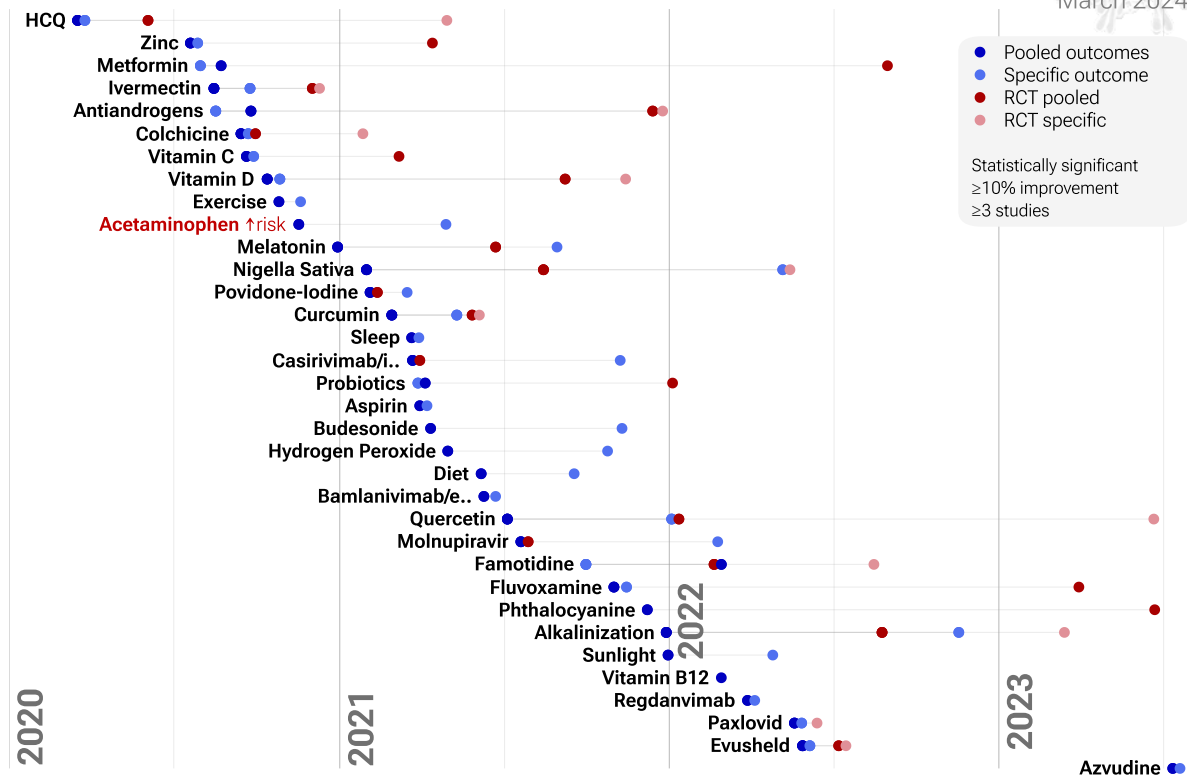
Time when COVID-19 studies showed efficacy

Legend:
- Pooled outcomes
- Specific outcome
- RCT pooled
- RCT specific

Statistically significant
≥10% improvement
≥3 studies

Treatments (top to bottom): HCQ, Zinc, Metformin, Ivermectin, Antiandrogens, Colchicine, Vitamin C, Vitamin D, Exercise, Acetaminophen ↑risk, Melatonin, Nigella Sativa, Povidone-Iodine, Curcumin, Sleep, Casirivimab/i.., Probiotics, Aspirin, Budesonide, Hydrogen Peroxide, Diet, Bamlanivimab/e.., Quercetin, Molnupiravir, Famotidine, Fluvoxamine, Phthalocyanine, Alkalinization, Sunlight, Vitamin B12, Regdanvimab, Paxlovid, Evusheld, Azvudine

Time axis: 2020, 2021, 2022, 2023

Figure 13. 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.

