# Zinc for COVID-19: real-time meta analysis of 61 studies (44 treatment studies and 17 sufficiency studies)

## Abstract

Statistically significant lower risk is seen for mortality, ventilation, hospitalization, progression, recovery, and viral clearance. 18 studies from 18 independent teams in 9 countries show statistically significant improvements.

Meta analysis using the most serious outcome reported shows 27% [17-36%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, peer-reviewed studies, and after excluding studies using combined treatment.

17 sufficiency studies analyze outcomes based on serum levels, showing 74% [64-81%] lower risk for patients with higher zinc levels.

Results are robust — in exclusion sensitivity analysis 19 of 44 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

8 studies use combined treatments. After exclusion the risk reduction is 26% [15-35%] compared to 27% [17-36%].
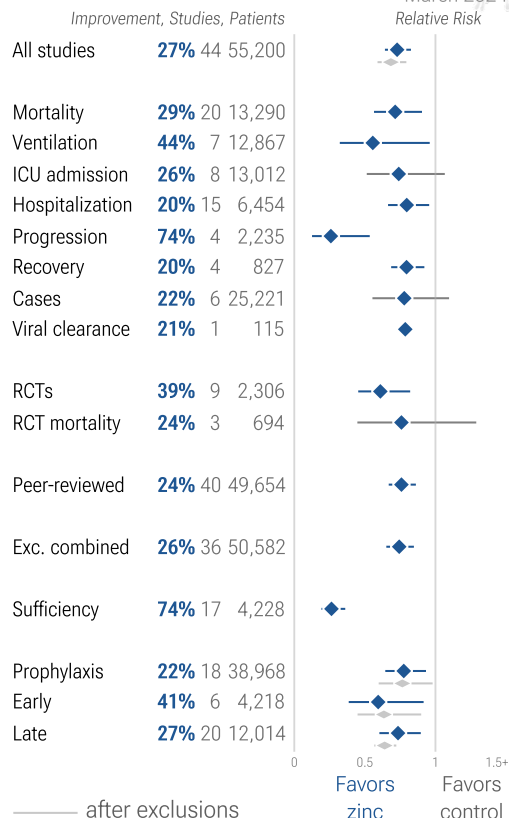
5 RCTs with 1,040 patients have not reported results (up to 3 years late).

The European Food Safety Authority has found evidence for a causal relationship between the intake of zinc and optimal immune system function $^{Galmés, Galmés (B)}$. Over-supplementation may be detrimental $^{karger.com}$. Bioaccessibility of supplements varies widely $^{Ośko}$.
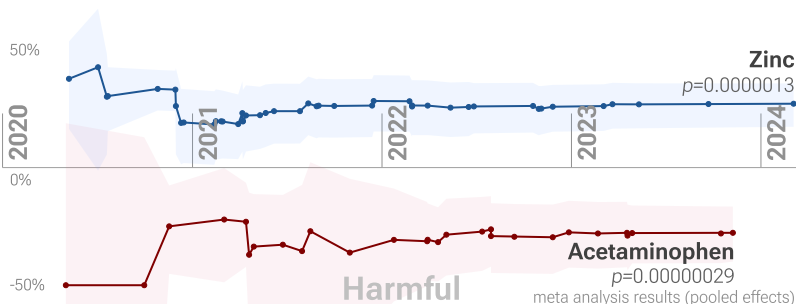
No treatment or intervention is 100% effective. All practical, effective, and safe means should be used based on risk/benefit analysis. Multiple treatments are typically used in combination, and other treatments are more effective. The quality of non-prescription supplements can vary widely $^{Crawford, Crighton}$.

All data to reproduce this paper and sources are in the appendix. Other meta analyses show significant improvements with zinc for mortality $^{Abuhelwa, Olczak-Pruc, Rheingold, Tabatabaeizadeh, Xie}$, severity $^{Fan}$, and cases $^{Fan}$.

**Zinc for COVID-19**

c19early.org
March 2024
*Relative Risk*

*Improvement, Studies, Patients*

| | Improvement | Studies | Patients |
|---|---|---|---|
| All studies | **27%** | 44 | 55,200 |
| Mortality | **29%** | 20 | 13,290 |
| Ventilation | **44%** | 7 | 12,867 |
| ICU admission | **26%** | 8 | 13,012 |
| Hospitalization | **20%** | 15 | 6,454 |
| Progression | **74%** | 4 | 2,235 |
| Recovery | **20%** | 4 | 827 |
| Cases | **22%** | 6 | 25,221 |
| Viral clearance | **21%** | 1 | 115 |
| RCTs | **39%** | 9 | 2,306 |
| RCT mortality | **24%** | 3 | 694 |
| Peer-reviewed | **24%** | 40 | 49,654 |
| Exc. combined | **26%** | 36 | 50,582 |
| Sufficiency | **74%** | 17 | 4,228 |
| Prophylaxis | **22%** | 18 | 38,968 |
| Early | **41%** | 6 | 4,218 |
| Late | **27%** | 20 | 12,014 |

0    0.5    1    1.5+
Favors zinc        Favors control

——— after exclusions

**Evolution of COVID-19 clinical evidence**

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100%

Effective

50%

**Zinc**
*p*=0.0000013

2020    2021    2022    2023    2024

0%

-50%

**Acetaminophen**
*p*=0.00000029

Harmful

meta analysis results (pooled effects)

**HIGHLIGHTS**

Zinc reduces risk for COVID-19 with very high confidence for mortality, progression, recovery, and in pooled analysis, high confidence for ventilation and hospitalization, low confidence for ICU admission and viral clearance, and very low confidence for cases. Over-supplementation may be detrimental.

Zinc was the 2nd treatment shown effective with ≥3 clinical studies in July 2020, now with $p = 0.0000013$ from 44 studies, and recognized in 10 countries.

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.

# 44 zinc COVID-19 studies (+5 unreported RCTs)

| Study | Improvement | RR [CI] | Outcome | Treatment | Control | Notes |
|---|---|---|---|---|---|---|
| Derwand | 79% | 0.21 [0.03-1.47] | death | 1/141 | 13/377 | CT[2] |
| Thomas (RCT) | -44% | 1.44 [0.36-5.71] | hosp. | 5/58 | 3/50 | COVIDAtoZ |
| Aldwihi | 24% | 0.76 [0.51-1.08] | hosp. | 53/199 | 184/539 | |
| Asimi | 97% | 0.03 [0.00-0.44] | ventilation | 0/270 | 9/86 | CT[2] |
| Mayberry | 53% | 0.47 [0.33-0.65] | death | 938 (n) | 1,090 (n) | |
| Abdallah (DB RCT) | 30% | 0.70 [0.36-1.31] | death | 15/231 | 22/239 | VIZIR |
| Boukef (DB RCT) | unknown, >1 year late | | | 150 (total) | | |
| **Early treatment** | **41%** | **0.59 [0.39-0.92]** | | 74/1,837 | 231/2,381 | **41% lower risk** |

Tau² = 0.13, I² = 60.6%, p = 0.018

| Study | Improvement | RR [CI] | Outcome | Treatment | Control | Notes |
|---|---|---|---|---|---|---|
| Carlucci | 38% | 0.62 [0.46-0.84] | death/HPC | 54/411 | 119/521 | |
| Krishnan | 18% | 0.82 [0.62-1.09] | death | 31/58 | 61/94 | |
| Yao | 34% | 0.66 [0.41-1.07] | death | 73/196 | 21/46 | |
| Frontera (PSM) | 37% | 0.63 [0.44-0.91] | death | 121/1,006 | 424/2,467 | CT[2] |
| Abd-Elsalam (RCT) | 1% | 0.99 [0.30-3.31] | death | 5/96 | 5/95 | data issues, see notes |
| Rosenthal | -16% | 1.16 [1.05-1.28] | death | n/a | n/a | |
| Darban (RCT) | 33% | 0.67 [0.14-3.17] | progression | 2/10 | 3/10 | ICU patients CT[2] |
| Patel (DB RCT) | 20% | 0.80 [0.15-4.18] | death | 2/15 | 3/18 | |
| Mulhem | 46% | 0.54 [0.43-0.68] | death | 256/1,596 | 260/1,623 | |
| Gadhiya | -41% | 1.41 [0.69-2.57] | death | 21/54 | 34/229 | |
| Al Sulaiman (ICU) | 36% | 0.64 [0.37-1.10] | death | 23/82 | 32/82 | ICU patients |
| Elavarasi | 65% | 0.35 [0.24-0.56] | death | 486 (n) | 1,201 (n) | |
| Assiri (ICU) | -81% | 1.81 [0.41-6.97] | death | 10/60 | 4/58 | ICU patients |
| Kaplan (RCT) | -14% | 1.14 [0.08-16.6] | ventilation | 1/14 | 1/16 | Reszinate CT[2] |
| Zangeneh (ICU) | -21% | 1.21 [0.51-2.90] | death | n/a | n/a | ICU patients |
| Alahmari | 30% | 0.70 [0.63-0.78] | hosp. time | 130 (n) | 847 (n) | |
| Doocy | 41% | 0.59 [0.19-1.85] | death | 3/28 | 21/116 | |
| Ibrahim Alhajjaji | 88% | 0.12 [0.01-2.24] | death | 0/44 | 4/57 | |
| Kyagambiddwa | 25% | 0.75 [0.44-1.25] | death | 20/89 | 22/73 | |
| Seely (DB RCT) | 48% | 0.52 [0.10-2.71] | progression | 2/42 | 4/44 | CT[2] |
| Sharmin (DB RCT) | unknown, >2 years late | | | 50 (est. total) | | |
| Correa (DB RCT) | unknown, >2 years late | | | 105 (total) | | |
| Güerri-Fern.. (RCT) | unknown, >1.5 years late | | | 75 (total) | | MARZINC |
| **Late treatment** | **27%** | **0.73 [0.60-0.90]** | | 624/4,417 | 1,018/7,597 | **27% lower risk** |

Tau² = 0.11, I² = 84.4%, p = 0.0024

| Study | Improvement | RR [CI] | Outcome | Treatment | Control | Notes |
|---|---|---|---|---|---|---|
| Louca | 1% | 0.99 [0.93-1.06] | cases | population-based cohort | | |
| Mahto | 37% | 0.63 [0.22-1.49] | IgG+ | 10/38 | 83/651 | |
| Bejan | 18% | 0.82 [0.22-3.13] | ventilation | 155 (n) | 9,074 (n) | |
| Holt | 7% | 0.93 [0.59-1.44] | cases | 21/750 | 425/14,477 | COVIDENCE UK |
| Abdulateef | 13% | 0.87 [0.38-1.97] | hosp. | 7/111 | 23/317 | |
| Seet (CLUS. RCT) | 50% | 0.50 [0.34-0.75] | symp. case | 33/634 | 64/619 | OT[1] |
| Israel | 100% | 0.00 [0.00-0.89] | hosp. | case control | | CT[2] |
| Bagheri | 60% | 0.40 [0.04-3.53] | severe case | 33 (n) | 477 (n) | |
| Gordon | 68% | 0.32 [0.01-7.87] | death | 0/104 | 1/96 | |
| Kumar | 20% | 0.80 [0.21-2.99] | death | 6/75 | 3/30 | |
| Nimer | -25% | 1.25 [0.87-1.77] | hosp. | 41/326 | 178/1,822 | |
| Shehab | 47% | 0.53 [0.19-1.47] | severe case | 4/65 | 22/188 | |
| Citu | 18% | 0.82 [0.12-5.68] | severe case | 2/74 | 2/61 | CT[2] |
| Stambouli (DB RCT) | 68% | 0.32 [0.03-2.95] | symp. case | 1/59 | 3/56 | |
| Adrean | -12% | 1.12 [0.74-1.70] | cases | 30/2,111 | 80/6,315 | |
| Sharif | 40% | 0.60 [0.46-0.77] | severe case | n/a | n/a | |
| Asoudeh | 57% | 0.43 [0.21-0.90] | severe case | 250 (all patients) | | |
| Seifi | 31% | 0.69 [0.52-0.94] | hosp. | n/a | n/a | per unit change |
| Ajili (DB RCT) | unknown, >3 years late | | | 660 (est. total) | | COVID-Milit |
| **Prophylaxis** | **22%** | **0.78 [0.64-0.93]** | | 155/4,535 | 884/34,183 | **22% lower risk** |

Tau² = 0.06, I² = 57.7%, p = 0.0071

| | | | | | | |
|---|---|---|---|---|---|---|
| **All studies** | **27%** | **0.73 [0.64-0.83]** | | 853/10,789 | 2,133/44,161 | **27% lower risk** |

[1] OT: comparison with other treatment
[2] CT: study uses combined treatment
Tau² = 0.08, I² = 78.2%, p < 0.0001

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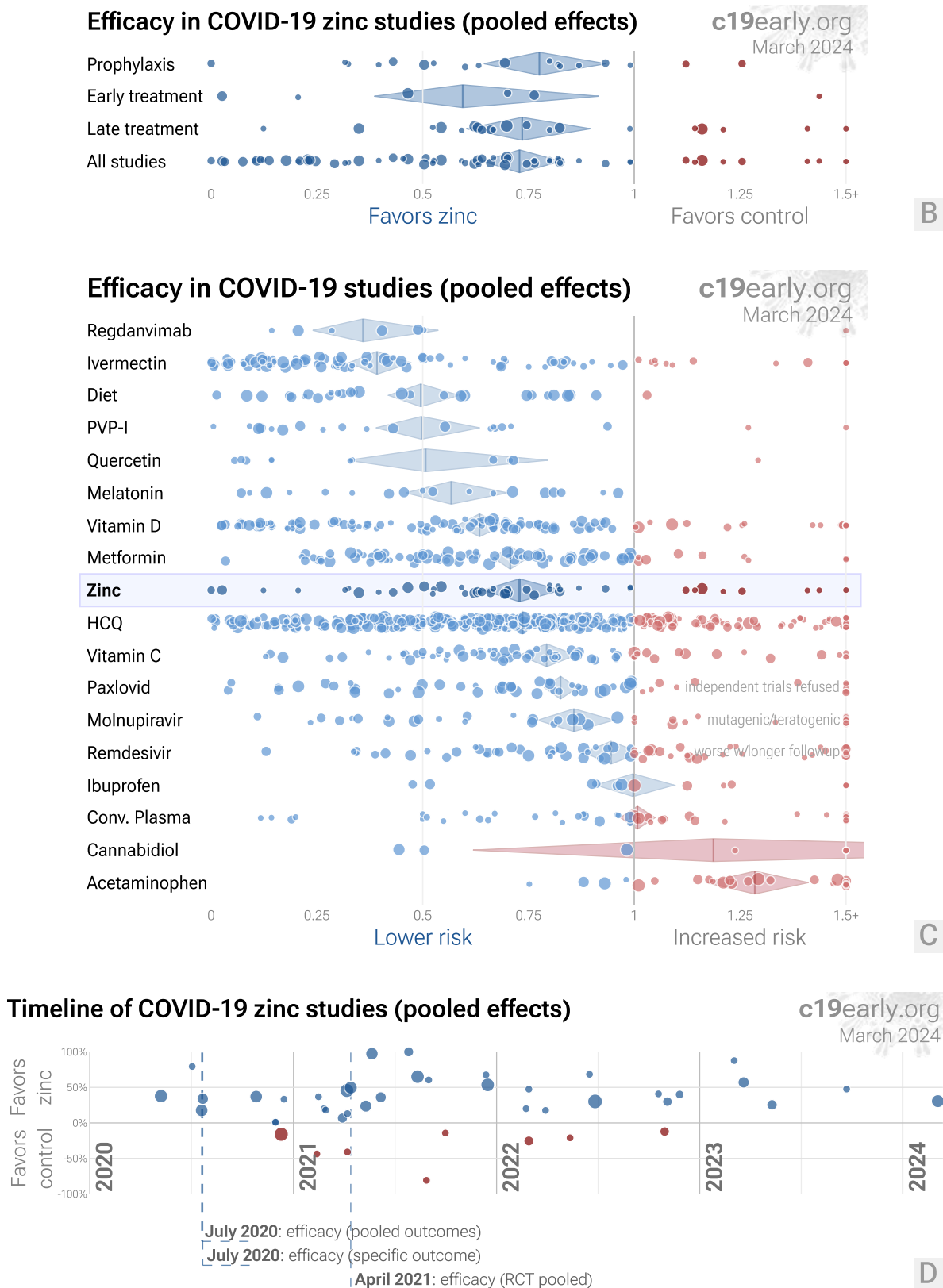(most serious outcome, see appendix)

Favors zinc ← → Favors control

0   0.25   0.5   0.75   1   1.25   1.5   1.75   2+

**Efficacy in COVID-19 zinc studies (pooled effects)**

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Prophylaxis
Early treatment
Late treatment
All studies

0    0.25    0.5    0.75    1    1.25    1.5+

Favors zinc                    Favors control

B

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

c19early.org
March 2024

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

0    0.25    0.5    0.75    1    1.25    1.5+

Lower risk                    Increased risk

C

**Timeline of COVID-19 zinc studies (pooled effects)**

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Favors zinc / Favors control

100%
50%
0%
-50%
-100%

2020    2021    2022    2023    2024

**July 2020**: efficacy (pooled outcomes)
**July 2020**: efficacy (specific outcome)
**April 2021**: efficacy (RCT pooled)

D

***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 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 7,063 proposed treatments show efficacy *c19early.org*. **D. Timeline of results in zinc studies.**

The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes, one or more specific outcome, and pooled outcomes in RCTs. Efficacy based on RCTs only was delayed by 8.8 months, compared to using all studies.

# Introduction

**Immediate treatment recommended.** SARS-CoV-2 infection primarily begins in the upper respiratory tract and may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems, which may lead to cytokine storm, pneumonia, ARDS, neurological issues *Hampshire, Scardua-Silva, Yang*, cardiovascular complications *Eberhardt*, organ failure, and death. Minimizing replication as early as possible is recommended.

**Many treatments are expected to modulate infection.** SARS-CoV-2 infection and replication involves the complex interplay of 50+ host and viral proteins and other factors *Note A, Malone, Murigneux, Lv, Lui, Niarakis*, providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 7,000 compounds may reduce COVID-19 risk *c19early.org (B)*, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

**Other infections.** Studies have shown efficacy with zinc for acute respiratory tract infections *Abioye* and the common cold *Hemilä*.

**Analysis.** We analyze all significant controlled studies of zinc for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random effects meta-analysis results for all studies, studies within each treatment stage, individual outcomes, peer-reviewed studies, Randomized Controlled Trials (RCTs), and higher quality studies.

**Treatment timing.** Figure 2 shows stages of possible treatment for COVID-19. **Prophylaxis** refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. **Early Treatment** refers to treatment immediately or soon after symptoms appear, while **Late Treatment** refers to more delayed treatment.



**Prophylaxis**
regularly take medication in advance
to prevent or minimize infections

**Early Treatment**
treat immediately on symptoms
or shortly thereafter

**Late Treatment**
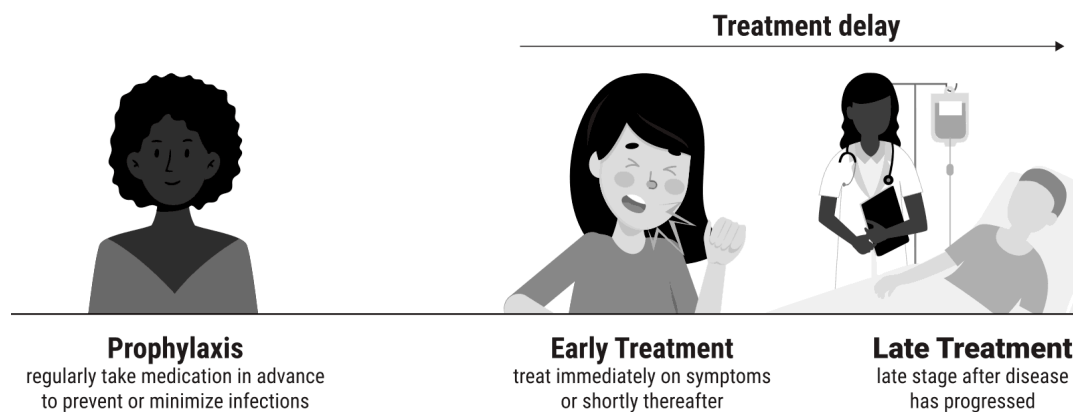late stage after disease
has progressed

*Figure 2.* Treatment stages.

# Preclinical Research

3 *In Silico* studies support the efficacy of zinc *Bess, El-Megharbel, Pormohammad*.

4 *In Vitro* studies support the efficacy of zinc *El-Megharbel, Hajdrik, Panchariya, te Velthuis*.

An *In Vivo* animal study supports the efficacy of zinc *El-Megharbel*.

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, for Randomized Controlled Trials, for peer-reviewed studies, with different exclusions, and for specific outcomes. Table 2 shows results by treatment stage. Figure 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, recovery, cases, viral clearance, sufficiency studies, peer reviewed studies, and all studies excluding combined treatment studies.

| | *Improvement* | *Studies* | *Patients* | *Authors* |
|---|---|---|---|---|
| All studies | **27%** [17-36%] **** | 44 | 55,200 | 459 |
| After exclusions | **32%** [21-41%] **** | 28 | 34,461 | 308 |
| Peer-reviewed studies | **24%** [14-33%] **** | 40 | 49,654 | 404 |
| Excluding combined treatment | **26%** [15-35%] **** | 36 | 50,582 | 385 |
| Randomized Controlled Trials | **39%** [18-55%] ** | 9 | 2,306 | 124 |
| | | | | |
| Mortality | **29%** [10-44%] ** | 20 | 13,290 | 199 |
| Ventilation | **44%** [4-68%] * | 7 | 12,867 | 59 |
| ICU admission | **26%** [-7-49%] | 8 | 13,012 | 88 |
| Hospitalization | **20%** [4-34%] * | 15 | 6,454 | 131 |
| Recovery | **20%** [8-31%] ** | 4 | 827 | 55 |
| Cases | **22%** [-10-45%] | 6 | 25,221 | 105 |
| | | | | |
| RCT mortality | **24%** [-29-55%] | 3 | 694 | 46 |
| RCT hospitalization | **4%** [-8-14%] | 4 | 514 | 57 |

*Table 1.* Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, with different exclusions, and for specific outcomes. Results show the percentage improvement with treatment and the 95% confidence interval. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

|  | Early treatment | Late treatment | Prophylaxis |
|---|---|---|---|
| All studies | 41% [8-61%] * | 27% [10-40%] ** | 22% [7-36%] ** |
| After exclusions | 37% [10-55%] * | 36% [28-43%] **** | 23% [2-40%] * |
| Peer-reviewed studies | 37% [10-55%] * | 21% [2-36%] * | 22% [7-36%] ** |
| Excluding combined treatment | 34% [7-54%] * | 25% [6-40%] * | 23% [6-36%] ** |
| Randomized Controlled Trials | 21% [-41-55%] | 21% [-60-61%] | 50% [26-67%] *** |
|  |  |  |  |
| Mortality | 50% [33-63%] **** | 24% [2-41%] * | 30% [-137-79%] |
| Ventilation | 86% [-66-99%] | 20% [-16-45%] | 18% [-213-78%] |
| ICU admission | 59% [48-68%] **** | 6% [-5-15%] | 30% [-154-81%] |
| Hospitalization | 66% [-4-89%] | 15% [-5-31%] | 13% [-26-40%] |
| Recovery | 23% [4-37%] * | 11% [-19-34%] |  |
| Cases |  |  | 22% [-10-45%] |
|  |  |  |  |
| RCT mortality | 30% [-31-64%] | 8% [-144-65%] |  |
| RCT hospitalization | 16% [-254-80%] | 4% [-8-14%] |  |

**Table 2.** Random effects meta-analysis results by treatment stage. Results show the percentage improvement with treatment, the 95% confidence interval, and the number of studies for the stage. * $p<0.05$  ** $p<0.01$  *** $p<0.001$  **** $p<0.0001$.

