

Ivermectin for COVID-19: real-time meta analysis of 63 studies

Covid Analysis, Aug 16, 2021, Version 110 – twitter personality response, updated
Together Trial (v1 Nov 26, 2020)

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- Meta analysis using the most serious outcome reported shows 72% [55-82%] and 86% [75-92%] improvement for early treatment and prophylaxis, with similar results after exclusion based sensitivity analysis and restriction to peer-reviewed studies or Randomized Controlled Trials.
- Statistically significant improvements are seen for mortality, hospitalization, recovery, cases, and viral clearance. 27 studies show statistically significant improvements in isolation. The probability that an ineffective treatment generated results as positive as the 63 studies is estimated to be 1 in 1 trillion.

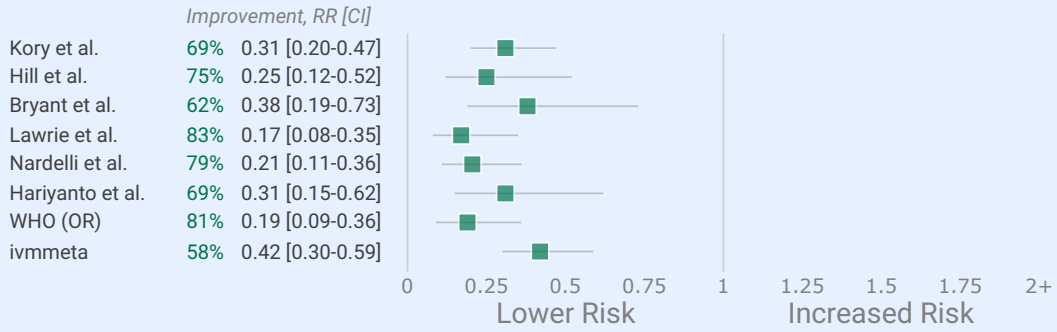
| | <i>Studies</i> | <i>Prophylaxis</i> | <i>Early treatment</i> | <i>Late treatment</i> | <i>Patients</i> |
|-------------------------------------|----------------|---------------------|------------------------|-----------------------|-----------------|
| <u>All studies</u> | 63 | 86% [75-92%] | 72% [55-82%] | 40% [24-52%] | 26,422 |
| <u>Peer-reviewed</u> | 42 | 86% [73-93%] | 75% [61-84%] | 43% [21-59%] | 16,455 |
| <u>Randomized Controlled Trials</u> | 31 | 84% [25-96%] | 61% [46-71%] | 30% [2-50%] | 6,561 |

Percentage improvement with ivermectin treatment

- While many treatments have some level of efficacy, they do not replace vaccines and other measures to avoid infection. Only 29% of ivermectin studies show zero events in the treatment arm.
- Elimination of COVID-19 is a race against viral evolution. No treatment, vaccine, or intervention is 100% available and effective for all current and future variants. All practical, effective, and safe means should be used. Those denying the efficacy of treatments share responsibility for the increased risk of COVID-19 becoming endemic; and the increased mortality, morbidity, and collateral damage.
- The evidence base is much larger and has much lower conflict of interest than typically used to approve drugs.
- All data to reproduce this paper and sources are in the appendix. See [*Bryant, Hariyanto, Hill, Kory, Lawrie, Nardelli*] for other meta analyses with similar results confirming efficacy.

Ivermectin meta analysis mortality results

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Evidence base used for other COVID-19 approvals

| Medication | Studies | Patients | Improvement |
|-------------------------------|---------|----------|--------------|
| <u>Budesonide (UK)</u> | 1 | 1,779 | 17% |
| <u>Remdesivir (USA)</u> | 1 | 1,063 | 31% |
| <u>Casiri/imdevimab (USA)</u> | 1 | 799 | 66% |
| <i>Ivermectin evidence</i> | 63 | 26,398 | 68% [60-75%] |

Ivermectin COVID-19 early treatment and prophylaxis studies

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| | Improvement, RR [CI] | Treatment | Control | Dose (4d) | | |
|---------------------|------------------------|-------------|-------------------------|-----------|-------|---------------------------------|
| Chowdhury (RCT) | 81% 0.19 [0.01-3.96] | hosp. | 0/60 | 2/56 | 14mg | OT ¹ CT ² |
| Espitia-Hernandez | 97% 0.03 [0.01-0.11] | viral+ | 0/28 | 7/7 | 12mg | CT ² |
| Carvallo | 85% 0.15 [0.02-1.28] | death | 1/32 | 3/14 | 36mg | CT ² |
| Mahmud (DB RCT) | 86% 0.14 [0.01-2.75] | death | 0/183 | 3/183 | 12mg | CT ² |
| Szente Fonseca | -14% 1.14 [0.75-1.66] | hosp. | 340 (n) | 377 (n) | 24mg | |
| Cadegiani | 78% 0.22 [0.01-4.48] | death | 0/110 | 2/137 | 42mg | CT ² |
| Ahmed (DB RCT) | 85% 0.15 [0.01-2.70] | symptoms | 0/17 | 3/19 | 48mg | |
| Chaccour (DB RCT) | 53% 0.47 [0.19-1.16] | symp. prob. | 12 (n) | 12 (n) | 28mg | |
| Afsar | 92% 0.08 [0.00-1.32] | symptoms | 0/37 | 7/53 | 48mg | |
| Babalola (DB RCT) | 64% 0.36 [0.10-1.27] | viral+ | 40 (n) | 20 (n) | 24mg | OT ¹ |
| Ravikirti (DB RCT) | 89% 0.11 [0.01-2.05] | death | 0/55 | 4/57 | 24mg | |
| Bukhari (RCT) | 82% 0.18 [0.07-0.46] | viral+ | 4/41 | 25/45 | 12mg | |
| Samaha (RCT) | 86% 0.14 [0.01-2.70] | hosp. | 0/50 | 3/50 | 12mg | |
| Mohan (DB RCT) | 62% 0.38 [0.08-1.75] | no recov. | 2/40 | 6/45 | 28mg | |
| Biber (DB RCT) | 70% 0.30 [0.03-2.76] | hosp. | 1/47 | 3/42 | 36mg | |
| Elalfy | 87% 0.13 [0.06-0.27] | viral+ | 7/62 | 44/51 | 36mg | CT ² |
| López-Me.. (DB RCT) | 67% 0.33 [0.01-8.11] | death | 0/200 | 1/198 | 84mg | |
| Roy | 6% 0.94 [0.52-1.93] | recov. time | 14 (n) | 15 (n) | n/a | CT ² |
| Chahla (CLUS. RCT) | 87% 0.13 [0.03-0.54] | no disch. | 2/110 | 20/144 | 24mg | |
| Mourya | 89% 0.11 [0.05-0.25] | viral+ | 5/50 | 47/50 | 48mg | |
| Loue (QR) | 70% 0.30 [0.04-2.20] | death | 1/10 | 5/15 | 14mg | |
| Merino (QR) | 74% 0.26 [0.11-0.61] | hosp. | population-based cohort | | 24mg | |
| Faisal (RCT) | 68% 0.32 [0.14-0.72] | no recov. | 6/50 | 19/50 | 48mg | |
| Aref (RCT) | 63% 0.37 [0.22-0.62] | recov. time | 57 (n) | 57 (n) | | |
| Krolewiecki (RCT) | -152% 2.52 [0.11-58.1] | ventilation | 1/27 | 0/14 | 168mg | |
| Vallejos (DB RCT) | -33% 1.33 [0.30-5.72] | death | 4/250 | 3/251 | 24mg | |
| Together.. (DB RCT) | 18% 0.82 [0.44-1.52] | death | 18/677 | 22/678 | 84mg | |

Early treatment 72% 0.28 [0.18-0.45] 52/2,599 229/2,640 **72% improvement**

Tau² = 0.82; I² = 80.8%

| | Improvement, RR [CI] | Treatment | Control | Dose (1m) | | |
|-------------------|-----------------------|-------------|------------|-----------|------|-----------------|
| Shouman (RCT) | 91% 0.09 [0.03-0.23] | symp. case | 15/203 | 59/101 | 36mg | |
| Carvallo | 96% 0.04 [0.00-0.63] | cases | 0/131 | 11/98 | 14mg | CT ² |
| Behera | 54% 0.46 [0.29-0.71] | cases | 41/117 | 145/255 | 42mg | |
| Carvallo | 100% 0.00 [0.00-0.02] | cases | 0/788 | 237/407 | 48mg | CT ² |
| Hellwig (ECO.) | 78% 0.22 [0.05-0.89] | cases | ecological | | 14mg | |
| Bernigaud | 99% 0.01 [0.00-0.10] | death | 0/69 | 150/3,062 | 84mg | |
| Alam | 91% 0.09 [0.04-0.25] | cases | 4/58 | 44/60 | 12mg | |
| Vallejos | 73% 0.27 [0.15-0.48] | cases | 13/389 | 61/486 | 48mg | MD ³ |
| Chahla (RCT) | 95% 0.05 [0.00-0.80] | m/s case | 0/117 | 10/117 | 48mg | CT ² |
| Behera | 83% 0.17 [0.12-0.23] | cases | 45/2,199 | 133/1,147 | 42mg | |
| Tanioka (ECO.) | 88% 0.12 [0.03-0.51] | death | ecological | | 14mg | |
| Seet (CLUS. RCT) | 50% 0.50 [0.33-0.76] | severe case | 32/617 | 64/619 | 12mg | OT ¹ |
| Morgenstern (PSM) | 80% 0.20 [0.01-4.15] | hosp. | 0/271 | 2/271 | 56mg | |
| Mondal | 88% 0.12 [0.01-0.55] | symp. case | 128 (n) | 1,342 (n) | n/a | |

Prophylaxis 86% 0.14 [0.08-0.25] 150/5,087 916/7,965 **86% improvement**

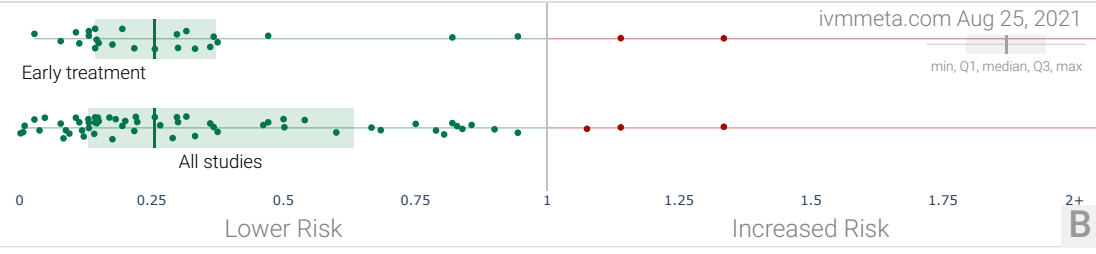
Tau² = 0.59; I² = 83.9%

All studies 79% 0.21 [0.15-0.31] 202/7,686 1,145/10,605 **79% improvement**

¹ OT: ivermectin vs. other treatment
² CT: study uses combined treatment
³ MD: minimal detail available currently
 Tau² = 0.88; I² = 88.6%; Z = 8.05

Effect extraction pre-specified, see appendix

Lower Risk Increased Risk **A**



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min, Q1, median, Q3, max

0 0.25 0.5 0.75 1 1.25 1.5 1.75 2+ **B**

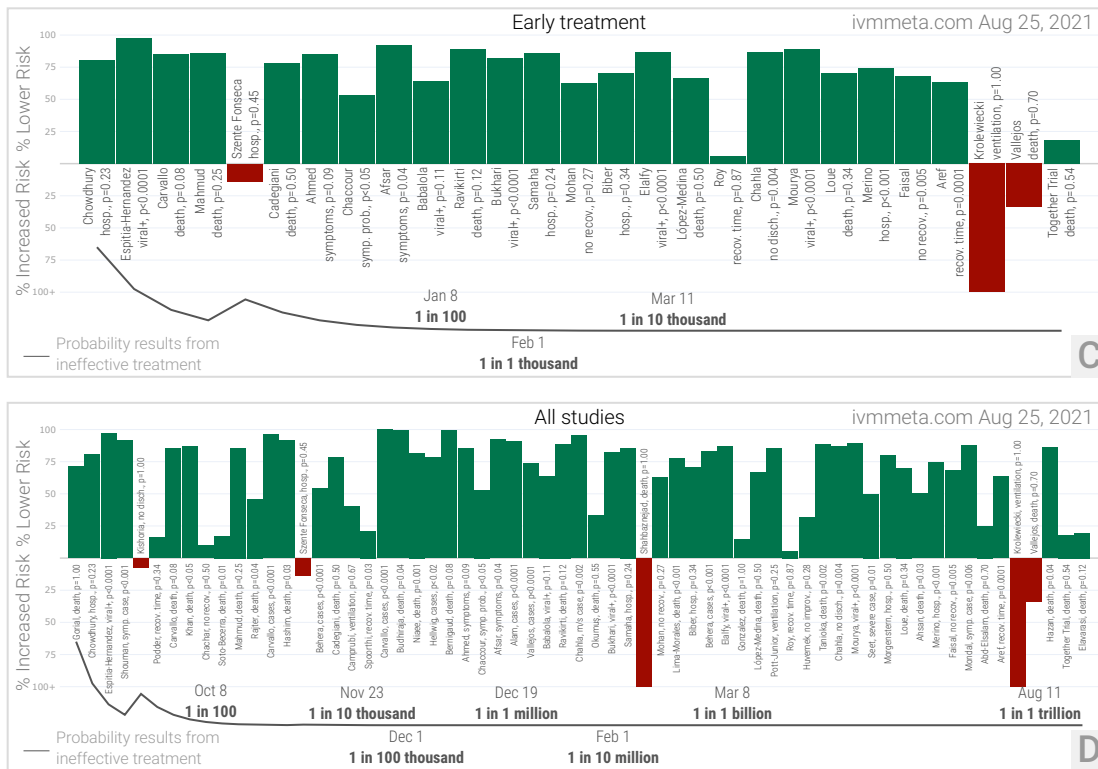


Figure 1. A. Random effects meta-analysis excluding late treatment. This plot shows pooled effects, analysis for individual outcomes is below, and more details on pooled effects can be found in the heterogeneity section. Effect extraction is pre-specified, using the most serious outcome reported. Simplified dosages are shown for comparison, these are the total dose in the first four days for treatment, and the monthly dose for prophylaxis, for a 70kg person. For details of effect extraction and full dosage information see the [appendix](#). **B.** Scatter plot showing the distribution of effects reported in early treatment studies and in all studies. **C and D.** Chronological history of all reported effects, with the probability that the observed frequency of positive results occurred due to random chance from an ineffective treatment.

Introduction

We analyze all significant studies concerning the use of ivermectin 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, for studies within each treatment stage, for mortality results, for COVID-19 case results, for viral clearance results, for peer-reviewed studies, for Randomized Controlled Trials (RCTs), and after exclusions.

We also perform a simple analysis of the distribution of study effects. If treatment was not effective, the observed effects would be randomly distributed (or more likely to be negative if treatment is harmful). We can compute the probability that the observed percentage of positive results (or higher) could occur due to chance with an ineffective treatment (the probability of $\geq k$ heads in n coin tosses, or the one-sided sign test / binomial test). Analysis of publication bias is important and adjustments may be needed if there is a bias toward publishing positive results.

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

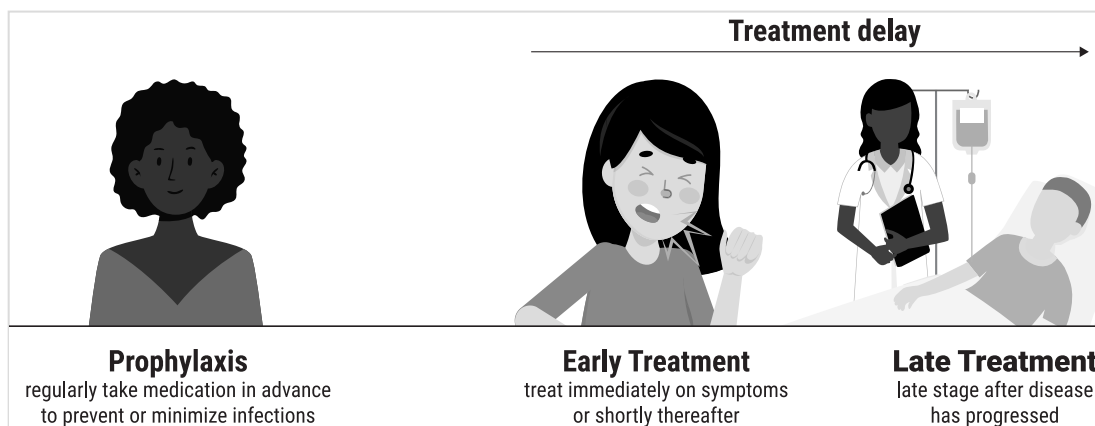


Figure 2. Treatment stages.

