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

@CovidAnalysis, November 2023
https://c19early.org/b9meta.html

- 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 confounding 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.

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 confounding 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 57 treatments.
### 11 vitamin B9 COVID-19 studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Improvement, RR [CI]</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bejan</td>
<td>9% 0.91 [0.33-2.53]</td>
<td>death</td>
<td>353 (n)</td>
</tr>
<tr>
<td>Meisel</td>
<td>27% 0.73 [0.26-2.04]</td>
<td>death</td>
<td>20 (n)</td>
</tr>
<tr>
<td>Bleik-Bueno</td>
<td>-87% 1.87 [1.51-2.33]</td>
<td>death</td>
<td>8,570 (all patients)</td>
</tr>
<tr>
<td>Deschaseau-Tangy</td>
<td>16% 0.84 [0.72-0.98]</td>
<td>cases</td>
<td>7,766 (all patients)</td>
</tr>
<tr>
<td>Monseret</td>
<td>-13% 2.32 [1.36-4.08]</td>
<td>death</td>
<td>n/a</td>
</tr>
<tr>
<td>Nimer</td>
<td>28% 0.72 [0.42-1.23]</td>
<td>hosp.</td>
<td>16/213</td>
</tr>
<tr>
<td>MacFadden</td>
<td>0% 1.00 [0.93-1.07]</td>
<td>cases</td>
<td>n/a</td>
</tr>
<tr>
<td>Loucera</td>
<td>1% 0.99 [0.81-1.20]</td>
<td>death</td>
<td>624 (n)</td>
</tr>
<tr>
<td>Topless</td>
<td>-54% 2.64 [2.15-3.24]</td>
<td>death</td>
<td>n/a</td>
</tr>
<tr>
<td>Farag (CLUS, RCT)</td>
<td>88% 0.12 [0.04-0.36]</td>
<td>cases</td>
<td>4/224</td>
</tr>
<tr>
<td>Akbar</td>
<td>-18% 1.18 [0.83-1.66]</td>
<td>cases</td>
<td>316 (n)</td>
</tr>
</tbody>
</table>

**Prophylaxis**

-11%  1.11 [0.85-1.47]  201,753  223,062,265

**All studies**

-11%  1.11 [0.85-1.47]  201,753  223,062,265

1 CT: study uses combined treatment

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

Favors vitamin B9  Favors control

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

- **Ivermectin**
- **PVP-I**
- **Quercetin**
- **Melatonin**
- **Sunlight**
- **Exercise**
- **Fluvoxamine**
- **Vitamin D**
- **Metformin**
- **Zinc**
- **HCQ**
- **Sotrovimab**
- **Vitamin C**
- **Paxlovid**
- **Molnupiravir**
- **Remdesivir**
- **Ibuprofen**
- **Conv. Plasma**
- **Vitamin B9**
- **Cannabidiol**
- **Acetaminophen**

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**Effect extraction pre-specified**

- Variant dependent
- Independent trials refused
- Mutagenic/teratogenic
- Worse/w/longer followup
- Independent trials refused
**Introduction**

We analyze all significant studies concerning the use 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).

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.

**Preclinical Research**

7 **In Silico** studies support the efficacy of vitamin B9 [Chen, Eskandari, Hosseini, Kumar, Pandya, Serseg, Ugurel].

An **In Vitro** study supports the efficacy of vitamin B9 [Chen].

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, with different exclusions, 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.

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Studies</th>
<th>Patients</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>-11% [-47-15%]</td>
<td>11</td>
<td>54,354</td>
</tr>
<tr>
<td>Peer-reviewed studies</td>
<td>-10% [-49-19%]</td>
<td>10</td>
<td>44,354</td>
</tr>
<tr>
<td>Randomized Controlled Trials</td>
<td>88% [64-96%] ***</td>
<td>1</td>
<td>363</td>
</tr>
<tr>
<td>Mortality</td>
<td>-53% [-14-0-2%]</td>
<td>6</td>
<td>34,077</td>
</tr>
<tr>
<td>Cases</td>
<td>4% [-31-29%]</td>
<td>5</td>
<td>18,129</td>
</tr>
</tbody>
</table>

Table 1. Random effects meta-analysis for all studies, with different exclusions, 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

