Vitamin B12 for COVID-19: real-time meta analysis of 4 studies
@CovidAnalysis, November 2023
https://c19early.org/b12meta.html

- Meta analysis using the most serious outcome reported shows 30% (5-48%) lower risk.
- No treatment or intervention is 100% effective. All practical, effective, and safe means should be used based on risk/benefit analysis. Multiple treatments are typically used in combination, and other treatments are more effective. There has been no early treatment studies to date. There is very limited data to date, with only one RCT, 2 treatment studies, and 2 prophylaxis studies.
- All data to reproduce this paper and sources are in the appendix.

Vitamin B12 for COVID-19

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage</th>
<th>Studies</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement, Studies, Patients</td>
<td>30%</td>
<td>4</td>
<td>11,407</td>
</tr>
<tr>
<td>Mortality</td>
<td>34%</td>
<td>1</td>
<td>9,206</td>
</tr>
<tr>
<td>Ventilation</td>
<td>35%</td>
<td>1</td>
<td>9,229</td>
</tr>
<tr>
<td>ICU admission</td>
<td>30%</td>
<td>2</td>
<td>9,301</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>11%</td>
<td>3</td>
<td>11,930</td>
</tr>
<tr>
<td>RCTs</td>
<td>75%</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>Prophylaxis Late</td>
<td>26%</td>
<td>2</td>
<td>11,354</td>
</tr>
<tr>
<td>Prophylaxis Early</td>
<td>77%</td>
<td>2</td>
<td>53</td>
</tr>
</tbody>
</table>

Favors vitamin B12
Favors control

Evolution of COVID-19 clinical evidence

Vitamin B12
p=0.023

Acetaminophen
p=0.00000094

HIGHLIGHTS

Vitamin B12 reduces risk for COVID-19 with high confidence for pooled analysis, low confidence for recovery, and very low confidence for hospitalization.

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.
### Efficacy in COVID-19 vitamin B12 studies (pooled effects)

**Prophylaxis**
- Nimer: 24% (0.76, 0.52-1.10), 35/395 vs. 184/1,753

**Late treatment**
- Erfani (RCT): 75% (0.25, 0.03-2.01), 1/17 vs. 4/17

**All studies**
- 30% (0.70, 0.52-0.95), 37/1,035 vs. 198/10,372

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**Effect extraction pre-specified**

- Tau^2 = 0.00, I^2 = 0.0%, p = 0.023
- Most serious outcome, see appendix

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**Favors vitamin B12**
- 4 vitamin B12 COVID-19 studies

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**Efficacy in COVID-19 studies (pooled effects)**
- Ivermectin
- PVP-I
- Quercetin
- Melatonin
- Sunlight
- Exercise
- Fluvoxamine
- Vitamin D
- Vitamin B12
- Metformin
- Zinc
- HCQ
- Sotrovimab
- Vitamin C
- Paxlovid
- Molnupiravir
- Remdesivir
- Ibuprofen
- Conv. Plasma
- Vitamin B9
- Cannabidiol
- Acetaminophen

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**Lower risk**
- Increased risk
**Timeline of COVID-19 vitamin B12 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. 0.7% of 5,722 proposed treatments show efficacy c19early.org. D. Timeline of results in vitamin B12 studies. The marked date indicates the time when efficacy was known with a statistically significant improvement of $\geq 10\%$ from $\geq 3$ studies for pooled outcomes.

**Introduction**

Vitamin B12 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.\cite{EFSA, Galmés, Galmés (B)}

We analyze all significant studies concerning the use of vitamin B12 for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random effects meta-analysis results for all studies, studies within each treatment stage, individual outcomes, 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.

**Figure 2.** Treatment stages.
Preclinical Research

In Silico studies support the efficacy of vitamin B12 \cite{Kandeel, Pandya}.

Preclinical research is an important part of the development of treatments, however results may be very different in clinical trials. Preclinical results are not used in this paper.

Results

Table 1 summarizes the results for all stages combined, after exclusions, and for specific outcomes. Table 2 shows results by treatment stage. Figure 3, 4, 5, 6, and 7 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, and hospitalization.