Results

Figure 3, 4, and 5 show results by treatment stage. Figure 6, 7, 8, 9, 10, 11, 12, and 13 show forest plots for a random effects meta-analysis of all studies with pooled effects, and for studies reporting mortality results, ICU admission, mechanical ventilation, hospitalization, recovery, COVID-19 cases, and viral clearance results only. Figure 14 shows results for peer reviewed trials only and Figure 15 shows results restricted to serious outcomes. Table 1 summarizes the results.

| Treatment time | Number of studies reporting positive effects | Total number of studies | Percentage of studies reporting positive effects | Probability of an equal or greater percentage of positive results from an ineffective treatment | Random effects meta-analysis results |
|-----------------|--|-------------------------|--|---|--|
| Early treatment | 24 | 27 | 88.9% | 1 in 41 thousand | 72% improvement RR 0.28 [0.18-0.45] p < 0.0001 |
| Late treatment | 20 | 22 | 90.9% | 1 in 17 thousand | 40% improvement RR 0.60 [0.48-0.76] p < 0.0001 |
| Prophylaxis | 14 | 14 | 100% | 1 in 16 thousand | 86% improvement RR 0.14 [0.08-0.25] p < 0.0001 |
| All studies | 58 | 63 | 92.1% | 1 in 1 trillion | 68% improvement RR 0.32 [0.25-0.40] p < 0.0001 |

Table 1. Results by treatment stage.

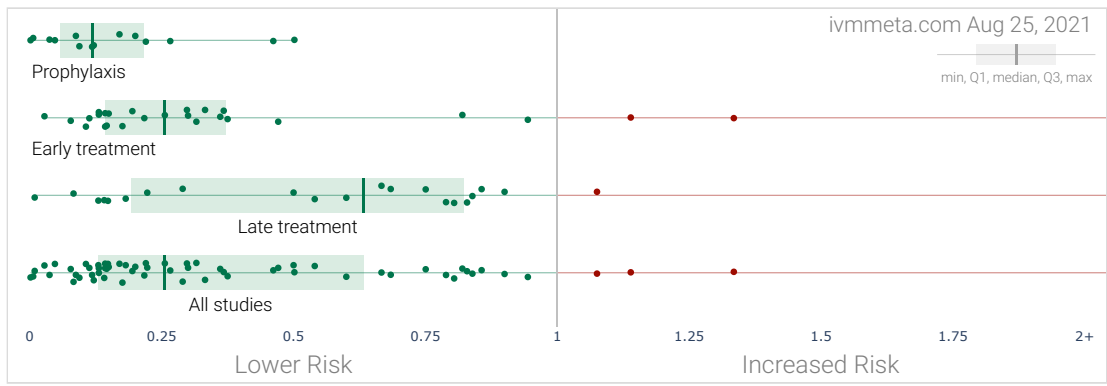


Figure 3. Results by treatment stage.

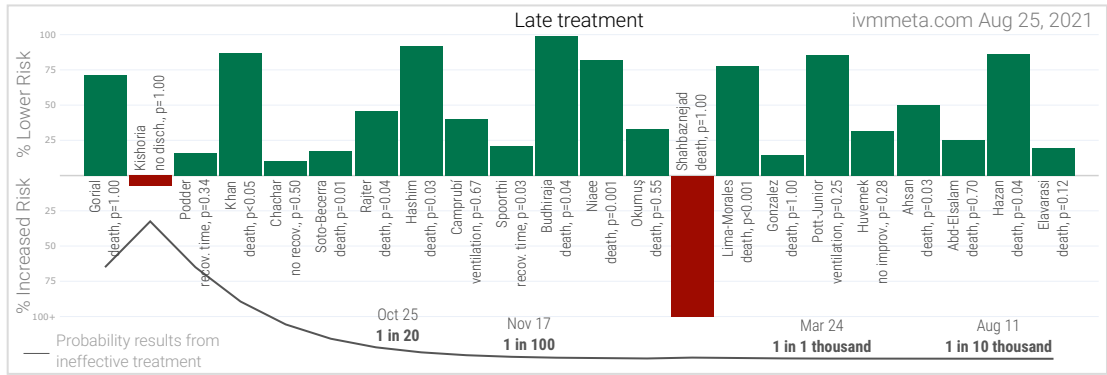
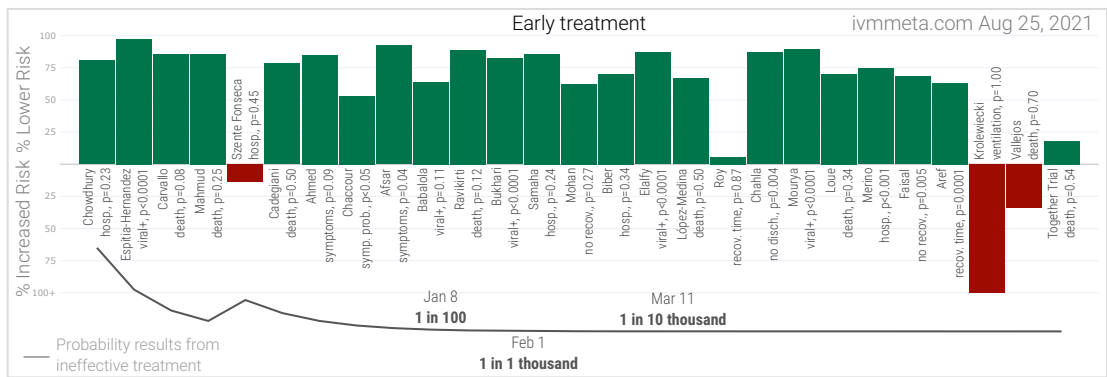


Figure 4. Chronological history of early and late treatment results, with the probability that the observed frequency of positive results occurred due to random chance from an ineffective treatment.

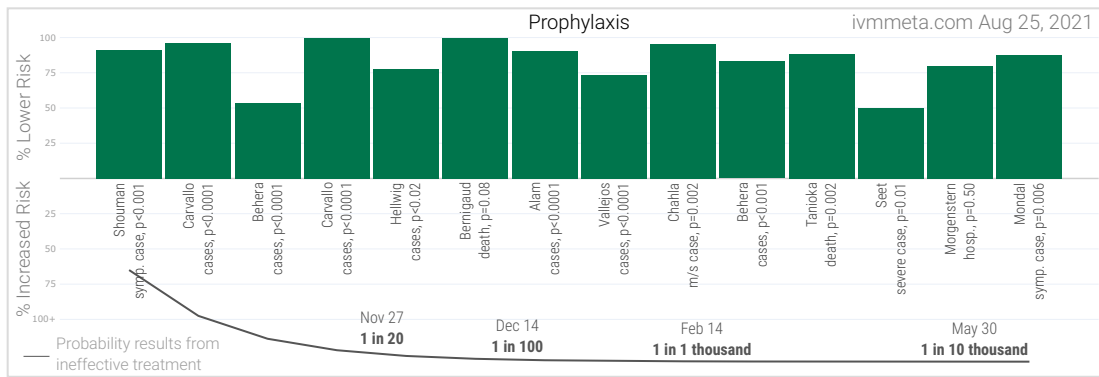


Figure 5. Chronological history of prophylaxis results.

All 63 ivermectin COVID-19 studies

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| | Improvement, RR [CI] | Treatment | Control | Dose (4d) | |
|---------------------|------------------------|-------------|-------------------------|-----------|---------------------------------|
| Chowdhury (RCT) | 81% 0.19 [0.01-3.96] | hosp. | 0/60 2/56 | 14mg | OT ¹ CT ² |
| Espitia-Hernandez | 97% 0.03 [0.01-0.11] | viral+ | 0/28 7/7 | 12mg | CT ² |
| Carvallo | 85% 0.15 [0.02-1.28] | death | 1/32 3/14 | 36mg | CT ² |
| Mahmud (DB RCT) | 86% 0.14 [0.01-2.75] | death | 0/183 3/183 | 12mg | CT ² |
| Szente Fonseca | -14% 1.14 [0.75-1.66] | hosp. | 340 (n) 377 (n) | 24mg | CT ² |
| Cadegiani | 78% 0.22 [0.01-4.48] | death | 0/110 2/137 | 42mg | CT ² |
| Ahmed (DB RCT) | 85% 0.15 [0.01-2.70] | symptoms | 0/17 3/19 | 48mg | |
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| Afsar | 92% 0.08 [0.00-1.32] | symptoms | 0/37 7/53 | 48mg | |
| Babalola (DB RCT) | 64% 0.36 [0.10-1.27] | viral+ | 40 (n) 20 (n) | 24mg | OT ¹ |
| Ravikirti (DB RCT) | 89% 0.11 [0.01-2.05] | death | 0/55 4/57 | 24mg | |
| Bukhari (RCT) | 82% 0.18 [0.07-0.46] | viral+ | 4/41 25/45 | 12mg | |
| Samaha (RCT) | 86% 0.14 [0.01-2.70] | hosp. | 0/50 3/50 | 12mg | |
| Mohan (DB RCT) | 62% 0.38 [0.08-1.75] | no recov. | 2/40 6/45 | 28mg | |
| Biber (DB RCT) | 70% 0.30 [0.03-2.76] | hosp. | 1/47 3/42 | 36mg | |
| Elalfy | 87% 0.13 [0.06-0.27] | viral+ | 7/62 44/51 | 36mg | CT ² |
| López-Me.. (DB RCT) | 67% 0.33 [0.01-8.11] | death | 0/200 1/198 | 84mg | |
| Roy | 6% 0.94 [0.52-1.93] | recov. time | 14 (n) 15 (n) | n/a | CT ² |
| Chahla (CLUS. RCT) | 87% 0.13 [0.03-0.54] | no disch. | 2/110 20/144 | 24mg | |
| Mourya | 89% 0.11 [0.05-0.25] | viral+ | 5/50 47/50 | 48mg | |
| Loue (QR) | 70% 0.30 [0.04-2.20] | death | 1/10 5/15 | 14mg | |
| Merino (QR) | 74% 0.26 [0.11-0.61] | hosp. | population-based cohort | 24mg | |
| Faisal (RCT) | 68% 0.32 [0.14-0.72] | no recov. | 6/50 19/50 | 48mg | |
| Aref (RCT) | 63% 0.37 [0.22-0.62] | recov. time | 57 (n) 57 (n) | | |
| Krolewiecki (RCT) | -152% 2.52 [0.11-58.1] | ventilation | 1/27 0/14 | 168mg | |
| Vallejos (DB RCT) | -33% 1.33 [0.30-5.72] | death | 4/250 3/251 | 24mg | |
| Together.. (DB RCT) | 18% 0.82 [0.44-1.52] | death | 18/677 22/678 | 84mg | |

Early treatment 72% 0.28 [0.18-0.45] 52/2,599 229/2,640 **72% improvement**

Tau² = 0.82; I² = 80.8%

| | Improvement, RR [CI] | Treatment | Control | Dose (4d) | |
|---------------------|------------------------|-------------|--------------------|-----------|---------------------------------|
| Gorial | 71% 0.29 [0.01-5.76] | death | 0/16 2/71 | 14mg | |
| Kishoria (RCT) | -8% 1.08 [0.57-2.02] | no disch. | 11/19 7/13 | 12mg | |
| Podder (RCT) | 16% 0.84 [0.55-1.12] | recov. time | 32 (n) 30 (n) | 14mg | |
| Khan | 87% 0.13 [0.02-1.01] | death | 1/115 9/133 | 12mg | |
| Chachar (RCT) | 10% 0.90 [0.44-1.83] | no recov. | 9/25 10/25 | 36mg | |
| Soto-Becerra | 17% 0.83 [0.71-0.97] | death | 92/203 1,438/2,630 | 14mg | |
| Rajter (PSM) | 46% 0.54 [0.27-0.99] | death | 13/98 24/98 | 14mg | |
| Hashim (SB RCT) | 92% 0.08 [0.00-1.44] | death | 0/59 6/70 | 28mg | CT ² |
| Camprubí | 40% 0.60 [0.18-2.01] | ventilation | 3/13 5/13 | 14mg | |
| Spoorthi | 21% 0.79 [0.62-1.01] | recov. time | 50 (n) 50 (n) | n/a | CT ² |
| Budhiraja | 99% 0.01 [0.00-0.15] | death | 0/34 103/942 | n/a | |
| Niaee (DB RCT) | 82% 0.18 [0.06-0.55] | death | 4/120 11/60 | 28mg | |
| Okumuş (DB RCT) | 33% 0.67 [0.27-1.64] | death | 6/30 9/30 | 56mg | |
| Shahbazn.. (DB RCT) | -197% 2.97 [0.13-70.5] | death | 1/35 0/34 | 14mg | |
| Lima-Morales | 78% 0.22 [0.12-0.41] | death | 15/481 52/287 | 12mg | CT ² |
| Gonzalez (DB RCT) | 14% 0.86 [0.29-2.56] | death | 5/36 6/37 | 12mg | |
| Pott-Junior (RCT) | 85% 0.15 [0.01-1.93] | ventilation | 1/27 1/4 | 14mg | |
| Huvemek (DB RCT) | 32% 0.68 [0.38-1.23] | no improv. | 13/50 19/50 | 84mg | |
| Ahsan | 50% 0.50 [0.28-0.90] | death | 17/110 17/55 | 21mg | CT ² |
| Abd-El salam (RCT) | 25% 0.75 [0.17-3.06] | death | 3/82 4/82 | 36mg | |
| Hazan | 86% 0.14 [0.01-2.19] | death | 0/24 synthetic | 24mg | CT ² SC ⁴ |
| Elavarasi | 20% 0.80 [0.61-1.06] | death | 48/283 311/1,475 | n/a | |

Late treatment 40% 0.60 [0.48-0.76] 242/1,942 2,034/6,189 **40% improvement**

Tau² = 0.11; I² = 58.2%

| | Improvement, RR [CI] | Treatment | Control | Dose (1m) | |
|-------------------|-----------------------|-------------|--------------------|-----------|-----------------|
| Shouman (RCT) | 91% 0.09 [0.03-0.23] | symp. case | 15/203 59/101 | 36mg | |
| Carvallo | 96% 0.04 [0.00-0.63] | cases | 0/131 11/98 | 14mg | CT ² |
| Behera | 54% 0.46 [0.29-0.71] | cases | 41/117 145/255 | 42mg | |
| Carvallo | 100% 0.00 [0.00-0.02] | cases | 0/788 237/407 | 48mg | CT ² |
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| Alam | 91% 0.09 [0.04-0.25] | cases | 4/58 44/60 | 12mg | |
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| Morgenstern (PSM) | 80% 0.20 [0.01-4.15] | hosp. | 0/271 2/271 | 56mg | |

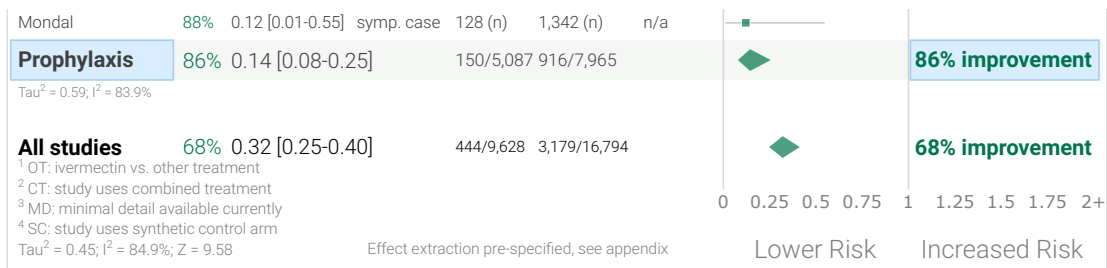


Figure 6. Random effects meta-analysis for all studies. This plot shows pooled effects, analysis for individual outcomes is below, and more details on pooled effects can be found in the heterogeneity section. Effect extraction is pre-specified, using the most serious outcome reported. Simplified dosages are shown for comparison, these are the total dose in the first four days for treatment, and the monthly dose for prophylaxis, for a 70kg person. For details of effect extraction and full dosage information see the [appendix](#).