<table>
<thead>
<tr>
<th>Improvement, RR [CI]</th>
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</tr>
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<td>27% [0.73 [0.26-2.04]</td>
<td>death</td>
</tr>
<tr>
<td>Bleik-Bueno</td>
<td>-87% [1.87 [1.51-2.33]</td>
<td>death</td>
</tr>
<tr>
<td>Deschasaux-Tanguy</td>
<td>16% [0.84 [0.72-0.98]</td>
<td>cases</td>
</tr>
<tr>
<td>Monserrat ... (PSM)</td>
<td>-132% [2.32 [1.36-4.08]</td>
<td>death</td>
</tr>
<tr>
<td>Nimer</td>
<td>28% [0.72 [0.42-1.23]</td>
<td>hosp.</td>
</tr>
<tr>
<td>MacFadden</td>
<td>0% [1.00 [0.93-1.07]</td>
<td>cases</td>
</tr>
<tr>
<td>Loucera</td>
<td>1% [0.99 [0.81-1.20]</td>
<td>cases</td>
</tr>
<tr>
<td>Topless</td>
<td>-16% [2.64 [2.15-3.24]</td>
<td>death</td>
</tr>
<tr>
<td>Farag (CLUS. RCT)</td>
<td>88% [0.12 [0.04-0.36]</td>
<td>cases</td>
</tr>
<tr>
<td>Akbar</td>
<td>-18% [1.18 [0.83-1.66]</td>
<td>cases</td>
</tr>
</tbody>
</table>

Prophylaxis | -11% [1.11 [0.85-1.47] |

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Improvement, RR (CI)</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bejan</td>
<td>9% [0.91-2.53]</td>
<td>353 (n)</td>
<td>8,853 (n)</td>
</tr>
<tr>
<td>Meisel</td>
<td>27% [0.73-2.04]</td>
<td>23 (n)</td>
<td>310 (n)</td>
</tr>
<tr>
<td>Bliek-Bueno</td>
<td>-87% [1.51-3.33]</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Monserrat ... (PSM)</td>
<td>-132% [2.32-4.08]</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Loucera</td>
<td>1% [0.81-1.20]</td>
<td>624 (n)</td>
<td>15,344 (n)</td>
</tr>
<tr>
<td>Topless</td>
<td>-164% [2.15-3.24]</td>
<td>population-based cohort</td>
<td></td>
</tr>
</tbody>
</table>

**Prophylaxis** -53% [0.98-2.40] 0/1,000 0/24,507

**All studies** -53% [0.98-2.40] 0/1,000 0/24,507

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

### 1 vitamin B9 COVID-19 mechanical ventilation result

<table>
<thead>
<tr>
<th>Study</th>
<th>Improvement, RR (CI)</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bejan</td>
<td>1% [0.99-2.53]</td>
<td>356 (n)</td>
<td>8,911 (n)</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>1% [0.99-2.53]</td>
<td>0/356</td>
<td>0/8,911</td>
</tr>
</tbody>
</table>

**All studies** 1% [0.99-2.53] 0/356 0/8,911

**Figure 5.** Random effects meta-analysis for ventilation.

### 1 vitamin B9 COVID-19 ICU result

<table>
<thead>
<tr>
<th>Study</th>
<th>Improvement, RR (CI)</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bejan</td>
<td>17% [0.83-2.02]</td>
<td>356 (n)</td>
<td>8,911 (n)</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>17% [0.83-2.02]</td>
<td>0/356</td>
<td>0/8,911</td>
</tr>
</tbody>
</table>

**All studies** 17% [0.83-2.02] 0/356 0/8,911

**Figure 6.** Random effects meta-analysis for ICU admission.
Figure 7. Random effects meta-analysis for hospitalization.

Table: 1 vitamin B9 COVID-19 hospitalization result

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Improvement, RR [CI]</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis</td>
<td>28% 0.72 [0.42-1.23]</td>
<td>16/213 203/1,935</td>
</tr>
<tr>
<td>Nimer</td>
<td>28% 0.72 [0.42-1.23]</td>
<td>16/213 203/1,935</td>
</tr>
<tr>
<td>All studies</td>
<td>28% 0.72 [0.42-1.23]</td>
<td>16/213 203/1,935</td>
</tr>
</tbody>
</table>

Figure 8. Random effects meta-analysis for cases.