# 44 zinc COVID-19 studies (+5 unreported RCTs)

| | Improvement, RR [CI] | | | Treatment | Control | | |
|---|---|---|---|---|---|---|---|
| Derwand | 79% | 0.21 [0.03-1.47] | death | 1/141 | 13/377 | | CT[2] |
| Thomas (RCT) | -44% | 1.44 [0.36-5.71] | hosp. | 5/58 | 3/50 | COVIDAtoZ | |
| Aldwihi | 24% | 0.76 [0.51-1.08] | hosp. | 53/199 | 184/539 | | |
| Asimi | 97% | 0.03 [0.00-0.44] | ventilation | 0/270 | 9/86 | | CT[2] |
| Mayberry | 53% | 0.47 [0.33-0.65] | death | 938 (n) | 1,090 (n) | | |
| Abdallah (DB RCT) | 30% | 0.70 [0.36-1.31] | death | 15/231 | 22/239 | VIZIR | |
| Boukef (DB RCT) | unknown, >1 year late | | | 150 (total) | | | |
| **Early treatment** | **41%** | **0.59 [0.39-0.92]** | | **74/1,837** | **231/2,381** | | **41% lower risk** |

Tau$^2$ = 0.13, I$^2$ = 60.6%, p = 0.018

| | Improvement, RR [CI] | | | Treatment | Control | | |
|---|---|---|---|---|---|---|---|
| Carlucci | 38% | 0.62 [0.46-0.84] | death/HPC | 54/411 | 119/521 | | |
| Krishnan | 18% | 0.82 [0.62-1.09] | death | 31/58 | 61/94 | | |
| Yao | 34% | 0.66 [0.41-1.07] | death | 73/196 | 21/46 | | |
| Frontera (PSM) | 37% | 0.63 [0.44-0.91] | death | 121/1,006 | 424/2,467 | | CT[2] |
| Abd-Elsalam (RCT) | 1% | 0.99 [0.30-3.31] | death | 5/96 | 5/95 | data issues, see notes | |
| Rosenthal | -16% | 1.16 [1.05-1.28] | death | n/a | n/a | | |
| Darban (RCT) | 33% | 0.67 [0.14-3.17] | progression | 2/10 | 3/10 | ICU patients CT[2] | |
| Patel (DB RCT) | 20% | 0.80 [0.15-4.18] | death | 2/15 | 3/18 | | |
| Mulhem | 46% | 0.54 [0.43-0.68] | death | 256/1,596 | 260/1,623 | | |
| Gadhiya | -41% | 1.41 [0.69-2.57] | death | 21/54 | 34/229 | | |
| Al Sulaiman (ICU) | 36% | 0.64 [0.37-1.10] | death | 23/82 | 32/82 | ICU patients | |
| Elavarasi | 65% | 0.35 [0.24-0.56] | death | 486 (n) | 1,201 (n) | | |
| Assiri (ICU) | -81% | 1.81 [0.41-6.97] | death | 10/60 | 4/58 | ICU patients | |
| Kaplan (RCT) | -14% | 1.14 [0.08-16.6] | ventilation | 1/14 | 1/16 | Reszinate | CT[2] |
| Zangeneh (ICU) | -21% | 1.21 [0.51-2.90] | death | n/a | n/a | ICU patients | |
| Alahmari | 30% | 0.70 [0.63-0.78] | hosp. time | 130 (n) | 847 (n) | | |
| Doocy | 41% | 0.59 [0.19-1.85] | death | 3/28 | 21/116 | | |
| Ibrahim Alhajjaji | 88% | 0.12 [0.01-2.24] | death | 0/44 | 4/57 | | |
| Kyagambiddwa | 25% | 0.75 [0.44-1.25] | death | 20/89 | 22/73 | | |
| Seely (DB RCT) | 48% | 0.52 [0.10-2.71] | progression | 2/42 | 4/44 | | CT[2] |
| Sharmin (DB RCT) | unknown, >2 years late | | | 50 (est. total) | | | |
| Correa (DB RCT) | unknown, >2 years late | | | 105 (total) | | | |
| Güerri-Fern.. (RCT) | unknown, >1.5 years late | | | 75 (total) | | MARZINC | |
| **Late treatment** | **27%** | **0.73 [0.60-0.90]** | | **624/4,417** | **1,018/7,597** | | **27% lower risk** |

Tau$^2$ = 0.11, I$^2$ = 84.4%, p = 0.0024

| | Improvement, RR [CI] | | | Treatment | Control | | |
|---|---|---|---|---|---|---|---|
| Louca | 1% | 0.99 [0.93-1.06] | cases | population-based cohort | | | |
| Mahto | 37% | 0.63 [0.22-1.49] | IgG+ | 10/38 | 83/651 | | |
| Bejan | 18% | 0.82 [0.22-3.13] | ventilation | 155 (n) | 9,074 (n) | | |
| Holt | 7% | 0.93 [0.59-1.44] | cases | 21/750 | 425/14,477 | COVIDENCE UK | |
| Abdulateef | 13% | 0.87 [0.38-1.97] | hosp. | 7/111 | 23/317 | | |
| Seet (CLUS. RCT) | 50% | 0.50 [0.34-0.75] | symp. case | 33/634 | 64/619 | | OT[1] |
| Israel | 100% | 0.00 [0.00-0.89] | hosp. | case control | | | CT[2] |
| Bagheri | 60% | 0.40 [0.04-3.53] | severe case | 33 (n) | 477 (n) | | |
| Gordon | 68% | 0.32 [0.01-7.87] | death | 0/104 | 1/96 | | |
| Kumar | 20% | 0.80 [0.21-2.99] | death | 6/75 | 3/30 | | |
| Nimer | -25% | 1.25 [0.87-1.77] | hosp. | 41/326 | 178/1,822 | | |
| Shehab | 47% | 0.53 [0.19-1.47] | severe case | 4/65 | 22/188 | | |
| Citu | 18% | 0.82 [0.12-5.68] | severe case | 2/74 | 2/61 | | CT[2] |
| Stambouli (DB RCT) | 68% | 0.32 [0.03-2.95] | symp. case | 1/59 | 3/56 | | |
| Adrean | -12% | 1.12 [0.74-1.70] | cases | 30/2,111 | 80/6,315 | | |
| Sharif | 40% | 0.60 [0.46-0.77] | severe case | n/a | n/a | | |
| Asoudeh | 57% | 0.43 [0.21-0.90] | severe case | 250 (all patients) | | | |
| Seifi | 31% | 0.69 [0.52-0.94] | hosp. | n/a | n/a | | per unit change |
| Ajili (DB RCT) | unknown, >3 years late | | | 660 (est. total) | | COVID-Milit | |
| **Prophylaxis** | **22%** | **0.78 [0.64-0.93]** | | **155/4,535** | **884/34,183** | | **22% lower risk** |

Tau$^2$ = 0.06, I$^2$ = 57.7%, p = 0.0071

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **All studies** | **27%** | **0.73 [0.64-0.83]** | | **853/10,789** | **2,133/44,161** | | **27% lower risk** |

[1] OT: comparison with other treatment
[2] CT: study uses combined treatment
Tau$^2$ = 0.08, I$^2$ = 78.2%, p < 0.0001

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

0   0.25   0.5   0.75   1   1.25   1.5   1.75   2+
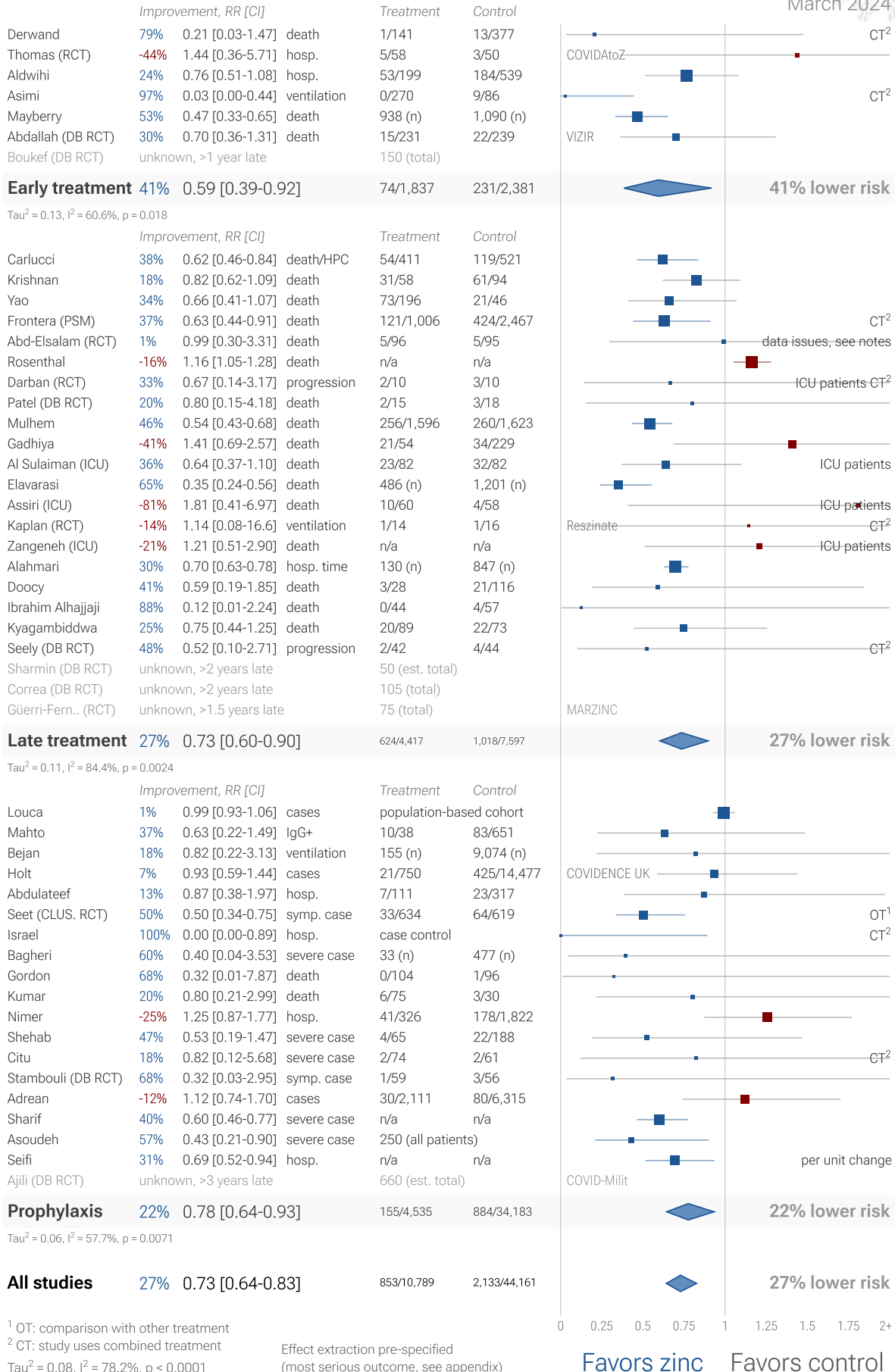
Favors zinc          Favors control

***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 see the appendix.
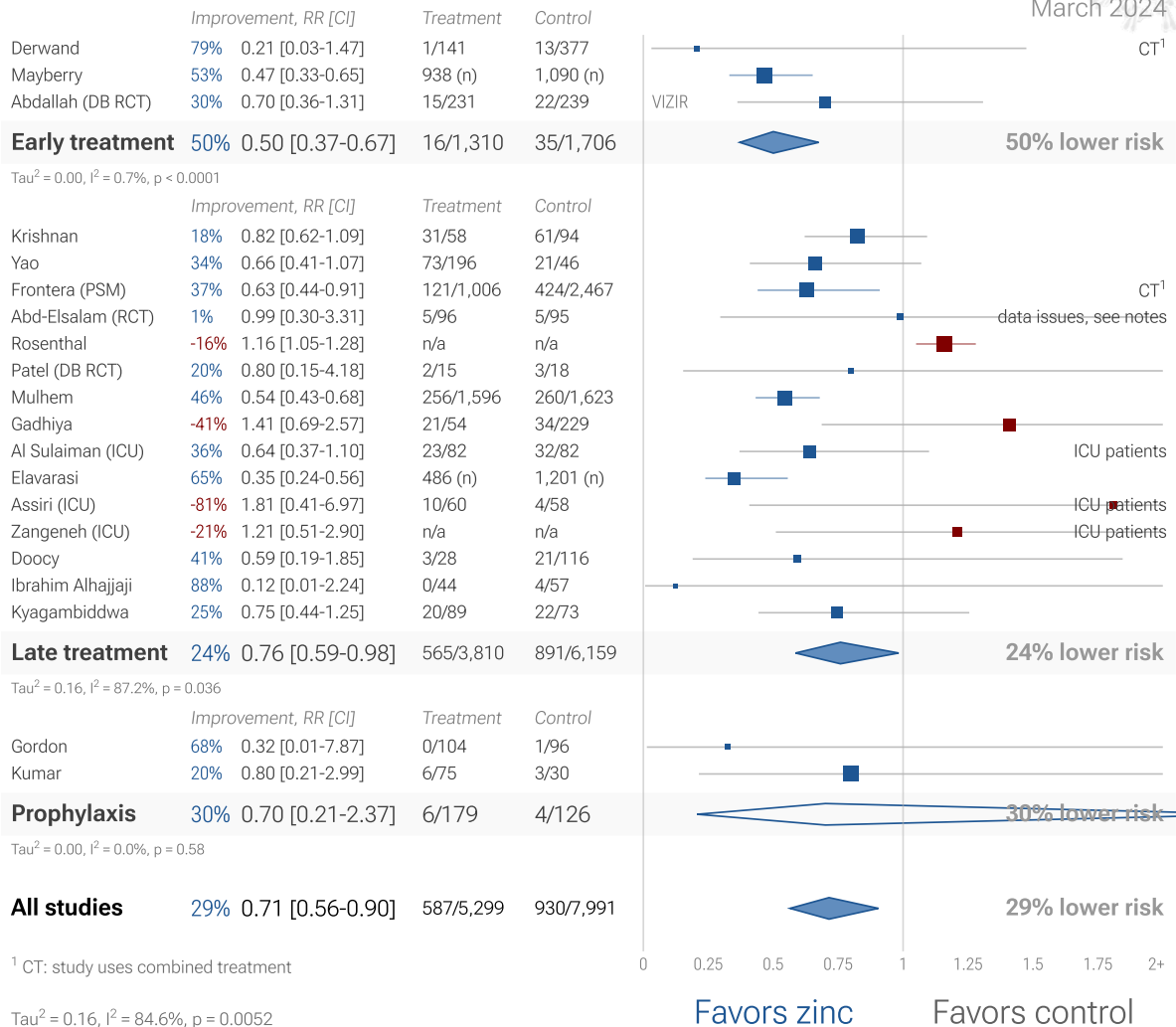
## 20 zinc COVID-19 mortality results

| | Improvement, RR [CI] | | Treatment | Control | |
|---|---|---|---|---|---|
| Derwand | 79% | 0.21 [0.03-1.47] | 1/141 | 13/377 | CT[1] |
| Mayberry | 53% | 0.47 [0.33-0.65] | 938 (n) | 1,090 (n) | |
| Abdallah (DB RCT) | 30% | 0.70 [0.36-1.31] | 15/231 | 22/239 | VIZIR |
| **Early treatment** | **50%** | **0.50 [0.37-0.67]** | 16/1,310 | 35/1,706 | **50% lower risk** |

Tau² = 0.00, I² = 0.7%, p < 0.0001

| | Improvement, RR [CI] | | Treatment | Control | |
|---|---|---|---|---|---|
| Krishnan | 18% | 0.82 [0.62-1.09] | 31/58 | 61/94 | |
| Yao | 34% | 0.66 [0.41-1.07] | 73/196 | 21/46 | |
| Frontera (PSM) | 37% | 0.63 [0.44-0.91] | 121/1,006 | 424/2,467 | CT[1] |
| Abd-Elsalam (RCT) | 1% | 0.99 [0.30-3.31] | 5/96 | 5/95 | data issues, see notes |
| Rosenthal | -16% | 1.16 [1.05-1.28] | n/a | n/a | |
| Patel (DB RCT) | 20% | 0.80 [0.15-4.18] | 2/15 | 3/18 | |
| Mulhem | 46% | 0.54 [0.43-0.68] | 256/1,596 | 260/1,623 | |
| Gadhiya | -41% | 1.41 [0.69-2.57] | 21/54 | 34/229 | |
| Al Sulaiman (ICU) | 36% | 0.64 [0.37-1.10] | 23/82 | 32/82 | ICU patients |
| Elavarasi | 65% | 0.35 [0.24-0.56] | 486 (n) | 1,201 (n) | |
| Assiri (ICU) | -81% | 1.81 [0.41-6.97] | 10/60 | 4/58 | ICU patients |
| Zangeneh (ICU) | -21% | 1.21 [0.51-2.90] | n/a | n/a | ICU patients |
| Doocy | 41% | 0.59 [0.19-1.85] | 3/28 | 21/116 | |
| Ibrahim Alhajjaji | 88% | 0.12 [0.01-2.24] | 0/44 | 4/57 | |
| Kyagambiddwa | 25% | 0.75 [0.44-1.25] | 20/89 | 22/73 | |
| **Late treatment** | **24%** | **0.76 [0.59-0.98]** | 565/3,810 | 891/6,159 | **24% lower risk** |

Tau² = 0.16, I² = 87.2%, p = 0.036

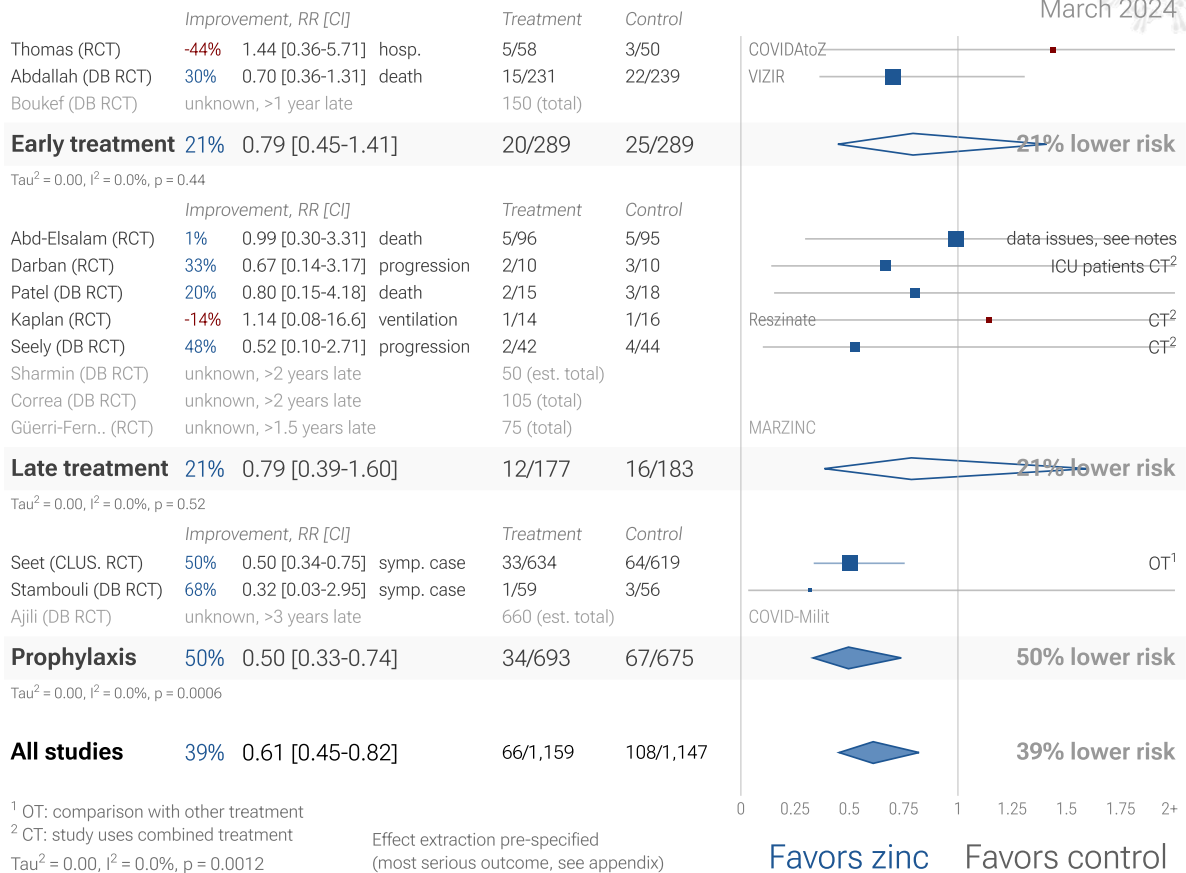| | Improvement, RR [CI] | | Treatment | Control | |
|---|---|---|---|---|---|
| Gordon | 68% | 0.32 [0.01-7.87] | 0/104 | 1/96 | |
| Kumar | 20% | 0.80 [0.21-2.99] | 6/75 | 3/30 | |
| **Prophylaxis** | **30%** | **0.70 [0.21-2.37]** | 6/179 | 4/126 | **30% lower risk** |

Tau² = 0.00, I² = 0.0%, p = 0.58

| | | | | | |
|---|---|---|---|---|---|
| **All studies** | **29%** | **0.71 [0.56-0.90]** | 587/5,299 | 930/7,991 | **29% lower risk** |

[1] CT: study uses combined treatment

Tau² = 0.16, I² = 84.6%, p = 0.0052

| 0 | 0.25 | 0.5 | 0.75 | 1 | 1.25 | 1.5 | 1.75 | 2+ |

Favors zinc    Favors control

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

## 7 zinc COVID-19 mechanical ventilation results

| | Improvement, RR [CI] | | Treatment | Control | | |
|---|---|---|---|---|---|---|
| Asimi | 97% | 0.03 [0.00-0.44] | 0/270 | 9/86 | | CT[1] |
| Mayberry | 64% | 0.36 [0.27-0.47] | 938 (n) | 1,090 (n) | | |
| **Early treatment** | **86%** | **0.14 [0.01-1.66]** | **0/1,208** | **9/1,176** | | 86% lower risk |

Tau$^2$ = 2.37, I$^2$ = 69.2%, p = 0.12

| | Improvement, RR [CI] | | Treatment | Control | | |
|---|---|---|---|---|---|---|
| Carlucci | 18% | 0.82 [0.54-1.25] | 29/411 | 62/521 | | |
| Abd-Elsalam (RCT) | 34% | 0.66 [0.19-2.26] | 4/96 | 6/95 | | data issues, see notes |
| Kaplan (RCT) | -14% | 1.14 [0.08-16.6] | 1/14 | 1/16 | Reszinate | CT[1] |
| Ibrahim Alhajjaji | 26% | 0.74 [0.23-2.37] | 4/44 | 7/57 | | |
| **Late treatment** | **20%** | **0.80 [0.55-1.16]** | **38/565** | **76/689** | | 20% lower risk |

Tau$^2$ = 0.00, I$^2$ = 0.0%, p = 0.24

| | Improvement, RR [CI] | | Treatment | Control | | |
|---|---|---|---|---|---|---|
| Bejan | 18% | 0.82 [0.22-3.13] | 155 (n) | 9,074 (n) | | |
| **Prophylaxis** | **18%** | **0.82 [0.22-3.13]** | **155 (n)** | **9,074 (n)** | | 18% lower risk |

Tau$^2$ = 0.00, I$^2$ = 0.0%, p = 0.78

| | | | | | | |
|---|---|---|---|---|---|---|
| **All studies** | **44%** | **0.56 [0.32-0.96]** | **38/1,928** | **85/10,939** | | 44% lower risk |

[1] CT: study uses combined treatment

Tau$^2$ = 0.24, I$^2$ = 63.1%, p = 0.035

Favors zinc    Favors control

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

## 8 zinc COVID-19 ICU results

| | Improvement, RR [CI] | | Treatment | Control | | |
|---|---|---|---|---|---|---|
| Mayberry | 60% | 0.40 [0.31-0.52] | 938 (n) | 1,090 (n) | | |
| Abdallah (DB RCT) | 54% | 0.46 [0.23-0.88] | 12/231 | 27/239 | VIZIR | |
| **Early treatment** | **59%** | **0.41 [0.32-0.52]** | **12/1,169** | **27/1,329** | | 59% lower risk |

Tau$^2$ = 0.00, I$^2$ = 0.0%, p < 0.0001

| | Improvement, RR [CI] | | Treatment | Control | | |
|---|---|---|---|---|---|---|
| Carlucci | 23% | 0.77 [0.53-1.10] | 38/411 | 82/521 | | |
| Darban (RCT) | 6% | 0.94 [0.84-1.06] | 10 (n) | 10 (n) | | ICU patients CT[1] |
| Al Sulaiman (ICU) | -25% | 1.25 [0.84-1.87] | 82 (n) | 82 (n) | | ICU patients |
| Kaplan (RCT) | -14% | 1.14 [0.08-16.6] | 1/14 | 1/16 | Reszinate | CT[1] |
| Ibrahim Alhajjaji | 3% | 0.97 [0.45-2.10] | 9/44 | 12/57 | | |
| **Late treatment** | **6%** | **0.94 [0.85-1.05]** | **48/561** | **95/686** | | 6% lower risk |

Tau$^2$ = 0.00, I$^2$ = 0.0%, p = 0.28

| | Improvement, RR [CI] | | Treatment | Control | | |
|---|---|---|---|---|---|---|
| Bejan | 30% | 0.70 [0.19-2.54] | 155 (n) | 9,112 (n) | | |
| **Prophylaxis** | **30%** | **0.70 [0.19-2.54]** | **155 (n)** | **9,112 (n)** | | 30% lower risk |

Tau$^2$ = 0.00, I$^2$ = 0.0%, p = 0.6

| | | | | | | |
|---|---|---|---|---|---|---|
| **All studies** | **26%** | **0.74 [0.51-1.07]** | **60/1,885** | **122/11,127** | | 26% lower risk |

[1] CT: study uses combined treatment

Tau$^2$ = 0.18, I$^2$ = 83.9%, p = 0.11

Favors zinc    Favors control

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

## 15 zinc COVID-19 hospitalization results

| | Improvement, RR [CI] | | | Treatment | Control | | |
|---|---|---|---|---|---|---|---|
| Derwand | 82% | 0.18 [0.07-0.54] | hosp. | 4/141 | 58/377 | | CT[1] |
| Thomas (RCT) | -44% | 1.44 [0.36-5.71] | hosp. | 5/58 | 3/50 | COVIDAtoZ | |
| Aldwihi | 24% | 0.76 [0.51-1.08] | hosp. | 53/199 | 184/539 | | |
| Asimi | 99% | 0.01 [0.00-0.16] | hosp. | 0/270 | 24/86 | | CT[1] |
| Abdallah (DB RCT) | 69% | 0.31 [0.03-2.61] | hosp. | 1/85 | 4/100 | VIZIR | |
| **Early treatment** | **66%** | **0.34 [0.11-1.04]** | | 63/753 | 273/1,152 | | **66% lower risk** |

Tau² = 1.04, I² = 77.6%, p = 0.058

| | Improvement, RR [CI] | | | Treatment | Control | | |
|---|---|---|---|---|---|---|---|
| Abd-Elsalam (RCT) | 4% | 0.96 [0.86-1.08] | hosp. time | 96 (n) | 95 (n) | | data issues, see notes |
| Al Sulaiman (ICU) | -6% | 1.06 [0.85-1.33] | hosp. time | 82 (n) | 82 (n) | | ICU patients |
| Kaplan (RCT) | -14% | 1.14 [0.08-16.6] | hosp. | 1/14 | 1/16 | Reszinate | CT[1] |
| Alahmari | 30% | 0.70 [0.63-0.78] | hosp. time | 130 (n) | 847 (n) | | |
| Ibrahim Alhajjaji | 29% | 0.71 [0.54-0.94] | hosp. time | 44 (n) | 57 (n) | | |
| **Late treatment** | **15%** | **0.85 [0.69-1.05]** | | 1/366 | 1/1,097 | | **15% lower risk** |

Tau² = 0.04, I² = 82.0%, p = 0.13

| | Improvement, RR [CI] | | | Treatment | Control | | |
|---|---|---|---|---|---|---|---|
| Abdulateef | 13% | 0.87 [0.38-1.97] | hosp. | 7/111 | 23/317 | | |
| Israel | 100% | 0.00 [0.00-0.89] | hosp. | case control | | | CT[1] |
| Bagheri | 41% | 0.59 [0.14-1.61] | hosp. | 4/33 | 167/477 | | |
| Nimer | -25% | 1.25 [0.87-1.77] | hosp. | 41/326 | 178/1,822 | | |
| Seifi | 31% | 0.69 [0.52-0.94] | hosp. | n/a | n/a | | per unit change |
| **Prophylaxis** | **13%** | **0.87 [0.60-1.26]** | | 52/470 | 368/2,616 | | **13% lower risk** |

Tau² = 0.07, I² = 49.6%, p = 0.47

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **All studies** | **20%** | **0.80 [0.66-0.96]** | | 116/1,589 | 642/4,865 | | **20% lower risk** |

[1] CT: study uses combined treatment

Tau² = 0.05, I² = 72.5%, p = 0.014

Favors zinc    Favors control

*Figure 7.* Random effects meta-analysis for hospitalization.