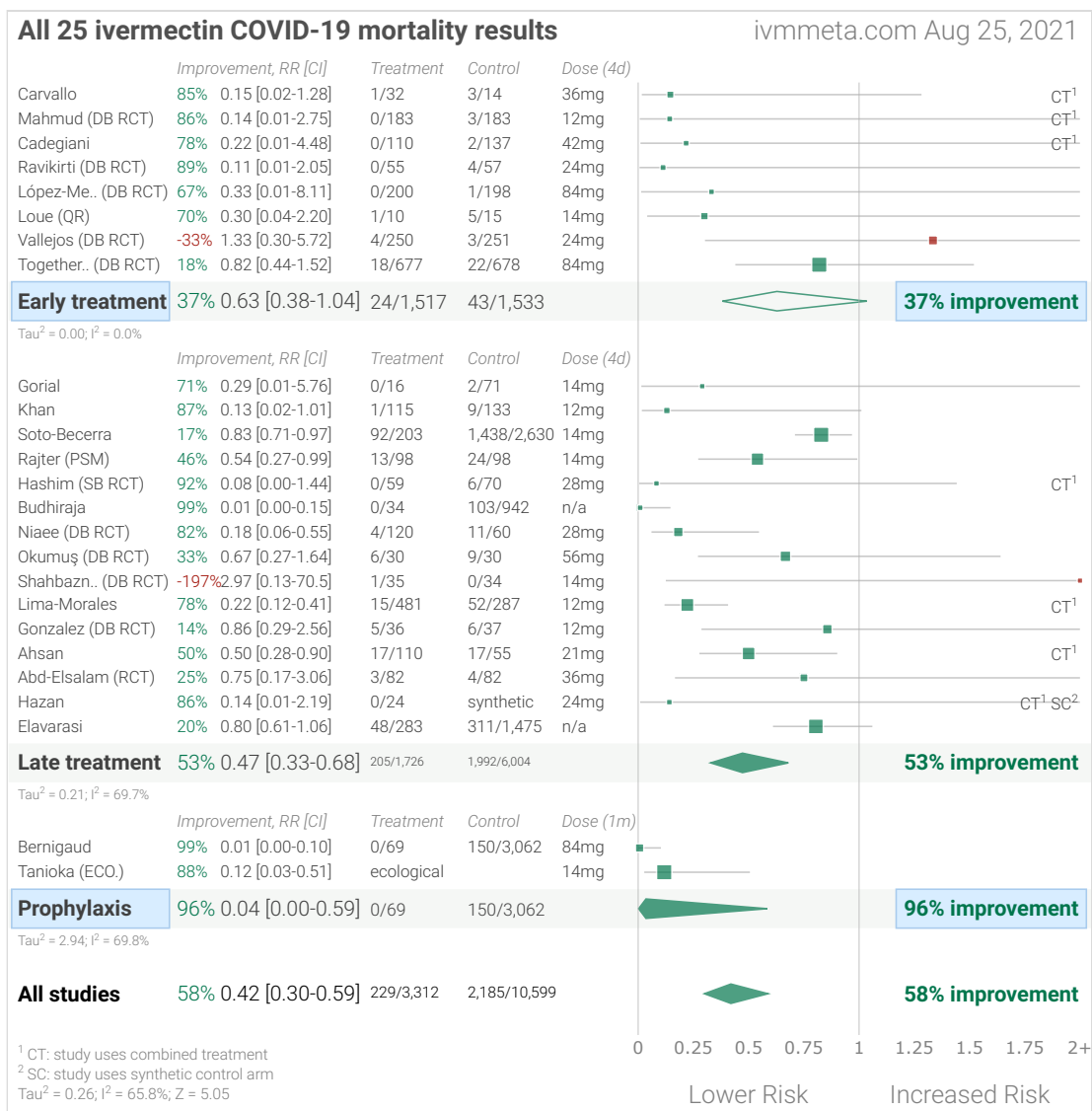


Figure 7. Random effects meta-analysis for mortality results only.

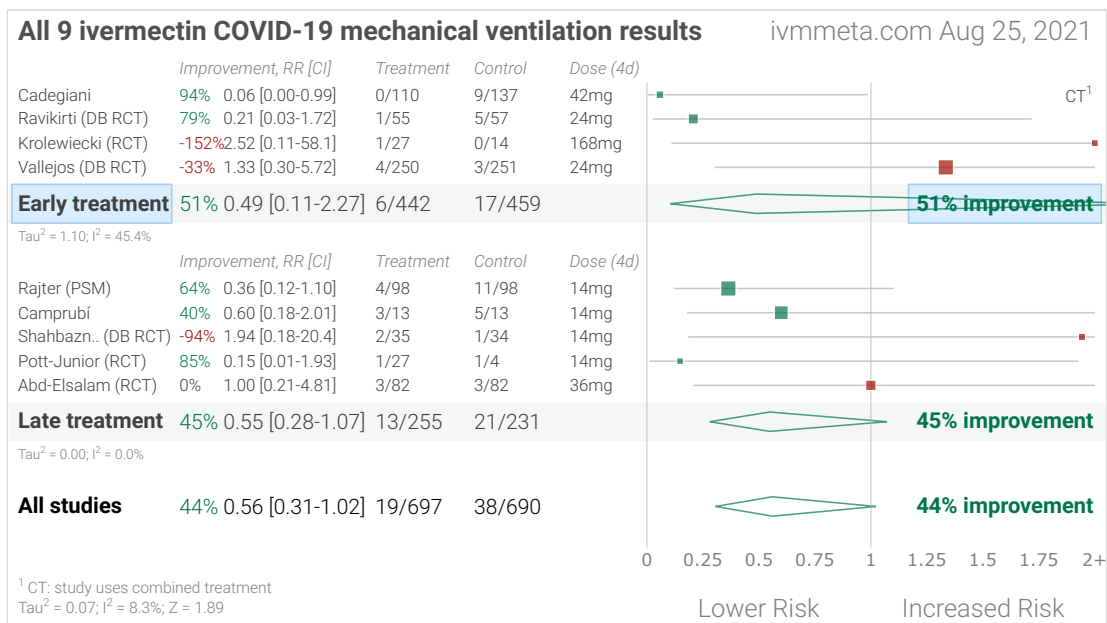


Figure 8. Random effects meta-analysis for mechanical ventilation results only.

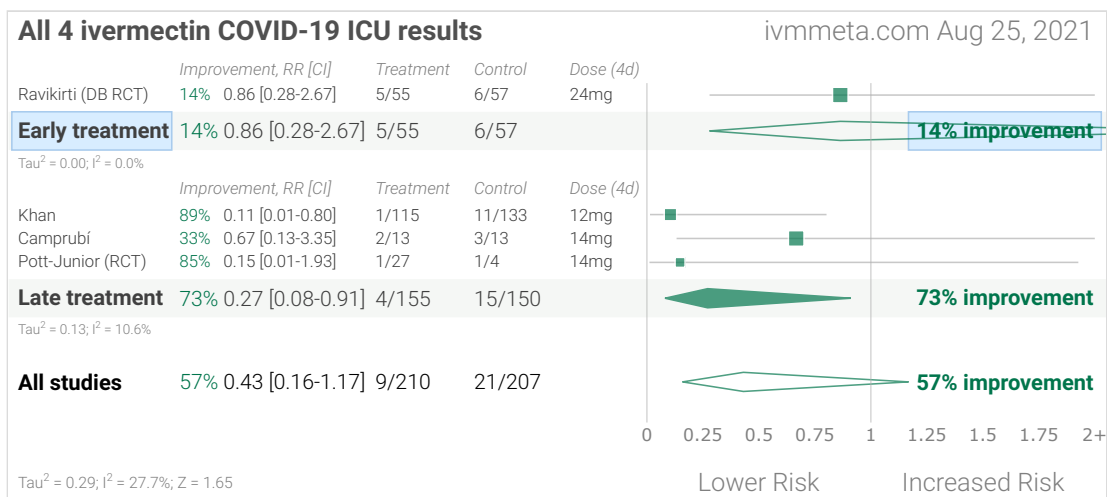


Figure 9. Random effects meta-analysis for ICU admission results only.

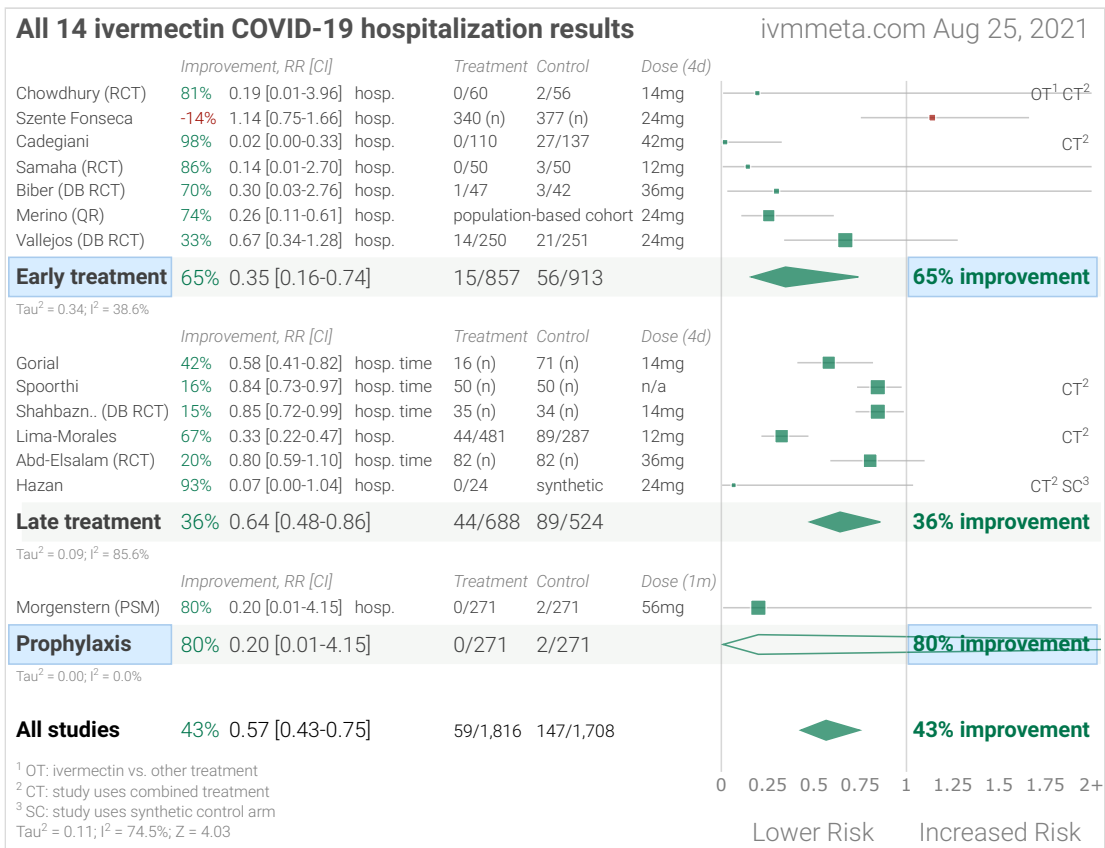


Figure 10. Random effects meta-analysis for hospitalization results only.

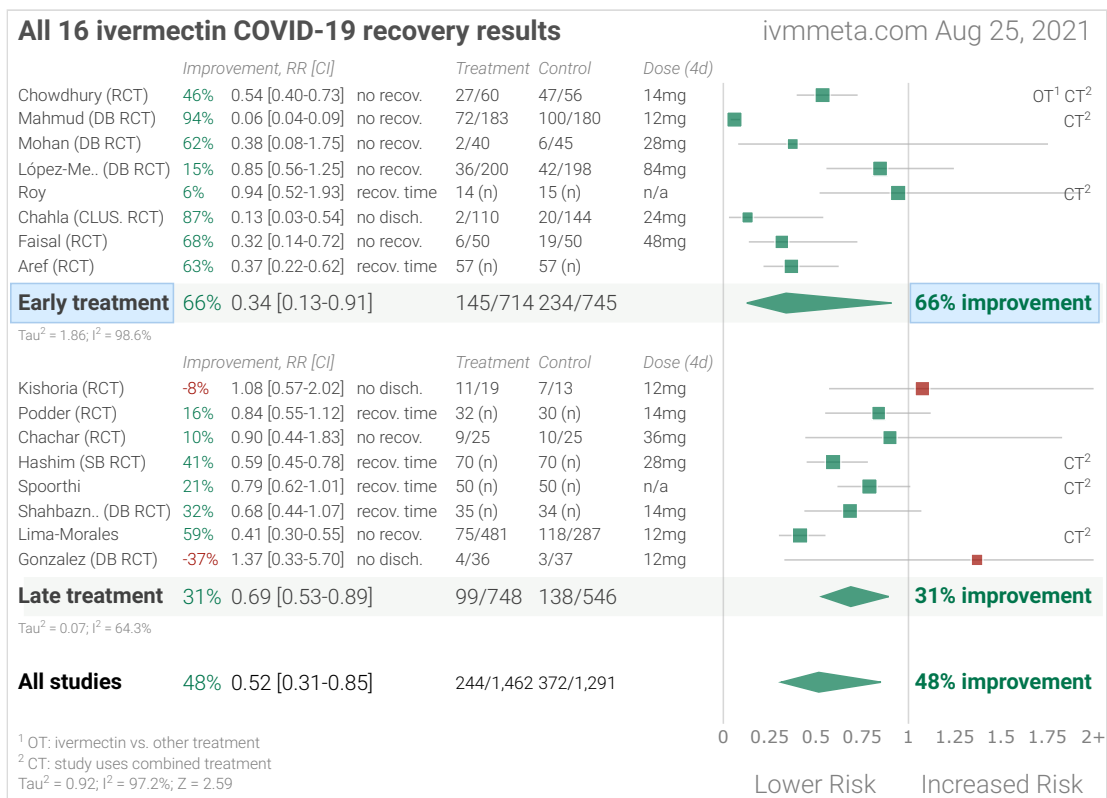


Figure 11. Random effects meta-analysis for recovery results only.

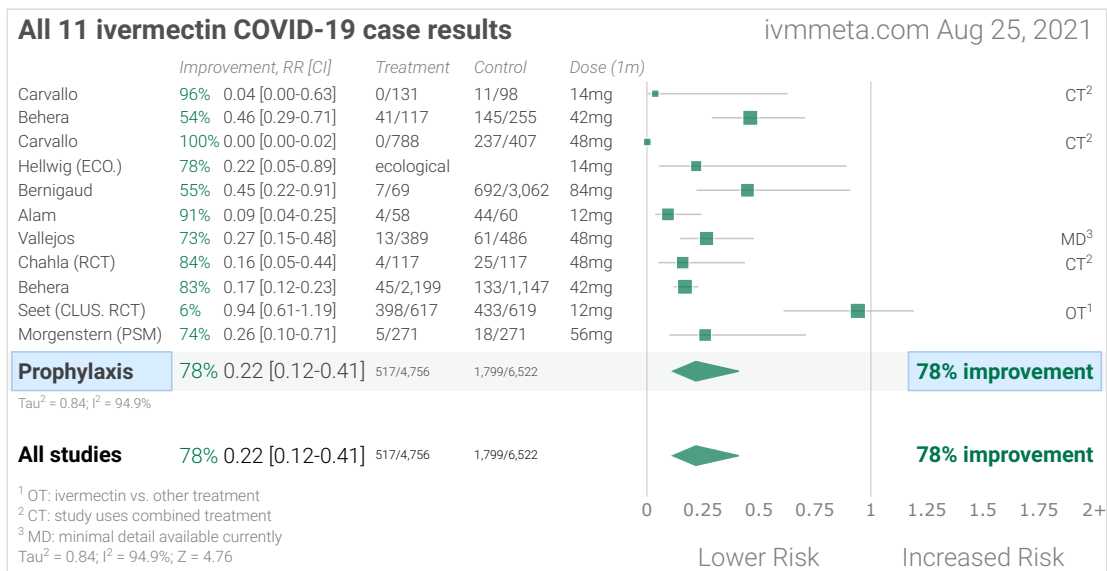


Figure 12. Random effects meta-analysis for COVID-19 case results only.