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

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

Discussion

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

incentive for scientists that value media recognition), and there are many reports of difficulty publishing positive results *Boulware, Meeus, Meneguesso*. 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 14 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.
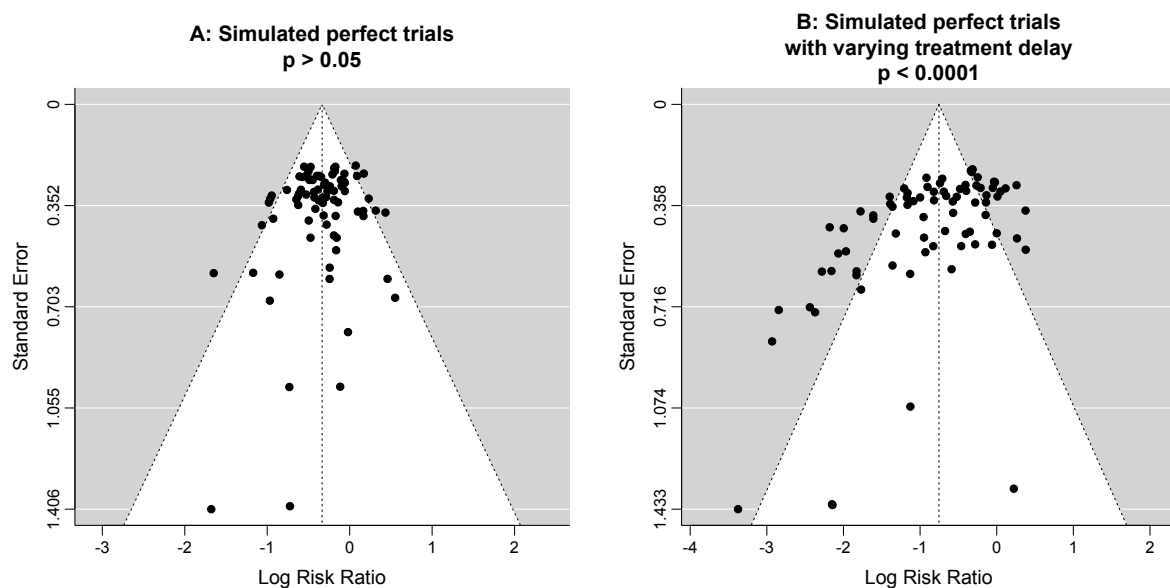
Figure 14. Example funnel plot analysis for simulated perfect trials.

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

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

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

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

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

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone *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, vaccine, or intervention is 100% available and effective for all current and future variants. Efficacy may vary significantly with different variants and within different populations. All treatments have potential side effects. Propensity to experience side effects may be predicted in advance by qualified physicians. We do not provide medical advice. Before taking any medication, consult a qualified physician who can compare all options, provide personalized advice, and provide details of risks and benefits based on individual medical history and situations.

Notes. 1 of 11 studies combine treatments. The results of vitamin B9 alone may differ. None of the RCTs use combined treatment.

Reviews. Multiple reviews cover vitamin B9 for COVID-19, presenting additional background on mechanisms and related results, including *Karakousis, Scaglione*.
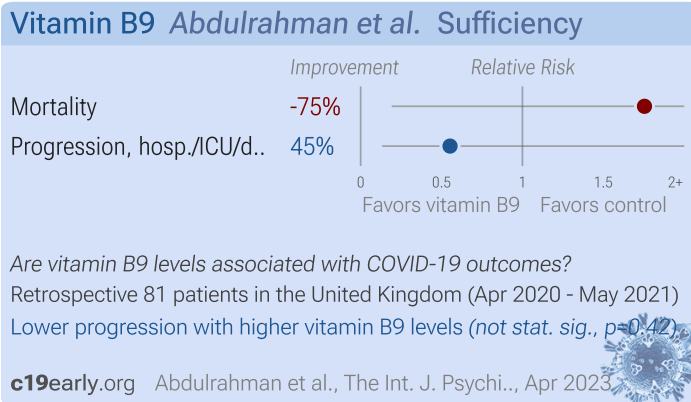
Conclusion