## 4 zinc COVID-19 progression results

| | Improvement, RR [CI] | | Treatment | Control | | |
|---|---|---|---|---|---|---|
| Mayberry | 85% | 0.15 [0.10-0.22] | 938 (n) | 1,090 (n) | | |
| **Early treatment** | **85%** | **0.15 [0.10-0.22]** | 938 (n) | 1,090 (n) | | **85% lower risk** |

Tau² = 0.00, I² = 0.0%, p < 0.0001

| | Improvement, RR [CI] | | Treatment | Control | | |
|---|---|---|---|---|---|---|
| Darban (RCT) | 33% | 0.67 [0.14-3.17] | 2/10 | 3/10 | | ICU patients CT[1] |
| Ibrahim Alhajjaji | 73% | 0.27 [0.10-0.74] | 4/44 | 19/57 | | |
| Seely (DB RCT) | 48% | 0.52 [0.10-2.71] | 2/42 | 4/44 | | CT[1] |
| **Late treatment** | **62%** | **0.38 [0.18-0.81]** | 8/96 | 26/111 | | **62% lower risk** |

Tau² = 0.00, I² = 0.0%, p = 0.013

| | | | | | | |
|---|---|---|---|---|---|---|
| **All studies** | **74%** | **0.26 [0.13-0.53]** | 8/1,034 | 26/1,201 | | **74% lower risk** |

[1] CT: study uses combined treatment

Tau² = 0.26, I² = 50.0%, p = 0.00028

Favors zinc    Favors control

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

## 4 zinc COVID-19 recovery results

| | Improvement | RR [CI] | | Treatment | Control | | | |
|---|---|---|---|---|---|---|---|---|
| Thomas (RCT) | 12% | 0.88 [0.67-1.16] | recov. time | 58 (n) | 50 (n) | | COVIDAtoZ | |
| Abdallah (DB RCT) | 29% | 0.71 [0.57-0.88] | no recov. | 82/231 | 120/239 | | VIZIR | |
| **Early treatment** | **23%** | **0.77 [0.63-0.96]** | | **82/289** | **120/289** | | | **23% lower risk** |

Tau² = 0.01, I² = 33.2%, p = 0.018

| | Improvement | RR [CI] | | Treatment | Control | | | |
|---|---|---|---|---|---|---|---|---|
| Abd-Elsalam (RCT) | 6% | 0.94 [0.55-1.62] | no recov. | 20/96 | 21/95 | | data issues, see notes | |
| Seely (DB RCT) | 14% | 0.86 [0.61-1.22] | no recov. | 34 (n) | 24 (n) | | CT[1] | |
| **Late treatment** | **11%** | **0.89 [0.66-1.19]** | | **20/130** | **21/119** | | | **11% lower risk** |

Tau² = 0.00, I² = 0.0%, p = 0.42

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **All studies** | **20%** | **0.80 [0.69-0.92]** | | **102/419** | **141/408** | | | **20% lower risk** |

[1] CT: study uses combined treatment

Tau² = 0.00, I² = 0.0%, p = 0.0024

Favors zinc — Favors control



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

## 6 zinc COVID-19 case results

| | Improvement | RR [CI] | | Treatment | Control | | |
|---|---|---|---|---|---|---|---|
| Louca | 1% | 0.99 [0.93-1.06] | cases | population-based cohort | | | |
| Holt | 7% | 0.93 [0.59-1.44] | cases | 21/750 | 425/14,477 | COVIDENCE UK | |
| Seet (CLUS. RCT) | 50% | 0.50 [0.34-0.75] | symp. case | 33/634 | 64/619 | | OT[1] |
| Gordon | 85% | 0.15 [0.02-0.58] | symp. case | 2/104 | 9/96 | | |
| Stambouli (DB RCT) | 68% | 0.32 [0.03-2.95] | symp. case | 1/59 | 3/56 | | |
| Adrean | -12% | 1.12 [0.74-1.70] | cases | 30/2,111 | 80/6,315 | | |
| Ajili (DB RCT) | unknown, >3 years late | | | 660 (est. total) | | COVID-Milit | |
| **Prophylaxis** | **22%** | **0.78 [0.55-1.10]** | | **87/3,658** | **581/21,563** | | **22% lower risk** |

Tau² = 0.10, I² = 72.1%, p = 0.15

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **All studies** | **22%** | **0.78 [0.55-1.10]** | | **87/3,658** | **581/21,563** | | **22% lower risk** |

[1] OT: comparison with other treatment

Tau² = 0.10, I² = 72.1%, p = 0.15

Favors zinc — Favors control



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

## 1 zinc COVID-19 viral clearance result

| | Improvement | RR [CI] | | Treatment | Control | | |
|---|---|---|---|---|---|---|---|
| Stambouli (DB RCT) | 21% | 0.79 [0.73-0.84] | viral load | 59 (n) | 56 (n) | | |
| **Prophylaxis** | **21%** | **0.79 [0.73-0.84]** | | **59 (n)** | **56 (n)** | | **21% lower risk** |

Tau² = 0.00, I² = 0.0%, p < 0.0001

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **All studies** | **21%** | **0.79 [0.73-0.84]** | | **59 (n)** | **56 (n)** | | **21% lower risk** |

Tau² = 0.00, I² = 0.0%, p < 0.0001

Favors zinc — Favors control



***Figure 11.*** Random effects meta-analysis for viral clearance.

# 17 zinc COVID-19 sufficiency studies

| | Improvement, RR [CI] | | | High Levels | Low Levels | |
|---|---|---|---|---|---|---|
| Yasui | 92% | 0.07 [0.01-0.54] | ventilation | 1/20 | 6/9 | |
| Jothimani | 90% | 0.10 [0.01-1.76] | death | 0/20 | 5/27 | |
| Vogel-González | 77% | 0.23 [0.10-0.51] | death | 9/191 | 12/58 | |
| Tomasa-Irriguible | 49% | 0.51 [0.19-1.02] | ventilation | 7/31 | 49/89 | |
| Gonçalves (ICU) | 82% | 0.18 [0.08-0.36] | severe case | 7/55 | 145/214 | ICU patients |
| Fromonot | 89% | 0.11 [0.02-0.48] | hosp. | 6/110 | 7/42 | |
| Du Laing | 79% | 0.21 [0.06-0.74] | death | 3/49 | 7/24 | |
| Ramos | 24% | 0.76 [0.38-1.52] | cases | 5/9 | 8/11 | |
| Ekemen Keleş | 75% | 0.25 [0.10-0.59] | hosp. | 10/89 | 5/11 | |
| Voelkle | 77% | 0.23 [0.06-0.72] | death/ICU | 5/35 | 10/22 | |
| Doğan | 77% | 0.23 [0.09-0.61] | cases | case control | | |
| Jiménez | 55% | 0.45 [0.13-1.58] | progression | 30 (n) | 70 (n) | |
| Wu | 71% | 0.29 [0.12-0.73] | death | 10/1,447 | 20/1,447 | |
| İşler | 88% | 0.12 [0.01-0.95] | cases | case control | | |
| Wozniak (ICU) | 47% | 0.53 [0.15-1.67] | death | 59 (n) | 59 (n) | ICU patients |
| Rozemeijer | 97% | 0.03 [0.00-0.68] | ICU | case control | | |
| Fujita | 86% | 0.14 [0.03-0.59] | oxygen | n/a | n/a | |
| **All studies** | **74%** | **0.26 [0.19-0.36]** | | 63/2,145 | 274/2,083 | **74% lower risk** |

Tau$^2$ = 0.14, I$^2$ = 34.1%, p < 0.0001

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

Favors zinc    Favors control

**Figure 12.** Random effects meta-analysis for sufficiency studies. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.

| | Improvement, RR [CI] | | | Treatment | Control | | |
|---|---|---|---|---|---|---|---|
| Derwand | 79% | 0.21 [0.03-1.47] | death | 1/141 | 13/377 | | CT[2] |
| Thomas (RCT) | -44% | 1.44 [0.36-5.71] | hosp. | 5/58 | 3/50 | COVIDAtoZ | |
| Aldwihi | 24% | 0.76 [0.51-1.08] | hosp. | 53/199 | 184/539 | | |
| Mayberry | 53% | 0.47 [0.33-0.65] | death | 938 (n) | 1,090 (n) | | |
| Abdallah (DB RCT) | 30% | 0.70 [0.36-1.31] | death | 15/231 | 22/239 | VIZIR | |
| **Early treatment** | **37%** | **0.63 [0.45-0.90]** | | **74/1,567** | **222/2,295** | | **37% lower risk** |

Tau$^2$ = 0.06, I$^2$ = 48.7%, p = 0.01

| | Improvement, RR [CI] | | | Treatment | Control | | |
|---|---|---|---|---|---|---|---|
| Carlucci | 38% | 0.62 [0.46-0.84] | death/HPC | 54/411 | 119/521 | | |
| Krishnan | 18% | 0.82 [0.62-1.09] | death | 31/58 | 61/94 | | |
| Yao | 34% | 0.66 [0.41-1.07] | death | 73/196 | 21/46 | | |
| Abd-Elsalam (RCT) | 1% | 0.99 [0.30-3.31] | death | 5/96 | 5/95 | | data issues, see notes |
| Rosenthal | -16% | 1.16 [1.05-1.28] | death | n/a | n/a | | |
| Darban (RCT) | 33% | 0.67 [0.14-3.17] | progression | 2/10 | 3/10 | | ICU patients CT[2] |
| Patel (DB RCT) | 20% | 0.80 [0.15-4.18] | death | 2/15 | 3/18 | | |
| Mulhem | 46% | 0.54 [0.43-0.68] | death | 256/1,596 | 260/1,623 | | |
| Gadhiya | -41% | 1.41 [0.69-2.57] | death | 21/54 | 34/229 | | |
| Al Sulaiman (ICU) | 36% | 0.64 [0.37-1.10] | death | 23/82 | 32/82 | | ICU patients |
| Assiri (ICU) | -81% | 1.81 [0.41-6.97] | death | 10/60 | 4/58 | | ICU patients |
| Zangeneh (ICU) | -21% | 1.21 [0.51-2.90] | death | n/a | n/a | | ICU patients |
| Alahmari | 30% | 0.70 [0.63-0.78] | hosp. time | 130 (n) | 847 (n) | | |
| Doocy | 41% | 0.59 [0.19-1.85] | death | 3/28 | 21/116 | | |
| Ibrahim Alhajjaji | 88% | 0.12 [0.01-2.24] | death | 0/44 | 4/57 | | |
| Kyagambiddwa | 25% | 0.75 [0.44-1.25] | death | 20/89 | 22/73 | | |
| Seely (DB RCT) | 48% | 0.52 [0.10-2.71] | progression | 2/42 | 4/44 | | CT[2] |
| **Late treatment** | **21%** | **0.79 [0.64-0.98]** | | **502/2,911** | **593/3,913** | | **21% lower risk** |

Tau$^2$ = 0.10, I$^2$ = 84.0%, p = 0.03

| | Improvement, RR [CI] | | | Treatment | Control | | |
|---|---|---|---|---|---|---|---|
| Louca | 1% | 0.99 [0.93-1.06] | cases | population-based cohort | | | |
| Mahto | 37% | 0.63 [0.22-1.49] | IgG+ | 10/38 | 83/651 | | |
| Bejan | 18% | 0.82 [0.22-3.13] | ventilation | 155 (n) | 9,074 (n) | | |
| Holt | 7% | 0.93 [0.59-1.44] | cases | 21/750 | 425/14,477 | COVIDENCE UK | |
| Abdulateef | 13% | 0.87 [0.38-1.97] | hosp. | 7/111 | 23/317 | | |
| Seet (CLUS. RCT) | 50% | 0.50 [0.34-0.75] | symp. case | 33/634 | 64/619 | | OT[1] |
| Israel | 100% | 0.00 [0.00-0.89] | hosp. | case control | | | CT[2] |
| Bagheri | 60% | 0.40 [0.04-3.53] | severe case | 33 (n) | 477 (n) | | |
| Gordon | 68% | 0.32 [0.01-7.87] | death | 0/104 | 1/96 | | |
| Kumar | 20% | 0.80 [0.21-2.99] | death | 6/75 | 3/30 | | |
| Nimer | -25% | 1.25 [0.87-1.77] | hosp. | 41/326 | 178/1,822 | | |
| Shehab | 47% | 0.53 [0.19-1.47] | severe case | 4/65 | 22/188 | | |
| Citu | 18% | 0.82 [0.12-5.68] | severe case | 2/74 | 2/61 | | CT[2] |
| Stambouli (DB RCT) | 68% | 0.32 [0.03-2.95] | symp. case | 1/59 | 3/56 | | |
| Adrean | -12% | 1.12 [0.74-1.70] | cases | 30/2,111 | 80/6,315 | | |
| Sharif | 40% | 0.60 [0.46-0.77] | severe case | n/a | n/a | | |
| Asoudeh | 57% | 0.43 [0.21-0.90] | severe case | 250 (all patients) | | | |
| Seifi | 31% | 0.69 [0.52-0.94] | hosp. | n/a | n/a | | per unit change |
| **Prophylaxis** | **22%** | **0.78 [0.64-0.93]** | | **155/4,535** | **884/34,183** | | **22% lower risk** |

Tau$^2$ = 0.06, I$^2$ = 57.7%, p = 0.0071

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **All studies** | **24%** | **0.76 [0.67-0.86]** | | **731/9,013** | **1,699/40,391** | | **24% lower risk** |

[1] OT: comparison with other treatment
[2] CT: study uses combined treatment
Tau$^2$ = 0.07, I$^2$ = 76.3%, p < 0.0001

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

0    0.25    0.5    0.75    1    1.25    1.5    1.75    2+

Favors zinc    Favors control

**Figure 13.** Random effects meta-analysis for peer reviewed studies. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. *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.

## 36 zinc COVID-19 studies excluding combined treatment



| | Improvement, RR [CI] | | Treatment | Control | |
|---|---|---|---|---|---|
| Thomas (RCT) | -44% | 1.44 [0.36-5.71] hosp. | 5/58 | 3/50 | COVIDAtoZ |
| Aldwihi | 24% | 0.76 [0.51-1.08] hosp. | 53/199 | 184/539 | |
| Mayberry | 53% | 0.47 [0.33-0.65] death | 938 (n) | 1,090 (n) | |
| Abdallah (DB RCT) | 30% | 0.70 [0.36-1.31] death | 15/231 | 22/239 | VIZIR |
| **Early treatment** | **34%** | **0.66 [0.46-0.93]** | **73/1,426** | **209/1,918** | **34% lower risk** |

Tau$^2$ = 0.06, I$^2$ = 54.3%, p = 0.017

| | Improvement, RR [CI] | | Treatment | Control | |
|---|---|---|---|---|---|
| Carlucci | 38% | 0.62 [0.46-0.84] death/HPC | 54/411 | 119/521 | |
| Krishnan | 18% | 0.82 [0.62-1.09] death | 31/58 | 61/94 | |
| Yao | 34% | 0.66 [0.41-1.07] death | 73/196 | 21/46 | |
| Abd-Elsalam (RCT) | 1% | 0.99 [0.30-3.31] death | 5/96 | 5/95 | data issues, see notes |
| Rosenthal | -16% | 1.16 [1.05-1.28] death | n/a | n/a | |
| Patel (DB RCT) | 20% | 0.80 [0.15-4.18] death | 2/15 | 3/18 | |
| Mulhem | 46% | 0.54 [0.43-0.68] death | 256/1,596 | 260/1,623 | |
| Gadhiya | -41% | 1.41 [0.69-2.57] death | 21/54 | 34/229 | |
| Al Sulaiman (ICU) | 36% | 0.64 [0.37-1.10] death | 23/82 | 32/82 | ICU patients |
| Elavarasi | 65% | 0.35 [0.24-0.56] death | 486 (n) | 1,201 (n) | |
| Assiri (ICU) | -81% | 1.81 [0.41-6.97] death | 10/60 | 4/58 | ICU patients |
| Zangeneh (ICU) | -21% | 1.21 [0.51-2.90] death | n/a | n/a | ICU patients |
| Alahmari | 30% | 0.70 [0.63-0.78] hosp. time | 130 (n) | 847 (n) | |
| Doocy | 41% | 0.59 [0.19-1.85] death | 3/28 | 21/116 | |
| Ibrahim Alhajjaji | 88% | 0.12 [0.01-2.24] death | 0/44 | 4/57 | |
| Kyagambiddwa | 25% | 0.75 [0.44-1.25] death | 20/89 | 22/73 | |
| **Late treatment** | **25%** | **0.75 [0.60-0.94]** | **498/3,345** | **586/5,060** | **25% lower risk** |

Tau$^2$ = 0.12, I$^2$ = 87.0%, p = 0.011

| | Improvement, RR [CI] | | Treatment | Control | |
|---|---|---|---|---|---|
| Louca | 1% | 0.99 [0.93-1.06] cases | population-based cohort | | |
| Mahto | 37% | 0.63 [0.22-1.49] IgG+ | 10/38 | 83/651 | |
| Bejan | 18% | 0.82 [0.22-3.13] ventilation | 155 (n) | 9,074 (n) | |
| Holt | 7% | 0.93 [0.59-1.44] cases | 21/750 | 425/14,477 | COVIDENCE UK |
| Abdulateef | 13% | 0.87 [0.38-1.97] hosp. | 7/111 | 23/317 | |
| Seet (CLUS. RCT) | 50% | 0.50 [0.34-0.75] symp. case | 33/634 | 64/619 | OT[1] |
| Bagheri | 60% | 0.40 [0.04-3.53] severe case | 33 (n) | 477 (n) | |
| Gordon | 68% | 0.32 [0.01-7.87] death | 0/104 | 1/96 | |
| Kumar | 20% | 0.80 [0.21-2.99] death | 6/75 | 3/30 | |
| Nimer | -25% | 1.25 [0.87-1.77] hosp. | 41/326 | 178/1,822 | |
| Shehab | 47% | 0.53 [0.19-1.47] severe case | 4/65 | 22/188 | |
| Stambouli (DB RCT) | 68% | 0.32 [0.03-2.95] symp. case | 1/59 | 3/56 | |
| Adrean | -12% | 1.12 [0.74-1.70] cases | 30/2,111 | 80/6,315 | |
| Sharif | 40% | 0.60 [0.46-0.77] severe case | n/a | n/a | |
| Asoudeh | 57% | 0.43 [0.21-0.90] severe case | 250 (all patients) | | |
| Seifi | 31% | 0.69 [0.52-0.94] hosp. | n/a | n/a | per unit change |
| **Prophylaxis** | **23%** | **0.77 [0.64-0.94]** | **153/4,461** | **882/34,122** | **23% lower risk** |

Tau$^2$ = 0.06, I$^2$ = 62.7%, p = 0.0081

| | | | | | |
|---|---|---|---|---|---|
| **All studies** | **26%** | **0.74 [0.65-0.85]** | **724/9,232** | **1,677/41,100** | **26% lower risk** |

[1] OT: comparison with other treatment

Tau$^2$ = 0.08, I$^2$ = 80.5%, p < 0.0001

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

0   0.25   0.5   0.75   1   1.25   1.5   1.75   2+

Favors zinc        Favors control

***Figure 14.*** Random effects meta-analysis for all studies excluding combined treatment studies. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.

# Randomized Controlled Trials (RCTs)

Figure 15 shows a comparison of results for RCTs and non-RCT studies. Random effects meta analysis of RCTs shows 39% improvement, compared to 26% for other studies. Figure 16, 17, and 18 show forest plots for random effects meta-analysis of all Randomized Controlled Trials, RCT mortality results, and RCT hospitalization results. RCT results are included in Table 1 and Table 2.
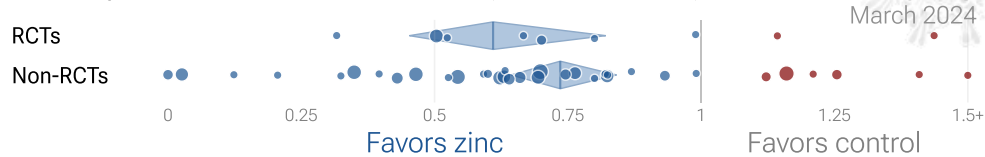
**Figure 15.** Results for RCTs and non-RCT studies.



# 9 zinc COVID-19 Randomized Controlled Trials

| | Improvement, RR [CI] | | Treatment | Control | |
|---|---|---|---|---|---|
| Thomas (RCT) | -44% 1.44 [0.36-5.71] | hosp. | 5/58 | 3/50 | COVIDAtoZ |
| Abdallah (DB RCT) | 30% 0.70 [0.36-1.31] | death | 15/231 | 22/239 | VIZIR |
| Boukef (DB RCT) | unknown, >1 year late | | 150 (total) | | |
| **Early treatment** | 21% 0.79 [0.45-1.41] | | 20/289 | 25/289 | 21% lower risk |

Tau² = 0.00, I² = 0.0%, p = 0.44

| | Improvement, RR [CI] | | Treatment | Control | |
|---|---|---|---|---|---|
| Abd-Elsalam (RCT) | 1% 0.99 [0.30-3.31] | death | 5/96 | 5/95 | data issues, see notes |
| Darban (RCT) | 33% 0.67 [0.14-3.17] | progression | 2/10 | 3/10 | ICU patients CT² |
| Patel (DB RCT) | 20% 0.80 [0.15-4.18] | death | 2/15 | 3/18 | |
| Kaplan (RCT) | -14% 1.14 [0.08-16.6] | ventilation | 1/14 | 1/16 | Reszinate CT² |
| Seely (DB RCT) | 48% 0.52 [0.10-2.71] | progression | 2/42 | 4/44 | CT² |
| Sharmin (DB RCT) | unknown, >2 years late | | 50 (est. total) | | |
| Correa (DB RCT) | unknown, >2 years late | | 105 (total) | | |
| Güerri-Fern.. (RCT) | unknown, >1.5 years late | | 75 (total) | | MARZINC |
| **Late treatment** | 21% 0.79 [0.39-1.60] | | 12/177 | 16/183 | 21% lower risk |

Tau² = 0.00, I² = 0.0%, p = 0.52

| | Improvement, RR [CI] | | Treatment | Control | |
|---|---|---|---|---|---|
| Seet (CLUS. RCT) | 50% 0.50 [0.34-0.75] | symp. case | 33/634 | 64/619 | OT[1] |
| Stambouli (DB RCT) | 68% 0.32 [0.03-2.95] | symp. case | 1/59 | 3/56 | |
| Ajili (DB RCT) | unknown, >3 years late | | 660 (est. total) | | COVID-Milit |
| **Prophylaxis** | 50% 0.50 [0.33-0.74] | | 34/693 | 67/675 | 50% lower risk |

Tau² = 0.00, I² = 0.0%, p = 0.0006

| | | | | | |
|---|---|---|---|---|---|
| **All studies** | 39% 0.61 [0.45-0.82] | | 66/1,159 | 108/1,147 | 39% lower risk |

[1] OT: comparison with other treatment
[2] CT: study uses combined treatment
Tau² = 0.00, I² = 0.0%, p = 0.0012

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

**Figure 16.** 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 see the appendix.

## 3 zinc COVID-19 RCT mortality results

| | Improvement, RR [CI] | | Treatment | Control | | |
|---|---|---|---|---|---|---|
| Abdallah (DB RCT) | 30% | 0.70 [0.36-1.31] | 15/231 | 22/239 | VIZIR | |
| **Early treatment** | 30% | 0.70 [0.36-1.31] | 15/231 | 22/239 | | 30% lower risk |

Tau² = 0.00, I² = 0.0%, p = 0.27

| | Improvement, RR [CI] | | Treatment | Control | | |
|---|---|---|---|---|---|---|
| Abd-Elsalam (RCT) | 1% | 0.99 [0.30-3.31] | 5/96 | 5/95 | | data issues, see notes |
| Patel (DB RCT) | 20% | 0.80 [0.15-4.18] | 2/15 | 3/18 | | |
| **Late treatment** | 8% | 0.92 [0.35-2.44] | 7/111 | 8/113 | | 8% lower risk |

Tau² = 0.00, I² = 0.0%, p = 0.87

| | | | | | |
|---|---|---|---|---|---|
| **All studies** | 24% | 0.76 [0.45-1.29] | 22/342 | 30/352 | 24% lower risk |

Tau² = 0.00, I² = 0.0%, p = 0.31

Favors zinc    Favors control

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

## 4 zinc COVID-19 RCT hospitalization results

| | Improvement, RR [CI] | | | Treatment | Control | | |
|---|---|---|---|---|---|---|---|
| Thomas (RCT) | -44% | 1.44 [0.36-5.71] | hosp. | 5/58 | 3/50 | COVIDAtoZ | |
| Abdallah (DB RCT) | 69% | 0.31 [0.03-2.61] | hosp. | 1/85 | 4/100 | VIZIR | |
| **Early treatment** | 16% | 0.84 [0.20-3.54] | | 6/143 | 7/150 | | 16% lower risk |

Tau² = 0.32, I² = 27.1%, p = 0.83

| | Improvement, RR [CI] | | | Treatment | Control | | |
|---|---|---|---|---|---|---|---|
| Abd-Elsalam (RCT) | 4% | 0.96 [0.86-1.08] | hosp. time | 96 (n) | 95 (n) | | data issues, see notes |
| Kaplan (RCT) | -14% | 1.14 [0.08-16.6] | hosp. | 1/14 | 1/16 | Reszinate | CT[1] |
| **Late treatment** | 4% | 0.96 [0.86-1.08] | | 1/110 | 1/111 | | 4% lower risk |

Tau² = 0.00, I² = 0.0%, p = 0.56

| | | | | | |
|---|---|---|---|---|---|
| **All studies** | 4% | 0.96 [0.86-1.08] | 7/253 | 8/261 | 4% lower risk |

[1] CT: study uses combined treatment

Tau² = 0.00, I² = 0.0%, p = 0.55

Favors zinc    Favors control

**Figure 18.** Random effects meta-analysis for RCT hospitalization results.

**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, reporting, and the potential for fraud. All of these biases have been observed with COVID-19 RCTs. There is no guarantee that a specific RCT provides a higher level of evidence.

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

experimental drug compared with those funded by nonprofit organizations. For COVID-19, some major philanthropic organizations are largely funded by investments with extreme conflicts of interest for and against specific COVID-19 interventions.

**RCTs for novel acute diseases requiring rapid treatment.** High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way. Every treatment RCT to date involves delayed treatment. Among the 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.

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

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

## Unreported RCTs

5 zinc RCTs have not reported results *Ajili, Boukef, Correa, Güerri-Fernández, Sharmin*. The trials report a total of 1,040 patients, with 3 trials having actual enrollment of 330, and the remainder estimated. The results are delayed from 1 year to over 3 years.

## Exclusions

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

The studies excluded are as below. Figure 19 shows a forest plot for random effects meta-analysis of all studies after exclusions.

*Abd-Elsalam*, multiple potential data reliability issues.

*Abdulateef*, unadjusted results with no group details.

*Asimi*, excessive unadjusted differences between groups.

*Assiri*, unadjusted results with no group details.

*Doocy*, unadjusted results with no group details.

*Gadhiya*, substantial unadjusted confounding by indication likely.

*Holt*, significant unadjusted confounding possible.

*Ibrahim Alhajjaji*, excessive unadjusted differences between groups.

*Israel*, treatment or control group size extremely small.

*Krishnan*, unadjusted results with no group details.

*Kumar*, unadjusted results with no group details.

*Kyagambiddwa*, unadjusted results with no group details.

*Mulhem*, substantial unadjusted confounding by indication likely; substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

*Rosenthal*, confounding by indication is likely and adjustments do not consider COVID-19 severity at baseline.

*Seifi*, the hospitalization result is only provided with respect to continuous values and the confidence interval is not reported for the case result.

*Shehab*, unadjusted results with no group details.