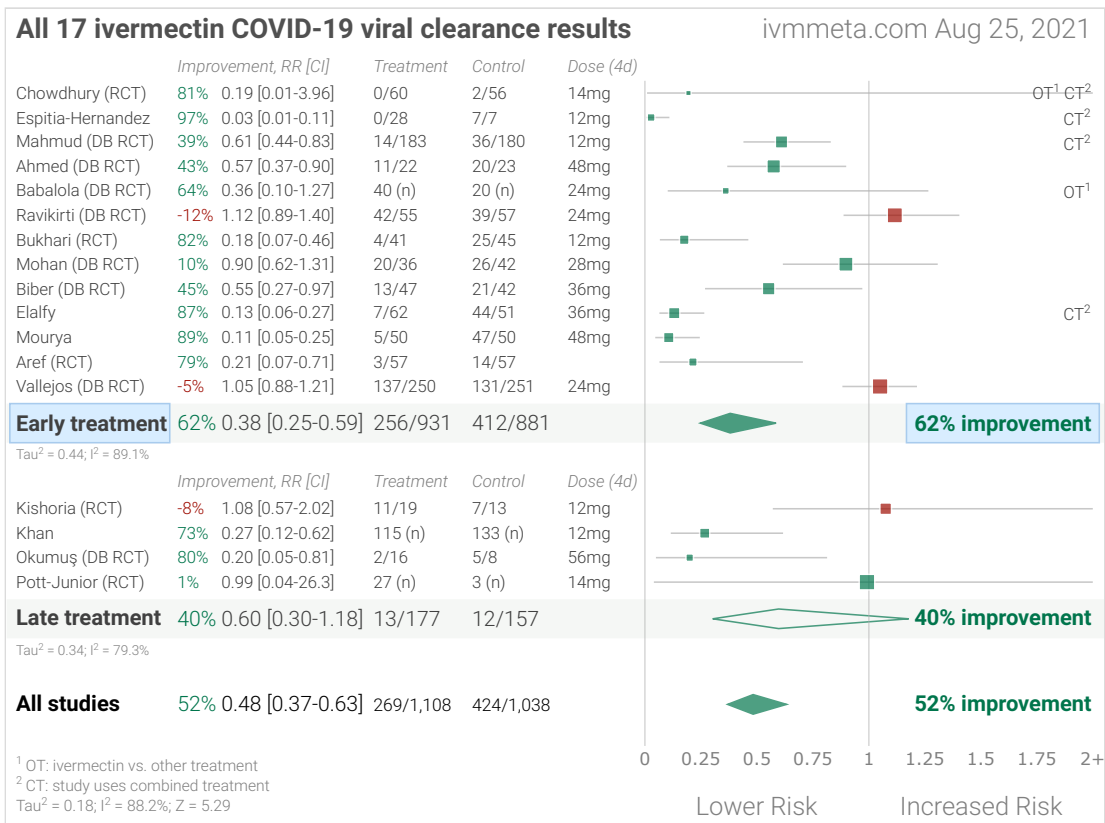


Figure 13. Random effects meta-analysis for viral clearance results only.

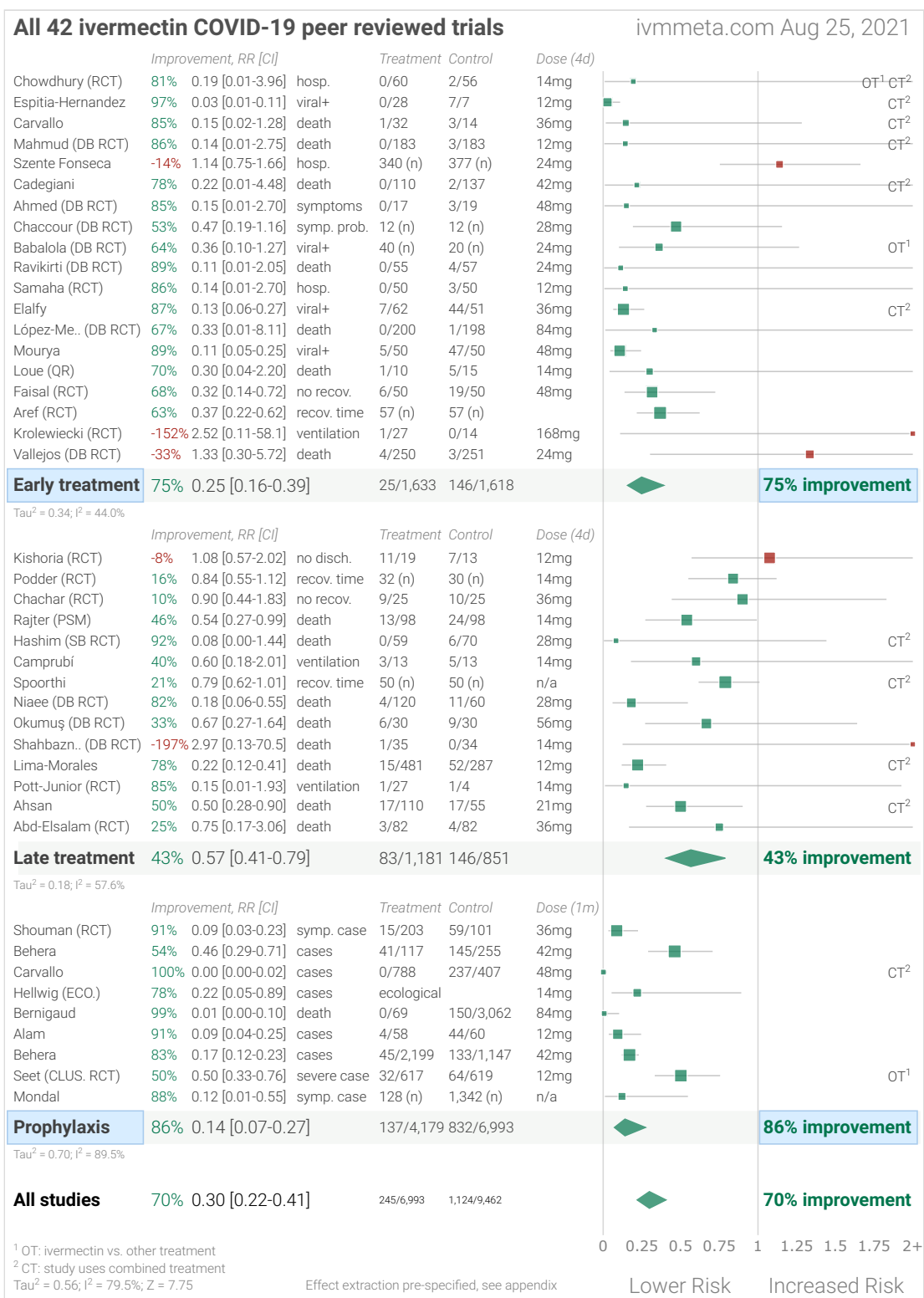


Figure 14. Random effects meta-analysis for peer reviewed trials only. Effect extraction is pre-specified, using the most serious outcome reported, see the [appendix](#) for details.

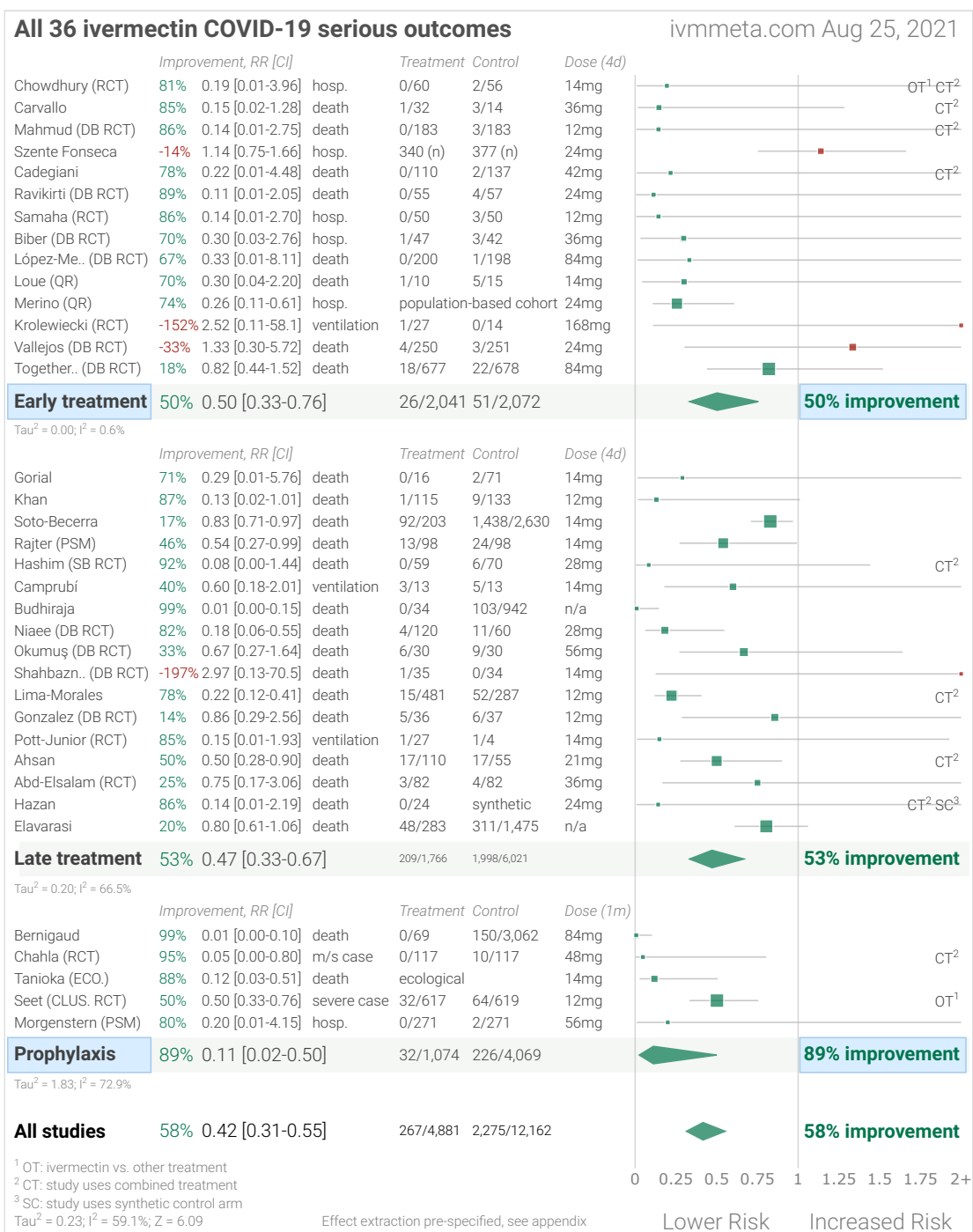


Figure 15. Random effects meta-analysis for serious outcomes only. Effect extraction is pre-specified, using the most serious outcome reported, see the [appendix](#) for details.

Randomized Controlled Trials (RCTs)

Results restricted to Randomized Controlled Trials (RCTs) are shown in Figure 16, 17, 18, and 19, and Table 2. RCT results are similar to non-RCT results. Evidence shows that non-RCT trials can also provide reliable results. [Concato] find that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. [Anglemyer] summarized reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. [Lee] shows that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or Internet survey bias could have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see [Deaton, Nichol].

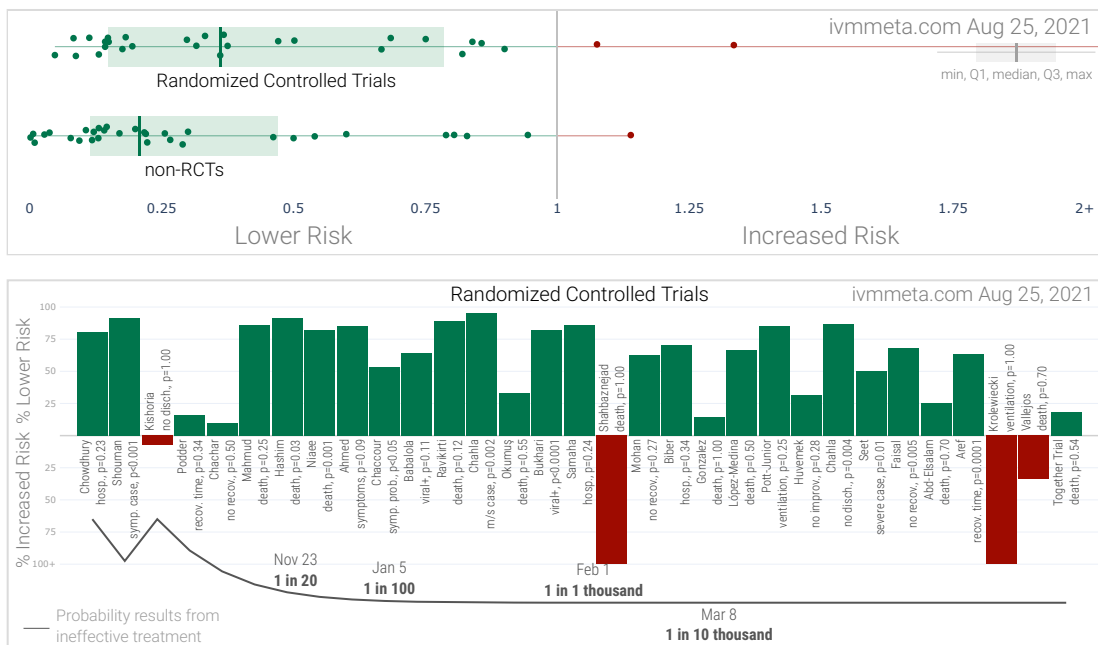


Figure 16. Randomized Controlled Trials. The distribution of results for RCTs is similar to the distribution for all other studies.

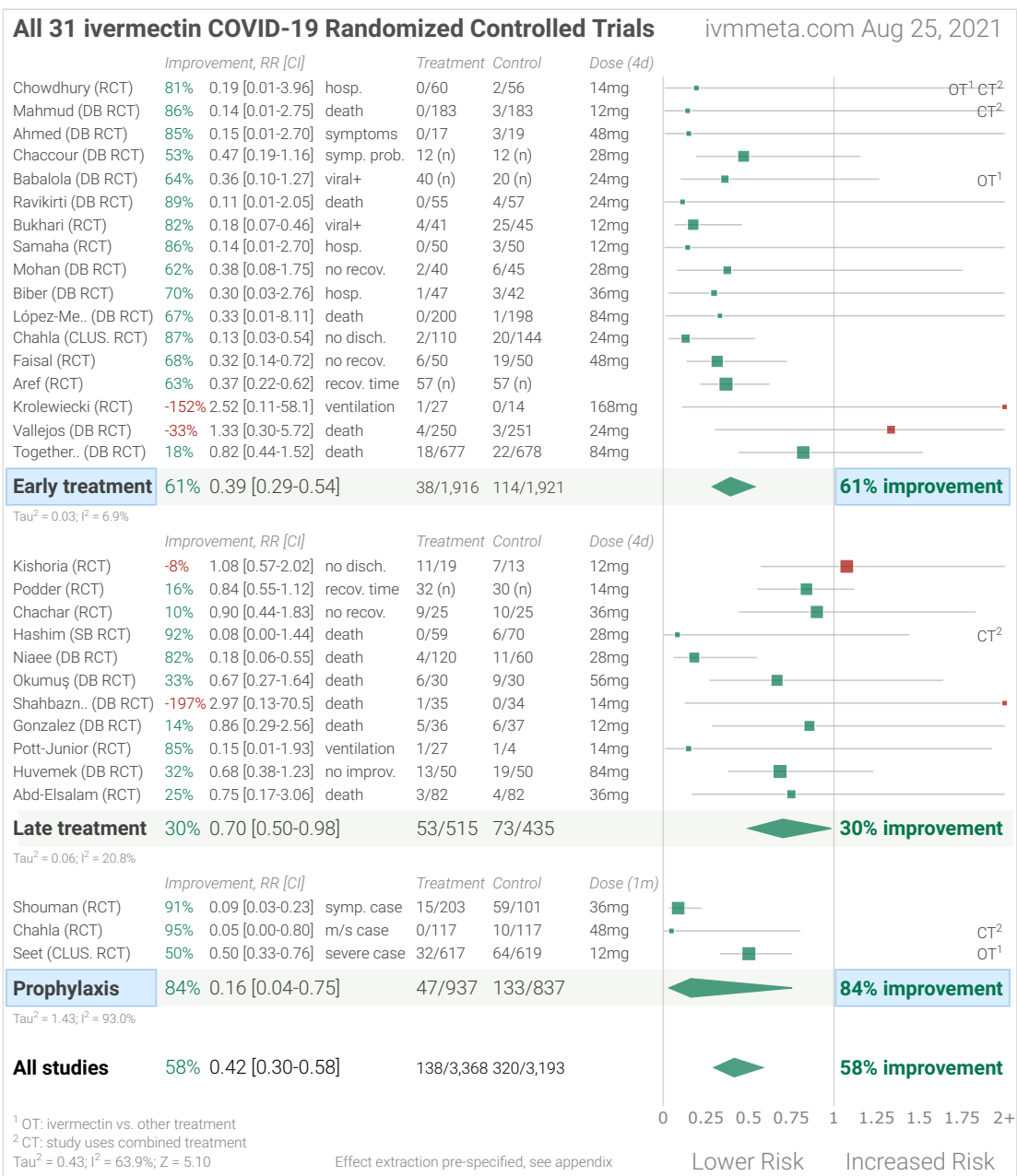


Figure 17. Random effects meta-analysis for Randomized Controlled Trials only. Effect extraction is pre-specified, using the most serious outcome reported, see the [appendix](#) for details.