Meta analysis using the most serious outcome reported shows 11% [-15-47%] higher risk, without reaching statistical significance. 4 sufficiency studies analyze outcomes based on serum levels, showing 12% [2-21%] 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 *Deschasaux-Tanguy, Farag*, as do sufficiency studies. Folic acid may not be the most effective or safest form for supplementation *Scaglione*. Studies show that a significant fraction of people have genetic variations limiting the ability to convert folic acid to the active form.
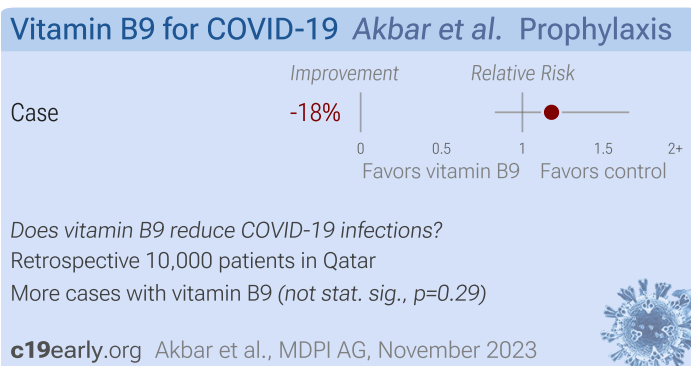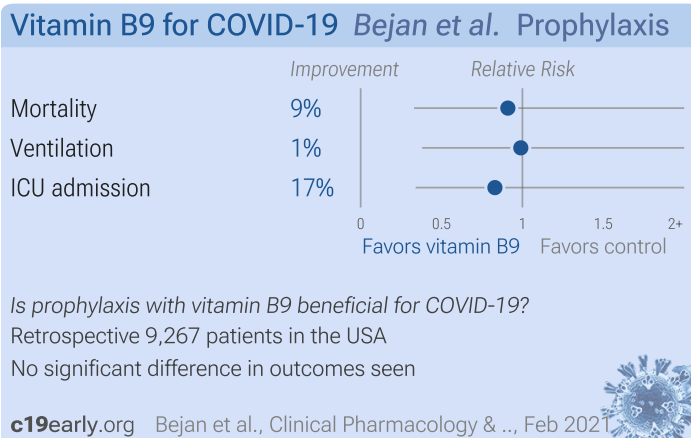
Study Notes

Abdulrahman

Vitamin B9 *Abdulrahman et al.* **Sufficiency**

	Improvement	Relative Risk
Mortality	-75%	
Progression, hosp./ICU/d..	45%	

0   0.5   1   1.5   2+
Favors vitamin B9   Favors control

Are vitamin B9 levels associated with COVID-19 outcomes?
Retrospective 81 patients in the United Kingdom (Apr 2020 - May 2021)
Lower progression with higher vitamin B9 levels *(not stat. sig., p=0.42)*

c19early.org   Abdulrahman et al., The Int. J. Psychi.., Apr 2023

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

Akbar

Vitamin B9 for COVID-19 *Akbar et al.* **Prophylaxis**

	Improvement	Relative Risk
Case	-18%	

0   0.5   1   1.5   2+
Favors vitamin B9   Favors control

Does vitamin B9 reduce COVID-19 infections?
Retrospective 10,000 patients in Qatar
More cases with vitamin B9 *(not stat. sig., p=0.29)*

c19early.org   Akbar et al., MDPI AG, November 2023

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

Vitamin B9 for COVID-19 *Bejan et al.* **Prophylaxis**

	Improvement	Relative Risk
Mortality	9%	
Ventilation	1%	
ICU admission	17%	

0   0.5   1   1.5   2+
Favors vitamin B9   Favors control

Is prophylaxis with vitamin B9 beneficial for COVID-19?
Retrospective 9,267 patients in the USA
No significant difference in outcomes seen

c19early.org   Bejan et al., Clinical Pharmacology & .., Feb 2021

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

Bliek-Bueno

Vitamin B9 *Bliek-Bueno et al.* Prophylaxis

	Improvement	*Relative Risk*
Mortality, combined	-87%	
Mortality, Campania	-170%	
Mortality, Aragon	-59%	