## 28 zinc COVID-19 studies after exclusions

| | Improvement, RR [CI] | | Treatment | Control | |
|---|---|---|---|---|---|
| Derwand | 79% | 0.21 [0.03-1.47] | death | 1/141 | 13/377 | CT[2] |
| Thomas (RCT) | -44% | 1.44 [0.36-5.71] | hosp. | 5/58 | 3/50 | COVIDAtoZ |
| Aldwihi | 24% | 0.76 [0.51-1.08] | hosp. | 53/199 | 184/539 | |
| Mayberry | 53% | 0.47 [0.33-0.65] | death | 938 (n) | 1,090 (n) | |
| Abdallah (DB RCT) | 30% | 0.70 [0.36-1.31] | death | 15/231 | 22/239 | VIZIR |
| **Early treatment** | **37%** | **0.63 [0.45-0.90]** | | 74/1,567 | 222/2,295 | **37% lower risk** |

Tau$^2$ = 0.06, I$^2$ = 48.7%, p = 0.01

| | Improvement, RR [CI] | | Treatment | Control | |
|---|---|---|---|---|---|
| Carlucci | 38% | 0.62 [0.46-0.84] | death/HPC | 54/411 | 119/521 | |
| Yao | 34% | 0.66 [0.41-1.07] | death | 73/196 | 21/46 | |
| Frontera (PSM) | 37% | 0.63 [0.44-0.91] | death | 121/1,006 | 424/2,467 | CT[2] |
| Darban (RCT) | 33% | 0.67 [0.14-3.17] | progression | 2/10 | 3/10 | ICU patients CT[2] |
| Patel (DB RCT) | 20% | 0.80 [0.15-4.18] | death | 2/15 | 3/18 | |
| Al Sulaiman (ICU) | 36% | 0.64 [0.37-1.10] | death | 23/82 | 32/82 | ICU patients |
| Elavarasi | 65% | 0.35 [0.24-0.56] | death | 486 (n) | 1,201 (n) | |
| Kaplan (RCT) | -14% | 1.14 [0.08-16.6] | ventilation | 1/14 | 1/16 | Reszinate CT[2] |
| Zangeneh (ICU) | -21% | 1.21 [0.51-2.90] | death | n/a | n/a | ICU patients |
| Alahmari | 30% | 0.70 [0.63-0.78] | hosp. time | 130 (n) | 847 (n) | |
| Seely (DB RCT) | 48% | 0.52 [0.10-2.71] | progression | 2/42 | 4/44 | CT[2] |
| **Late treatment** | **36%** | **0.64 [0.57-0.72]** | | 278/2,392 | 607/5,252 | **36% lower risk** |

Tau$^2$ = 0.01, I$^2$ = 20.5%, p < 0.0001

| | Improvement, RR [CI] | | Treatment | Control | |
|---|---|---|---|---|---|
| Louca | 1% | 0.99 [0.93-1.06] | cases | population-based cohort | | |
| Mahto | 37% | 0.63 [0.22-1.49] | IgG+ | 10/38 | 83/651 | |
| Bejan | 18% | 0.82 [0.22-3.13] | ventilation | 155 (n) | 9,074 (n) | |
| Seet (CLUS. RCT) | 50% | 0.50 [0.34-0.75] | symp. case | 33/634 | 64/619 | OT[1] |
| Bagheri | 60% | 0.40 [0.04-3.53] | severe case | 33 (n) | 477 (n) | |
| Gordon | 68% | 0.32 [0.01-7.87] | death | 0/104 | 1/96 | |
| Nimer | -25% | 1.25 [0.87-1.77] | hosp. | 41/326 | 178/1,822 | |
| Citu | 18% | 0.82 [0.12-5.68] | severe case | 2/74 | 2/61 | CT[2] |
| Stambouli (DB RCT) | 68% | 0.32 [0.03-2.95] | symp. case | 1/59 | 3/56 | |
| Adrean | -12% | 1.12 [0.74-1.70] | cases | 30/2,111 | 80/6,315 | |
| Sharif | 40% | 0.60 [0.46-0.77] | severe case | n/a | n/a | |
| Asoudeh | 57% | 0.43 [0.21-0.90] | severe case | 250 (all patients) | | |
| **Prophylaxis** | **23%** | **0.77 [0.60-0.98]** | | 117/3,534 | 411/19,171 | **23% lower risk** |

Tau$^2$ = 0.08, I$^2$ = 68.6%, p = 0.034

| | | | | | |
|---|---|---|---|---|---|
| **All studies** | **32%** | **0.68 [0.59-0.79]** | 469/7,493 | 1,240/26,718 | **32% lower risk** |

$^1$ OT: comparison with other treatment
$^2$ CT: study uses combined treatment
Tau$^2$ = 0.07, I$^2$ = 74.9%, p < 0.0001

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

Favors zinc    Favors control

**Figure 19.** Random effects meta-analysis for all studies after exclusions. 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 see the appendix.

## Heterogeneity

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

**Treatment delay.** The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours *McLean, Treanor*. Baloxavir studies for influenza also show that treatment delay is critical — *Ikematsu et al.* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden et al.* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and *Kumar (B) et al.* report only 2.5 hours improvement for inpatient treatment.

| Treatment delay | Result |
|---|---|
| Post exposure prophylaxis | **86% fewer cases** *Ikematsu* |
| <24 hours | -33 hours symptoms *Hayden* |
| 24-48 hours | -13 hours symptoms *Hayden* |
| Inpatients | -2.5 hours to improvement *Kumar (B)* |

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

Figure 20 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.



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

c19early.org
March 2024

p<0.00000000001
mixed-effects meta-regression, most serious sufficiently powered outcome
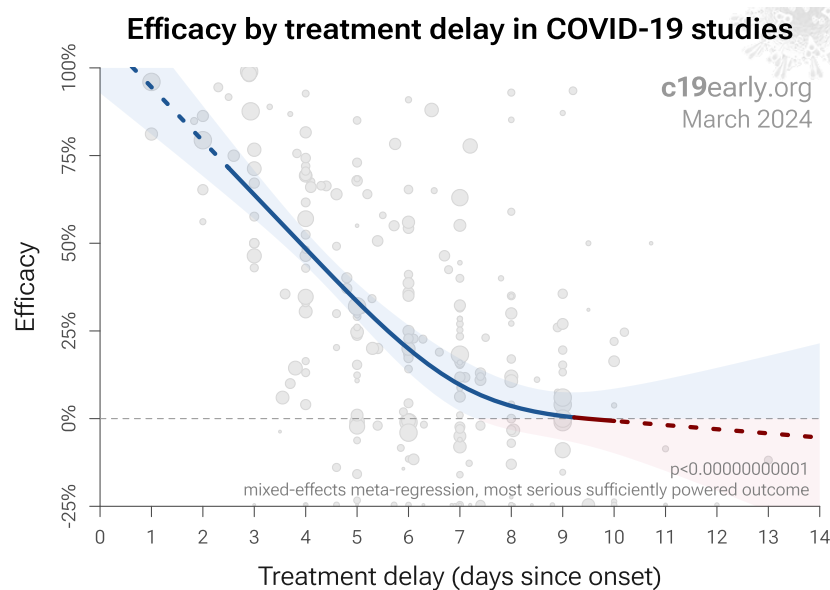
**Figure 20.** Early treatment is more effective. Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

**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 et al.*).

**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.** Efficacy may depend critically on the distribution of SARS-CoV-2 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 supplements, other medications, or other kinds of treatment such as prone positioning. Treatments may be synergistic [Alsaidi, Andreani, De Forni, Fiaschi, Jeffreys, Jitobaom, Jitobaom (B), Ostrov, Said, Thairu, Wan], therefore efficacy may depend strongly on combined treatments.

**Medication quality.** The quality of medications may vary significantly between manufacturers and production batches, which may significantly affect efficacy and safety. *Williams et al.* analyze ivermectin from 11 different sources, showing highly variable antiparasitic efficacy across different manufacturers. *Xu et al.* analyze a treatment from two different manufacturers, showing 9 different impurities, with significantly different concentrations for each manufacturer. Non-prescription supplements may show very wide variations in quality [Crawford, Crighton].

**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 21. 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 4 months faster (6 months for RCTs).** Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 85% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 3.7 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.
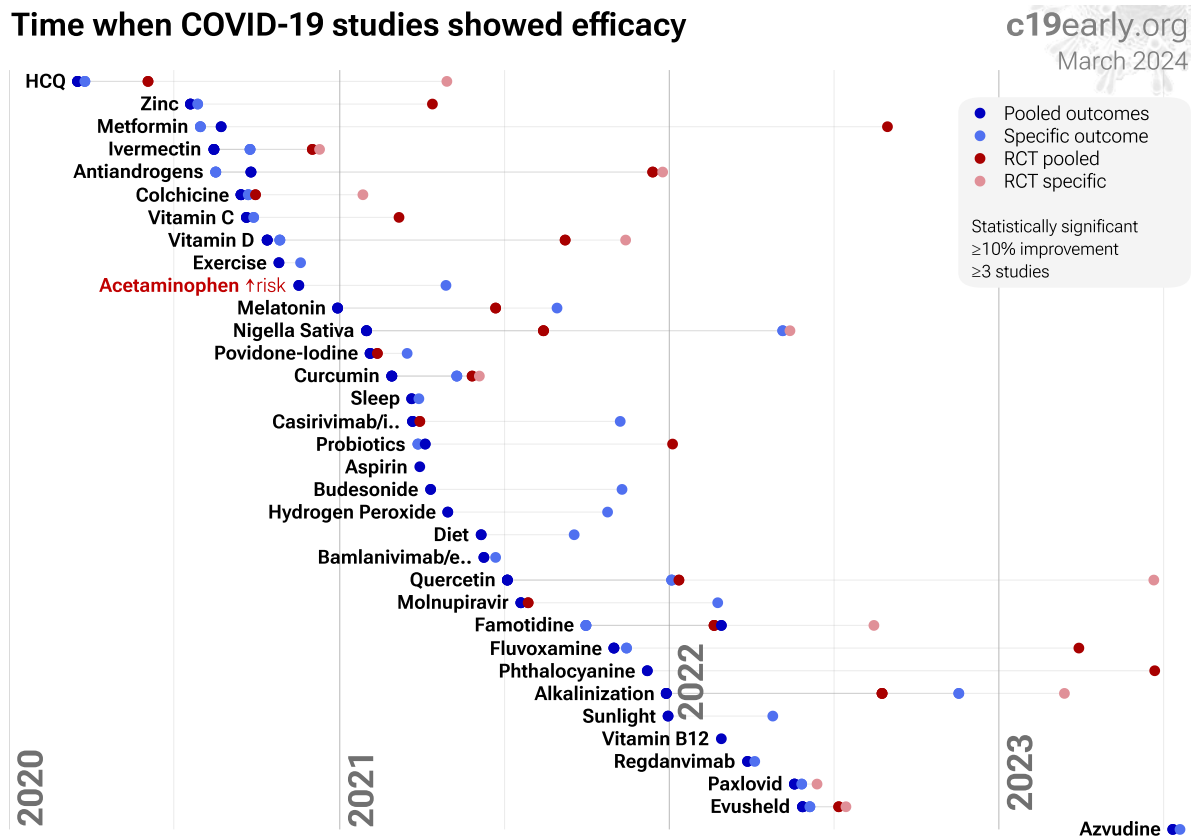
*Figure 21.* The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies. Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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

**Results for other viruses.** Studies have also shown efficacy with zinc for acute respiratory tract infections [Abioye] and the common cold [Hemilä].

**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].

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 22 shows a scatter plot of results for prospective and retrospective treatment studies. Prospective studies show 31% [12-46%] improvement in meta analysis, compared to 27% [16-36%] for retrospective studies, showing no significant difference, with results to date favoring a possible negative publication bias.
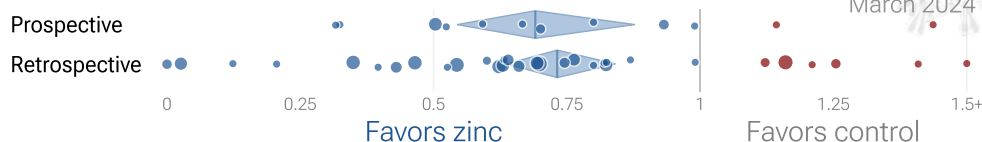


*Figure 22.* Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.

**Late treatment bias.** Studies for zinc were primarily late treatment studies, in contrast with typical patented treatments that were tested with early treatment as recommended.
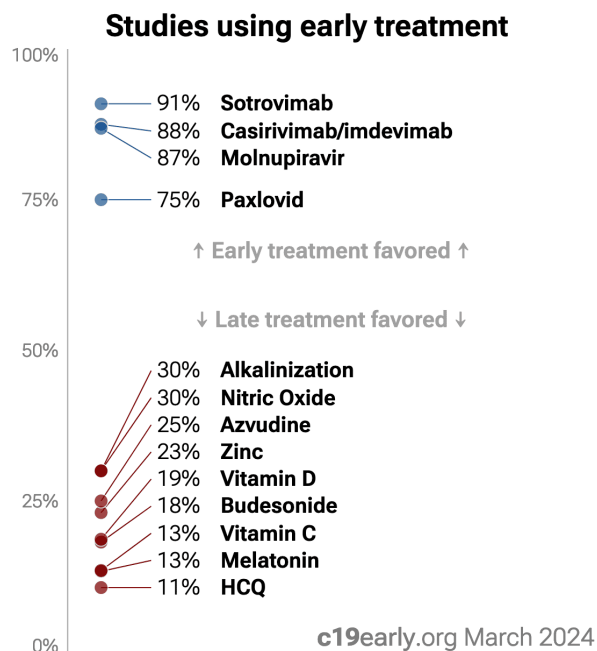


*Figure 23.* Patented treatments received mostly early treatment studies, while low cost treatments were typically tested for late treatment.

**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 24 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.
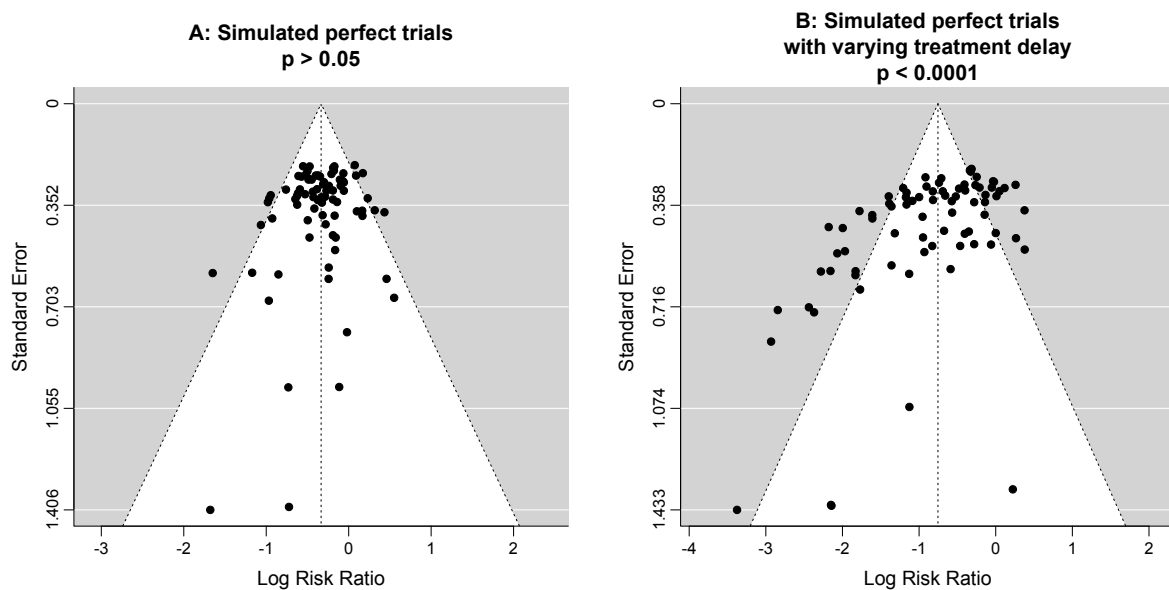


*Figure 24.* Example funnel plot analysis for simulated perfect trials.

**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. Zinc for COVID-19 lacks this because it is an inexpensive and widely available supplement. In contrast, most COVID-19 zinc 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 zinc trials represent the optimal conditions for efficacy.

**Physician case series results.** Table 4 shows the reported results of physicians that use early treatments for COVID-19, compared to the results for a non-treating physician. The treatments used vary. Physicians typically use a combination of treatments, with almost all reporting use of ivermectin and/or HCQ, and most using additional treatments, including zinc. These results are subject to selection and ascertainment bias and more accurate analysis requires details of the patient populations and followup, however results are consistently better across many teams, and consistent with the extensive controlled trial evidence that shows a significant reduction in risk with many early treatments, and improved results with the use of multiple treatments in combination.

| LATE TREATMENT | | | | | | |
|---|---|---|---|---|---|---|
| Physician / Team | Location | Patients | Hospitalization | | Mortality | |
| Dr. David Uip (*) | Brazil | 2,200 | 38.6% (850) | Ref. | 2.5% (54) | Ref. |
| EARLY TREATMENT - 39 physicians/teams | | | | | | |
| Physician / Team | Location | Patients | Hospitalization | Improvement | Mortality | Improvement |
| Dr. Roberto Alfonso Accinelli <br> 0/360 deaths for treatment within 3 days | Peru | 1,265 | | | 0.6% (7) | 77.5% |
| Dr. Mohammed Tarek Alam <br> patients up to 84 years old | Bangladesh | 100 | | | 0.0% (0) | 100.0% |
| Dr. Oluwagbenga Alonge | Nigeria | 310 | | | 0.0% (0) | 100.0% |
| Dr. Raja Bhattacharya <br> up to 88yo, 81% comorbidities | India | 148 | | | 1.4% (2) | 44.9% |
| Dr. Flavio Cadegiani | Brazil | 3,450 | 0.1% (4) | 99.7% | 0.0% (0) | 100.0% |
| Dr. Alessandro Capucci | Italy | 350 | 4.6% (16) | 88.2% | | |
| Dr. Shankara Chetty | South Africa | 8,000 | | | 0.0% (0) | 100.0% |
| Dr. Deborah Chisholm | USA | 100 | | | 0.0% (0) | 100.0% |
| Dr. Ryan Cole | USA | 400 | 0.0% (0) | 100.0% | 0.0% (0) | 100.0% |
| Dr. Marco Cosentino <br> vs. 3-3.8% mortality during period; earlier treatment better | Italy | 392 | 6.4% (25) | 83.5% | 0.3% (1) | 89.6% |
| Dr. Jeff Davis | USA | 6,000 | | | 0.0% (0) | 100.0% |
| Dr. Dhanajay | India | 500 | | | 0.0% (0) | 100.0% |
| Dr. Bryan Tyson & Dr. George Fareed | USA | 20,000 | 0.0% (6) | 99.9% | 0.0% (4) | 99.2% |
| Dr. Raphael Furtado | Brazil | 170 | 0.6% (1) | 98.5% | 0.0% (0) | 100.0% |
| Dr. Heather Gessling | USA | 1,500 | | | 0.1% (1) | 97.3% |
| Dr. Ellen Guimarães | Brazil | 500 | 1.6% (8) | 95.9% | 0.4% (2) | 83.7% |
| Dr. Syed Haider | USA | 4,000 | 0.1% (5) | 99.7% | 0.0% (0) | 100.0% |
| Dr. Mark Hancock | USA | 24 | | | 0.0% (0) | 100.0% |
| Dr. Sabine Hazan | USA | 1,000 | | | 0.0% (0) | 100.0% |
| Dr. Mollie James | USA | 3,500 | 1.1% (40) | 97.0% | 0.0% (1) | 98.8% |
| Dr. Roberta Lacerda | Brazil | 550 | 1.5% (8) | 96.2% | 0.4% (2) | 85.2% |
| Dr. Katarina Lindley | USA | 100 | 5.0% (5) | 87.1% | 0.0% (0) | 100.0% |
| Dr. Ben Marble | USA | 150,000 | | | 0.0% (4) | 99.9% |
| Dr. Edimilson Migowski | Brazil | 2,000 | 0.3% (7) | 99.1% | 0.1% (2) | 95.9% |
| Dr. Abdulrahman Mohana | Saudi Arabia | 2,733 | | | 0.0% (0) | 100.0% |
| Dr. Carlos Nigro | Brazil | 5,000 | 0.9% (45) | 97.7% | 0.5% (23) | 81.3% |
| Dr. Benoit Ochs | Luxembourg | 800 | | | 0.0% (0) | 100.0% |
| Dr. Ortore | Italy | 240 | 1.2% (3) | 96.8% | 0.0% (0) | 100.0% |
| Dr. Valerio Pascua <br> one death for a patient presenting on the 5th day in need of supplemental oxygen | Honduras | 415 | 6.3% (26) | 83.8% | 0.2% (1) | 90.2% |
| Dr. Sebastian Pop | Romania | 300 | | | 0.0% (0) | 100.0% |
| Dr. Brian Proctor | USA | 869 | 2.3% (20) | 94.0% | 0.2% (2) | 90.6% |

| | | | | | | |
|---|---|---|---|---|---|---|
| Dr. Anastacio Queiroz | Brazil | 700 | | | 0.0% (0) | 100.0% |
| Dr. Didier Raoult | France | 8,315 | 2.6% (214) | 93.3% | 0.1% (5) | 97.6% |
| Dr. Karin Ried<br>up to 99yo, 73% comorbidities, av. age 63 | Turkey | 237 | | | 0.4% (1) | 82.8% |
| Dr. Roman Rozencwaig<br>patients up to 86 years old | Canada | 80 | | | 0.0% (0) | 100.0% |
| Dr. Vipul Shah | India | 8,000 | | | 0.1% (5) | 97.5% |
| Dr. Silvestre Sobrinho | Brazil | 116 | 8.6% (10) | 77.7% | 0.0% (0) | 100.0% |
| Dr. Unknown | Brazil | 957 | 1.7% (16) | 95.7% | 0.2% (2) | 91.5% |
| Dr. Vladimir Zelenko | USA | 2,200 | 0.5% (12) | 98.6% | 0.1% (2) | 96.3% |
| Mean improvement with early treatment protocols | | 237,521 | Hospitalization | 94.1% | Mortality | 94.7% |

*Table 4.* Physician results with early treatment protocols compared to no early treatment. (*) Dr. Uip reportedly prescribed early treatment for himself, but not for patients *medicospelavidacovid19.com.br*.

**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 the 44 studies compare against other treatments, which may reduce the effect seen. 8 of 44 studies combine treatments. The results of zinc alone may differ. 3 of 9 RCTs use combined treatment. Other meta analyses show significant improvements with zinc for mortality *Abuhelwa, Olczak-Pruc, Rheingold, Tabatabaeizadeh, Xie*, severity *Fan*, and cases *Fan*.

**Reviews.** Many reviews cover zinc for COVID-19, presenting additional background on mechanisms and related results, including *Arora, Briassoulis, Derwand, DiGuilio, Foshati, Joachimiak, Schloss, Sethuram*.

## NIH

NIH provides an analysis of zinc for COVID-19 *covid19treatmentguidelines.nih.gov*, concluding that there is insufficient evidence to recommend for or against use. However, they appear not to have looked at the majority of the evidence. For example, considering RCTs providing clinical results for COVID-19 and zinc, they reference only *Abd-Elsalam, Abdallah, Thomas*, and appear not to know about 6 other RCTs *Darban, Kaplan, Patel, Seely, Seet, Stambouli* as shown in Figure 25. Notably, the NIH selection is not based on quality, for example including *Abd-Elsalam et al.*, with data reliability issues, and not including *Seet et al.*, a much larger and higher quality trial.



**Figure 25.** Analysis by NIH is missing 6 RCTs.

## Conclusion

Zinc is an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality, ventilation, hospitalization, progression, recovery, and viral clearance. 18 studies from 18 independent teams in 9 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 27% [17-36%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, peer-reviewed studies, and after excluding studies using combined treatment. 17 sufficiency studies analyze outcomes based on serum levels, showing 74% [64-81%] lower risk for patients with higher zinc levels. Results are robust — in exclusion sensitivity analysis 19 of 44 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

8 studies use combined treatments. After exclusion the risk reduction is 26% [15-35%] compared to 27% [17-36%].

The European Food Safety Authority has found evidence for a causal relationship between the intake of zinc and optimal immune system function *Galmés, Galmés (B)*. Over-supplementation may be detrimental *karger.com*. Bioaccessibility of supplements varies widely *Ośko*.

Other meta analyses show significant improvements with zinc for mortality *Abuhelwa, Olczak-Pruc, Rheingold, Tabatabaeizadeh, Xie*, severity *Fan*, and cases *Fan*.

## Study Notes

### Abd-Elsalam



Zinc *Abd-Elsalam et al.* LATE TREATMENT RCT

|  | Improvement | Relative Risk |
| --- | --- | --- |
| Mortality | 1% | |
| Ventilation | 34% | |
| Recovery | 6% | |
| Hospitalization time | 4% | |

Favors zinc    Favors control

Is **late** treatment with zinc beneficial for COVID-19?
RCT 191 patients in Egypt (June - August 2020)
Trial underpowered for serious outcomes

**c19**early.org   Abd-Elsalam et al., Biological Trace E.., Nov 2020
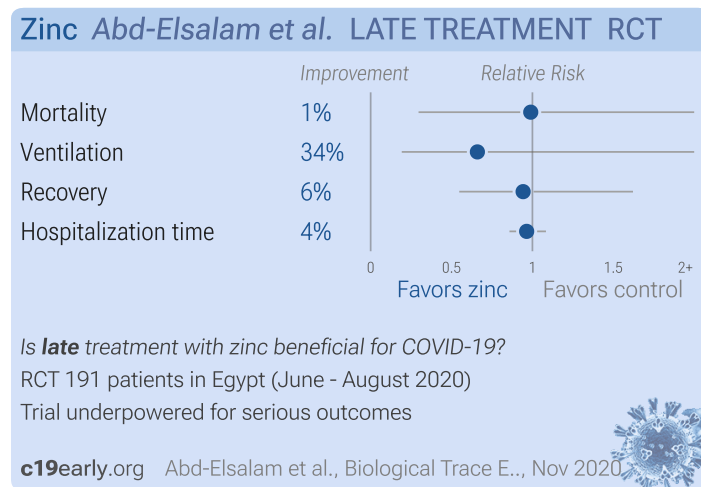
*Abd-Elsalam*: 191 patient RCT in Egypt comparing the addition of zinc to HCQ, not showing a significant difference. No information on baseline zinc values was recorded. Egypt has a low rate of zinc deficiency so supplementation may be less likely to be helpful *ncbi.nlm.nih.gov, ncbi.nlm.nih.gov (B)*. For several issues with this trial, see *osf.io*. See also *link.springer.com*. The primary outcome was changed from viral clearance to "improvement or mortality" in the last month of the trial. The pre-specified outcome was not reported.

**Abdallah**



**Zinc VIZIR EARLY TREATMENT DB RCT**

| | Improvement | Relative Risk |
|---|---|---|
| Mortality | 30% | |
| Death/ICU | 38% | |
| ICU admission | 54% | |
| Oxygen therapy, day 30 | 42% | |
| Oxygen therapy, day 15 | 23% | |
| Recovery, day 30 | 29% | |
| Recovery, day 15 | 14% | |
| Hospitalization, outpatients | 69% | |
| Hospitalization time, inpat.. | 33% | |
| Recovery time, outpatients | 25% | |

0   0.5   1   1.5   2+
Favors zinc    Favors control
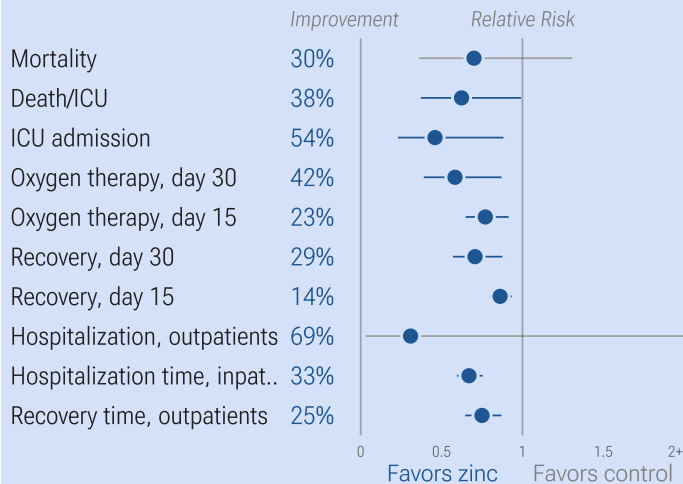
*Is early treatment with zinc beneficial for COVID-19?*
Double-blind RCT 470 patients in Tunisia (February - May 2022)
**Lower death/ICU *(p=0.04)* and ICU admission *(p=0.01)***

**c19**early.org   Abdallah et al., Clinical Infectious D.., Nov 2022

*Abdallah*: RCT 470 patients with symptoms ≤7 days, showing significantly lower ICU admission and combined mortality/ICU admission with zinc treatment. Greater benefit was seen for patients treated within 3 days. 25mg elemental zinc bid for 15 days.

See also *academic.oup.com* and the author's reply *academic.oup.com (B)*.