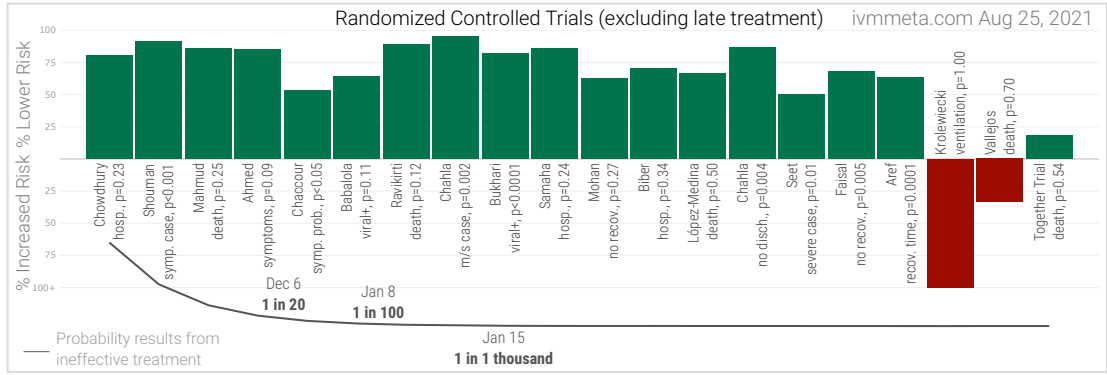
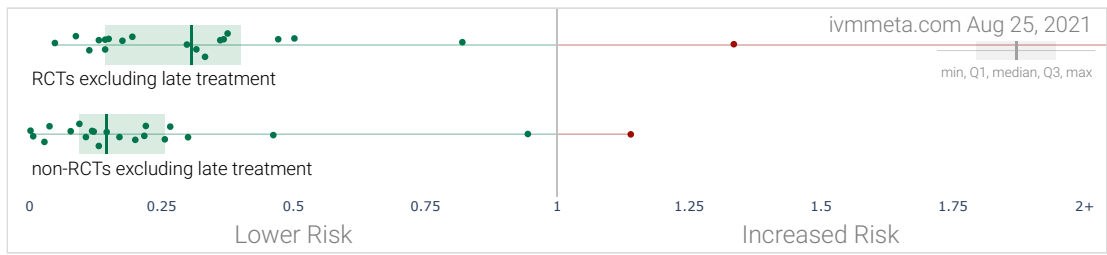


Figure 19. RCTs excluding late treatment.

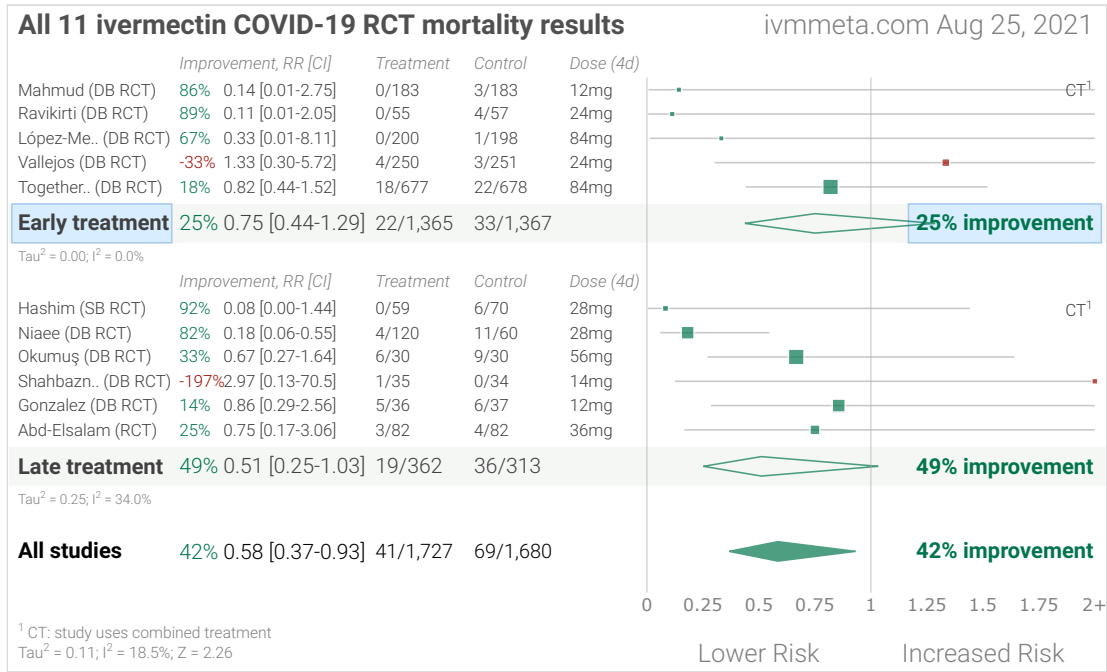


Figure 18. Random effects meta-analysis for Randomized Controlled Trial mortality results only.

| Treatment time | Number of studies reporting positive effects | Total number of studies | Percentage of studies reporting positive effects | Probability of an equal or greater percentage of positive results from an ineffective treatment | Random effects meta-analysis results |
|---|--|-------------------------|--|---|---|
| Randomized Controlled Trials | 27 | 31 | 87.1% | 1 in 59 thousand | 58% improvement RR 0.42 [0.30-0.58] p < 0.0001 |
| Randomized Controlled Trials (excluding late treatment) | 18 | 20 | 90.0% | 1 in 5 thousand | 69% improvement RR 0.31 [0.20-0.48] p < 0.0001 |

Table 2. Summary of RCT results.

Exclusions

To avoid bias in the selection of studies, we include all studies in the main analysis. Here we show the results after excluding studies with critical issues likely to alter results, non-standard studies, and studies where very minimal detail is currently available. Our bias evaluation is based on full 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 may underemphasize serious issues not captured in the checklists, and overemphasize issues unlikely to alter outcomes in specific cases (for example, lack of blinding for an objective mortality outcome, or certain specifics of randomization with a very large effect size). However, these approaches can be very high quality when well done, especially when the authors carefully review each study in detail [Bryant].

[Soto-Becerra] is a database analysis covering anyone with ICD-10 COVID-19 codes, which includes asymptomatic PCR+ patients. Therefore many patients in the control group are likely asymptomatic with regards to SARS-CoV-2, but in the hospital for another reason. For those that had symptomatic COVID-19, there is also likely significant confounding by indication. KM curves show that the treatment groups were in more serious condition, with more than the total excess mortality at 30 days occurring on day 1. All treatments are worse than the control group at 30 days, while at the latest followup all treatments show lower mortality than control. The machine learning system used also appears over-parameterized and likely to result in significant overfitting and inaccurate results. There is also no real control group in this study - patients receiving the treatments after 48 hours were put in the control group. Authors also state that outcomes within 24 hours were excluded, however the KM curves show significant mortality at day 1 (only for the treatment groups). Several protocol violations have also been reported in this study [Yim]. Note that this study provides both 30 day mortality and weighted KM curves up to day 43 for ivermectin, we use the day 43 results as per our protocol.

[López-Medina] has many issues. The primary outcome was changed mid-trial from clinical deterioration to complete resolution of symptoms including "not hospitalized and no limitation of activities" as a negative outcome. Critically, temporary side effects of a successful treatment may be considered as a negative outcome, which could result in falsely concluding that the treatment is not effective. Such an outcome is also not very meaningful in terms of assessing how treatment affects the incidence of serious outcomes. With the low risk patient population in this study, there is

also little room for improvement - 58% recovered within the first 2 days to "not hospitalized and no limitation of activities" or better. There was only one death (in the control arm). This study also gave ivermectin to the control arm for 38 patients and it is unknown if the full extent of the error was identified, or if there were additional undiscovered errors. The side effect data reported in this trial raises major concerns, with more side effects reported in the placebo arm, suggesting that more placebo patients may have received treatment. Ivermectin was widely used in the population and available OTC at the time of the study. The study protocol allows other treatments but does not report on usage. The name of the study drug was concealed by referring to it as "D11AX22". The presentation of this study also appears to be significantly biased. While all outcomes show a benefit for ivermectin, the abstract fails to mention that much larger benefits are seen for serious outcomes, including the original primary outcome, and that the reason for not reaching statistical significance is the low number of events in a low risk population where most recover quickly without treatment.

[Shahbaznejad] had only one death that occurred in a patient that was critically ill at the time of admission and died within the first 24 hours.

[Vallejos] reports prophylaxis results, however only very minimal details are currently available in a news report. We include these results for additional confirmation of the efficacy observed in other trials, however this study is excluded here. *[Hellwig]* analyze African countries and COVID-19 cases in October 2020 as a function of whether widespread prophylactic use of ivermectin is used for parasitic infections. *[Tanioka]* perform a similar analysis for COVID-19 mortality in January 2021. These studies are excluded because they are not clinical trials. *[Galan]* perform an RCT comparing ivermectin and other treatments with very late stage severe condition hospitalized patients, not showing significant differences between the treatments. Authors were unable to add a control arm due to ethical issues. The closest control comparison we could find is *[Baqui]*, which shows 43% hospital mortality in the northern region of Brazil where the study was performed, from which we can estimate the mortality with ivermectin in this study as 47% lower, RR 0.53. Further, the study is restricted to more severe cases, hence the expected mortality, and therefore the benefit of treatment, may be higher. *[Kishoria]* restrict inclusion to patients that did not respond to standard treatment, provide no details on the time of the discharge status, and there are very large unadjusted differences in the groups, with over twice as many patients in the ivermectin group with age >40, and all patients over 60 in the ivermectin group.

Summarizing, the studies excluded are as follows, and the resulting forest plot is shown in Figure 20.

[Ahsan], unadjusted results with no group details.

[Carvallo], minimal details of groups provided.

[Elavarasi], unadjusted results with no group details.

[Hazan], study uses a synthetic control arm.

[Hellwig], not a typical trial, analysis of African countries that used or did not use ivermectin prophylaxis for parasitic infections.

[Kishoria], excessive unadjusted differences between groups.

[López-Medina], strong evidence of patients in the control group self-medicating, ivermectin widely used in the population at that time, and the study drug identity was concealed by using the name D11AX22.

[Roy], no serious outcomes reported and fast recovery in treatment and control groups, there is little room for a treatment to improve results.

[Soto-Becerra], substantial unadjusted confounding by indication likely, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.

[Tanioka], not a typical trial, analysis of African countries that used or did not use ivermectin prophylaxis for parasitic infections.

[Together Trial], preliminary report with minimal details.

[Vallejos], detail too minimal.

All 51 ivermectin COVID-19 studies with exclusions

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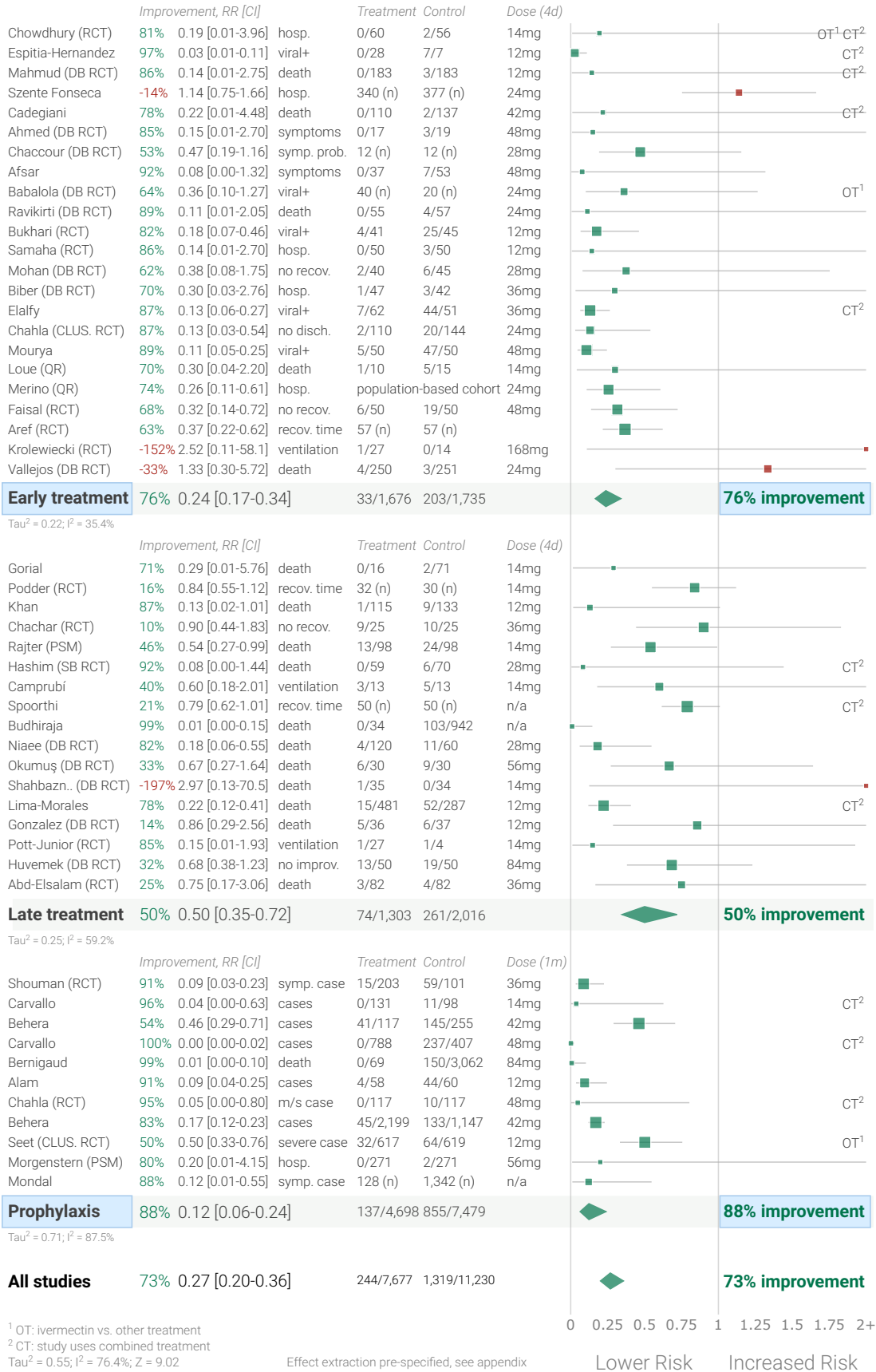


Figure 20. Random effects meta-analysis excluding studies with significant issues. Effect extraction is pre-specified, using the most serious outcome reported, see the [appendix](#) for details.

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. Figure 21 shows an example where efficacy declines as a function of treatment delay. Other medications might be beneficial for late stage complications, while early use may not be effective or 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].

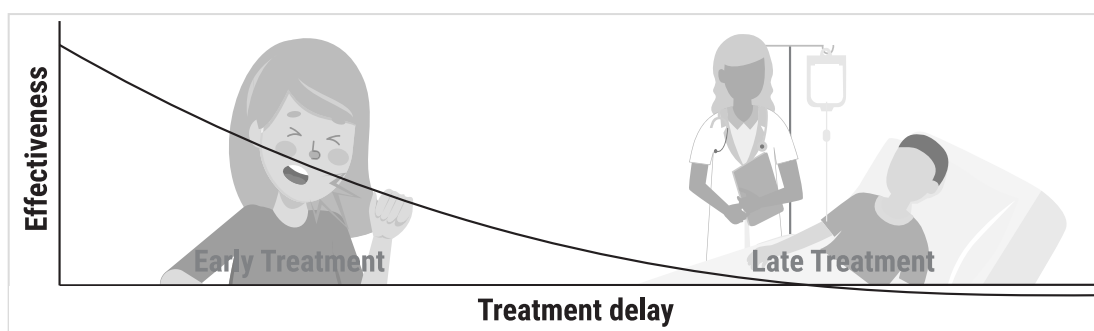


Figure 21. Effectiveness may depend critically on treatment delay.

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

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

Variants. There are thousands of different variants of SARS-CoV-2 and efficacy may depend critically on the distribution of variants encountered by the patients in a study.

Regimen. Effectiveness may depend strongly on the dosage and treatment regimen. Higher dosages have been found to be more successful for ivermectin [Hill]. Method of administration may also be critical. [Guzzo] show that the plasma concentration of ivermectin is much higher when administered with food (Figure 22: geometric mean AUC 2.6 times higher). Many ivermectin studies specify fasting, or they do not specify administration. Fasting administration is expected to reduce effectiveness for COVID-19 due to lower plasma and tissue concentrations. Note that this is different to anthelmintic use in the gastrointestinal tract where fasting is recommended.