Table: 5 vitamin B9 COVID-19 case results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Improvement, RR [CI]</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topless</td>
<td>-51% 1.51 [1.42-1.61]</td>
<td>4/540 20/9,823</td>
</tr>
<tr>
<td>Deschasaux-Tanguy</td>
<td>16% 0.84 [0.72-0.98]</td>
<td>7,766 (all patients)</td>
</tr>
<tr>
<td>MacFadden</td>
<td>0% 1.00 [0.93-1.07]</td>
<td>n/a n/a</td>
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<tr>
<td>Farag (CLUS, RCT)</td>
<td>88% 0.12 [0.04-0.36]</td>
<td>4/224 20/139</td>
</tr>
<tr>
<td>Akbar</td>
<td>-18% 1.18 [0.83-1.66]</td>
<td>316 (n) 9,684 (n)</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>4% 0.96 [0.71-1.31]</td>
<td>4/540 20/9,823</td>
</tr>
<tr>
<td>All studies</td>
<td>4% 0.96 [0.71-1.31]</td>
<td>4/540 20/9,823</td>
</tr>
</tbody>
</table>

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.

Table: 4 vitamin B9 COVID-19 sufficiency studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Improvement, RR [CI]</th>
<th>High Levels</th>
<th>Low Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdulrahman</td>
<td>-75% 1.75 [0.19-16.7]</td>
<td>72 (n) 9 (n)</td>
<td></td>
</tr>
<tr>
<td>Doğan</td>
<td>56% 0.44 [0.04-4.51]</td>
<td>2/54 1/12</td>
<td></td>
</tr>
<tr>
<td>Voekle</td>
<td>12% 0.88 [0.78-0.99]</td>
<td>n/a n/a</td>
<td></td>
</tr>
<tr>
<td>Meisel</td>
<td>15% 0.85 [0.41-1.75]</td>
<td>296 (n) 38 (n)</td>
<td></td>
</tr>
<tr>
<td>All studies</td>
<td>12% 0.88 [0.79-0.98]</td>
<td>2/422 1/59</td>
<td></td>
</tr>
</tbody>
</table>

Effect extraction pre-specified (most serious outcome, see appendix)
Figure 10. Random effects meta-analysis for peer reviewed studies. Zeraatkar 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. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.

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 and Table 2. 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. Understanding bias is critical to interpreting study results. 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.

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 enrolment 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 57 treatments we have analyzed, 64% 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, 39 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 39 treatments with statistically significant efficacy/harm, 24 have been confirmed in RCTs, with a mean delay of 5.7 months. For the 15 unconfirmed treatments, 4 have zero RCTs to date. The point estimates for the remaining 11 are all consistent with the overall results (benefit or harm), with 9 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.

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.

<table>
<thead>
<tr>
<th>Treatment delay</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post exposure prophylaxis</td>
<td>86% fewer cases][Ikematsu]</td>
</tr>
<tr>
<td>&lt;24 hours</td>
<td>-33 hours symptoms][Hayden]</td>
</tr>
<tr>
<td>24-48 hours</td>
<td>-13 hours symptoms][Hayden]</td>
</tr>
<tr>
<td>Inpatients</td>
<td>-2.5 hours to improvement][Kumar (B)]</td>
</tr>
</tbody>
</table>

Table 3. 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 57 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

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, 39 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 89% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 3.4 months. When restricting to RCTs only, 52% 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.

**Time when COVID-19 studies showed efficacy**

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, Meneghesso]. 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.](image-url)
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, Biancatelli, De Forni, Gasmi, Jeffrey, Jitobaom, Jitobaom (B), Ostrov, Thairu. 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.
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 confounding 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, as do sufficiency studies. Folic acid may not be the most effective or safest form for supplementation. 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

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)

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

Akbar

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

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**

*Bejan et al.* Prophylaxis

<table>
<thead>
<tr>
<th>Vitamin B9 for COVID-19</th>
<th>Improvement</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>9%</td>
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<tr>
<td>Ventilation</td>
<td>1%</td>
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<tr>
<td>ICU admission</td>
<td>17%</td>
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</table>

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

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

**Bliek-Bueno**

*Bliek-Bueno et al.* Prophylaxis

<table>
<thead>
<tr>
<th>Vitamin B9</th>
<th>Improvement</th>
<th>Relative Risk</th>
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</thead>
<tbody>
<tr>
<td>Mortality, combined</td>
<td>-87%</td>
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<td>Mortality, Campania</td>
<td>-170%</td>
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<tr>
<td>Mortality, Aragon</td>
<td>-59%</td>
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</tbody>
</table>

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)*

*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**

*Deschasaux-Tanguy et al.* Prophylaxis

<table>
<thead>
<tr>
<th>Vitamin B9</th>
<th>Improvement</th>
<th>Relative Risk per SD change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>16%</td>
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</tr>
</tbody>
</table>

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

*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**

<table>
<thead>
<tr>
<th></th>
<th>Improvement</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>56%</td>
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<tr>
<td>ICU admission</td>
<td>-11%</td>
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</table>

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)

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**

<table>
<thead>
<tr>
<th></th>
<th>Improvement</th>
<th>Relative Risk</th>
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</thead>
<tbody>
<tr>
<td>Case, 1000µg</td>
<td>88%</td>
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<tr>
<td>Case, 500µg</td>
<td>66%</td>
<td></td>
</tr>
</tbody>
</table>

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

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**

<table>
<thead>
<tr>
<th></th>
<th>Improvement</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

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

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**

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

Meisel

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

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)

Monserrat Villatoro

**Vitamin B9 Monserrat Villatoro et al. Prophylaxis**

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

*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.