**Abdulateef**



**Zinc for COVID-19 *Abdulateef et al.* Prophylaxis**

| | Improvement | Relative Risk |
|---|---|---|
| Hospitalization | 13% | |

0   0.5   1   1.5   2+
Favors zinc    Favors control
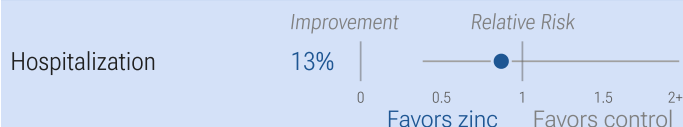
*Is prophylaxis with zinc beneficial for COVID-19?*
Retrospective 428 patients in Iraq (July - August 2020)
Study underpowered to detect differences

**c19**early.org   Abdulateef et al., Open Medicine, April 2021

*Abdulateef*: Survey of 428 recovered COVID-19 patients in Iraq, showing fewer hospital visits for patients on prophylactic vitamin C or D. Hospitalization was lower for those on vitamin C, D, or zinc, without statistical significance.

## Adrean



Zinc for COVID-19 *Adrean et al.* Prophylaxis

| | Improvement | Relative Risk |
|---|---|---|
| Case | -12% | |
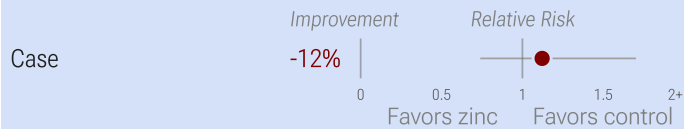
Does zinc reduce COVID-19 infections?
Retrospective 8,426 patients in the USA (April 2020 - April 2021)
No significant difference in cases

**c19**early.org  Adrean et al., Cureus, October 2022
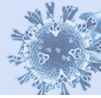
*Adrean*: Retrospective 8,426 patients in the USA, showing no significant difference in cases with zinc prophylaxis. Severity results were not reported due to the small number of events.

## Ajili

*Ajili*: Estimated 660 participant zinc prophylaxis RCT with results not reported over 3 years after estimated completion.

## Al Sulaiman



Zinc for COVID-19 *Al Sulaiman et al.* ICU PATIENTS

| | Improvement | Relative Risk |
|---|---|---|
| Mortality | 36% | |
| Mortality (b) | 48% | |
| ICU time | -25% | |
| Hospitalization time | -6% | |
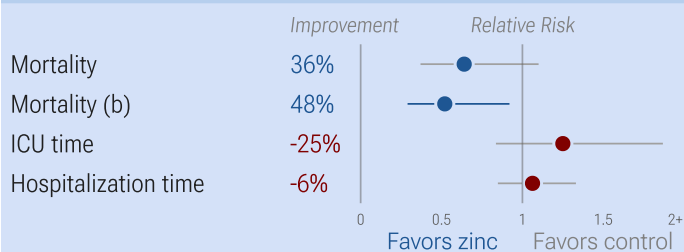
Is **very late** treatment with zinc beneficial for COVID-19?
PSM retrospective 164 patients in Saudi Arabia (Mar 2020 - Mar 2021)
Lower mortality (*p=0.11*) and longer ICU admission (*p=0.28*), not sig.

**c19**early.org  Al Sulaiman et al., Critical Care, Jun 2021

*Al Sulaiman*: Retrospective 266 ICU patients showing lower mortality with zinc treatment (very close to statistical significance), and higher odds of acute kidney injury. NRC21R/287/07.

## Alahmari



Zinc for COVID-19 *Alahmari et al.* LATE TREATMENT

| | Improvement | Relative Risk |
|---|---|---|
| Hospitalization time | 30% | |
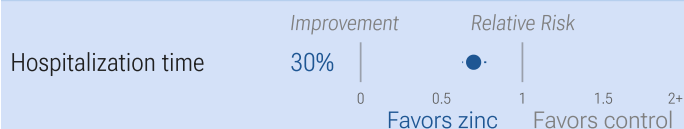
Is **late** treatment with zinc beneficial for COVID-19?
Retrospective 977 patients in Saudi Arabia (May - July 2020)
**Shorter hospitalization with zinc (*p<0.000001*)**

**c19**early.org  Alahmari et al., Healthcare, June 2022
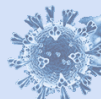
*Alahmari*: Retrospective 977 hospitalized patients in Saudi Arabia, showing significantly shorter hospitalization with zinc treatment.

## Aldwihi



Zinc for COVID-19 *Aldwihi et al.* EARLY TREATMENT

Hospitalization — Improvement 24% — Relative Risk

Is early treatment with zinc beneficial for COVID-19?
Retrospective 738 patients in Saudi Arabia (August - October 2020)
Lower hospitalization with zinc *(not stat. sig., p=0.16)*

**c19**early.org Aldwihi et al., Int. J. Environmental .., May 2021
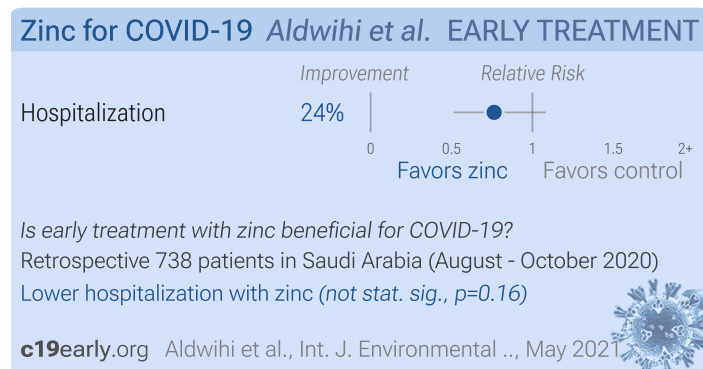
*Aldwihi*: Retrospective survey-based analysis of 738 COVID-19 patients in Saudi Arabia, showing lower hospitalization with vitamin C, turmeric, zinc, and nigella sativa, and higher hospitalization with vitamin D. For vitamin D, most patients continued prophylactic use. For vitamin C, the majority of patients continued prophylactic use. For nigella sativa, the majority of patients started use during infection. Authors do not specify the fraction of prophylactic use for turmeric and zinc.

## Asimi



Zinc for COVID-19 *Asimi et al.* EARLY TREATMENT

Improvement — Relative Risk
Ventilation 97%
Hospitalization 99%
Severe case 100%

Is early treatment with zinc + vitamin D and selenium beneficial for COVID-19?
Retrospective 356 patients in Bosnia and Herzegovina
**Lower ventilation *(p<0.0001)* and hospitalization *(p<0.0001)***

**c19**early.org Asimi et al., Endocrine Abstracts, May 2021

*Asimi*: Retrospective 356 Hashimoto's thyroiditis outpatients, 270 taking vitamin D, zinc, and selenium, showing significantly lower hospitalization with treatment. Authors adjust for age, gender, BMI, and smoking status, reporting statistically significant associations with p<0.001 for hospitalization and mechanical ventilation, however they do not report the adjusted risks.

## Asoudeh



Zinc for COVID-19 *Asoudeh et al.* Prophylaxis

Severe case — Improvement 57% — Relative Risk

Is prophylaxis with zinc beneficial for COVID-19?
Retrospective 250 patients in Iran (June - September 2021)
**Lower severe cases with zinc *(p=0.03)***

**c19**early.org Asoudeh et al., Clinical Nutrition ESPEN, Mar 2023
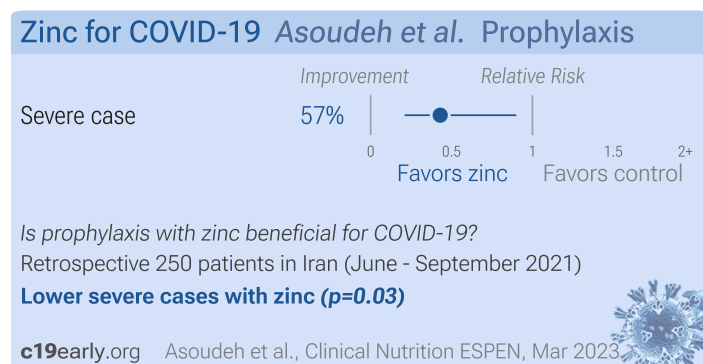
*Asoudeh*: Retrospective 250 recovered COVID-19 patients, showing lower risk of severe cases with higher zinc intake.

## Assiri

**Zinc for COVID-19** *Assiri et al.* **ICU PATIENTS**

| | Improvement | Relative Risk |
|---|---|---|
| Mortality | -81% | |

0    0.5    1    1.5    2+
Favors zinc    Favors control

Is **very late** treatment with zinc beneficial for COVID-19?
Retrospective 118 patients in Saudi Arabia
Higher mortality with zinc *(not stat. sig., p=0.44)*

**c19**early.org   Assiri et al., J. Infection and Public.., Aug 2021
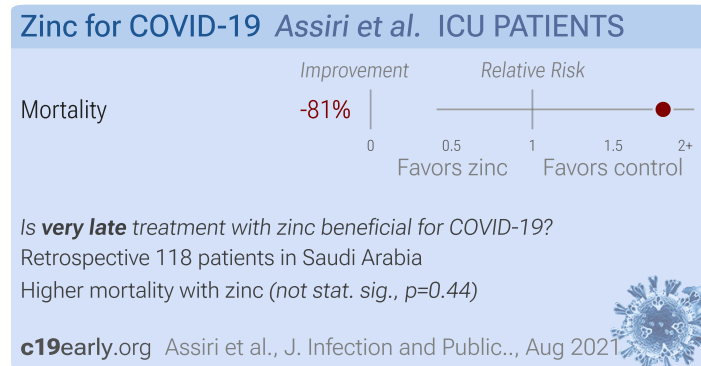
*Assiri*: Retrospective 118 ICU patients in Saudi Arabia showing no significant differences in unadjusted results with zinc, vitamin D, and favipiravir treatment.

## Bagheri

**Zinc for COVID-19** *Bagheri et al.* **Prophylaxis**

| | Improvement | Relative Risk |
|---|---|---|
| Severe case | 60% | |
| Hospitalization | 41% | |

0    0.5    1    1.5    2+
Favors zinc    Favors control

Is prophylaxis with zinc beneficial for COVID-19?
Retrospective 510 patients in Iran
Lower severe cases *(p=0.41)* and hospitalization *(p=0.37)*, not sig.

**c19**early.org   Bagheri et al., J. Family & Reproducti.., Sep 2021
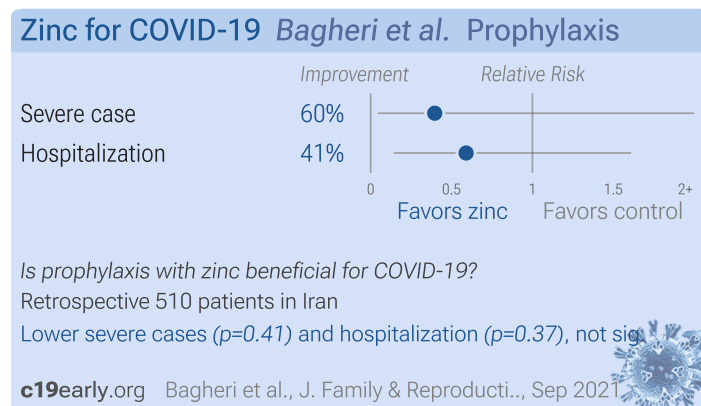
*Bagheri*: Retrospective 510 patients in Iran, showing lower risk of severity with vitamin D (statistically significant) and zinc (not statistically significant) supplementation. IR.TUMS.VCR.REC.1398.1063.

## Bejan

**Zinc for COVID-19** *Bejan et al.* **Prophylaxis**

| | Improvement | Relative Risk |
|---|---|---|
| Ventilation | 18% | |
| ICU admission | 30% | |

0    0.5    1    1.5    2+
Favors zinc    Favors control

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

**c19**early.org   Bejan et al., Clinical Pharmacology & .., Feb 2021
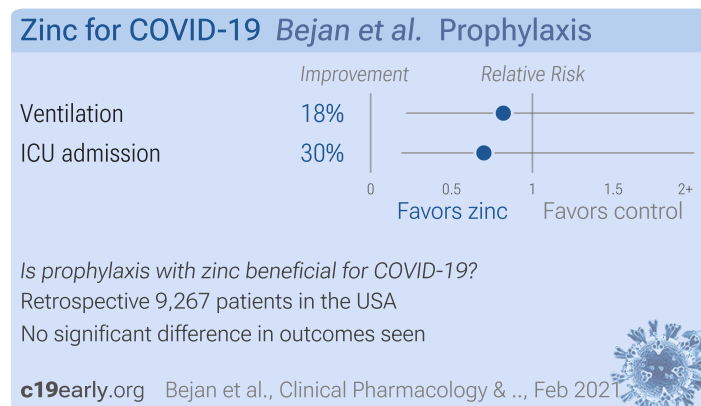
*Bejan*: Retrospective 9,748 COVID-19 patients in the USA showing lower ventilation and ICU admission with zinc prophylaxis, without statistical significance.

## Boukef

*Boukef*: 150 patient zinc early treatment RCT with results not reported over 1 year after completion.

## Carlucci



**Zinc for COVID-19** *Carlucci et al.* LATE TREATMENT

| | Improvement | Relative Risk |
|---|---|---|
| Death/hospice | 38% | |
| Ventilation | 18% | |
| ICU admission | 23% | |

Scale: 0, 0.5, 1, 1.5, 2+
Favors zinc — Favors control

*Is **late** treatment with zinc beneficial for COVID-19?*
Retrospective 932 patients in the USA
**Lower death/hospice with zinc (p=0.002)**

**c19**early.org  Carlucci et al., J. Med. Microbiol., S.., May 2020
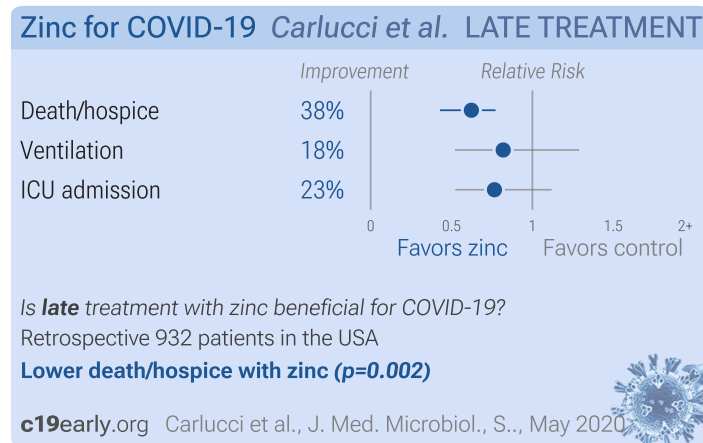
*Carlucci*: Retrospective 932 patients showing that the addition of zinc to HCQ+AZ reduced mortality / transfer to hospice, ICU admission, and the need for ventilation.

## Citu



**Zinc for COVID-19** *Citu et al.* Prophylaxis

| | Improvement | Relative Risk |
|---|---|---|
| Severe case | 18% | |

Scale: 0, 0.5, 1, 1.5, 2+
Favors zinc — Favors control

*Is prophylaxis with zinc + calcium beneficial for COVID-19?*
Retrospective 135 patients in Romania (April 2020 - February 2022)
Study underpowered to detect differences

**c19**early.org  Citu et al., Nutrients, March 2022
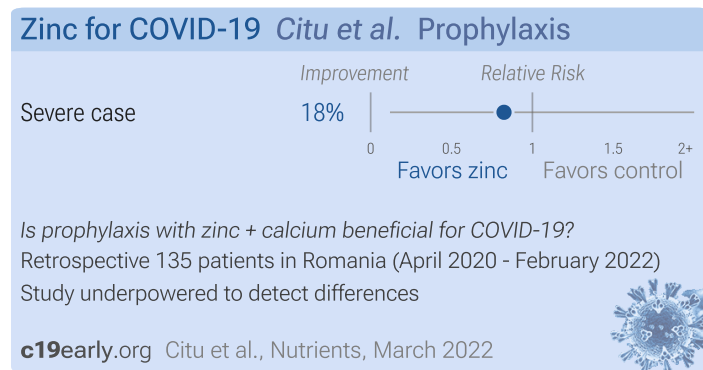
*Citu*: Retrospective 448 pregnant women with COVID-19. Patients with calcium, zinc, and magnesium supplementation, or magnesium only, had a significantly higher titer of SARS-CoV-2 anti-RBD antibodies. There was no statistically significant difference in severe cases based on supplementation.

## Correa

*Correa*: 105 patient zinc late treatment RCT with results not reported over 2 years after completion.

## Darban



**Zinc** *Darban et al.* ICU PATIENTS RCT

|  | Improvement | Relative Risk |
|---|---|---|
| Progression | 33% | |
| ICU time | 6% | |

0    0.5    1    1.5    2+
Favors zinc    Favors control

*Is **very late** treatment with zinc + melatonin and vitamin C beneficial for COVID-19?*
RCT 20 patients in Iran (April - June 2020)
Trial underpowered to detect differences

**c19**early.org   Darban et al., J. Cellular & Molecular.., Dec 2020
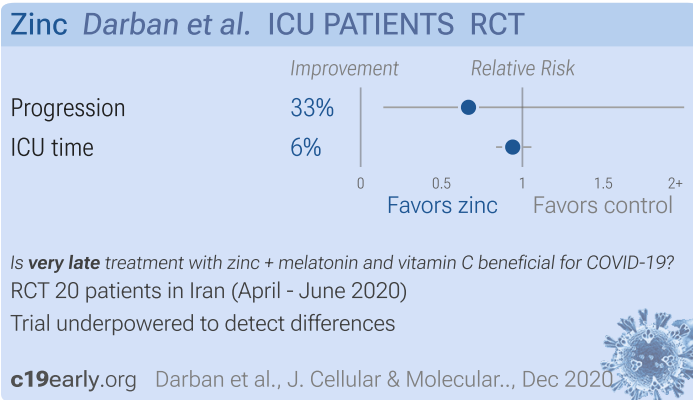
*Darban*: Small RCT in Iran with 20 ICU patients, 10 treated with high-dose vitamin C, melatonin, and zinc, not showing significant differences.

## Derwand



**Zinc for COVID-19** *Derwand et al.* EARLY TREATMENT

|  | Improvement | Relative Risk |
|---|---|---|
| Mortality | 79% | |
| Hospitalization | 82% | |

0    0.5    1    1.5    2+
Favors zinc    Favors control

*Is early treatment with zinc + HCQ and azithromycin beneficial for COVID-19?*
Retrospective 518 patients in the USA
**Lower hospitalization with zinc + HCQ and azithromycin (p=0.001)**

**c19**early.org   Derwand et al., Int. J. Antimicrobial .., Jul 2020

*Derwand (B)*: 79% lower mortality and 82% lower hospitalization with early HCQ+AZ+Z. Retrospective 518 patients (141 treated, 377 control).

## Doocy



**Zinc for COVID-19** *Doocy et al.* LATE TREATMENT

|  | Improvement | Relative Risk |
|---|---|---|
| Mortality | 41% | unadjusted |

0    0.5    1    1.5    2+
Favors zinc    Favors control

*Is **late** treatment with zinc beneficial for COVID-19?*
Prospective study of 144 patients in multiple countries (Dec 2020 - Jun 2021)
Lower mortality with zinc *(not stat. sig., p=0.41)*

**c19**early.org   Doocy et al., PLOS Global Public Health, Oct 2022
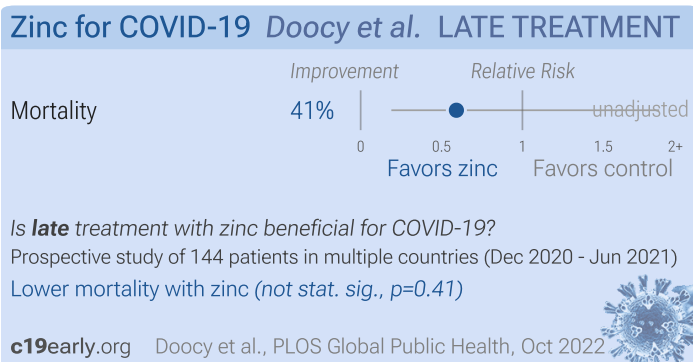
*Doocy*: Prospective study of 144 hospitalized COVID-19 patients in the DRC and South Sudan, showing lower mortality with zinc treatment, without statistical significance.

## Doğan

### Zinc for COVID-19 *Doğan et al.* Sufficiency

|  | Improvement | Relative Risk |
|---|---|---|
| Case | 77% |  |

Favors zinc — Favors control

*Are zinc levels associated with COVID-19 outcomes?*
Prospective study of 176 patients in Turkey (Jul - Oct 2021)
**Fewer cases with higher zinc levels (p=0.0031)**

**c19**early.org  Doğan et al., J. Tropical Pediatrics, Aug 2022
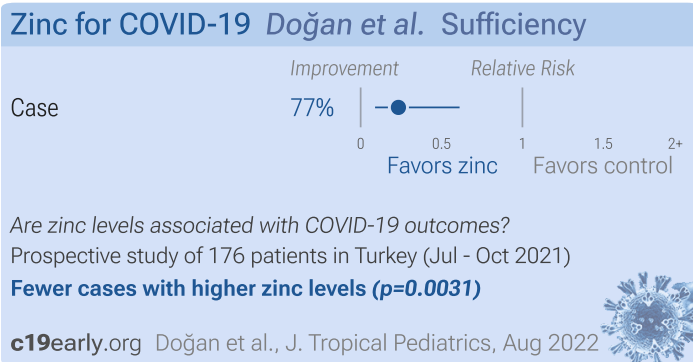
*Doğan*: Prospective study of 88 pediatric COVID-19 patients and 88 healthy controls, showing significantly lower zinc and vitamin D levels in COVID-19 patients.

## Du Laing

### Zinc for COVID-19 *Du Laing et al.* Sufficiency

|  | Improvement | Relative Risk |
|---|---|---|
| Mortality | 79% |  |
| Mortality (b) | 78% |  |

Favors zinc — Favors control

*Are zinc levels associated with COVID-19 outcomes?*
Retrospective 73 patients in Belgium
**Lower mortality with higher zinc levels (p=0.012)**

**c19**early.org  Du Laing et al., Nutrients, September 2021
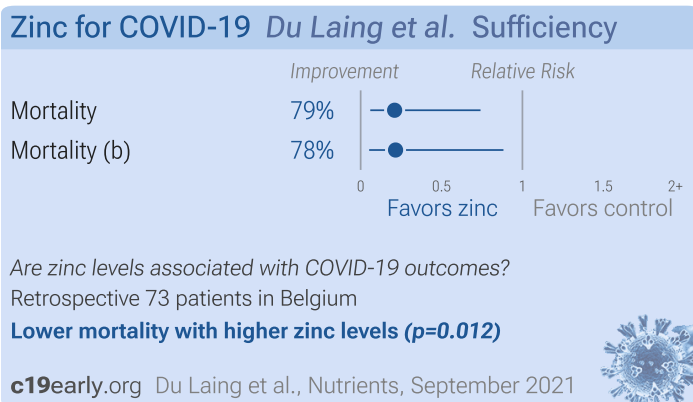
*Du Laing*: Retrospective 73 hospitalized COVID-19 patients in Belgium, showing higher risk of mortality with selenium deficiency and zinc deficiency.

## Ekemen Keleş

### Zinc for COVID-19 *Ekemen Keleş et al.* Sufficiency

|  | Improvement | Relative Risk |
|---|---|---|
| Hospitalization | 75% |  |

Favors zinc — Favors control

*Are zinc levels associated with COVID-19 outcomes?*
Prospective study of 100 patients in Turkey (Aug - Nov 2020)
**Lower hospitalization with higher zinc levels (p=0.011)**

**c19**early.org  Ekemen Keleş et al., European J. Pedia.., Jan 2022
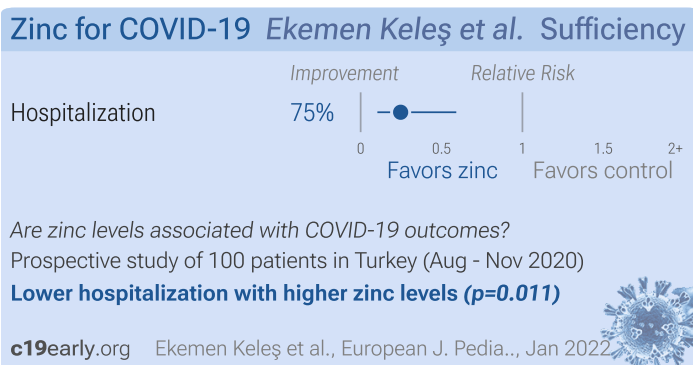
*Ekemen Keleş*: Prospective study of 100 COVID+ pediatric patients in Turkey, showing significantly increased risk of hospitalization for patients with zinc deficiency.

## Elavarasi

### Zinc for COVID-19  *Elavarasi et al.*  LATE TREATMENT

|  | Improvement | Relative Risk |
| --- | --- | --- |
| Mortality | 65% | |

Favors zinc — Favors control
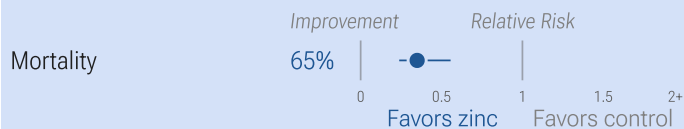
*Is **late** treatment with zinc beneficial for COVID-19?*
Retrospective 1,687 patients in India
**Lower mortality with zinc (p=0.0000016)**

**c19**early.org  Elavarasi et al., medRxiv, August 2021
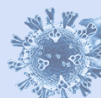
*Elavarasi*: Retrospective 2017 hospitalized patients in India, showing lower mortality with zinc treatment.

## Fromonot

### Zinc for COVID-19  *Fromonot et al.*  Sufficiency

|  | Improvement | Relative Risk |
| --- | --- | --- |
| Hospitalization | 89% | |
| Case | 28% | |

Favors zinc — Favors control
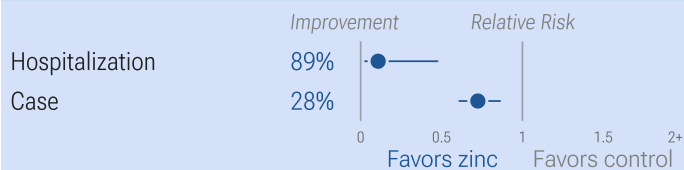
*Are zinc levels associated with COVID-19 outcomes?*
Prospective study of 240 patients in France
**Lower hospitalization (p=0.002) and fewer cases (p=0.003)**

**c19**early.org  Fromonot et al., Clinical Nutrition, May 2021
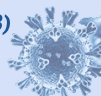
*Fromonot*: Analysis of 240 consecutive patients in France, showing significantly higher zinc deficiency in COVID-19 patients, and significantly greater risk of hospitalization for COVID-19 patients with zinc deficiency. 2020PI087.

## Frontera

### Zinc for COVID-19  *Frontera et al.*  LATE TREATMENT

|  | Improvement | Relative Risk |
| --- | --- | --- |
| Mortality | 37% | |
| Mortality (b) | 24% | |

Favors zinc — Favors control
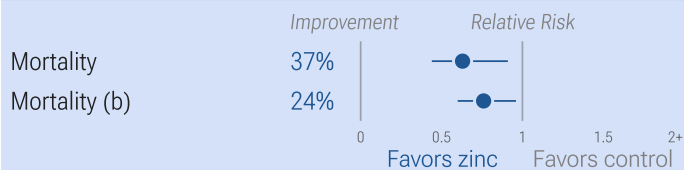
*Is **late** treatment with zinc + HCQ beneficial for COVID-19?*
PSM retrospective 3,473 patients in the USA
**Lower mortality with zinc + HCQ (p=0.015)**

**c19**early.org  Frontera et al., Research Square, October 2020
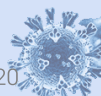
*Frontera*: Retrospective 3,473 hospitalized patients showing 37% lower mortality with HCQ+zinc.