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

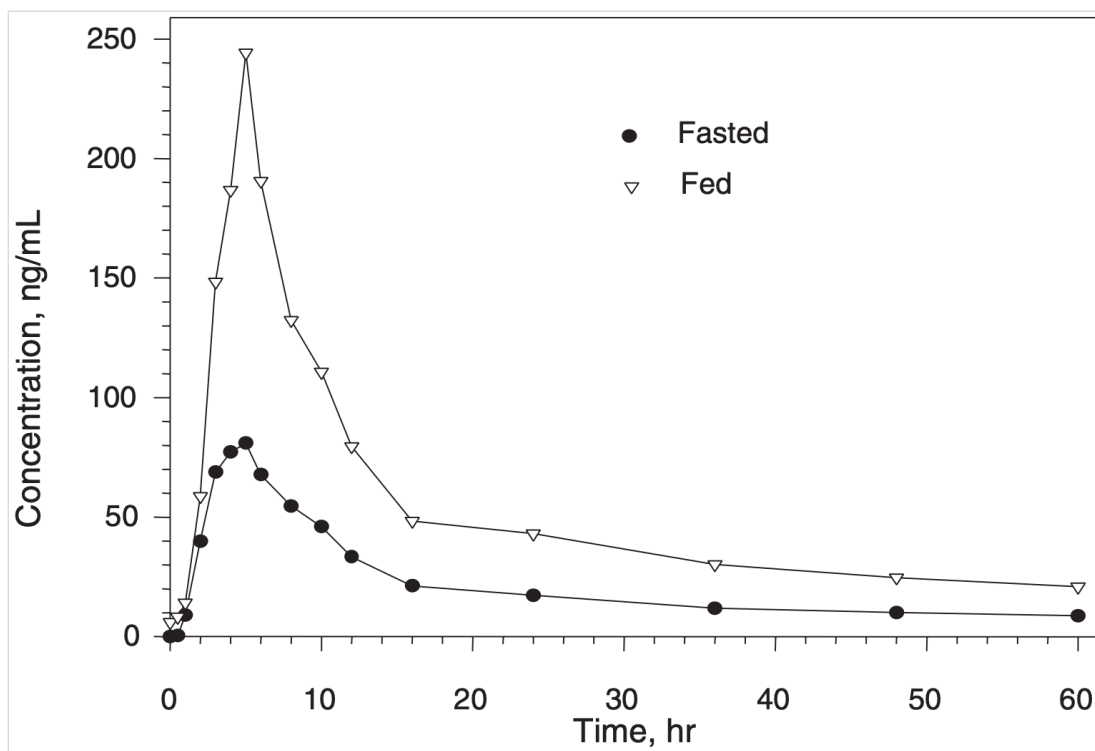


Figure 22. Mean plasma concentration (ng/ml) profiles of ivermectin following single oral doses of 30mg (fed and fasted administration), from [Guzzo].

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 the treatment may be very effective when used earlier.

In general, by combining heterogeneous studies, as all meta analyses do, we run the risk of obscuring an effect by including studies where the treatment is less effective, not effective, or harmful.

When including studies where a treatment is less effective we expect the estimated effect size to be lower than that for the optimal case. We do not *a priori* expect that pooling all studies will create a positive result for an effective treatment. Looking at all studies is valuable for providing an overview of all research, and important to avoid cherry-picking, but the resulting estimate does not apply to specific cases such as early treatment in high-risk populations.

Ivermectin studies vary widely in all the factors above, which makes the consistently positive results even more remarkable. A failure to detect an association after combining heterogeneous studies does not mean the treatment is not effective (it may only work in certain cases), however the reverse is not true – an identified association is valid, although the magnitude of the effect may be larger for more optimal cases, and lower for less optimal cases. As above, the probability that an ineffective treatment generated results as positive as the 63 studies to date is estimated to be 1 in 1 trillion. This result benefits from the fact that ivermectin shows some degree of efficacy for COVID-

19 in a wide variety of cases. It also likely benefits from the fact that relatively few ivermectin trials to date have been designed in a way that favors poor results. However, more trials designed in this way are expected, for example the TOGETHER trial is testing ivermectin in locations known to have a high degree of self-medication and using low doses compared to current clinical recommendations as updated for current variants. As with a companion trial, this trial may also include very low-risk patients, include relatively late treatment while identifying as an early treatment trial, and use an active placebo (vitamin C). While we present results for all studies in this paper, the individual outcome and treatment time analyses are more relevant for specific use cases.

Discussion

Publication bias. Publishing is often biased towards positive results, which we would need to adjust for when analyzing the percentage of positive results. For ivermectin, there is currently not enough data to evaluate publication bias with high confidence. One method to evaluate bias is to compare prospective vs. retrospective studies. Prospective studies are 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 23 shows a scatter plot of results for prospective and retrospective studies. The median effect size for prospective studies is 70% improvement, compared to 76% for retrospective studies, showing no significant difference. [Bryant] also perform a funnel plot analysis, which they found did not suggest evidence of publication bias.

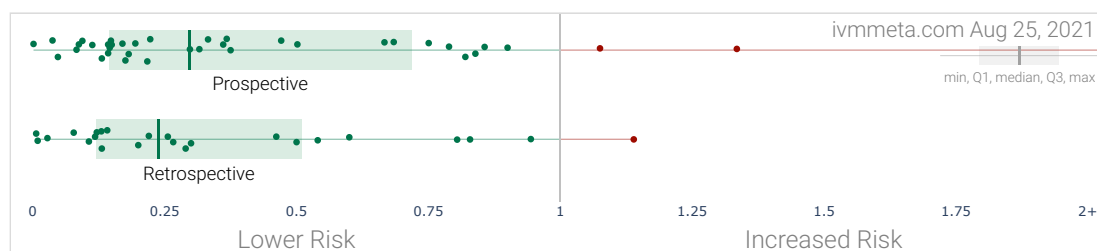


Figure 23. Prospective vs. retrospective studies.

News coverage of ivermectin studies is extremely biased. Only one study to date has received significant press coverage in western media [López-Medina], which is neither the largest or the least biased study, and is one of the two studies with the most critical issues as discussed earlier.

3 of the 63 studies compare against other treatments rather than placebo. Currently ivermectin shows better results than these other treatments, however ivermectin may show greater improvement when compared to placebo. 15 of 63 studies combine treatments, for example ivermectin + doxycycline. The results of ivermectin alone may differ. 4 of 31 RCTs use combined treatment, three with doxycycline, and one with iota-carrageenan. 1 of 63 studies currently have minimal published details available.

Typical meta analyses involve subjective selection criteria, effect extraction rules, and study bias evaluation, which can be used to bias results towards a specific outcome. In order to avoid bias we include all studies and use a pre-specified method to extract results from all studies (we also

present results after exclusions). The results to date are overwhelmingly positive, very consistent, and very insensitive to potential selection criteria, effect extraction rules, and/or bias evaluation.

Additional meta analyses confirming the effectiveness of ivermectin can be found in [Bryant, Hill, Kory, Lawrie]. Figure 24 shows a comparison of mortality results across meta analyses. [Kory] also review epidemiological data and provide suggested treatment regimens.

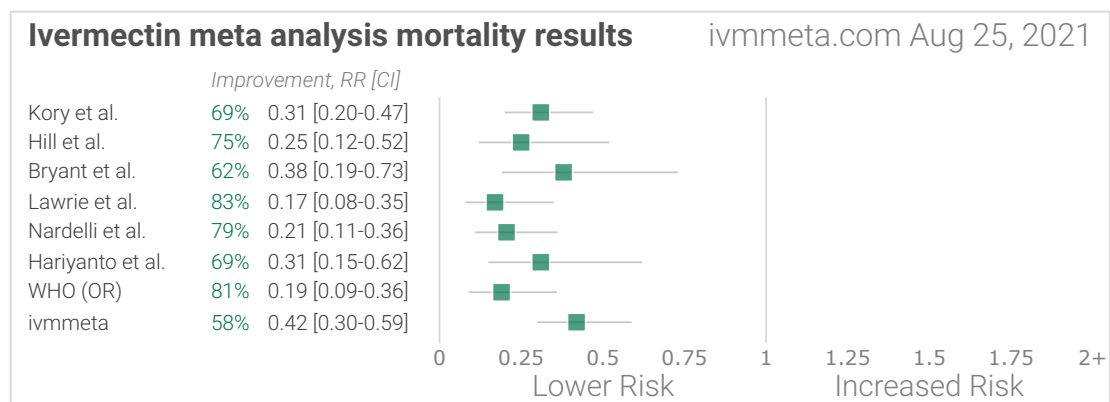


Figure 24. Comparison of mortality results from different meta analyses. OR converted to RR for [Kory, Nardelli]. OR displayed for [WHO]. WHO provides two results, one based on 5 studies and one based on 7, with no explanation for the difference. The result based on 7 studies is shown here, for which the details required to calculate the RR are not provided.

The evidence supporting ivermectin for COVID-19 far exceeds the typical amount of evidence used for the approval of treatments. [Lee] shows that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Table 3 and Table 4 compare the amount of evidence for ivermectin compared to that used for other COVID-19 approvals, and that used by WHO for the approval of ivermectin for scabies and strongyloidiasis. Table 5 compares US CDC recommendations for ibuprofen and ivermectin.

| Indication | Studies | Patients | Status |
|-----------------------------|---------|----------|----------|
| Strongyloidiasis [Kory (B)] | 5 | 591 | Approved |
| Scabies [Kory (B)] | 10 | 852 | Approved |
| COVID-19 | 63 | 26,398 | Pending |
| COVID-19 RCTs | 31 | 6,561 | |

Table 3. WHO ivermectin approval status.

| Medication | Studies | Patients | Improvement | Status |
|-------------------------------|---------|----------|--------------|----------|
| <u>Budesonide (UK)</u> | 1 | 1,779 | 17% | Approved |
| <u>Remdesivir (USA)</u> | 1 | 1,063 | 31% | Approved |
| <u>Casiri/imdevimab (USA)</u> | 1 | 799 | 66% | Approved |
| <i>Ivermectin evidence</i> | 63 | 26,398 | 68% [60-75%] | Pending |

Table 4. Evidence base used for other COVID-19 approvals compared with the ivermectin evidence base.

| | <i>Ibuprofen</i> | <i>Ivermectin (for scabies)</i> | <i>Ivermectin (for COVID-19)</i> |
|-----------------|------------------|---------------------------------|----------------------------------|
| Lives saved | 0 | 0 | >500,000 |
| Deaths per year | ~450 | <1 | <1 |
| CDC recommended | Yes | Yes | No |
| Based on | 0 RCTs | 10 RCTs 852 patients | 31 RCTs 6,561 patients |

Table 5. Comparison of CDC recommendations [Kory (B)].

WHO Analysis

WHO updated their treatment recommendations on 3/30/2021 [WHO]. For ivermectin they reported a mortality odds ratio of 0.19 [0.09-0.36] based on 7 studies with 1,419 patients. They do not specify which trials they included. The report is inconsistent, with a forest plot that only shows 4 studies with mortality results. WHO's recommendation has not been updated for 147 days.

Despite this extremely positive result, they recommended only using ivermectin in clinical trials. The analysis contains many flaws [Kory (C)]:

- Of the 63 studies (31 RCTs), they only included 16.
- They excluded all 14 prophylaxis studies (3 RCTs).
- There was no protocol for data exclusion.
- Trials included in the original UNITAID search protocol [Hill] were excluded.
- They excluded all epidemiological evidence, although WHO has considered such evidence in the past.
- They combine early treatment and late treatment studies and do not provide heterogeneity information. As above, early treatment is more successful, so pooling late treatment studies will obscure the effectiveness of early treatment. They chose not to do subgroup analysis by disease

severity across trials, although treatment delay is clearly a critical factor in COVID-19 treatment, the analysis is easily done (as above), and it is well known that the studies for ivermectin and many other treatments clearly show greater effectiveness for early treatment.

- WHO downgraded the quality of trials compared to the UNITAID systematic review team [Hill] and a separate international expert guideline group that has long worked with the WHO [Bryant].
- They disregarded their own guidelines that stipulate quality assessments should be upgraded when there is evidence of a large magnitude effect (which there is), and when there is evidence of a dose-response relationship (which there is). They claim there is no dose-response relationship, while the UNITAID systematic review team found a clear relationship [Hill].
- Their risk of bias assessments do not match the actual risk of bias in studies. For example they classify [López-Medina] as low risk of bias, however this study has many issues making the results unreliable [Covid Analysis], even prompting an open letter from over 170 physicians concluding that the study is fatally flawed [Open Letter]. [Gonzalez] is also classified as low risk of bias, but is a study with very late stage severe condition high-comorbidity patients. There is a clear treatment delay-response relationship and very late stage treatment is not expected to be as effective as early treatment. Conversely, much higher quality studies were classified as high risk of bias.
- Although WHO's analysis is called a "living guideline", it is rarely updated and very out of date. As of May 14, 2021, four of the missing RCTs are known to WHO and labeled "RCTs pending data extraction" [COVID-NMA]. We added these 4, 4, 2, and one month earlier.
- A single person served as Methods Chair, member of the Guidance Support Collaborator Committee, and member of the Living Systematic Review/NMA team.
- Public statements from people involved in the analysis suggest substantial bias. For example, a co-chair reportedly said that "the data available was sparse and likely based on chance" [Reuters]. As above, the data is comprehensive, and we estimate the probability that an ineffective treatment generated results as positive as observed to be 1 in 1 trillion. The clinical team lead refers to their analysis of ivermectin as "fighting this overuse of unproven therapies ... without evidence of efficacy" [Reuters], despite the extensive evidence of efficacy from the 63 studies by 613 scientists with 26,398 patients. People involved may be more favorable to late stage treatment of COVID-19, for example the co-chair recommended treating severe COVID-19 with remdesivir [Rochweg].

In summary, although WHO's analysis predicts that over 2 million fewer people would be dead if ivermectin was used from early in the pandemic, they recommend against use outside trials. This appears to be based primarily on excluding the majority of the evidence, and by assigning bias estimates that do not match the actual risk of bias in studies.

Use early in the pandemic was proposed by Kitasato University including the co-discoverer of ivermectin, Dr. Satoshi Ōmura. They requested Merck conduct clinical trials of ivermectin for COVID-19 in Japan, because Merck has priority to submit an application for an expansion of ivermectin's indications. Merck declined [Yagisawa].

Merck Analysis

Merck has recommended against ivermectin [Merck], however this recommendation has not been updated for 201 days.

They stated that there is "no scientific basis for a potential therapeutic effect against COVID-19 from pre-clinical studies". This is contradicted by many papers and studies, including [Arévalo, Bello, Choudhury, de Melo, DiNicolantonio, DiNicolantonio (B), Errecalde, Eweas, Francés-Monerris, Heidary, Jans, Jeffreys, Kalfas, Kory, Lehrer, Li, Mody, Mountain Valley MD, Qureshi, Saha, Surnar, Udofia, Wehbe, Yesilbag, Zaidi, Zatlouka].

They state that there is "no meaningful evidence for clinical activity or clinical efficacy in patients with COVID-19 disease". This is contradicted by numerous studies including [Afsar, Alam, Aref, Babalola, Behera, Behera (B), Bernigaud, Budhiraja, Bukhari, Cadegiani, Carvalho (B), Carvalho (C), Chaccour, Chahla, Chahla (B), Chowdhury, Elalfy, Espitia-Hernandez, Faisal, Hashim, Huvemek, Khan, Lima-Morales, Loue, Mahmud, Merino, Mohan, Mondal, Morgenstern, Mourya, Niaee, Okumuş, Ravikirti, Samaha, Seet].

They also claim that there is "a concerning lack of safety data in the majority of studies". Safety analysis is found in [Descotes, Errecalde, Guzzo, Kory, Madrid], and safety data can be found in most studies, including [Abd-Elsalam, Afsar, Ahmed, Aref, Babalola, Behera (B), Bhattacharya, Biber, Bukhari, Camprubí, Carvalho, Chaccour, Chahla (B), Chowdhury, Elalfy, Espitia-Hernandez, Gorial, Hazan, Huvemek, Khan, Kishoria, Krolewiecki, Lima-Morales, Loue, López-Medina, Mahmud, Mohan, Morgenstern, Mourya, Niaee, Okumuş, Pott-Junior, Seet, Shahbaznejad, Shouman, Spoorthi, Szenté Fonseca, Vallejos (B)].