0   0.5   1   1.5   2+
Favors vitamin B9   Favors control

Is prophylaxis with vitamin B9 + Vitamin B12 beneficial for COVID-19?
Retrospective 8,570 patients in multiple countries (Mar - Apr 2020)
Higher mortality with vitamin B9 + Vitamin B12 *(p<0.000001)*

c19early.org   Bliek-Bueno et al., Int. J. Environmen.., Nov 2021

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

Vitamin B9 *Deschasaux-Tanguy et al.* Prophylaxis

	Improvement	*Relative Risk*	
Case	16%		per SD change

0   0.5   1   1.5   2+
Favors vitamin B9   Favors control

Does vitamin B9 reduce COVID-19 infections?
Retrospective 7,766 patients in France
Fewer cases with vitamin B9 *(p=0.02)*

c19early.org   Deschasaux-Tanguy et al., BMC Medicine, Nov 2021
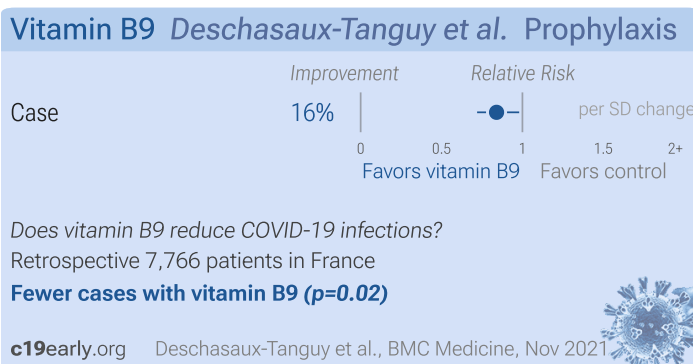
Deschasaux-Tanguy: Analysis of 7,766 adults in France, showing higher intakes of vitamin C, folate, vitamin K, dietary fibre, and fruit and vegetables associated with lower seropositivity.

Doğan

Vitamin B9 for COVID-19 *Doğan et al.* Sufficiency

	Improvement	*Relative Risk*
Mortality	56%	
ICU admission	-11%	

0   0.5   1   1.5   2+
Favors vitamin B9   Favors control

Are vitamin B9 levels associated with COVID-19 outcomes?
Retrospective 66 patients in Turkey (January - March 2022)
Lower mortality with higher vitamin B9 levels *(not stat. sig., p=0.46)*

c19early.org   Doğan et al., Sağlık Akademisi Kastamonu, Apr 2022

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

Farag

Vitamin B9 *Farag et al.* Prophylaxis RCT

	Improvement	Relative Risk
Case, 1000μg	88%	
Case, 500μg	66%	

0   0.5   1   1.5   2+
Favors vitamin B9   Favors control

Does vitamin B9 reduce COVID-19 infections?
RCT 363 patients in Egypt (May - June 2020)
Fewer cases with vitamin B9 *(p=0.000004)*

c19early.org   Farag et al., Microbes and Infectious .., Nov 2022
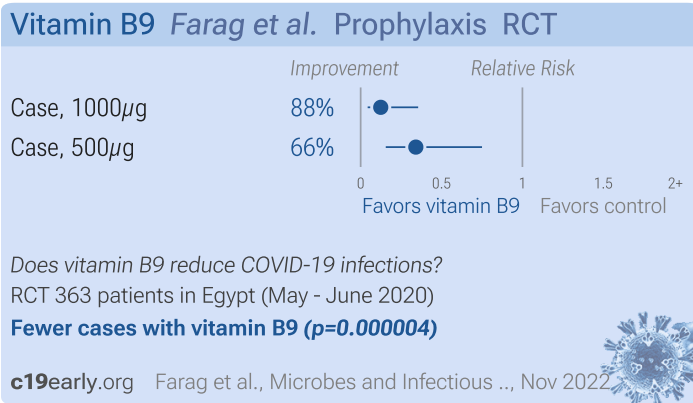
Farag: Cluster RCT 526 healthcare workers in Egypt, showing lower COVID-19 cases with folic acid supplementation, and a dose-response relationship. Each wave of health care workers was randomized within 14 day isolation periods, introducing potential confounding by time.