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Studies</th>
<th>Patients</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>30% (5-48%) *</td>
<td>4</td>
<td>11,407</td>
</tr>
<tr>
<td>Randomized Controlled Trials</td>
<td>75% [-101-97%]</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>ICU admission</td>
<td>30% [-64-70%]</td>
<td>2</td>
<td>9,301</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>11% [-9-28%]</td>
<td>3</td>
<td>11,930</td>
</tr>
</tbody>
</table>

Table 1. Random effects meta-analysis for all stages combined, after exclusions, and for specific outcomes. Results show the percentage improvement with treatment and the 95% confidence interval. *p<0.05.

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Late treatment</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>77% [9-94%] *</td>
<td>26% [-2-46%]</td>
</tr>
<tr>
<td>Randomized Controlled Trials</td>
<td>75% [-101-97%]</td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>75% [-101-97%]</td>
<td>16% [-60-56%]</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>-1% [-41-28%]</td>
<td>18% [-6-37%]</td>
</tr>
</tbody>
</table>

Table 2. Random effects meta-analysis results by treatment stage. Results show the percentage improvement with treatment, the 95% confidence interval, and the number of studies for the stage. *p<0.05.
4 vitamin B12 COVID-19 studies

**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.

1 vitamin B12 COVID-19 mortality result

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

1 vitamin B12 COVID-19 mechanical ventilation result

**Figure 5.** Random effects meta-analysis for ventilation.
**Randomized Controlled Trials (RCTs)**

Figure 8 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. Analysis of double-blind RCTs has identified extreme levels of bias. 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 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 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).

Non-RCT studies have been shown to be reliable. Evidence shows that non-RCT trials can also provide reliable results. Concato find that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. Anglmyer summarized reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. Lee shows that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or Internet survey bias could have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see Beaton, Nichol.

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.

1 vitamin B12 COVID-19 Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Improvement, RR [CI]</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erfani (RCT) 75%</td>
<td>0.25 [0.03-2.01] ICU 1/17 4/17</td>
<td></td>
</tr>
<tr>
<td>Late treatment 75%</td>
<td>0.25 [0.03-2.01] 1/17 4/17</td>
<td></td>
</tr>
<tr>
<td>All studies 75%</td>
<td>0.25 [0.03-2.01] 1/17 4/17</td>
<td></td>
</tr>
</tbody>
</table>

Figure 8. 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 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. 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 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</td>
</tr>
</tbody>
</table>

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

Figure 9 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.

**Efficacy by treatment delay in COVID-19 studies**

*Figure 9. Early treatment is more effective. Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 57 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 LópezMédina).

**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 10. 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.
The time when COVID-19 studies showed efficacy

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020</td>
<td>HCQ</td>
<td>Low</td>
</tr>
<tr>
<td>2021</td>
<td>Zinc</td>
<td>High</td>
</tr>
<tr>
<td>2022</td>
<td>Ivermectin</td>
<td>High</td>
</tr>
<tr>
<td>2023</td>
<td>Pooled</td>
<td>High</td>
</tr>
</tbody>
</table>

**Figure 10.** 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 show 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. For vitamin B12, there is currently not enough data to evaluate publication bias with high confidence.
One method to evaluate bias is to compare prospective vs. retrospective studies. Prospective studies are more likely to be published regardless of the result, while retrospective studies are more likely to exhibit bias. For example, researchers may perform preliminary analysis with minimal effort and the results may influence their decision to continue. Retrospective studies also provide more opportunities for the specifics of data extraction and adjustments to influence results.

Figure 11 shows a scatter plot of results for prospective and retrospective studies.

![Efficacy in COVID-19 vitamin B12 studies (pooled effects)](image)

**Efficacy in COVID-19 vitamin B12 studies (pooled effects)**

**Figure 11.** Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.

Funnel plot analysis. Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 12 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 $p < 0.05$. 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.

![Funnel plot analysis for simulated perfect trials](image)

**Figure 12.** 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 B12 for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 vitamin B12 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 B12 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. 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.

**Conclusion**

Meta analysis using the most serious outcome reported shows 30% [5-48%] lower risk.
Study Notes

Bejan

**Vitamin B12 for COVID-19**  
*Bejan et al.* Prophylaxis

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>34%</td>
</tr>
<tr>
<td>Ventilation</td>
<td>35%</td>
</tr>
<tr>
<td>ICU admission</td>
<td>16%</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>10%</td>
</tr>
</tbody>
</table>

*Is prophylaxis with vitamin B12 beneficial for COVID-19?*  
Retrospective 9,748 patients in the USA  
Lower mortality (*p*=0.3) and ventilation (*p*=0.26), not sig.