Merck has a number of conflicts of interest:

- Merck has committed to give ivermectin away for free "as much as needed, for as long as needed" in the Mectizan® Donation Program [Merck (B)], to help eliminate river blindness.
- Merck has their own new COVID-19 treatments MK-7110 (formerly CD24Fc) [Adams] and Molnupiravir (MK-4482) [Wikipedia]. Merck has a ~\$1.2B agreement to supply molnupiravir to the US government, if it receives EUA or approval [Khan (B)].
- Ivermectin is off-patent, there are many manufacturers, and Merck is unlikely to be able to compete with low cost manufacturers.
- Promoting the use of low cost off-patent medications compared to new products may be undesirable to some shareholders.
- Japan requested Merck conduct clinical trials early in the pandemic and they declined. Merck may be reluctant to admit this mistake [Yagisawa].

FDA Analysis

The US FDA recommended against ivermectin on March 5, 2021, however they state that "*The FDA has not reviewed data to support use of ivermectin in COVID-19 patients to treat or to prevent COVID-19*". This recommendation has not been updated for 172 days.

The FDA notes that they "*received multiple reports of patients who have required medical support and been hospitalized after self-medicating with ivermectin intended for horses*". The number of reports was 4 [Pfeiffer]. For comparison, acetaminophen overdose results in ~33,000 yearly hospitalizations in the USA (~12,000 unintentional) [Charilaou]. The FDA's recommendation may increase cases of self-medication with animal ivermectin, because it reduces the percentage of prescribing physicians.

They say that "*Ivermectin is not an anti-viral*", however many studies contradict this [Ahmed, Aref, Babalola, Biber, Bukhari, Caly, Chowdhury, Elalfy, Espitia-Hernandez, Khan, Mahmud, Mohan, Mourya, Okumus], including 9 RCTs.

They note that "*some initial research is underway*", however there had been many studies completed and published prior to the FDA recommendation [Afsar, Ahmed, Alam, Babalola, Behera, Bernigaud, Biber, Budhiraja, Bukhari, Cadebiani, Camprubí, Carvallo, Chaccour, Chachar, Chahla (B), Chowdhury, Elalfy, Espitia-Hernandez, Gonzalez, Gorial, Hashim, Hellwig, Khan, Lima-Morales, López-Medina, Mahmud, Mohan, Niaee, Okumus, Podder, Rajter, Ravikirti, Samaha, Shouman, Spoorthi], including 19 RCTs.

Conclusion

Ivermectin is an effective treatment for COVID-19. The probability that an ineffective treatment generated results as positive as the 63 studies to date is estimated to be 1 in 1 trillion. As expected for an effective treatment, early treatment is more successful, with an estimated reduction of 72% in the effect measured using random effects meta-analysis (RR 0.28 [0.18-0.45]). 37% and 96% lower mortality is observed for early treatment and prophylaxis (RR 0.63 [0.38-1.04] and 0.04 [0.00-0.59]). Statistically significant improvements are seen for mortality, hospitalization, recovery, cases, and viral clearance. The consistency of positive results across a wide variety of heterogeneous studies is remarkable, with 92% of the 63 studies reporting positive effects (27 statistically significant in isolation).

Responses

Twitter personality response. An influential Twitter personality, epidemiologist, podcaster, and journalist has made a number of incorrect, misleading, hyperbolic, and unsupported statements, including for example:

- that excluding Elgazzar et al. completely changes the results (excluding 1 of 64 studies has very little effect, and the exclusion actually improves the treatment delay-response relationship)
- making basic errors suggesting very superficial reading of studies, for example claiming the RR in Szente Fonseca is the risk of being treated

- making basic errors suggesting very superficial reading of this paper, for example claiming that a result for prophylaxis studies is based on the number of patients from all studies
- equating a positive effect that is not statistically significant at a specific level with "no effect", a misunderstanding of statistics
- equating a high degree of COVID-19 in a country partially adopting a treatment with a lack of efficacy, disregarding obvious confounding such as heavily affected areas being more likely to adopt treatment (analysis of results in regions or time periods adopting treatment, while not equivalent to controlled studies, is more informative and shows efficacy [*Chamie-Quintero, Chamie-Quintero (B), Merino, Ontai*])
- confusing heterogeneity due to dose, treatment delay, etc. and due to bias
- disregarding treatment delay to dilute or obscure effects by including late treatment (author has also used this method with other treatments)
- disregarding the existence of specific outcome analyses, RCT analysis, and exclusion-based sensitivity analysis
- misunderstanding funnel plot analysis and explanations other than selective reporting (and providing no evidence of unreported negative studies, while there is substantial evidence of difficulty publishing positive studies [*Jerusalem Post*])
- suggesting that it is impossible to combine evidence from mortality and hospitalization (for example), but combining late treatment and early treatment in order to obscure efficacy (if a treatment reduces disease severity requiring hospitalization, reduced mortality in at-risk populations is expected, whereas lack of efficacy several days after onset can not be extrapolated to early treatment — treatments for a viral infection are often less effective when delayed)
- making serious claims about individual studies without contacting authors (for example claiming patients were excluded for reaching the endpoint too quickly, whereas authors report exclusions due to baseline negative status)
- suggesting that a specific symptom such as cough should be used (they would prefer a less positive result for the study)
- suggesting that viral load is more important than symptomatic results
- suggesting that mortality should be used in populations with zero mortality (for low-risk populations with no mortality, reduction in mortality is not possible, this does not mean a reduction in hospitalization, for example, is not valuable)
- suggesting that, for example, in a study of viral load where all patients recover, it is not valuable if treated patients recover faster (or are less likely to transmit the virus to others)
- suggesting that study selected outcomes should have priority rather than using a consistent pre-specified protocol, disregarding the added bias and the fact that this actually improves results for ivermectin (for example the very small event count negative serious outcomes in Krolewiecki and Vallejos would no longer have priority).

We note that this personality has taken a public position against early treatments for COVID-19 since at least July 2020. Given this longstanding and influential negative position, they may tend to view information with a negative filter and confirmation bias, and may be reluctant to admit errors. They acknowledge not having read all of the studies (and appear to have very superficially read others). They submitted zero feedback to us, suggesting that they know their comments are incorrect or that they have a motivation other than correcting errors. Author claims that they could

not contact us, however there are over 50 feedback links throughout this article. We also note that the author is not open to critical feedback and routinely blocks Twitter users correcting their mistakes or expressing anything critical on their feed.

Meta analysis should not combine heterogeneous studies. All meta analyses combine heterogeneous studies, because all studies differ in one or more ways, including patient demographics, treatment delay distribution, effect measured, SARS-CoV-2 variants, and treatment regimens (note that this is different to heterogeneity caused by bias). Combining heterogeneous studies may obscure efficacy - for example if treatment within 24 hours is twice as effective as treatment within 48 hours and we include studies with later treatment; or if a treatment is effective at reducing mortality but has no effect on viral clearance and we include viral clearance studies. Including studies that are further from the optimal treatment situation will reduce the observed effect size. This can be seen in the treatment delay analysis - late treatment is less effective and including late treatment studies lowers the effect size. For any negative meta analysis, we must consider if the treatment is effective but only in a subset of the situations covered by the studies (or a situation not covered by any study, for example few treatments have studies with a treatment delay ≤ 24 hours).

Inconclusive meta analyses. [Popp, Roman] provide meta analyses that show positive effects without reaching statistical significance. These analyses are highly flawed as detailed in the references. The primary methods used to avoid reaching statistical significance is exclusion of the majority of the evidence base, and division of the remaining subset. It is invalid to use partial evidence from a small subset of studies and then claim there is not enough evidence. Given the increased mortality, morbidity, and collateral damage, and the increased risk of COVID-19 being endemic, negative recommendations based on positive but inconclusive small subsets of data are unsupportable.

Early/late vs. mild/moderate/severe. Some analyses classify treatment based on early/late administration (as we do here), while others distinguish between mild/moderate/severe cases. We note that 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.

In Vitro evidence on required concentration. Some people claim that [Caly] shows that therapeutic concentrations are not easily reached in humans. This is incorrect. The authors explain why their *in vitro* study cannot be used to determine the effective dose *in vivo*, and state that the concentration required is very unlikely to be an issue [Wagstaff]. The study used monkey kidney cells (the only choice at the time of the experiments), which lack adaptive immune responses and do not produce interferon. Authors also note that ivermectin accumulates in lung and other tissues, that subsequent experiments with lung cells show many times greater concentrations, and that the average lung concentration shown in modeling studies exceeds the effective level shown in their research. Authors note that ivermectin works with the immune system and a 1:1 ratio of drug to virus is unlikely to be required. In [Bray], author reply that "ivermectin's key direct target in mammalian cells is a not a viral component, but a host protein important in intracellular transport; the fact that it is a host-directed agent (HDA) is almost certainly the basis of its broad-spectrum activity against a number of different RNA viruses *in vitro*. The way a HDA can reduce viral load is by inhibiting a key cellular process that the virus hijacks to enhance infection by suppressing the host antiviral response. Reducing viral load by even a modest amount by using a HDA at low dose early in infection can be the key to enabling the body's immune system to begin to mount the full antiviral response before the infection takes control." In further research, authors note that they find efficacy for prophylactic use, and that smaller repeated doses are more effective than a single larger dose [Wagstaff].

Revisions

This paper is data driven, all graphs and numbers are dynamically generated. We will update the paper as new studies are released or with any corrections. Please submit updates and corrections at <https://ivmmeta.com/>.

12/2: We added [*Ahmed*].

12/7: We added [*Chaccour*].

12/11: We added [*Soto-Becerra*].

12/16: We added [*Afsar*].

12/17: We added [*Alam*].

12/26: We added [*Carvalho (B), Vallejos*].

12/27: We added the total number of authors and patients.

12/29: We added meta analysis excluding late treatment.

12/31: We added additional details about the studies in the appendix.

1/2: We added dosage information and we added the number of patients to the forest plots.

1/5: We added direct links to the study details in the forest plots.

1/6: We added [*Babalola*].

1/7: We added direct links to the study details in the chronological plots.

1/9: We added [*Ravikirti*]. Due to the much larger size of the control group in [*Bernigaud*], we limited the size of the control group to be the same as the treatment group for calculation of the total number of patients.

1/10: We put all prophylaxis studies in a single group.

1/11: We added [*Chahla (B)*].

1/12: We added [*Okumuş*].

1/15: We added the effect measured for each study in the forest plots.

1/16: We moved the analysis with exclusions to the main text, and added additional commentary.

1/17: We added [*Bukhari*].

1/19: We added [*Samaha, Shahbaznejad*]. [*Chaccour*] was updated to the journal version of the paper.

1/25: We updated [*Vallejos*] with the recently released results.

1/26: We updated [*Shouman*] with the journal version of the article.

2/2: We added [*Mohan*].

2/5: We updated [*Bukhari*] to the preprint.

2/10: We added [*Lima-Morales*].

2/11: We added more details on the analysis of prospective vs. retrospective studies.

2/12: We added [*Biber*].

2/14: We added analysis restricted to COVID-19 case outcomes, and we added additional results in the abstract.

2/15: We added [*Behera (B)*].

2/16: We updated [*Behera*] to the journal version of the paper.

2/17: We added [*Elalfy*], and we added analysis restricted to viral clearance outcomes, and mortality results restricted to RCTs.

2/18: We updated [*Babalola*] to the journal version of the paper.

2/23: We added [*Gonzalez*].

2/24: We added a comparison of the evidence base and WHO approval status for the use of ivermectin with scabies and COVID-19. We updated [*Okumuş*] with the Research Square preprint.

2/27: We added analysis restricted to peer reviewed studies.

3/2: We updated [*Vallejos*] with the latest results [*Vallejos (C)*].

3/3: We updated the graphs to indicate the time period for the dosage column, now showing the dosage over one month for prophylaxis and over four days for other studies.

3/4: We added [*López-Medina*], and we added more information in the abstract.

3/5: We added discussion of pooled effects (we show both pooled effects and individual outcome results).

3/6: We added [*Chowdhury*] and we identify studies that compare with another treatment.

3/10: We added [*Pott-Junior*].

3/12: We added [*Bryant, Roy*].

3/17: We added [*Nardelli*].

3/25: We added [*Huvmek*].

3/26: We added [*Tanioka*].

3/28: We highlighted and added discussion for studies that use combined treatments.

3/30: We added [Chahla].

3/31: We updated [Chahla (B)] to the preprint.

4/4: We added event counts to the forest plots.

4/5: We added [Mourya].

4/7: We identified studies where minimal detail is currently available in the forest plots.

4/9: We corrected a duplicate entry for [Bukhari].

4/10: We added [Kishoria].

4/14: We added [Seet].

4/16: We added [Morgenstern].

4/18: We updated [Morgenstern] to the preprint.

4/25: We updated [Biber] to the latest results reported at the International Ivermectin for Covid Conference.

4/26: We added notes on heterogeneity.

4/27: We added analysis restricted to hospitalization results and a comparison with the evidence base used in the approval of other COVID-19 treatments.

4/28: We added the WHO meta analysis results for comparison.

4/30: We added analysis of the WHO meta analysis and updated [Kory] to the journal version.

5/4: We added [Loue].

5/5: We previously limited the size of the control group in [Bernigaud] to be the same as the treatment group for calculation of the total number of patients. This is now also reflected and noted in the forest plots.

5/5: We updated [Okumuş] to the journal paper.

5/6: We updated discussion based on peer review including discussion of heterogeneity, exclusion based sensitivity analysis, and search criteria.

5/6: We added mechanical ventilation and ICU admission analysis.

5/6: We added a comparison of CDC recommendations.

5/6: We updated [Chahla] to the Research Square preprint.

5/7: We updated [Shahbaznejad] to the journal version, which includes additional outcomes not reported earlier.

5/8: We added [Merino].

5/10: We added additional information in the abstract.

5/10: We added [*Faisal*].

5/13: We updated [*Mahmud*] to the journal version.

5/15: We updated the discussion of the WHO analysis.

5/17: We added [*Szente Fonseca*].

5/18: We added analysis of Merck's recommendation.

5/26: [*Samaha*] was updated to the journal version.

5/31: [*Biber*] was updated to the preprint.

6/2: We added [*Abd-Elsalam*].

6/5: We added [*Ahsan*].

6/7: We added [*Hariyanto*].

6/15: We added [*Aref*].

6/18: We added [*Krolewiecki*].

6/19: [*Gonzalez*] was incorrectly included in the peer-reviewed analysis.

6/19: We updated [*Bryant*] to the journal version.

6/21: We added more information to the abstract.

7/2: We updated [*Niaee*] to the journal version.

7/3: We added [*Vallejos (B)*].

7/6: We previously limited the size of the control group for [*Bernigaud*] when calculating the total number of patients, however this was confusing for many people that did not read the details. We now show the original counts and note the larger size of the control group in the text.

7/8: We updated [*Cadegiani*] to the journal version.

7/9: We added [*Hazan*].

7/15: Elgazzar et al. was retracted and has been removed.

7/16: We updated [*Ravikirti*] with the journal version of the article.

7/20: We updated [*Hashim*] with the journal version of the article.

7/29: We added discussion in the responses section.

7/31: We added discussion in the responses section related to *in vitro* evidence and therapeutic concentrations.

8/2: We added analysis restricted to serious outcomes and analysis restricted to recovery, and we added discussion in the [responses](#) section.

8/3: We added discussion in the [responses](#) section.

8/4: We added discussion of the FDA recommendation.

8/5: We added [*Mondal*].

8/6: We updated [*Behera (B)*] with the journal version of the article.

8/8: We updated discussion in the responses.

8/12: We added [*Elavarasi, Together Trial*].

8/15: We updated discussion and made the abstract more concise.

8/16: We updated [*Together Trial*] with event counts.

Appendix 1. Methods and Study Results

We performed ongoing searches of PubMed, medRxiv, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Collabovid, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19ivermectin.com, which regularly receives submissions of studies upon publication. Search terms were ivermectin and COVID-19 or SARS-CoV-2, or simply ivermectin. Automated searches are performed every hour with notifications of new matches. The broad search terms result in a large volume of new studies on a daily basis which are reviewed for inclusion. All studies regarding the use of ivermectin for COVID-19 that report a comparison with a control group are included in the main analysis. Sensitivity analysis is performed, excluding studies with critical 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 calculations for that study. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days are used. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms were not used (the next most serious outcome is used – no studies were excluded). For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcome is considered more important than PCR testing status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available (after most or all patients have recovered there is no room for an effective treatment to do better). When results provide an odds ratio, we computed the relative risk when possible, or converted to a relative risk according to [*Zhang*]. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported including propensity score matching (PSM), the PSM results are used. 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 all expressed with RR < 1.0 suggesting effectiveness. Most results are the relative risk of something negative. If studies report relative times, results are expressed as the ratio of the time for the ivermectin group versus the time for the control group. Calculations are done in Python (3.9.6) with scipy (1.6.2), pythonmeta (1.23), numpy (1.21.1), statsmodels (0.12.2), and plotly (4.14.3).