Loucera

Vitamin B9 for COVID-19 *Loucera et al.* Prophylaxis

	Improvement	Relative Risk
Mortality	1%	

0   0.5   1   1.5   2+
Favors vitamin B9   Favors control

Is prophylaxis with vitamin B9 beneficial for COVID-19?
Retrospective 15,968 patients in Spain (January - November 2020)
No significant difference in mortality

c19early.org   Loucera et al., Virology J., August 2022
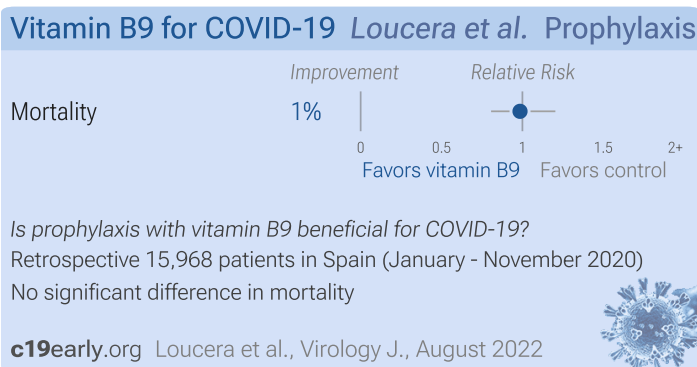
Loucera: Retrospective 15,968 COVID-19 hospitalized patients in Spain, showing no significant difference in mortality with existing use of folic acid. Since only hospitalized patients are included, results do not reflect different probabilities of hospitalization across treatments.

MacFadden

Vitamin B9 for COVID-19 *MacFadden et al.* Prophylaxis

	Improvement	Relative Risk
Case	0%	

0   0.5   1   1.5   2+
Favors vitamin B9   Favors control

Does vitamin B9 reduce COVID-19 infections?
Retrospective study in Canada (January - December 2020)
No significant difference in cases

c19early.org   MacFadden et al., Open Forum Infectiou.., Mar 2022
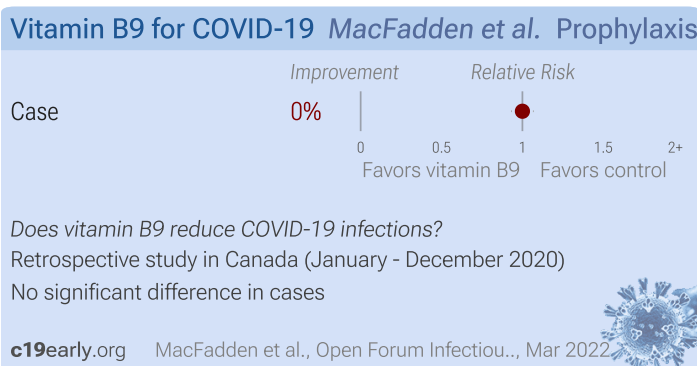
MacFadden: Retrospective 26,121 cases and 2,369,020 controls ≥65yo in Canada, showing no significant difference in cases with chronic use of vitamin B9.

Meisel

Vitamin B9 for COVID-19 *Meisel et al.* Prophylaxis

	Improvement	Relative Risk
Mortality	27%	
Death/intubation	6%	
Mortality, 5.9ng/mL	15%	levels
Death/intubation, 5.9ng/mL	40%	levels

0   0.5   1   1.5   2+
Favors vitamin B9   Favors control

Is prophylaxis with vitamin B9 beneficial for COVID-19?
Retrospective 334 patients in Israel (January - November 2020)
Lower mortality with vitamin B9 *(not stat. sig., p=0.54)*

c19early.org Meisel et al., Nutrients, March 2021

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

Monserrat Villatoro

Vitamin B9 *Monserrat Villatoro et al.* Prophylaxis

	Improvement	Relative Risk
Mortality	-132%	

0   0.5   1   1.5   2+
Favors vitamin B9   Favors control

Is prophylaxis with vitamin B9 beneficial for COVID-19?
PSM retrospective study in Spain
Higher mortality with vitamin B9 *(p=0.0027)*