*Bejan*: Retrospective 9,748 COVID-19 patients in the USA showing lower risk with vitamin B12 use, without statistical significance.

Erfani

**Vitamin B12**  
*Erfani et al.* LATE TREATMENT RCT

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>75%</td>
</tr>
<tr>
<td>Hospitalization time</td>
<td>-1%</td>
</tr>
</tbody>
</table>

*Is late treatment with vitamin B12 beneficial for COVID-19?*  
RCT 34 patients in Iran  
Lower ICU admission with vitamin B12 (not stat. sig., *p*=0.34)

*Erfani*: Small RCT 34 hospitalized patients in Iran showing improved inflammatory markers and lower ICU admission with vitamin B12 treatment, without statistical significance. There was no mortality.

Jang

**Vitamin B12 for COVID-19**  
*Jang et al.* ECMO PATIENTS

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery</td>
<td>78%</td>
</tr>
</tbody>
</table>

*Is late treatment with vitamin B12 beneficial for COVID-19?*  
Retrospective 19 patients in South Korea (February - April 2020)  
Improved recovery with vitamin B12 (*p*=0.041)

*Jang*: Improved recovery with vitamin B12 treatment in ECMO patients.
Jang: Retrospective 19 COVID-19 ECMO patients in South Korea, showing a higher rate of weaning from ECMO with vitamin B12 treatment, without statistical significance. Authors perform multivariate analysis but do not provide full results, only reporting $p > 0.05$.

Nimer

![Vitamin B12 for COVID-19](image)

Is prophylaxis with vitamin B12 beneficial for COVID-19?
Retrospective 2,148 patients in Jordan (March - July 2021)
Lower hospitalization ($p=0.15$) and severe cases ($p=0.06$), not sig.

Is prophylaxis with vitamin B12 beneficial for COVID-19?
Retrospective 2,148 patients in Jordan (March - July 2021)
Lower hospitalization ($p=0.15$) and severe cases ($p=0.06$), not sig.

Nimer: Retrospective 2,148 COVID-19 recovered patients in Jordan, showing lower risk of severity and hospitalization with vitamin B12 prophylaxis, without statistical significance.

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 B12, 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 B12 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 SpO$_2$ 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. 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 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.

A summary of study results is below. Please submit updates and corrections at https://c19early.org/b12meta.html.

Late treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

<table>
<thead>
<tr>
<th>Erfani, 9/14/2023, Randomized Controlled Trial, placebo-controlled, Iran, peer-reviewed, median age 52.6, 4 authors.</th>
<th>risk of ICU admission, 75.0% lower, RR 0.25, p = 0.34, treatment 1 of 17 (5.9%), control 4 of 17 (23.5%), NNT 5.7.</th>
<th>hospitalization time, 0.8% higher, relative time 1.01, p = 0.97, treatment mean 7.47 (±2.93) n=17, control mean 7.41 (±4.88) n=17.</th>
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<tr>
<td>Jang, 12/16/2020, retrospective, South Korea, peer-reviewed, median age 63.0, 10 authors, study period February 2020 - April 2020.</td>
<td>risk of no recovery, 78.3% lower, RR 0.22, p = 0.04, treatment 1 of 6 (16.7%), control 10 of 13 (76.9%), NNT 1.7, weaning from ECMO.</td>
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</table>

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>
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<tr>
<th>Bejan, 2/28/2021, retrospective, USA, peer-reviewed, mean age 42.0, 6 authors.</th>
<th>risk of death, 34.0% lower, OR 0.66, p = 0.30, treatment 617, control 8,589, adjusted per study, RR approximated with OR.</th>
<th>risk of mechanical ventilation, 35.0% lower, OR 0.65, p = 0.26, treatment 618, control 8,611, adjusted per study, RR approximated with OR.</th>
</tr>
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<tbody>
<tr>
<td>risk of ICU admission, 16.0% lower, OR 0.84, p = 0.61, treatment 625, control 8,642, adjusted per study, RR approximated with OR.</td>
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</tbody>
</table>
### References

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