*Monserrat Villatoro:* PSM retrospective 3,712 hospitalized patients in Spain, showing lower mortality with existing use of azithromycin, bempiramine, budesonide-formoterol fumarate, cefuroxime, colchicine, enoxaparin, ipratropium bromide, loratadine, mepyramine theophylline acetate, oral rehydration salts, and salsalate 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*

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.

**Topless**

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

Is prophylaxis with vitamin B9 beneficial for COVID-19?
Retrospective 376,254 patients in the United Kingdom
Higher mortality (p<0.0001) and more cases (p<0.0001)

**Voelkle**

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

Are vitamin B9 levels associated with COVID-19 outcomes?
Prospective study of 57 patients in Switzerland (Mar - Apr 2020)
Lower death/ICU with higher vitamin B9 levels (p=0.02)

---

*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.
Appendix 1. Methods and Data

We performed ongoing searches of PubMed, medRxiv, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Collabovid, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19early.org. Search terms were vitamin B9, filtered for papers containing the terms COVID-19 or SARS-CoV-2. Automated searches are performed every few hours with notification of new matches. 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 are used. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms were not used (the next most serious outcome is used — no studies were excluded). 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 outcome is considered more important than PCR testing 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 no room for an effective treatment to do better). If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO₂ is more important than cough. When results provide an odds ratio, we computed the relative risk when possible, or converted 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 including propensity score matching (PSM), the PSM results are used. Adjusted primary outcome 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 (3.11.6) with scipy (1.11.3), pythonmeta (1.26), numpy (1.26.1), statsmodels (0.14.0), and plotly (5.17.0).

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. 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.

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

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.
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.

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Study Design</th>
<th>Country</th>
<th>Procedure</th>
<th>Mean Age</th>
<th>Authors</th>
<th>Study Period</th>
<th>Outcomes</th>
<th>Risk Change</th>
<th>OR, p Value</th>
<th>RR Approximated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akbar, 11/7/2023</td>
<td>retrospective,</td>
<td>Qatar, preprint</td>
<td>mean age 40.3, 9 authors</td>
<td>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.</td>
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<td>Bejan, 2/28/2021</td>
<td>retrospective,</td>
<td>USA, peer-reviewed,</td>
<td>mean age 42.0, 6 authors</td>
<td>risk of death, 9.0% lower, OR 0.91, p = 0.87, treatment 353, control 8,853, adjusted per study, RR approximated with OR.</td>
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<td>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.</td>
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<td>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.</td>
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<td>Biek-Bueno, 11/10/2021</td>
<td>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.</td>
<td>risk of death, 87.4% higher, OR 1.87, p &lt; 0.001, combined, RR approximated with OR.</td>
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<td>risk of death, 170.0% higher, OR 2.70, p &lt; 0.001, Campania, RR approximated with OR.</td>
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<td>risk of death, 59.0% higher, OR 1.59, p &lt; 0.001, Aragon, RR approximated with OR.</td>
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<tr>
<td>Deschasaux-Tanguy, 11/30/2021</td>
<td>retrospective, France, peer-reviewed, 95 authors.</td>
<td>risk of case, 16.0% lower, OR 0.84, p = 0.02, RR approximated with OR, per standard deviation change.</td>
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<tr>
<td>Farag, 11/20/2022</td>
<td>Cluster Randomized Controlled Trial, Egypt, peer-reviewed, mean age 37.5, 9 authors, study period 17 May, 2020 - 30 June, 2020, trial PACTR202005599385499.</td>
<td>risk of case, 87.6% lower, RR 0.12, p &lt; 0.001, treatment 4 of 224 (1.8%), control 20 of 139 (14.4%), NNT 7.9, 1000µg.</td>
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<td>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.</td>
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<tr>
<td>Loucera, 8/16/2022</td>
<td>retrospective, Spain, peer-reviewed, 8 authors, study period January 2020 - November 2020.</td>
<td>risk of death, 1.5% lower, HR 0.99, p = 0.88, treatment 624, control 15,344, Cox proportional hazards, day 30.</td>
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<tr>
<td>MacFadden, 3/29/2022</td>
<td>retrospective, Canada, peer-reviewed, 9 authors, study period 15 January, 2020 - 31 December, 2020.</td>
<td>risk of case, no change, OR 1.00, p = 1.00, RR approximated with OR.</td>
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<tr>
<td>Meisel, 3/2/2021</td>
<td>retrospective, Israel, peer-reviewed, 8 authors, study period 27 January, 2020 - 23 November, 2020.</td>
<td>risk of death, 27.0% lower, OR 0.73, p = 0.54, treatment 23, control 310, RR approximated with OR.</td>
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<td>risk of death/intubation, 6.0% lower, OR 0.94, p = 0.88, treatment 23, control 310, RR approximated with OR.</td>
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<tr>
<td>Monserrat Villatoro, 1/8/2022</td>
<td>retrospective, propensity score matching, Spain, peer-reviewed, 18 authors.</td>
<td>risk of death, 132.0% higher, OR 2.32, p = 0.003, RR approximated with OR.</td>
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</tbody>
</table>
Nimer, 2/28/2022, retrospective, Jordan, peer-reviewed, survey, 4 authors, study period March 2021 - July 2021.