c19early.org   Monserrat Villatoro et al., Pharmaceut.., Jan 2022
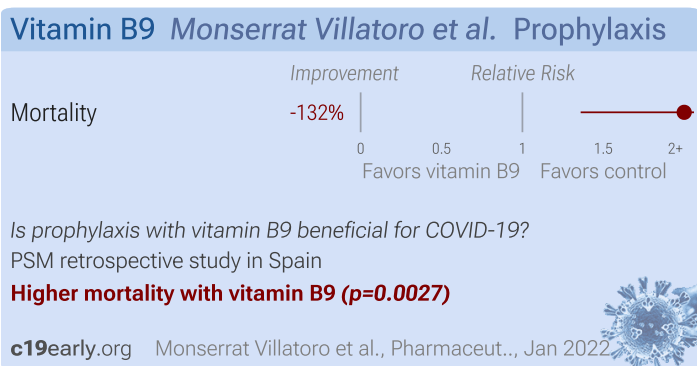
Monserrat Villatoro: PSM retrospective 3,712 hospitalized patients in Spain, showing lower mortality with existing use of azithromycin, bemiparine, budesonide-formoterol fumarate, cefuroxime, colchicine, enoxaparin, ipratropium bromide, loratadine, mepyramine theophylline acetate, oral rehydration salts, and salbutamol sulphate, and higher mortality with acetylsalicylic acid, digoxin, folic acid, mirtazapine, linagliptin, enalapril, atorvastatin, and allopurinol.

Nimer

Vitamin B9 for COVID-19 *Nimer et al.* Prophylaxis

	Improvement	Relative Risk
Hospitalization	28%	
Severe case	28%	

0   0.5   1   1.5   2+
Favors vitamin B9   Favors control

Is prophylaxis with vitamin B9 beneficial for COVID-19?
Retrospective 2,148 patients in Jordan (March - July 2021)
Lower hospitalization *(p=0.23)* and severe cases *(p=0.16)*, not sig.

c19early.org   Nimer et al., Bosnian J. Basic Medical.., Feb 2022

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

Tomasa-Irriguible

Tomasa-Irriguible: Estimated 300 patient vitamin B9 early treatment RCT with results expected soon (estimated completion over 3 months ago).

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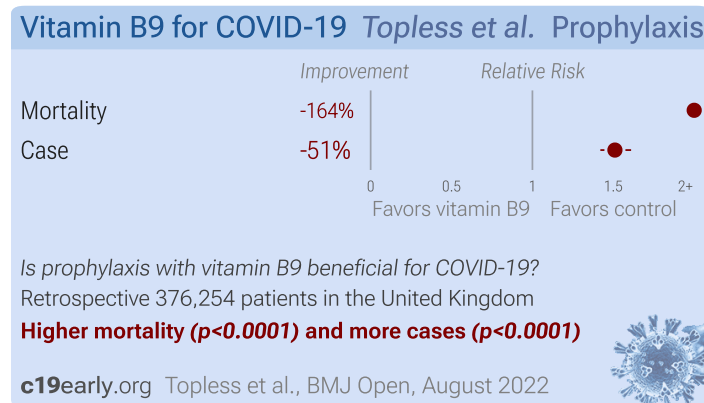
Topless: UK Biobank retrospective showing higher cases and mortality with folic acid supplementation.

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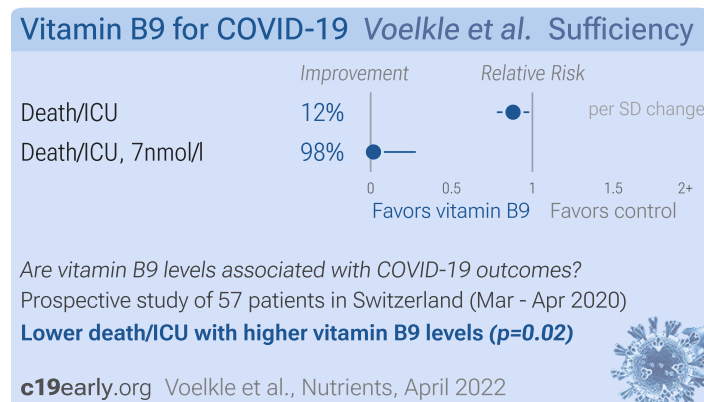
Voelkle: Prospective study of 57 consecutive hospitalized COVID-19 patients in Switzerland, showing lower risk of mortality/ICU admission with vitamin B9. Adjustments only considered age.

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. 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 (B)*. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 *Sweeting*. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.12.2) with scipy (1.12.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.1), and plotly (5.19.0).

Forest plots are computed using PythonMeta *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*.

A summary of study results is below. Please submit updates and corrections at https://c19early.org/b9meta.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.

Tomasa-Irriguible, 11/30/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Spain, trial NCT04751669 (history) (CoVIT).	Estimated 300 patient RCT with results unknown and over 3 months late.

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, preprint, mean age 40.3, 9 authors.	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.

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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