PSM aHR 0.63, p=0.015
regression aHR 0.76, p = 0.023

## Fujita



**Zinc for COVID-19** *Fujita et al.* Sufficiency

|  | Improvement | Relative Risk |
|---|---|---|
| Oxygen therapy | 86% | |

0   0.5   1   1.5   2+
Favors zinc   Favors control
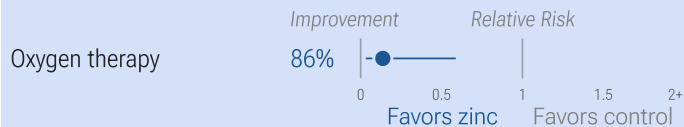
*Are zinc levels associated with COVID-19 outcomes?*
Retrospective study in Japan (March 2020 - April 2021)
**Lower need for oxygen therapy with higher zinc levels *(p=0.0074)***

**c19**early.org   Fujita et al., J. Infection and Chemot.., Mar 2024

*Fujita*: Retrospective 60 COVID-19 hospitalized patients in Japan showing higher risk of progression to pneumonia requiring oxygen therapy with zinc deficiency at the time of diagnosis.

## Gadhiya



**Zinc for COVID-19** *Gadhiya et al.* LATE TREATMENT

|  | Improvement | Relative Risk |
|---|---|---|
| Mortality | -41% | |

0   0.5   1   1.5   2+
Favors zinc   Favors control
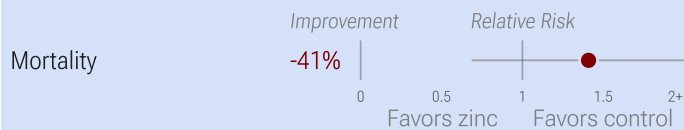
*Is **late** treatment with zinc beneficial for COVID-19?*
Retrospective 283 patients in the USA
Higher mortality with zinc *(not stat. sig., p=0.33)*

**c19**early.org   Gadhiya et al., BMJ Open, April 2021

*Gadhiya*: Retrospective 283 patients in the USA showing higher mortality with all treatments (not statistically significant). Confounding by indication is likely. In the supplementary appendix, authors note that the treatments were usually given for patients that required oxygen therapy. Oxygen therapy and ICU admission (possibly, the paper includes ICU admission for model 2 in some places but not others) were the only variables indicating severity used in adjustments.

## Gonçalves



**Zinc for COVID-19** *Gonçalves et al.* ICU PATIENTS

|  | Improvement | Relative Risk |
|---|---|---|
| Severe case | 82% | |

0   0.5   1   1.5   2+
Favors zinc   Favors control
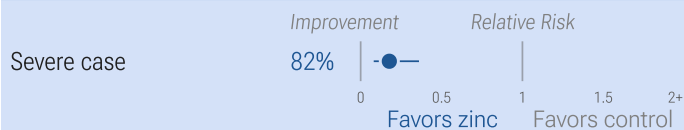
*Are zinc levels associated with COVID-19 outcomes?*
Retrospective 269 patients in Brazil
**Lower severe cases with higher zinc levels *(p=0.001)***

**c19**early.org   Gonçalves et al., Nutrition in Clinica.., Dec 2020

*Gonçalves*: Retrospective 169 ICU patients in Brazil, 214 with low zinc levels, showing an association between low zinc levels and severe ARDS. CAAE 30608,020.9.0000.8114.

## Gordon



**Zinc for COVID-19** *Gordon et al.* Prophylaxis

| | Improvement | Relative Risk |
|---|---|---|
| Mortality | 68% | |
| Symp. case | 85% | |

Favors zinc — Favors control

*Is prophylaxis with zinc beneficial for COVID-19?*
Prospective study of 200 patients in the USA
**Fewer symptomatic cases with zinc** *(p=0.022)*

**c19**early.org  Gordon et al., Frontiers in Medicine, Dec 2021
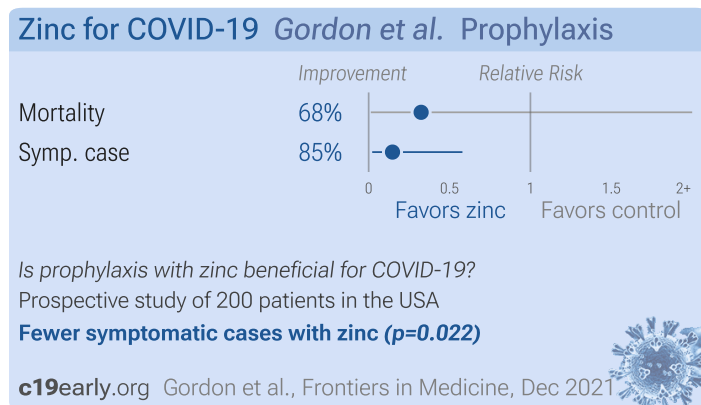
*Gordon*: Prospective study of zinc supplementation with 104 patients randomized to receive 10mg, 25mg, or 50mg of zinc picolinate daily, and a matched sample of 96 control patients from the adjacent clinic that did not routinely recommend/use zinc, showing significantly lower symptomatic COVID-19 with treatment.

## Güerri-Fernández

*Güerri-Fernández*: 75 patient zinc late treatment RCT with results not reported over 1.5 years after completion.

## Holt



**Zinc for COVID-19  COVIDENCE UK**  Prophylaxis

| | Improvement | Relative Risk |
|---|---|---|
| Case | 7% | |

Favors zinc    Favors control

*Does zinc reduce COVID-19 infections?*
Prospective study of 15,227 patients in the United Kingdom (May 2020 - Feb 2021)
No significant difference in cases

**c19**early.org  Holt et al., Thorax, March 2021
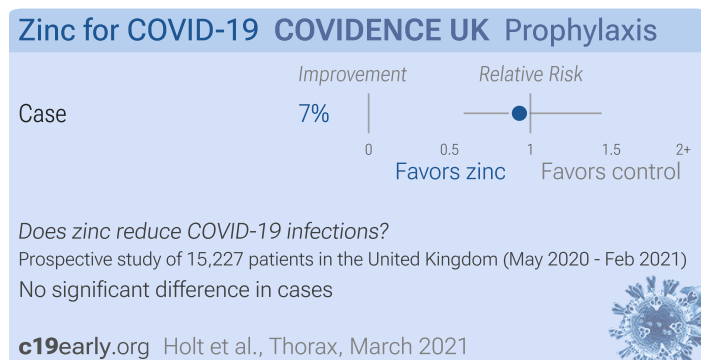
*Holt*: Prospective survey-based study with 15,227 people in the UK, showing lower risk of COVID-19 cases with vitamin A, vitamin D, zinc, selenium, probiotics, and inhaled corticosteroids; and higher risk with metformin and vitamin C. Statistical significance was not reached for any of these. Except for vitamin D, the results for treatments we follow were only adjusted for age, sex, duration of participation, and test frequency. NCT04330599. COVIDENCE UK.

## Ibrahim Alhajjaji

### Zinc *Ibrahim Alhajjaji et al.* LATE TREATMENT

|  | Improvement | Relative Risk |
|---|---|---|
| Mortality | 88% | |
| Ventilation | 26% | |
| ICU admission | 3% | |
| Respiratory failure | 73% | |
| Hospitalization time | 29% | |

0  0.5  1  1.5  2+
Favors zinc   Favors control
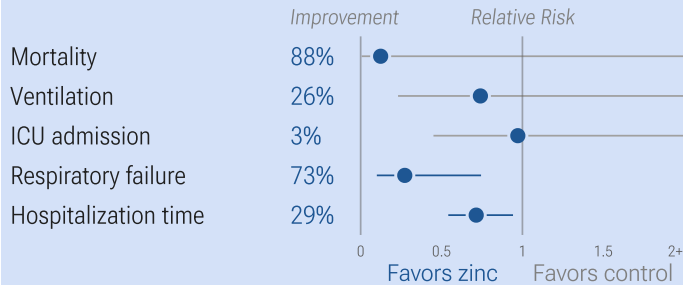
*Is **late** treatment with zinc beneficial for COVID-19?*
Retrospective 101 patients in Saudi Arabia (March 2020 - December 2021)
**Lower progression *(p=0.0042)* and shorter hospitalization *(p=0.017)***

**c19**early.org   Ibrahim Alhajjaji et al., Saudi Pharma.., Mar 2023

*Ibrahim Alhajjaji*: Retrospective 101 hospitalized pediatric patients in Saudi Arabia, showing zinc treatment associated with lower respiratory failure and shorter hospitalization in unadjusted results. Patients receiving zinc were older. Authors note elevated serum creatinine and the possibility of kidney injury.

## Israel

### Zinc for COVID-19 *Israel et al.* Prophylaxis

|  | Improvement | Relative Risk |
|---|---|---|
| Hospitalization | 100% | |

0  0.5  1  1.5  2+
Favors zinc   Favors control
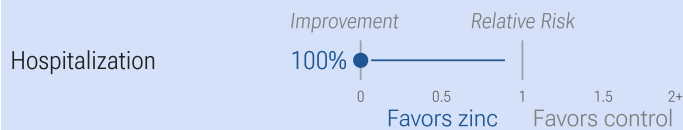
*Is prophylaxis with zinc + calcium beneficial for COVID-19?*
Retrospective 20,859 patients in Israel
**Lower hospitalization with zinc + calcium *(p=0.037)***

**c19**early.org   Israel et al., Epidemiology and Global.., Jul 2021

*Israel*: Case control study examining medication usage with a healthcare database in Israel, showing lower risk of hospitalization with calcium + zinc supplements (defined as being picked up within 35 days prior to PCR+), however only 10 patients took the supplements. Other patients may have acquired supplements outside of the healthcare system.

## İşler

### Zinc for COVID-19 *İşler et al.* Sufficiency

|  | Improvement | Relative Risk |
|---|---|---|
| Case | 88% | |

0  0.5  1  1.5  2+
Favors zinc   Favors control
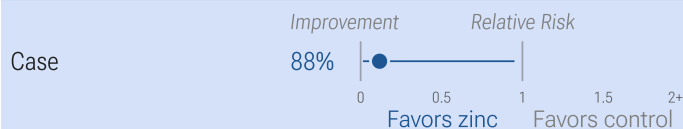
*Are zinc levels associated with COVID-19 outcomes?*
Retrospective 77 patients in Turkey
**Fewer cases with higher zinc levels *(p=0.045)***

**c19**early.org   İşler et al., Life and Medical Sciences, Jul 2023

İşler: Retrospective 51 COVID-19 patients and 26 healthy controls in Turkey, showing significantly lower zinc levels in COVID-19 patients, and zinc deficiency associated with COVID-19 in unadjusted results.

## Jiménez



Zinc for COVID-19 *Jiménez et al.* Sufficiency

| | Improvement | Relative Risk |
|---|---|---|
| Death/mechanical ventil.. | 55% | |

0   0.5   1   1.5   2+
Favors zinc   Favors control

*Are zinc levels associated with COVID-19 outcomes?*
Prospective study of 100 patients in Spain (September 2020 - April 2021)
Lower progression with higher zinc levels *(not stat. sig., p=0.22)*

**c19**early.org   Jiménez et al., J. Trace Elements in M.., May 2023

*Jiménez*: Prospective analysis of 100 hospitalized COVID-19 patients in Spain, showing higher risk of death/mechanical ventilation/ICU admission with zinc levels <79$\mu$g/dL, without statistical significance.

## Jothimani



Zinc for COVID-19 *Jothimani et al.* Sufficiency

| | Improvement | Relative Risk |
|---|---|---|
| Mortality | 90% | |
| ICU admission | 92% | |

0   0.5   1   1.5   2+
Favors zinc   Favors control

*Are zinc levels associated with COVID-19 outcomes?*
Prospective study of 47 patients in India
**Lower ICU admission with higher zinc levels *(p=0.015)***

**c19**early.org   Jothimani et al., Int. J. Infectious D.., Sep 2020
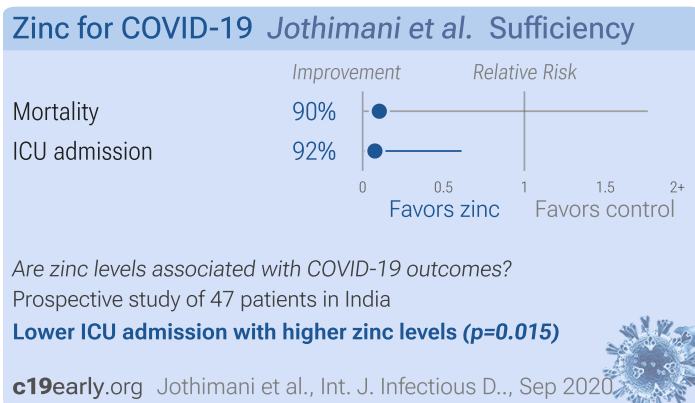
*Jothimani*: Prospective study of zinc levels in 47 hospitalized COVID-19 patients and 45 healthy controls. COVID-19 patients had significantly lower zinc levels (74.5 vs. 105.8 median µg/dl, p < 0.001). 57.4% of COVID-19 patients were zinc deficient, and they had higher rates of complications, ARDS, prolonged hospital stay, and increased mortality.

## Kaplan



Zinc  Reszinate  LATE TREATMENT  RCT

| | Improvement | Relative Risk |
|---|---|---|
| Ventilation | -14% | |
| ICU admission | -14% | |
| Hospitalization | -14% | |

0   0.5   1   1.5   2+
Favors zinc   Favors control

*Is **late** treatment with zinc + resveratrol beneficial for COVID-19?*
RCT 30 patients in the USA (September 2020 - January 2021)
Trial underpowered to detect differences

**c19**early.org   Kaplan et al., SSRN, 10.2139/ssrn.3934.., Oct 2021

*Kaplan*: Small RCT of zinc plus resveratrol in COVID-19+ outpatients, showing no significant differences in viral clearance or symptoms. Although the treatment group was older (46.3 vs. 38.5) and had more severe baseline symptoms, they had similar symptomatic recovery by the second week.

## Krishnan



Zinc for COVID-19 *Krishnan et al.* LATE TREATMENT

Mortality — Improvement 18% — Relative Risk

0   0.5   1   1.5   2+
Favors zinc   Favors control

Is **late** treatment with zinc beneficial for COVID-19?
Retrospective 152 patients in the USA
Lower mortality with zinc *(not stat. sig., p=0.18)*

**c19**early.org  Krishnan et al., J Clin Anesth., July 2020
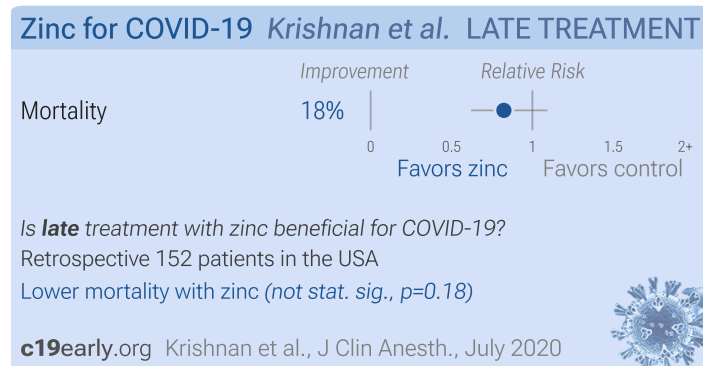
*Krishnan*: Retrospective 152 mechanically ventilated patients in the USA showing unadjusted lower mortality with vitamin C, vitamin D, HCQ, and zinc treatment, statistically significant only for vitamin C.

## Kumar



Zinc for COVID-19 *Kumar et al.* Prophylaxis

Mortality — Improvement 20% — Relative Risk — unadjusted

0   0.5   1   1.5   2+
Favors zinc   Favors control

Is prophylaxis with zinc beneficial for COVID-19?
Retrospective 105 patients in India (June - August 2021)
Study underpowered to detect differences

**c19**early.org  Kumar et al., Cureus, February 2022
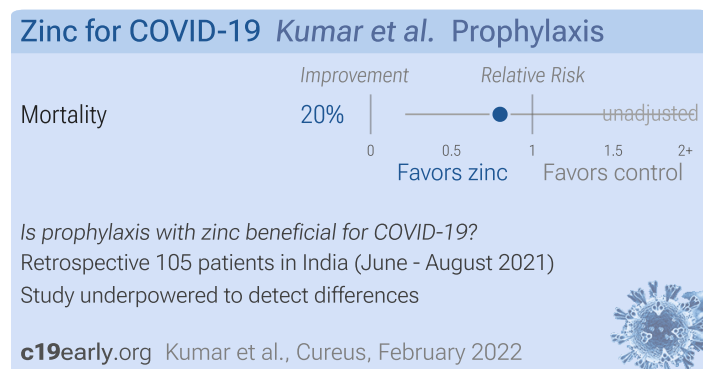
*Kumar*: Case control study of 105 COVID-19 patients in India, 55 with mucormycosis and 50 without, showing zinc prophylaxis and diabetes both associated with mucormycosis in unadjusted results. This is likely confounded because zinc supplementation is commonly used with diabetes *academic.oup.com (C)*, and Arora et al. show lower risk of mucormycosis with zinc prophylaxis, aOR 0.05 [0.01–0.19] *Arora (B)*. There was no significant difference in mortality based on zinc prophylaxis in unadjusted results.

## Kyagambiddwa



Zinc for COVID-19 *Kyagambiddwa et al.* LATE TREATMENT

Mortality — Improvement 25% — Relative Risk

0   0.5   1   1.5   2+
Favors zinc   Favors control

Is **late** treatment with zinc beneficial for COVID-19?
Retrospective 246 patients in Uganda (May 2020 - August 2022)
Lower mortality with zinc *(not stat. sig., p=0.28)*

**c19**early.org  Kyagambiddwa et al., Infection and Dru.., May 2023
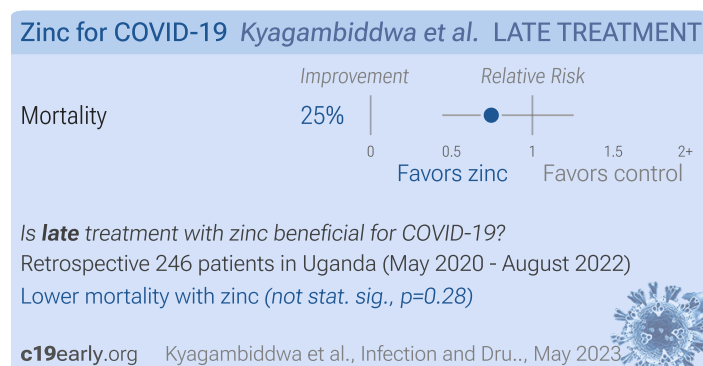
*Kyagambiddwa*: Retrospective 246 severe COVID-19 patients in Uganda, showing lower mortality with zinc treatment in unadjusted results, without statistical significance.

## Louca

### Zinc for COVID-19 *Louca et al.* Prophylaxis

| | Improvement | Relative Risk |
|---|---|---|
| Case | 1% | |

0    0.5    1    1.5    2+

Favors zinc    Favors control

*Does zinc reduce COVID-19 infections?*
Retrospective 372,720 patients in the United Kingdom
No significant difference in cases

**c19**early.org    Louca et al., BMJ Nutrition, Preventio.., Nov 2020
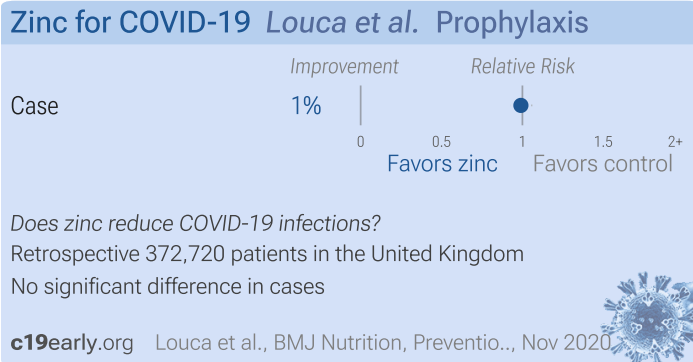
*Louca*: Survey analysis of dietary supplements showing no significant difference in PCR+ cases with zinc usage. These results are for PCR+ cases only, they do not reflect potential benefits for reducing the severity of cases. A number of biases could affect the results, for example users of the app may not be representative of the general population, and people experiencing symptoms may be more likely to install and use the app.

## Mahto

### Zinc for COVID-19 *Mahto et al.* Prophylaxis

| | Improvement | Relative Risk |
|---|---|---|
| IgG positive | 37% | |

0    0.5    1    1.5    2+

Favors zinc    Favors control

*Is prophylaxis with zinc beneficial for COVID-19?*
Retrospective 689 patients in India
Lower IgG positivity with zinc *(not stat. sig., p=0.35)*

**c19**early.org    Mahto et al., American J. Blood Research, Feb 2021
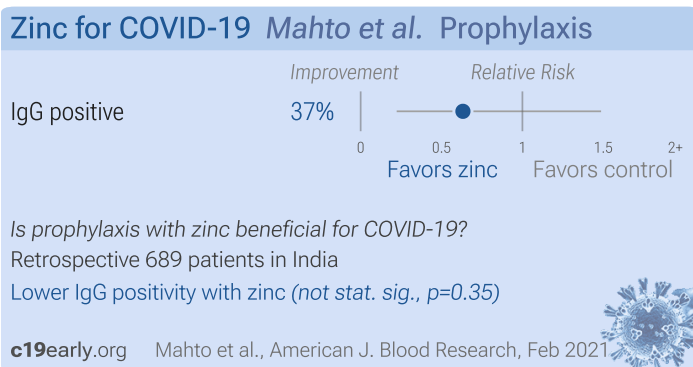
*Mahto*: Retrospective 689 healthcare workers in India, showing no significant difference in IgG positivity with zinc prophylaxis.

## Mayberry

### Zinc for COVID-19 *Mayberry et al.* EARLY TREATMENT

| | Improvement | Relative Risk | |
|---|---|---|---|
| Mortality | 53% | | |
| Ventilation | 64% | | |
| ICU admission | 60% | | |
| Death/ventilation/ICU | 58% | | primary |
| Progression to ARDS | 85% | | |

0    0.5    1    1.5    2+

Favors zinc    Favors control

*Is early treatment with zinc beneficial for COVID-19?*
Retrospective 2,028 patients in the USA (March 2020 - April 2021)
**Lower mortality *(p<0.0001)* and ventilation *(p<0.0001)***

**c19**early.org    Mayberry et al., Critical Care Medicine, Dec 2021

*Mayberry*: Retrospective 2,028 COVID patients in the USA, showing significantly lower mortality, ventilation, ICU admission, and progression to ARDS with zinc use, defined as at least one dose from one week prior to admission to 48 hours after admission.

## Mulhem



Zinc for COVID-19 *Mulhem et al.* LATE TREATMENT

|  | Improvement | Relative Risk |
|---|---|---|
| Mortality | 46% | |

Favors zinc    Favors control

*Is **late** treatment with zinc beneficial for COVID-19?*
Retrospective 3,219 patients in the USA
**Lower mortality with zinc *(p<0.000001)***

**c19**early.org   Mulhem et al., BMJ Open, April 2021
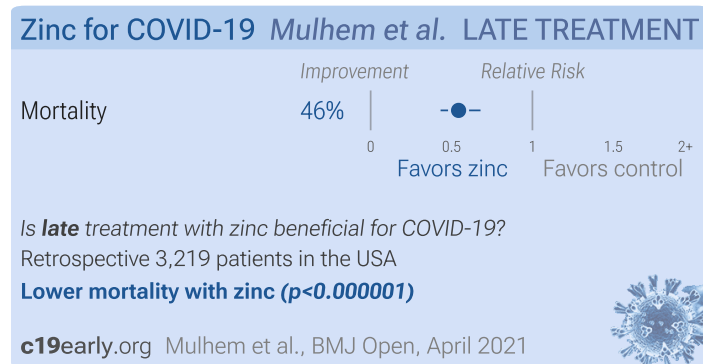
*Mulhem*: Retrospective database analysis of 3,219 hospitalized patients in the USA. Very different results in the time period analysis (Table S2), and results significantly different to other studies for the same medications (e.g., heparin OR 3.06 [2.44-3.83]) suggest significant confounding by indication and confounding by time.

## Nimer



Zinc for COVID-19 *Nimer et al.* Prophylaxis

|  | Improvement | Relative Risk |
|---|---|---|
| Hospitalization | -25% | |
| Severe case | -13% | |

Favors zinc    Favors control

*Is prophylaxis with zinc beneficial for COVID-19?*
Retrospective 2,148 patients in Jordan (March - July 2021)
Higher hospitalization with zinc *(not stat. sig., p=0.21)*

**c19**early.org   Nimer et al., Bosnian J. Basic Medical.., Feb 2022
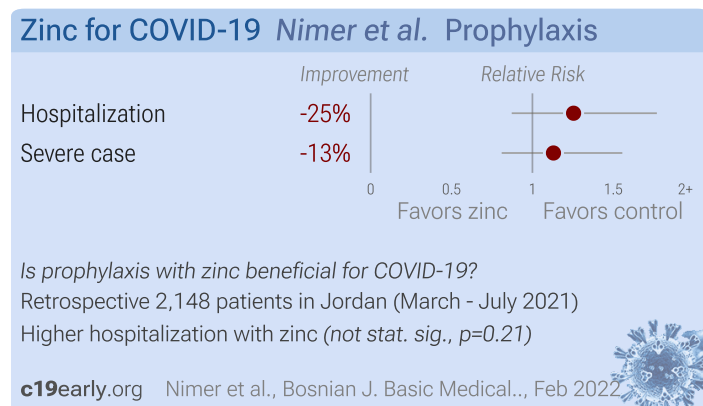
*Nimer*: Retrospective 2,148 COVID-19 recovered patients in Jordan, showing no significant differences in the risk of severity and hospitalization with zinc prophylaxis.

## Patel



Zinc *Patel et al.* LATE TREATMENT DB RCT

|  | Improvement | Relative Risk |
|---|---|---|
| Mortality | 20% | |

Favors zinc    Favors control

*Is **late** treatment with zinc beneficial for COVID-19?*
Double-blind RCT 33 patients in Australia
Trial underpowered to detect differences

**c19**early.org   Patel et al., J. Medical Virology, Feb 2021
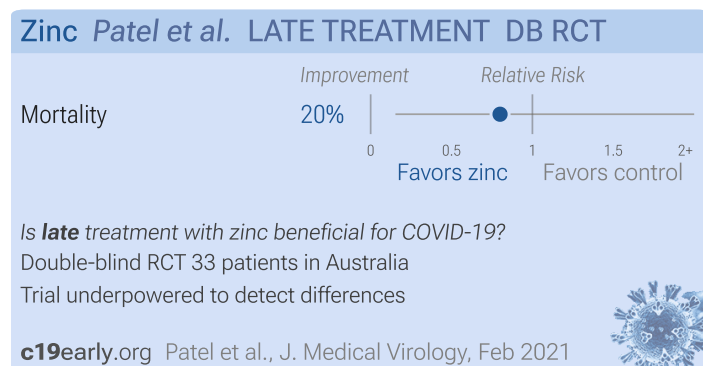
*Patel*: Small early terminated RCT with 33 hospitalized patients in Australia, 15 treated with zinc, showing no significant difference in clinical outcomes. Treatment increased zinc levels above the deficiency cutoff. Intravenous zinc 0.5mg/kg/day (elemental zinc concentration 0.24mg/kg/day) for up to 7 days. ACTRN12620000454976.