<table>
<thead>
<tr>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

Topless, 8/24/2022, retrospective, United Kingdom, peer-reviewed, 6 authors.

<table>
<thead>
<tr>
<th>Risk of death, 164.0% higher, OR 2.64, p &lt; 0.001, adjusted per study, multivariable, model 2, RR approximated with OR.</th>
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</thead>
<tbody>
<tr>
<td>Risk of case, 51.0% higher, OR 1.51, p &lt; 0.001, adjusted per study, multivariable, model 2, RR approximated with OR.</td>
</tr>
</tbody>
</table>

### Supplementary Data

### References


3. **Alsaidi** et al., Griffithsin and Carrageenan Combination Results in Antiviral Synergy against SARS-CoV-1 and 2 in a Pseudoviral Model, Marine Drugs, doi:10.3390/md19080418.


5. **Altman (B)** et al., How to obtain the confidence interval from a P value, BMJ, doi:10.1136/bmj.d2090.


10. **Boulware**, D., Comments regarding paper rejection, twitter.com/boulware_dr/status/1311331372884205570.


17. Egger et al., Bias in meta-analysis detected by a simple, graphical test, BMJ, doi:10.1136/bmj.315.7109.629.


20. Faria et al., Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil, Science, doi:10.1126/science.abh2644.


25. Hosseini et al., Computational molecular docking and virtual screening revealed promising SARS-CoV-2 drugs, Precision Clinical Medicine, doi:10.1093/pcmedi/pbab001.


42. Monserrat Villatoro et al., A Case-Control of Patients with COVID-19 to Explore the Association of Previous Hospitalization Use of Medication on the Mortality of COVID-19 Disease: A Propensity Score Matching Analysis, Pharmaceuticals, doi:10.3390/ph15010078.

43. Moreno et al., Assessment of regression-based methods to adjust for publication bias through a comprehensive simulation study, BMC Medical Research Methodology, doi:10.1186/1471-2288-9-2.


46. Ostrov et al., Highly Specific Sigma Receptor Ligands Exhibit Anti-Viral Properties in SARS-CoV-2 Infected Cells, Pathogens, doi:10.3390/pathogens10111514.


51. Rücker et al., Arcsine test for publication bias in meta-analyses with binary outcomes, Statistics in Medicine, doi:10.1002/sim.2971.

52. Scaglione et al., Folate, folic acid and 5-methyltetrahydrofolate are not the same thing, Xenobiotica, doi:10.3109/00498254.2013.845705.


61. Willett et al., The hyper-transmissible SARS-CoV-2 Omicron variant exhibits significant antigenic change, vaccine escape and a switch in cell entry mechanism, medRxiv, doi:10.1101/2022.01.03.21268111.

62. Williams, T., Not All Ivermectin Is Created Equal: Comparing The Quality of 11 Different Ivermectin Sources, Do Your Own Research, doyourownresearch.substack.com/p/not-all-ivermectin-is-created-equal.


64. Zavascki et al., Advanced ventilatory support and mortality in hospitalized patients with COVID-19 caused by Gamma (P.1) variant of concern compared to other lineages: cohort study at a reference center in Brazil, Research Square, doi:10.21203/rs.3.rs-910467/v1.