## Ramos



Zinc for COVID-19 *Ramos et al.* Sufficiency

| | Improvement | Relative Risk |
|---|---|---|
| Case | 24% | |

Favors zinc    Favors control

*Are zinc levels associated with COVID-19 outcomes?*
Retrospective 20 patients in Brazil
Study underpowered to detect differences

**c19**early.org    Ramos et al., Global J. Health Science, Nov 2021
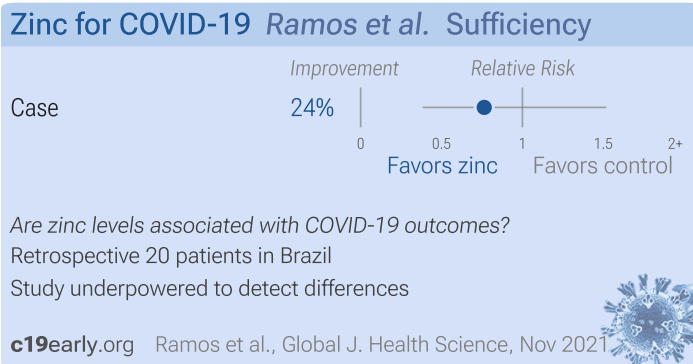
*Ramos*: Retrospective 13 COVID-19 patients and 7 controls in Brazil, showing no significant difference in zinc deficiency.

## Rosenthal



Zinc for COVID-19 *Rosenthal et al.* LATE TREATMENT

| | Improvement | Relative Risk |
|---|---|---|
| Mortality | -16% | |

Favors zinc    Favors control

*Is **late** treatment with zinc beneficial for COVID-19?*
Retrospective study in the USA
**Higher mortality with zinc (*p=0.003*)**

**c19**early.org    Rosenthal et al., JAMA Network Open, Dec 2020
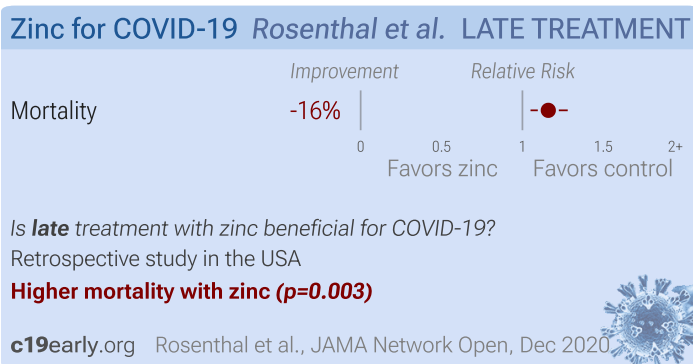
*Rosenthal*: Retrospective database analysis of 64,781 hospitalized patients in the USA, showing lower mortality with vitamin C or vitamin D (authors do not distinguish between the two), and higher mortality with zinc and HCQ, statistically significant for zinc. Authors excluded hospital-based outpatient visits, without explanation. Confounding by indication is likely, adjustments do not appear to include any information on COVID-19 severity at baseline.

## Rozemeijer



Zinc for COVID-19 *Rozemeijer et al.* Sufficiency

| | Improvement | Relative Risk |
|---|---|---|
| ICU admission | 97% | |

Favors zinc    Favors control

*Are zinc levels associated with COVID-19 outcomes?*
Prospective study of 25 patients in Netherlands
**Lower ICU admission with higher zinc levels (*p=0.028*)**

**c19**early.org    Rozemeijer et al., Nutrients, January 2024
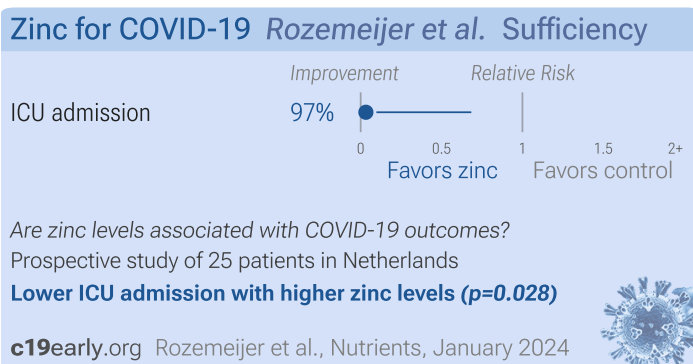
*Rozemeijer*: Prospective pilot study of 20 critically ill COVID-19 ICU patients showing high deficiency rates of 50-100% for vitamins A, B6, and D; zinc; and selenium at admission. Deficiencies of vitamins B6 and D, and low iron status, persisted after 3 weeks. Plasma levels of vitamins A and E, zinc, and selenium increased over time as inflammation resolved, suggesting redistribution may explain some observed deficiencies. All patients received daily micronutrient administration. Additional intravenous and oral micronutrient administration for 10 patients did not significantly

impact micronutrient levels or deficiency rates, however authors note that the administered doses may be too low. The form of vitamin D is not specified but may have been cholecalciferol which is expected to have a very long onset of action compared to more appropriate forms such as calcifediol or calcitriol.

**Seely**



**Zinc** *Seely et al.* LATE TREATMENT DB RCT

| | Improvement | Relative Risk |
|---|---|---|
| ER visit | 48% | |
| Mean cumulative sympt.. | 14% | |
| EQ-VAS average score <80 | 29% | |
| EQ5D improvement, Wk 1 | 29% | |
| EQ5D improvement, Wk 2 | 14% | |
| EQ5D improvement, Wk 3 | 50% | |
| EQ5D improvement, Wk 4 | -12% | |
| Recovery time | -4% | |
| PASC, 12 weeks | 12% | |
| PASC, 8 weeks | 36% | |
| PASC, 4 weeks | 1% | |

Favors zinc    Favors control

*Is **late** treatment with zinc + combined treatments beneficial for COVID-19?*
Double-blind RCT 90 patients in Canada (September 2021 - April 2022)
Patients likely mostly recovered before treatment received

**c19**early.org  Seely et al., BMJ Open, September 2023

*Seely*: Early terminated low-risk population (no hospitalization) very late treatment (mean 8 days) RCT with 44 patients treated with vitamin C, D, K, and zinc, and 46 control patients, showing no significant differences.

Authors acknowledge that the very late treatment is a major limitation, noting that in an ideal setting, *"patients would begin taking therapeutic interventions immediately after noticing symptoms"*. Authors note that patients already had a low symptom burden at baseline and that *"it is likely that the majority of the participants had almost fully recovered before starting treatment."*

Authors note that most participants were young, had few comorbidities and had excellent self-rated health at baseline, leaving less room for improvement.

There was low compliance with completing surveys. Data from only 64% of patients was in the main analysis.

Authors claim "high internal validity", but the loss of data was statistically significantly different between arms, without analysis or mention. Since the study involves widely available treatments, one possibility is that patients in the control arm who feel sick may be more likely to independently take the treatments (via supplementation or food/sun exposure), believing that they are in the control arm or that additional dosing is safe, and they may then feel it's inappropriate to continue submitting the surveys.

Discussion is biased, stating that "evidence for the use of these products in people with COVID-19 is limited", however there were 219 controlled studies at the time, including 8, 27, and 16 RCTs for vitamin C, D, and zinc. Authors claim high similarity between arms however there was 60% vs. 41% male patients, and 88% vs. 68% of patients that received a third dose.

Authors claim that treatment "showed no beneficial effects for overall health or symptom burden". However 48% lower

ER visits is beneficial, and most outcomes show a benefit. The only statistically significant effect was the loss of data, however significant clinical effects are not expected based on the small sample, very late treatment, event rates, and outcomes.

## Seet
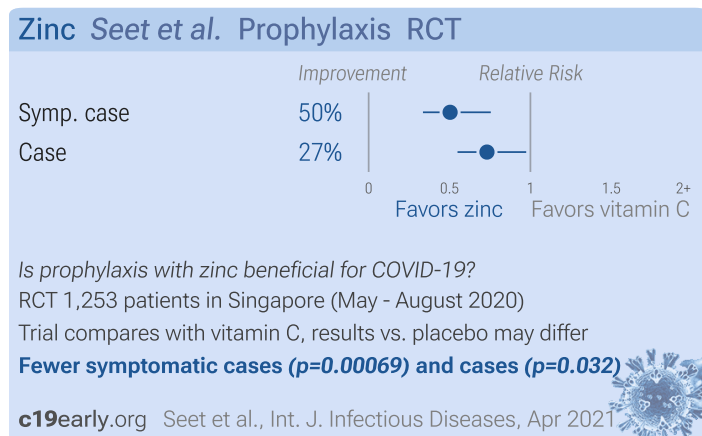


*Seet*: Prophylaxis RCT in Singapore with 3,037 low risk patients, showing lower serious cases, lower symptomatic cases, and lower confirmed cases of COVID-19 with all treatments (ivermectin, HCQ, PVP-I, and Zinc + vitamin C) compared to vitamin C.

Meta-analysis of vitamin C in 6 previous trials shows a benefit of 16%, so the actual benefit of ivermectin, HCQ, and PVP-I may be higher. Cluster RCT with 40 clusters.

There were no hospitalizations and no deaths. NCT04446104.

## Seifi
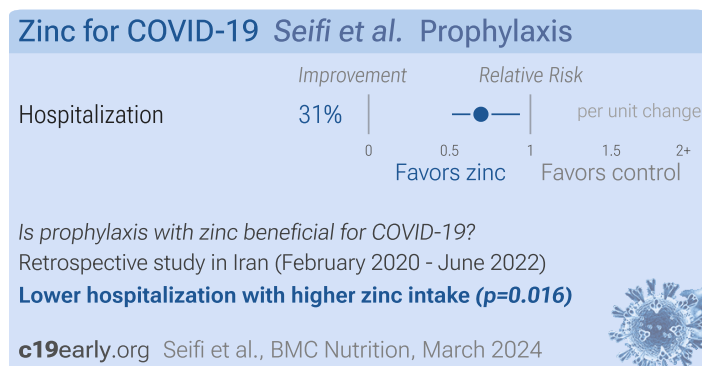


*Seifi*: Analysis of 1,957 older adults showing lower risk of COVID-19 hospitalization with higher dietary zinc intake. Each unit increase in zinc intake was associated with a 31% reduction in the risk of COVID-19 hospitalization after adjustments. A dynamical system model showed that consumption of zinc < 9.7mg per day was associated with a 1.5 times greater risk of COVID-19 infection.

## Sharif



**Zinc for COVID-19** *Sharif et al.* Prophylaxis

| | Improvement | Relative Risk |
|---|---|---|
| Severe case, zinc | 40% | |
| Severe case, C+D+zinc | 97% | |

Favors zinc    Favors control

*Is prophylaxis with zinc beneficial for COVID-19?*
Retrospective study in Bangladesh (December 2020 - February 2021)
**Lower severe cases with zinc** *(p=0.0001)*

**c19**early.org  Sharif et al., Nutrients, November 2022
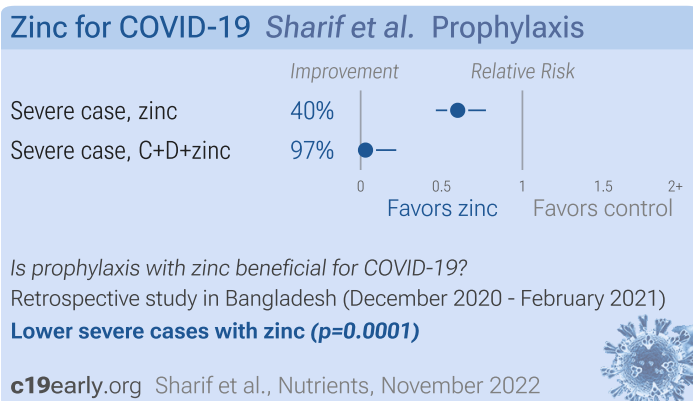
*Sharif*: Retrospective 962 COVID-19 patients in Bangladesh, showing significantly lower severity with vitamin C, vitamin D, and zinc supplementation, and improved results from the combination of all three.

## Sharmin

*Sharmin*: Estimated 50 patient zinc late treatment RCT with results not reported over 2 years after estimated completion.

## Shehab



**Zinc for COVID-19** *Shehab et al.* Prophylaxis

| | Improvement | Relative Risk |
|---|---|---|
| Severe case | 47% | unadjusted |

Favors zinc    Favors control

*Is prophylaxis with zinc beneficial for COVID-19?*
Retrospective 253 patients in multiple countries (Sep 2020 - Mar 2021)
Lower severe cases with zinc *(not stat. sig., p=0.24)*

**c19**early.org   Shehab et al., Tropical J. Pharmaceuti.., Feb 2022
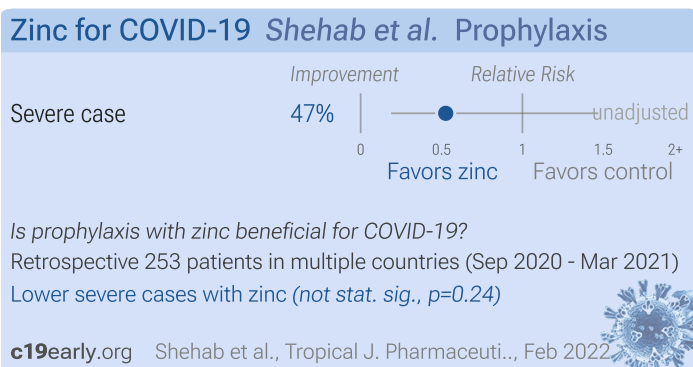
*Shehab*: Retrospective survey-based analysis of 349 COVID-19 patients, showing a lower risk of severe cases with vitamin D, zinc, turmeric, and honey prophylaxis in unadjusted analysis, without statistical significance. REC/UG/2020/03.

## Stambouli



**Zinc** *Stambouli et al.* Prophylaxis  DB RCT

| | Improvement | Relative Risk |
|---|---|---|
| Symp. case | 68% | |
| Case | 5% | |
| Ct values | 21% | |

Favors zinc    Favors control

*Is prophylaxis with zinc beneficial for COVID-19?*
Double-blind RCT 115 patients in Tunisia (November 2020 - February 2021)
**Improved viral load with zinc** *(p<0.000001)*

**c19**early.org  Stambouli et al., Int. J. Infectious D.., Jun 2022
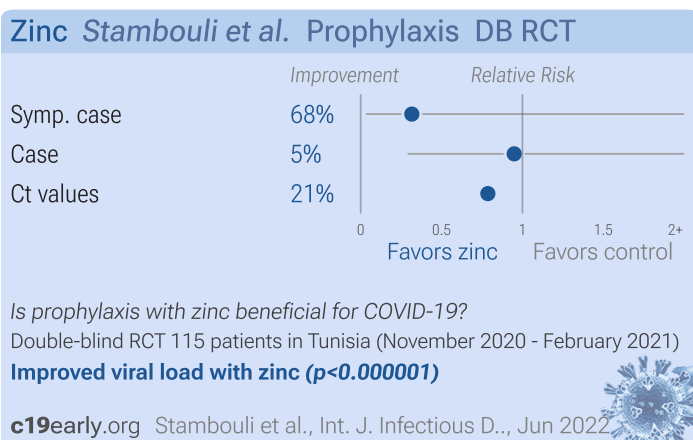
*Stambouli*: Prophylaxis RCT with 59 zinc + doxycycline, 56 doxycycline, and 57 placebo healthcare workers, showing lower symptomatic cases and significantly improved Ct values with the addition of zinc to doxycycline treatment. Doxycycline 100mg/day and zinc 15 mg/day.

## Thomas



Zinc COVIDAtoZ EARLY TREATMENT RCT

| | Improvement | Relative Risk |
|---|---|---|
| Hospitalization | -44% | |
| Recovery time | 12% | |

0   0.5   1   1.5   2+
Favors zinc   Favors control

primary

Is early treatment with zinc beneficial for COVID-19?
RCT 108 patients in the USA (April 2020 - February 2021)
Faster recovery with zinc (not stat. sig., p=0.38)

c19early.org    Thomas et al., JAMA Network Open, February 2021
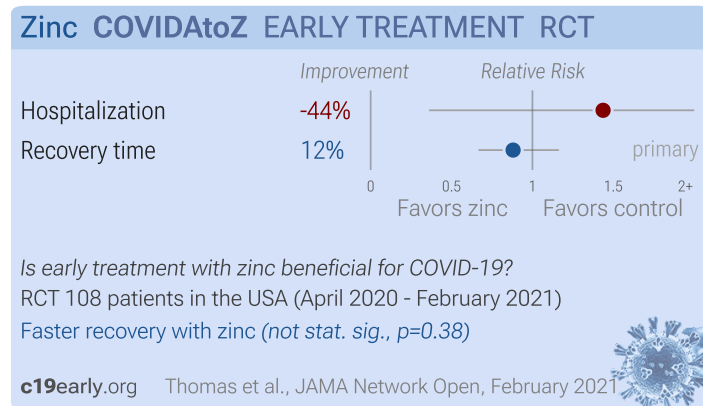
*Thomas*: Small 214 low-risk outpatient RCT showing non-statistically significant faster recovery with zinc and with vitamin C. Study performed in the USA where zinc deficiency is relatively uncommon. The zinc dosage is relatively low, 50mg zinc gluconate (7mg elemental zinc), one tenth of that shown to reduce the duration of colds in other studies *patrickholford.com*.

## Tomasa-Irriguible



Zinc *Tomasa-Irriguible et al.* Sufficiency

| | Improvement | Relative Risk |
|---|---|---|
| Ventilation | 49% | |
| ICU admission | 52% | |

0   0.5   1   1.5   2+
Favors zinc   Favors control

Are zinc levels associated with COVID-19 outcomes?
Retrospective 120 patients in Spain (March - May 2020)
Lower ICU admission with higher zinc levels (p=0.017)

c19early.org   Tomasa-Irriguible et al., Metabolites, Oct 2020
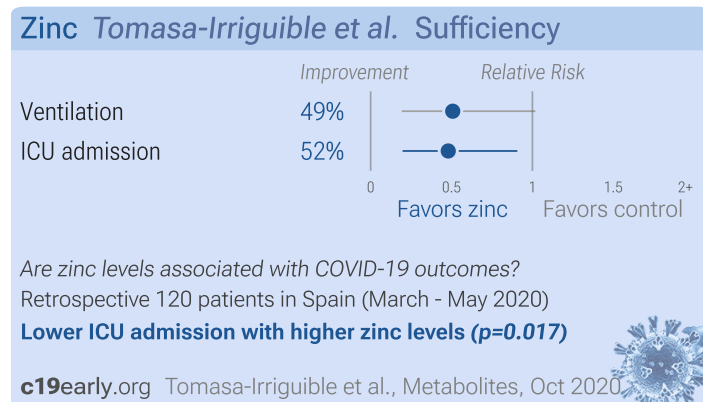
*Tomasa-Irriguible (B)*: Retrospective 120 hospitalized patients in Spain showing zinc deficiency associated with higher ICU admission.

## Tomasa-Irriguible

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

## Voelkle



**Zinc for COVID-19** *Voelkle et al.* Sufficiency

| | Improvement | Relative Risk |
|---|---|---|
| Death/ICU | 77% | |

0  0.5  1  1.5  2+
Favors zinc    Favors control
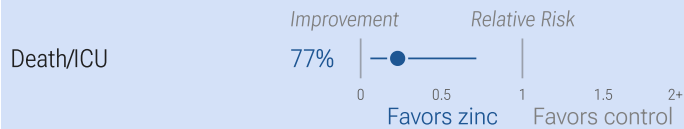
*Are zinc levels associated with COVID-19 outcomes?*
Prospective study of 57 patients in Switzerland (Mar - Apr 2020)
**Lower death/ICU with higher zinc levels *(p=0.007)***

**c19**early.org  Voelkle et al., Nutrients, April 2022
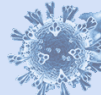
*Voelkle*: Prospective study of 57 consecutive hospitalized COVID-19 patients in Switzerland, showing higher risk of mortality/ICU admission with vitamin A, vitamin D, and zinc deficiency, with statistical significance only for vitamin A and zinc. Adjustments only considered age.

## Vogel-González



**Zinc for COVID-19** *Vogel-González et al.* Sufficiency

| | Improvement | Relative Risk |
|---|---|---|
| Mortality | 77% | |
| ICU admission | 71% | |
| Recovery time | 68% | |

0  0.5  1  1.5  2+
Favors zinc    Favors control
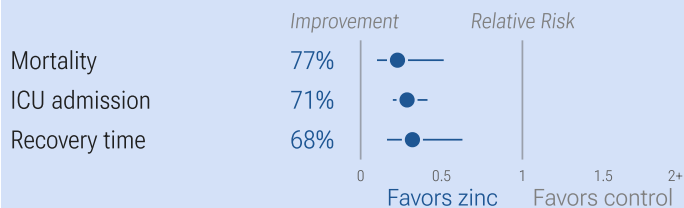
*Are zinc levels associated with COVID-19 outcomes?*
Retrospective 249 patients in Spain
**Lower mortality *(p=0.00048)* and ICU admission *(p<0.0001)***

**c19**early.org  Vogel-González et al., Nutrients, October 2020
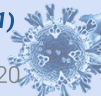
*Vogel-González*: Retrospective 249 PCR+ hospitalized patients in Spain, 58 with zinc levels on admission <50 µg/dL, showing higher mortality and ICU admission, and slower recovery with low zinc levels.

## Wozniak



**Zinc for COVID-19** *Wozniak et al.* ICU PATIENTS

| | Improvement | Relative Risk |
|---|---|---|
| Mortality | 47% | |
| Septic shock | 62% | |

0  0.5  1  1.5  2+
Favors zinc    Favors control
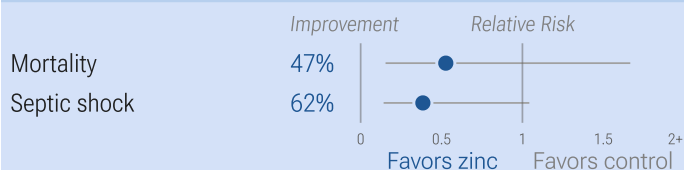
*Are zinc levels associated with COVID-19 outcomes?*
Retrospective 118 patients in Switzerland (March - May 2020)
Lower mortality *(p=0.3)* and progression *(p=0.06)*, not sig.

**c19**early.org  Wozniak et al., Nutrients, July 2023
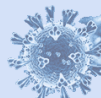
*Wozniak*: Retrospective 345 COVID-19 patients in Switzerland, showing significantly different zinc levels with ICU patients < hospitalized patients < outpatients.

For ICU patients, there was higher mortality, septic shock, and mechanical ventilation days with lower zinc levels, without statistical significance.

## Wu



Zinc for COVID-19 *Wu et al.* Sufficiency

| | Improvement | Relative Risk |
|---|---|---|
| Mortality | 71% | |
| Death/hospitalization | 27% | |
| Hospitalization | 18% | |

Favors zinc    Favors control

*Are zinc levels associated with COVID-19 outcomes?*
Retrospective 2,894 patients in multiple countries (Jan 2022 - Apr 2023)
**Lower mortality *(p=0.0048)* and death/hosp. *(p=0.03)***

**c19**early.org  Wu et al., J. Infection, June 2023
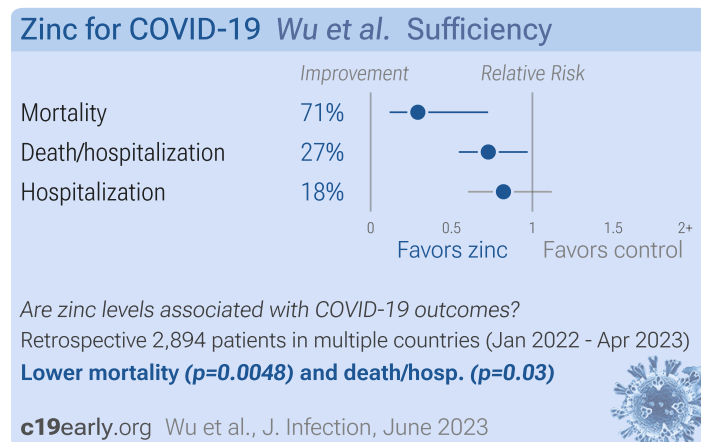
*Wu*: TriNetX PSM retrospective 10,935 COVID-19 patients, showing higher mortality with zinc deficiency.

## Yao



Zinc for COVID-19 *Yao et al.* LATE TREATMENT

| | Improvement | Relative Risk |
|---|---|---|
| Mortality | 34% | |

Favors zinc    Favors control

*Is **late** treatment with zinc beneficial for COVID-19?*
Retrospective 242 patients in the USA
Lower mortality with zinc *(not stat. sig., p=0.09)*

**c19**early.org  Yao et al., Chest, July 2020
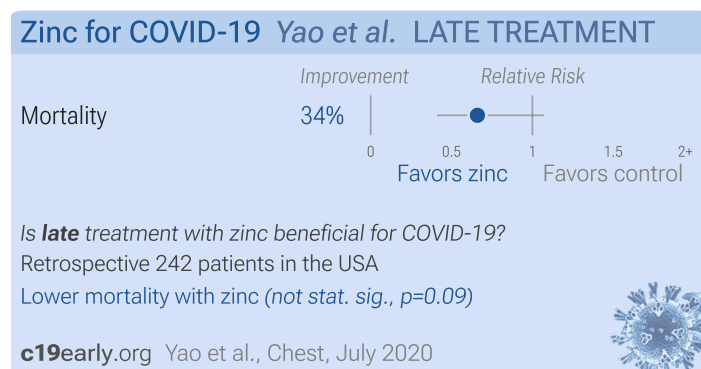
*Yao*: Retrospective 242 hospitalized patients in the USA showing adjusted hazard ratio for zinc treatment, aHR 0.66 [0.41-1.07]. *ncbi.nlm.nih.gov (C)* notes that the study would be more informative if baseline serum zinc levels were known.

## Yasui



Zinc for COVID-19 *Yasui et al.* Sufficiency

| | Improvement | Relative Risk |
|---|---|---|
| Ventilation | 92% | |

Favors zinc    Favors control

*Are zinc levels associated with COVID-19 outcomes?*
Retrospective 29 patients in Japan
**Lower ventilation with higher zinc levels *(p=0.0011)***

**c19**early.org  Yasui et al., Int. J. Infectious Disea.., Sep 2020
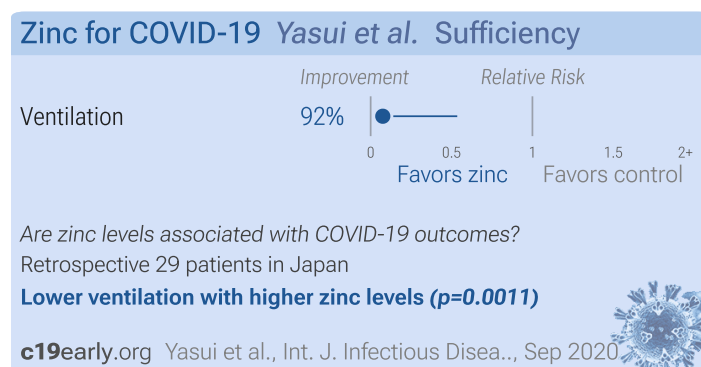
*Yasui*: Retrospective 62 hospitalized patients, 29 with serum zinc data, showing significantly lower serum zinc levels for severe COVID-19 cases (intubation) compared with mild and moderate cases, p = 0.005. Authors recommend zinc supplementation.

**Zangeneh**



Zinc for COVID-19 *Zangeneh et al.* ICU PATIENTS

| | Improvement | Relative Risk |
|---|---|---|
| Mortality | -21% | |

Favors zinc 0    0.5    1    1.5    2+ Favors control

Is **very late** treatment with zinc beneficial for COVID-19?
Retrospective study in Iran
No significant difference in mortality

**c19**early.org Zangeneh et al., Obesity Medicine, May 2022
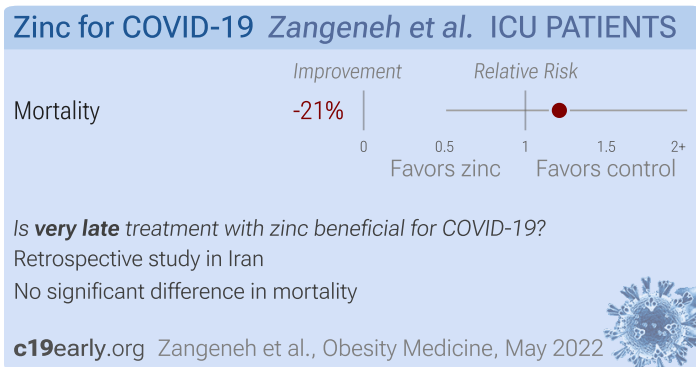
*Zangeneh*: Retrospective 193 ICU patients in Iran, showing no significant difference with zinc treatment.

# Appendix 1. Methods and Data

We perform ongoing searches of PubMed, medRxiv, Europe PMC, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19early.org. Search terms are zinc 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 zinc for COVID-19 that report a comparison with a control group are included in the main analysis. Sensitivity analysis is performed, excluding studies with major issues, epidemiological studies, and studies with minimal available information. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral test status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low $SpO_2$ is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to [Zhang]. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 [Sweeting]. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.12.2) with scipy (1.12.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.1), and plotly (5.19.0).

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].

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

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

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| *Abdallah*, 11/4/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Tunisia, peer-reviewed, mean age 54.2, 24 authors, study period 15 February, 2022 - 4 May, 2022, average treatment delay 4.6 days, trial NCT05212480 (history) (VIZIR). | risk of death, 29.9% lower, RR 0.70, *p* = 0.27, treatment 15 of 231 (6.5%), control 22 of 239 (9.2%), NNT 37, odds ratio converted to relative risk, day 30. |
| | risk of death/ICU, 37.6% lower, RR 0.62, *p* = 0.04, treatment 24 of 231 (10.4%), control 40 of 239 (16.7%), NNT 16, odds ratio converted to relative risk, day 30. |
| | risk of ICU admission, 54.0% lower, RR 0.46, *p* = 0.01, treatment 12 of 231 (5.2%), control 27 of 239 (11.3%), NNT 16, odds ratio converted to relative risk, day 30. |
| | risk of oxygen therapy, 41.7% lower, RR 0.58, *p* = 0.009, treatment 31 of 231 (13.4%), control 55 of 239 (23.0%), NNT 10, grade III, day 30, Figure 3. |
| | risk of oxygen therapy, 22.9% lower, RR 0.77, *p* = 0.003, treatment 108 of 231 (46.8%), control 145 of 239 (60.7%), NNT 7.2, grade III, day 15, Figure 3. |
| | risk of no recovery, 29.3% lower, RR 0.71, *p* = 0.002, treatment 82 of 231 (35.5%), control 120 of 239 (50.2%), NNT 6.8, grade II/III, day 30. |
| | risk of no recovery, 13.8% lower, RR 0.86, *p* < 0.001, treatment 180 of 231 (77.9%), control 216 of 239 (90.4%), NNT 8.0, grade II/III, day 15. |

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| | risk of hospitalization, 69.1% lower, RR 0.31, *p* = 0.30, treatment 1 of 85 (1.2%), control 4 of 100 (4.0%), NNT 35, odds ratio converted to relative risk, outpatients. |
| | hospitalization time, 33.0% lower, relative time 0.67, *p* < 0.001, treatment mean 7.1 (±3.4) n=146, control mean 10.6 (±2.8) n=134, inpatients. |
| | recovery time, 25.0% lower, relative time 0.75, *p* < 0.001, treatment mean 9.6 (±4.1) n=85, control mean 12.8 (±6.7) n=100, outpatients. |
| *Aldwihi*, 5/11/2021, retrospective, Saudi Arabia, peer-reviewed, survey, mean age 36.5, 8 authors, study period August 2020 - October 2020. | risk of hospitalization, 23.7% lower, RR 0.76, *p* = 0.16, treatment 53 of 199 (26.6%), control 184 of 539 (34.1%), NNT 13, adjusted per study, odds ratio converted to relative risk, multivariable. |
| *Asimi*, 5/22/2021, retrospective, Bosnia and Herzegovina, preprint, 3 authors, this trial uses multiple treatments in the treatment arm (combined with vitamin D and selenium) - results of individual treatments may vary, excluded in exclusion analyses: excessive unadjusted differences between groups. | risk of mechanical ventilation, 97.4% lower, RR 0.03, *p* < 0.001, treatment 0 of 270 (0.0%), control 9 of 86 (10.5%), NNT 9.6, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), unadjusted. |
| | risk of hospitalization, 99.0% lower, RR 0.010, *p* < 0.001, treatment 0 of 270 (0.0%), control 24 of 86 (27.9%), NNT 3.6, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), unadjusted. |
| | risk of severe case, 99.5% lower, RR 0.005, *p* < 0.001, treatment 0 of 270 (0.0%), control 51 of 86 (59.3%), NNT 1.7, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), unadjusted. |
| *Boukef*, 2/28/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Tunisia, trial NCT05670444 (history). | 150 patient RCT with results unknown and over 1 year late. |
| *Derwand (B)*, 7/3/2020, retrospective, USA, peer-reviewed, 3 authors, this trial uses multiple treatments in the treatment arm (combined with HCQ and azithromycin) - results of individual treatments may vary. | risk of death, 79.4% lower, RR 0.21, *p* = 0.12, treatment 1 of 141 (0.7%), control 13 of 377 (3.4%), NNT 37, odds ratio converted to relative risk. |
| | risk of hospitalization, 81.6% lower, RR 0.18, *p* < 0.001, treatment 4 of 141 (2.8%), control 58 of 377 (15.4%), NNT 8.0, odds ratio converted to relative risk. |
| *Mayberry*, 12/16/2021, retrospective, USA, peer-reviewed, 14 authors, study period March 2020 - April 2021. | risk of death, 53.5% lower, OR 0.47, *p* < 0.001, treatment 938, control 1,090, adjusted per study, multivariable, RR approximated with OR. |
| | risk of mechanical ventilation, 64.2% lower, OR 0.36, *p* < 0.001, treatment 938, control 1,090, adjusted per study, multivariable, RR approximated with OR. |
| | risk of ICU admission, 60.0% lower, OR 0.40, *p* < 0.001, treatment 938, control 1,090, adjusted per study, multivariable, RR approximated with OR. |

| | death/ventilation/ICU, 57.8% lower, OR 0.42, $p < 0.001$, treatment 938, control 1,090, adjusted per study, multivariable, primary outcome, RR approximated with OR. |
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| | progression to ARDS, 85.4% lower, OR 0.15, $p < 0.001$, treatment 938, control 1,090, adjusted per study, multivariable, RR approximated with OR. |
| *Thomas*, 2/12/2021, Randomized Controlled Trial, USA, peer-reviewed, 11 authors, study period 8 April, 2020 - 11 February, 2021, trial NCT04342728 (history) (COVIDAtoZ). | **risk of hospitalization, 43.7% higher, RR 1.44, $p = 0.72$,** treatment 5 of 58 (8.6%), control 3 of 50 (6.0%). |
| | recovery time, 11.9% lower, relative time 0.88, $p = 0.38$, treatment mean 5.9 (±4.9) n=58, control mean 6.7 (±4.4) n=50, mean time to a 50% reduction in symptoms, primary outcome. |
| *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. |

## 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.

| *Abd-Elsalam*, 11/29/2020, Randomized Controlled Trial, Egypt, peer-reviewed, 10 authors, study period 23 June, 2020 - 23 August, 2020, data issues, see notes, trial NCT04447534 (history), excluded in exclusion analyses: multiple potential data reliability issues. | **risk of death, 1.0% lower, RR 0.99, $p = 0.99$, treatment 5 of 96** (5.2%), control 5 of 95 (5.3%), NNT 1824. |
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| | risk of mechanical ventilation, 34.0% lower, RR 0.66, $p = 0.54$, treatment 4 of 96 (4.2%), control 6 of 95 (6.3%), NNT 47. |
| | risk of no recovery, 5.8% lower, RR 0.94, $p = 0.97$, treatment 20 of 96 (20.8%), control 21 of 95 (22.1%), NNT 79. |
| | hospitalization time, 3.6% lower, relative time 0.96, $p = 0.55$, treatment 96, control 95. |
| *Al Sulaiman*, 6/7/2021, retrospective, propensity score matching, Saudi Arabia, peer-reviewed, 10 authors, study period 1 March, 2020 - 31 March, 2021. | **risk of death, 36.0% lower, HR 0.64, $p = 0.11$, treatment 23 of** 82 (28.0%), control 32 of 82 (39.0%), NNT 9.1, adjusted per study, in-hospital, PSM, multivariable Cox proportional hazards. |
| | risk of death, 48.0% lower, HR 0.52, $p = 0.03$, treatment 19 of 82 (23.2%), control 31 of 82 (37.8%), NNT 6.8, adjusted per study, 30 day, PSM, multivariable Cox proportional hazards. |
| | ICU time, 25.0% higher, relative time 1.25, $p = 0.28$, treatment 82, control 82. |
| | hospitalization time, 6.2% higher, relative time 1.06, $p = 0.61$, treatment 82, control 82. |
| *Alahmari*, 6/27/2022, retrospective, Saudi Arabia, peer-reviewed, 7 authors, study period 1 May, 2020 - 30 July, 2020. | **hospitalization time, 30.2% lower, relative time 0.70, $p < 0.001$,** treatment mean 6.39 (±0.76) n=130, control mean 9.15 (±0.27) n=847. |

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| *Assiri*, 8/28/2021, retrospective, Saudi Arabia, peer-reviewed, 8 authors, excluded in exclusion analyses: unadjusted results with no group details. | risk of death, 80.8% higher, RR 1.81, *p* = 0.44, treatment 10 of 60 (16.7%), control 4 of 58 (6.9%), inverted to make RR<1 favor treatment, odds ratio converted to relative risk. |
| *Carlucci*, 5/8/2020, retrospective, USA, peer-reviewed, 6 authors. | risk of death/hospice, 37.7% lower, RR 0.62, *p* = 0.002, treatment 54 of 411 (13.1%), control 119 of 521 (22.8%), NNT 10, adjusted per study, odds ratio converted to relative risk, multivariate logistic regression. |
| | risk of mechanical ventilation, 18.0% lower, RR 0.82, *p* = 0.40, treatment 29 of 411 (7.1%), control 62 of 521 (11.9%), adjusted per study, odds ratio converted to relative risk, multivariate logistic regression. |
| | risk of ICU admission, 23.5% lower, RR 0.77, *p* = 0.17, treatment 38 of 411 (9.2%), control 82 of 521 (15.7%), adjusted per study, odds ratio converted to relative risk, multivariate logistic regression. |
| *Correa*, 10/30/2021, Double Blind Randomized Controlled Trial, trial NCT04902976 (history). | 105 patient RCT with results unknown and over 2 years late. |
| *Darban*, 12/15/2020, Randomized Controlled Trial, Iran, peer-reviewed, 8 authors, study period 7 April, 2020 - 8 June, 2020, this trial uses multiple treatments in the treatment arm (combined with melatonin and vitamin C) - results of individual treatments may vary, trial IRCT20151228025732N52. | risk of progression, 33.3% lower, RR 0.67, *p* = 1.00, treatment 2 of 10 (20.0%), control 3 of 10 (30.0%), NNT 10. |
| | ICU time, 6.0% lower, relative time 0.94, *p* = 0.30, treatment 10, control 10. |
| *Doocy*, 10/19/2022, prospective, multiple countries, peer-reviewed, 6 authors, study period December 2020 - June 2021, trial NCT04568499 (history), excluded in exclusion analyses: unadjusted results with no group details. | risk of death, 40.8% lower, RR 0.59, *p* = 0.41, treatment 3 of 28 (10.7%), control 21 of 116 (18.1%), NNT 14, unadjusted. |
| *Elavarasi*, 8/12/2021, retrospective, India, preprint, 26 authors. | risk of death, 65.1% lower, RR 0.35, *p* < 0.001, treatment 486, control 1,201, adjusted per study, odds ratio converted to relative risk, model 4, multivariate logistic regression, control prevalence approximated with overall prevalence. |
| *Frontera*, 10/26/2020, retrospective, propensity score matching, USA, preprint, median age 64.0, 14 authors, this trial uses multiple treatments in the treatment arm (combined with HCQ) - results of individual treatments may vary. | risk of death, 37.0% lower, HR 0.63, *p* = 0.01, treatment 121 of 1,006 (12.0%), control 424 of 2,467 (17.2%), NNT 19, adjusted per study, PSM. |
| | risk of death, 24.0% lower, HR 0.76, *p* = 0.02, treatment 121 of 1,006 (12.0%), control 424 of 2,467 (17.2%), NNT 19, adjusted per study, regression. |
| *Gadhiya*, 4/8/2021, retrospective, USA, peer-reviewed, 4 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely. | risk of death, 40.9% higher, RR 1.41, *p* = 0.33, treatment 21 of 54 (38.9%), control 34 of 229 (14.8%), adjusted per study, odds ratio converted to relative risk, multivariate logistic regression. |
| *Güerri-Fernández*, 5/25/2022, Randomized Controlled Trial, Spain, trial NCT05778383 (history) (MARZINC). | 75 patient RCT with results unknown and over 1.5 years late. |

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| *Ibrahim Alhajjaji*, 3/4/2023, retrospective, Saudi Arabia, peer-reviewed, 8 authors, study period 1 March, 2020 - 31 December, 2021, excluded in exclusion analyses: excessive unadjusted differences between groups. | risk of death, 87.6% lower, RR 0.12, $p$ = 0.13, treatment 0 of 44 (0.0%), control 4 of 57 (7.0%), NNT 14, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm). |
| | risk of mechanical ventilation, 26.0% lower, RR 0.74, $p$ = 0.75, treatment 4 of 44 (9.1%), control 7 of 57 (12.3%), NNT 31. |
| | risk of ICU admission, 2.8% lower, RR 0.97, $p$ = 1.00, treatment 9 of 44 (20.5%), control 12 of 57 (21.1%), NNT 167. |
| | respiratory failure, 72.7% lower, RR 0.27, $p$ = 0.004, treatment 4 of 44 (9.1%), control 19 of 57 (33.3%), NNT 4.1. |
| | hospitalization time, 28.6% lower, relative time 0.71, $p$ = 0.02, treatment 44, control 57. |
| *Kaplan*, 10/1/2021, Randomized Controlled Trial, USA, preprint, 12 authors, study period 21 September, 2020 - 22 January, 2021, average treatment delay 5.9 days, this trial uses multiple treatments in the treatment arm (combined with resveratrol) - results of individual treatments may vary, trial NCT04542993 (history) (Reszinate). | risk of mechanical ventilation, 14.3% higher, RR 1.14, $p$ = 1.00, treatment 1 of 14 (7.1%), control 1 of 16 (6.2%). |
| | risk of ICU admission, 14.3% higher, RR 1.14, $p$ = 1.00, treatment 1 of 14 (7.1%), control 1 of 16 (6.2%). |
| | risk of hospitalization, 14.3% higher, RR 1.14, $p$ = 1.00, treatment 1 of 14 (7.1%), control 1 of 16 (6.2%). |
| *Krishnan*, 7/20/2020, retrospective, USA, peer-reviewed, 13 authors, excluded in exclusion analyses: unadjusted results with no group details. | risk of death, 17.6% lower, RR 0.82, $p$ = 0.18, treatment 31 of 58 (53.4%), control 61 of 94 (64.9%), NNT 8.7. |
| *Kyagambiddwa*, 5/11/2023, retrospective, Uganda, peer-reviewed, mean age 39.0, 15 authors, study period May 2020 - August 2022, excluded in exclusion analyses: unadjusted results with no group details. | risk of death, 25.4% lower, RR 0.75, $p$ = 0.28, treatment 20 of 89 (22.5%), control 22 of 73 (30.1%), NNT 13. |
| *Mulhem*, 4/7/2021, retrospective, database analysis, USA, peer-reviewed, 3 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely; substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically. | risk of death, 45.6% lower, RR 0.54, $p$ < 0.001, treatment 256 of 1,596 (16.0%), control 260 of 1,623 (16.0%), adjusted per study, odds ratio converted to relative risk, logistic regression. |
| *Patel*, 2/25/2021, Double Blind Randomized Controlled Trial, Australia, peer-reviewed, 12 authors. | risk of death, 20.0% lower, RR 0.80, $p$ = 1.00, treatment 2 of 15 (13.3%), control 3 of 18 (16.7%), NNT 30. |
| *Rosenthal*, 12/10/2020, retrospective, database analysis, USA, peer-reviewed, 5 authors, excluded in exclusion analyses: confounding by indication is likely and adjustments do not consider COVID-19 severity at baseline. | risk of death, 16.0% higher, OR 1.16, $p$ = 0.003, adjusted per study, multivariable, RR approximated with OR. |
| *Seely*, 9/22/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Canada, peer-reviewed, mean age 39.9, 10 authors, study period | ER visit, 47.6% lower, RR 0.52, $p$ = 0.68, treatment 2 of 42 (4.8%), control 4 of 44 (9.1%), NNT 23. |

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| September 2021 - April 2022, this trial uses multiple treatments in the treatment arm (combined with vitamin C, D, K2, and zinc) - results of individual treatments may vary, trial NCT04780061 (history). | relative mean cumulative symptom score, 13.8% better, RR 0.86, *p* = 0.41, treatment mean 166.3 (±92.3) n=34, control mean 192.9 (±153.6) n=24. |
| | EQ-VAS average score <80, 29.4% lower, RR 0.71, *p* = 0.54, treatment 7 of 34 (20.6%), control 7 of 24 (29.2%), NNT 12, average daily EQ-VAS score <80. |
| | relative EQ5D improvement, 28.6% better, RR 0.71, *p* = 0.44, treatment 32, control 31, relative improvement in EQ5D, week 1. |
| | relative EQ5D improvement, 14.3% better, RR 0.86, *p* = 0.73, treatment 33, control 30, relative improvement in EQ5D, week 2. |
| | relative EQ5D improvement, 50.0% better, RR 0.50, *p* = 0.17, treatment 32, control 33, relative improvement in EQ5D, week 3. |
| | relative EQ5D improvement, 12.5% worse, RR 1.12, *p* = 0.47, treatment 30, control 25, relative improvement in EQ5D, week 4. |
| | recovery time, 4.0% higher, relative time 1.04, *p* = 0.81, treatment 34, control 24. |
| | risk of PASC, 12.1% lower, RR 0.88, *p* = 1.00, treatment 3 of 33 (9.1%), control 3 of 29 (10.3%), NNT 80, 12 weeks. |
| | risk of PASC, 35.7% lower, RR 0.64, *p* = 0.69, treatment 3 of 35 (8.6%), control 4 of 30 (13.3%), NNT 21, 8 weeks. |
| | risk of PASC, 0.6% lower, RR 0.99, *p* = 1.00, treatment 6 of 35 (17.1%), control 5 of 29 (17.2%), NNT 1015, 4 weeks. |
| *Sharmin*, 9/1/2021, Double Blind Randomized Controlled Trial, placebo-controlled, Bangladesh, trial NCT04558424 (history). | Estimated 50 patient RCT with results unknown and over 2 years late. |
| *Yao*, 7/22/2020, retrospective, USA, peer-reviewed, 9 authors. | risk of death, 34.0% lower, RR 0.66, *p* = 0.09, treatment 73 of 196 (37.2%), control 21 of 46 (45.7%), adjusted per study, multivariate Cox regression. |
| *Zangeneh*, 5/13/2022, retrospective, Iran, peer-reviewed, 3 authors. | risk of death, 21.0% higher, HR 1.21, *p* = 0.66, Cox proportional hazards. |

## 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.

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| *Abdulateef*, 4/8/2021, retrospective, Iraq, peer-reviewed, 7 authors, study period July 2020 - August 2020, excluded in exclusion analyses: unadjusted results with no group details. | risk of hospitalization, 13.1% lower, RR 0.87, *p* = 0.83, treatment 7 of 111 (6.3%), control 23 of 317 (7.3%), NNT 105, unadjusted. |

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| *Adrean*, 10/30/2022, retrospective, USA, peer-reviewed, survey, 6 authors, study period 1 April, 2020 - 9 April, 2021. | risk of case, 12.2% higher, RR 1.12, *p* = 0.58, treatment 30 of 2,111 (1.4%), control 80 of 6,315 (1.3%). |
| *Ajili*, 7/31/2020, Double Blind Randomized Controlled Trial, placebo-controlled, trial NCT04377646 (history) (COVID-Milit). | Estimated 660 patient RCT with results unknown and over 3 years late. |
| *Asoudeh*, 3/21/2023, retrospective, Iran, peer-reviewed, 10 authors, study period June 2021 - September 2021. | risk of severe case, 57.0% lower, OR 0.43, *p* = 0.03, adjusted per study, T3 vs. T1, multivariable, model 3, RR approximated with OR. |
| *Bagheri*, 9/1/2021, retrospective, Iran, peer-reviewed, 6 authors. | risk of severe case, 60.4% lower, OR 0.40, *p* = 0.41, treatment 33, control 477, adjusted per study, multinomial logistic regression, RR approximated with OR. |
| | risk of hospitalization, 41.0% lower, RR 0.59, *p* = 0.37, treatment 4 of 33 (12.1%), control 167 of 477 (35.0%), NNT 4.4, adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, binary logistic regression. |
| *Bejan*, 2/28/2021, retrospective, USA, peer-reviewed, mean age 42.0, 6 authors. | risk of mechanical ventilation, 18.0% lower, OR 0.82, *p* = 0.78, treatment 155, control 9,074, adjusted per study, RR approximated with OR. |
| | risk of ICU admission, 30.0% lower, OR 0.70, *p* = 0.60, treatment 155, control 9,112, adjusted per study, RR approximated with OR. |
| *Citu*, 3/30/2022, retrospective, Romania, peer-reviewed, survey, 14 authors, study period 14 April, 2020 - 14 February, 2022, this trial uses multiple treatments in the treatment arm (combined with calcium) - results of individual treatments may vary. | risk of severe case, 17.6% lower, RR 0.82, *p* = 1.00, treatment 2 of 74 (2.7%), control 2 of 61 (3.3%), NNT 174, Ca+Mg+Zn vs. Mg. |
| *Gordon*, 12/13/2021, prospective, USA, peer-reviewed, 2 authors. | risk of death, 67.6% lower, RR 0.32, *p* = 0.48, treatment 0 of 104 (0.0%), control 1 of 96 (1.0%), NNT 96, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm). |
| | risk of symptomatic case, 85.3% lower, RR 0.15, *p* = 0.02, treatment 2 of 104 (1.9%), control 9 of 96 (9.4%), NNT 13, adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk. |
| *Holt*, 3/30/2021, prospective, United Kingdom, peer-reviewed, 34 authors, study period 1 May, 2020 - 5 February, 2021, trial NCT04330599 (history) (COVIDENCE UK), excluded in exclusion analyses: significant unadjusted confounding possible. | risk of case, 6.8% lower, RR 0.93, *p* = 0.77, treatment 21 of 750 (2.8%), control 425 of 14,477 (2.9%), NNT 737, adjusted per study, odds ratio converted to relative risk, minimally adjusted, group sizes approximated. |
| *Israel*, 7/27/2021, retrospective, Israel, peer-reviewed, 10 authors, this trial uses multiple treatments in the treatment arm (combined with | risk of hospitalization, >99.99% lower, OR < 0.001, *p* = 0.04, treatment 0 of 6,953 (0.0%) cases, 10 of 13,906 (0.1%) controls, NNT 3.0, case control OR, PCR+, cohort 2. |

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| calcium) - results of individual treatments may vary, excluded in exclusion analyses: treatment or control group size extremely small. | |
| *Kumar*, 2/23/2022, retrospective, India, peer-reviewed, 10 authors, study period June 2021 - August 2021, excluded in exclusion analyses: unadjusted results with no group details. | risk of death, 20.0% lower, RR 0.80, *p* = 0.71, treatment 6 of 75 (8.0%), control 3 of 30 (10.0%), NNT 50, unadjusted. |
| *Louca*, 11/30/2020, retrospective, United Kingdom, peer-reviewed, 26 authors. | risk of case, 0.9% lower, RR 0.99, *p* = 0.80, odds ratio converted to relative risk, United Kingdom, all adjustment model. |
| *Mahto*, 2/15/2021, retrospective, India, peer-reviewed, 6 authors. | risk of IgG positive, 36.8% lower, RR 0.63, *p* = 0.35, treatment 10 of 38 (26.3%), control 83 of 651 (12.7%), adjusted per study, odds ratio converted to relative risk, multivariable. |
| *Nimer*, 2/28/2022, retrospective, Jordan, peer-reviewed, survey, 4 authors, study period March 2021 - July 2021. | risk of hospitalization, 25.4% higher, RR 1.25, *p* = 0.21, treatment 41 of 326 (12.6%), control 178 of 1,822 (9.8%), adjusted per study, odds ratio converted to relative risk, multivariable. |
| | risk of severe case, 13.0% higher, RR 1.13, *p* = 0.46, treatment 46 of 326 (14.1%), control 214 of 1,822 (11.7%), adjusted per study, odds ratio converted to relative risk, multivariable. |
| *Seet*, 4/14/2021, Cluster Randomized Controlled Trial, Singapore, peer-reviewed, 15 authors, study period 13 May, 2020 - 31 August, 2020, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04446104 (history). | risk of symptomatic case, 49.7% lower, RR 0.50, *p* < 0.001, treatment 33 of 634 (5.2%), control 64 of 619 (10.3%), NNT 19. |
| | risk of case, 26.9% lower, RR 0.73, *p* = 0.03, treatment 300 of 634 (47.3%), control 433 of 619 (70.0%), NNT 4.4, adjusted per study, odds ratio converted to relative risk, model 6. |
| *Seifi*, 3/4/2024, retrospective, Iran, peer-reviewed, mean age 49.7, 8 authors, study period February 2020 - June 2022, excluded in exclusion analyses: the hospitalization result is only provided with respect to continuous values and the confidence interval is not reported for the case result. | risk of hospitalization, 30.6% lower, OR 0.69, *p* = 0.02, RR approximated with OR, per unit change, per unit change. |
| *Sharif*, 11/26/2022, retrospective, Bangladesh, peer-reviewed, 14 authors, study period 13 December, 2020 - 4 February, 2021. | risk of severe case, 40.0% lower, OR 0.60, *p* < 0.001, adjusted per study, multivariable, RR approximated with OR. |
| | risk of severe case, 97.0% lower, OR 0.03, *p* = 0.005, adjusted per study, combined use of vitamin C, vitamin D, and zinc, multivariable, RR approximated with OR. |
| *Shehab*, 2/28/2022, retrospective, multiple countries, peer-reviewed, survey, 7 authors, study period September 2020 - March 2021, excluded in exclusion analyses: unadjusted results with no group details. | risk of severe case, 47.4% lower, RR 0.53, *p* = 0.24, treatment 4 of 65 (6.2%), control 22 of 188 (11.7%), NNT 18, unadjusted, severe vs. mild cases. |
| *Stambouli*, 6/17/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Tunisia, peer-reviewed, 22 authors, study period 12 November, 2020 - 10 February, 2021, trial NCT04584567 (history). | risk of symptomatic case, 68.4% lower, RR 0.32, *p* = 0.36, treatment 1 of 59 (1.7%), control 3 of 56 (5.4%), NNT 27, zinc + doxycycline vs. doxycycline. |

| | risk of case, 5.1% lower, RR 0.95, $p$ = 1.00, treatment 5 of 59 (8.5%), control 5 of 56 (8.9%), NNT 220, zinc + doxycycline vs. doxycycline. |
| --- | --- |
| | relative Ct values, 21.4% better, RR 0.79, $p < 0.001$, treatment mean 29.0 (±1.3) n=59, control mean 22.8 (±4.0) n=56, zinc + doxycycline vs. doxycycline. |

## 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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