The 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). The forest plots show simplified dosages for comparison, these are the total dose in the first four days for treatment, and the monthly dose for prophylaxis, for a 70kg person. For full dosage details see below.

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

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment, and treatment started within 5 days after the onset of symptoms, although 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*].

Note that the size of the control group in [*Bernigaud*] is significantly larger than the treatment group. We previously limited the size to be the same as that of the treatment group for calculation of the number of patients, however this was confusing to many people that did not read the details.

A summary of study results is below. Please submit updates and corrections at <https://ivmmeta.com/>.

Early treatment

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

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| <p>[<i>Afsar</i>], 12/15/2020, retrospective, Pakistan, South Asia, preprint, 6 authors, dosage 12mg days 1-6.</p> | <p>risk of fever at day 14, 92.2% lower, RR 0.08, $p = 0.04$, treatment 0 of 37 (0.0%), control 7 of 53 (13.2%), continuity correction due to zero event (with reciprocal of the contrasting arm).</p> |
| <p>[<i>Ahmed</i>], 12/2/2020, Double Blind Randomized Controlled Trial, Bangladesh, South Asia, peer-reviewed, mean age 42.0, 15 authors, dosage 12mg days 1-5, ivermectin + doxycycline group took only a single dose of ivermectin.</p> | <p>risk of unresolved symptoms, 85.0% lower, RR 0.15, $p = 0.09$, treatment 0 of 17 (0.0%), control 3 of 19 (15.8%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 7 fever ivermectin.</p> |
| | <p>risk of unresolved symptoms, 62.7% lower, RR 0.37, $p = 0.35$, treatment 1 of 17 (5.9%), control 3 of 19 (15.8%), day 7 fever ivermectin + doxycycline.</p> |

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| | <p>risk of no virological cure, 42.5% lower, RR 0.58, $p = 0.01$, treatment 11 of 22 (50.0%), control 20 of 23 (87.0%), day 7 ivermectin.</p> |
| | <p>risk of no virological cure, 20.0% lower, RR 0.80, $p = 0.28$, treatment 16 of 23 (69.6%), control 20 of 23 (87.0%), day 7 ivermectin + doxycycline.</p> |
| | <p>risk of no virological cure, 62.7% lower, RR 0.37, $p = 0.02$, treatment 5 of 22 (22.7%), control 14 of 23 (60.9%), day 14 ivermectin.</p> |
| | <p>risk of no virological cure, 35.7% lower, RR 0.64, $p = 0.24$, treatment 9 of 23 (39.1%), control 14 of 23 (60.9%), day 14 ivermectin + doxycycline.</p> |
| | <p>time to viral-, 23.6% lower, relative time 0.76, $p = 0.02$, treatment 22, control 23, ivermectin.</p> |
| | <p>time to viral-, 9.4% lower, relative time 0.91, $p = 0.27$, treatment 23, control 23, ivermectin + doxycycline.</p> |
| | <p>hospitalization time, 1.0% lower, relative time 0.99, ivermectin.</p> |
| | <p>hospitalization time, 4.1% higher, relative time 1.04, ivermectin + doxycycline.</p> |
| <p>[Aref], 6/15/2021, Randomized Controlled Trial, Egypt, Africa, peer-reviewed, 7 authors.</p> | <p>relative duration of fever, 63.2% lower, relative time 0.37, $p < 0.001$, treatment 57, control 57.</p> |
| | <p>risk of no virological cure, 78.6% lower, RR 0.21, $p = 0.004$, treatment 3 of 57 (5.3%), control 14 of 57 (24.6%).</p> |
| <p>[Babalola], 1/6/2021, Double Blind Randomized Controlled Trial, Nigeria, Africa, peer-reviewed, baseline oxygen requirements 8.3%, 10 authors, dosage 12mg or 6mg q84h for two weeks, this trial compares with another treatment - results may be better when compared to placebo.</p> | <p>adjusted risk of viral+ at day 5, 63.9% lower, RR 0.36, $p = 0.11$, treatment 40, control 20, adjusted per study.</p> |
| | <p>risk of no virological cure, 58.0% lower, RR 0.42, $p = 0.01$, treatment 20, control 20, 12mg - Cox proportional hazard model.</p> |
| | <p>risk of no virological cure, 40.5% lower, RR 0.60, $p = 0.12$, treatment 20, control 20, 6mg - Cox proportional hazard model.</p> |
| | <p>time to viral-, 49.2% lower, relative time 0.51,</p> |

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| | treatment 20, control 20, 12mg. |
| | time to viral-, 34.4% lower, relative time 0.66, treatment 20, control 20, 6mg. |
| <p>[Biber], 2/12/2021, Double Blind Randomized Controlled Trial, Israel, Middle East, preprint, 10 authors, dosage 12mg days 1-3, 15mg for patients >= 70kg.</p> | <p>risk of hospitalization, 70.2% lower, RR 0.30, $p = 0.34$, treatment 1 of 47 (2.1%), control 3 of 42 (7.1%).</p> |
| | <p>risk of no virological cure, 44.8% lower, RR 0.55, $p = 0.04$, treatment 13 of 47 (27.7%), control 21 of 42 (50.0%), adjusted per study, odds ratio converted to relative risk, multivariable logistic regression, day 6, Ct>30.</p> |
| | <p>risk of no virological cure, 70.2% lower, RR 0.30, $p = 0.14$, treatment 2 of 47 (4.3%), control 6 of 42 (14.3%), day 10, non-infectious samples (Ct>30 or non-viable culture).</p> |
| | <p>risk of no virological cure, 82.1% lower, RR 0.18, $p = 0.01$, treatment 2 of 47 (4.3%), control 10 of 42 (23.8%), day 8, non-infectious samples (Ct>30 or non-viable culture).</p> |
| | <p>risk of no virological cure, 75.6% lower, RR 0.24, $p = 0.02$, treatment 3 of 47 (6.4%), control 11 of 42 (26.2%), day 6, non-infectious samples (Ct>30 or non-viable culture).</p> |
| | <p>risk of no virological cure, 65.1% lower, RR 0.35, $p = 0.05$, treatment 4 of 28 (14.3%), control 9 of 22 (40.9%), day 4, non-infectious samples (Ct>30 or non-viable culture).</p> |
| | <p>risk of no virological cure, 51.9% lower, RR 0.48, $p = 0.08$, treatment 7 of 47 (14.9%), control 13 of 42 (31.0%), day 10, Ct>30.</p> |
| | <p>risk of no virological cure, 57.9% lower, RR 0.42, $p = 0.02$, treatment 8 of 47 (17.0%), control 17 of 42 (40.5%), day 8, Ct>30.</p> |
| | <p>risk of no virological cure, 44.7% lower, RR 0.55, $p = 0.05$, treatment 13 of 47 (27.7%), control 21 of 42 (50.0%), day 6, Ct>30.</p> |
| | <p>risk of no virological cure, 31.9% lower, RR 0.68, $p = 0.16$, treatment 13 of 28 (46.4%), control 15 of</p> |

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| | 22 (68.2%), day 4, Ct>30. |
| [Bukhari], 1/16/2021, Randomized Controlled Trial, Pakistan, South Asia, preprint, 10 authors, dosage 12mg single dose. | risk of no virological cure, 82.4% lower, RR 0.18, $p < 0.001$, treatment 4 of 41 (9.8%), control 25 of 45 (55.6%), day 7. |
| | risk of no virological cure, 38.7% lower, RR 0.61, $p < 0.001$, treatment 24 of 41 (58.5%), control 43 of 45 (95.6%), day 3. |
| [Cadejani], 11/4/2020, prospective, Brazil, South America, peer-reviewed, 4 authors, dosage 200µg/kg days 1-3, this trial uses multiple treatments in the treatment arm (combined with AZ, nitazoxanide (82), HCQ (22), spironolactone (66), dutasteride (4)) - results of individual treatments may vary. | risk of death, 78.3% lower, RR 0.22, $p = 0.50$, treatment 0 of 110 (0.0%), control 2 of 137 (1.5%), continuity correction due to zero event (with reciprocal of the contrasting arm), control group 1. |
| | risk of mechanical ventilation, 94.2% lower, RR 0.06, $p = 0.005$, treatment 0 of 110 (0.0%), control 9 of 137 (6.6%), continuity correction due to zero event (with reciprocal of the contrasting arm), control group 1. |
| | risk of hospitalization, 98.0% lower, RR 0.02, $p < 0.001$, treatment 0 of 110 (0.0%), control 27 of 137 (19.7%), continuity correction due to zero event (with reciprocal of the contrasting arm), control group 1. |
| [Carvalho], 9/15/2020, prospective, Argentina, South America, peer-reviewed, mean age 55.7, 3 authors, dosage 36mg days 1, 8, dose varied depending on patient condition - mild 24mg, moderate 36mg, severe 48mg, this trial uses multiple treatments in the treatment arm (combined with dexamethasone, enoxaparin, and aspirin) - results of individual treatments may vary. | moderate/severe patients, 85.4% lower, RR 0.15, $p = 0.08$, treatment 1 of 32 (3.1%), control 3 of 14 (21.4%), the only treatment death was a patient already in the ICU before treatment. |
| [Chaccour], 12/7/2020, Double Blind Randomized Controlled Trial, Spain, Europe, peer-reviewed, 23 authors, dosage 400µg/kg single dose. | symptom probability, 52.9% lower, RR 0.47, $p < 0.05$, treatment 12, control 12, relative probability of symptoms at day 28, mixed effects logistic regression, data in supplementary appendix. |
| | viral load, 94.6% lower, relative load 0.05, treatment 12, control 12, day 7 mid-recovery, data in supplementary appendix. |
| [Chahla], 3/30/2021, Cluster Randomized Controlled Trial, Argentina, South | risk of no discharge, 86.9% lower, RR 0.13, $p = 0.004$, treatment 2 of 110 (1.8%), control 20 of 144 |

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| <p>America, preprint, 9 authors, dosage 24mg days 1, 8, 15, 22.</p> | <p>(13.9%), adjusted per study, odds ratio converted to relative risk, logistic regression.</p> |
| <p>[Chowdhury], 7/14/2020, Randomized Controlled Trial, Bangladesh, South Asia, peer-reviewed, 6 authors, dosage 200µg/kg single dose, this trial compares with another treatment - results may be better when compared to placebo, this trial uses multiple treatments in the treatment arm (combined with doxycycline) - results of individual treatments may vary.</p> | <p>risk of hospitalization, 80.6% lower, RR 0.19, $p = 0.23$, treatment 0 of 60 (0.0%), control 2 of 56 (3.6%), continuity correction due to zero event (with reciprocal of the contrasting arm).</p> |
| | <p>risk of no recovery, 46.4% lower, RR 0.54, $p < 0.001$, treatment 27 of 60 (45.0%), control 47 of 56 (83.9%), mid-recovery day 5.</p> |
| | <p>recovery time, 15.2% lower, relative time 0.85, $p = 0.07$, treatment 60, control 56.</p> |
| | <p>risk of no virological cure, 80.6% lower, RR 0.19, $p = 0.23$, treatment 0 of 60 (0.0%), control 2 of 56 (3.6%), continuity correction due to zero event (with reciprocal of the contrasting arm).</p> |
| | <p>time to viral-, 4.3% lower, relative time 0.96, $p = 0.23$, treatment 60, control 56.</p> |
| <p>[Elalfy], 2/16/2021, retrospective, Egypt, Africa, peer-reviewed, 15 authors, dosage 18mg days 1, 4, 7, 10, 13, <90kg 18mg, 90-120kg 24mg, >120kg 30mg, this trial uses multiple treatments in the treatment arm (combined with nitazoxanide, ribavirin, and zinc) - results of individual treatments may vary.</p> | <p>risk of no virological cure, 86.9% lower, RR 0.13, $p < 0.001$, treatment 7 of 62 (11.3%), control 44 of 51 (86.3%), day 15.</p> |
| | <p>risk of no virological cure, 58.1% lower, RR 0.42, $p < 0.001$, treatment 26 of 62 (41.9%), control 51 of 51 (100.0%), day 7.</p> |
| <p>[Espitia-Hernandez], 8/15/2020, retrospective, Mexico, North America, peer-reviewed, mean age 45.1, 5 authors, dosage 6mg days 1-2, 8-9, this trial uses multiple treatments in the treatment arm (combined with azithromycin and cholecalciferol) - results of individual treatments may vary.</p> | <p>risk of viral+ at day 10, 97.2% lower, RR 0.03, $p < 0.001$, treatment 0 of 28 (0.0%), control 7 of 7 (100.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).</p> |
| <p>[Faisal], 5/10/2021, Randomized Controlled Trial, Pakistan, South Asia, peer-reviewed, 3 authors, dosage 12mg days 1-5.</p> | <p>risk of no recovery, 68.4% lower, RR 0.32, $p = 0.005$, treatment 6 of 50 (12.0%), control 19 of 50 (38.0%), 6-8 days, mid-recovery.</p> |
| | <p>risk of no recovery, 27.3% lower, RR 0.73, $p = 0.11$, treatment 24 of 50 (48.0%), control 33 of 50 (66.0%), 3-5 days.</p> |

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| | risk of no recovery, 75.0% lower, RR 0.25, $p = 0.09$, treatment 2 of 50 (4.0%), control 8 of 50 (16.0%), 9-10 days. |
| [Krolewiecki], 6/18/2021, Randomized Controlled Trial, Argentina, South America, peer-reviewed, 23 authors, dosage 600µg/kg days 1-5. | risk of mechanical ventilation, 151.9% higher, RR 2.52, $p = 1.00$, treatment 1 of 27 (3.7%), control 0 of 14 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm). |
| | risk of disease progression, 3.7% higher, RR 1.04, $p = 1.00$, treatment 2 of 27 (7.4%), control 1 of 14 (7.1%). |
| [Loue], 4/17/2021, retrospective quasi-randomized (patient choice), France, Europe, peer-reviewed, 2 authors, dosage 200µg/kg single dose. | risk of death, 70.0% lower, RR 0.30, $p = 0.34$, treatment 1 of 10 (10.0%), control 5 of 15 (33.3%). |
| | risk of COVID-19 severe case, 55.0% lower, RR 0.45, $p = 0.11$, treatment 3 of 10 (30.0%), control 10 of 15 (66.7%). |
| [López-Medina], 3/4/2021, Double Blind Randomized Controlled Trial, Colombia, South America, peer-reviewed, median age 37.0, 19 authors, dosage 300µg/kg days 1-5. | risk of death, 66.8% lower, RR 0.33, $p = 0.50$, treatment 0 of 200 (0.0%), control 1 of 198 (0.5%), continuity correction due to zero event (with reciprocal of the contrasting arm). |
| | risk of escalation of care, 60.8% lower, RR 0.39, $p = 0.10$, treatment 4 of 200 (2.0%), control 10 of 198 (5.1%), odds ratio converted to relative risk. |
| | risk of escalation of care with post-hoc <12h exclusion, 34.3% lower, RR 0.66, $p = 0.51$, treatment 4 of 200 (2.0%), control 6 of 198 (3.0%), odds ratio converted to relative risk. |
| | risk of deterioration by ≥ 2 points on an 8-point scale, 43.1% lower, RR 0.57, $p = 0.35$, treatment 4 of 200 (2.0%), control 7 of 198 (3.5%), odds ratio converted to relative risk. |
| | risk of fever post randomization, 24.8% lower, RR 0.75, $p = 0.33$, treatment 16 of 200 (8.0%), control 21 of 198 (10.6%), odds ratio converted to relative risk. |
| | risk of unresolved symptoms at day 21, 15.3% lower, RR 0.85, $p = 0.53$, treatment 36 of 200 (18.0%), control 42 of 198 (21.2%), odds ratio converted to relative risk, Cox proportional-hazard model. |

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| | <p>hazard ratio for lack of resolution of symptoms, 6.5% lower, RR 0.93, $p = 0.53$, treatment 200, control 198.</p> |
| | <p>relative median time to resolution of symptoms, 16.7% lower, relative time 0.83, treatment 200, control 198.</p> |
| <p>[Mahmud], 10/9/2020, Double Blind Randomized Controlled Trial, Bangladesh, South Asia, peer-reviewed, 15 authors, dosage 12mg single dose, this trial uses multiple treatments in the treatment arm (combined with doxycycline) - results of individual treatments may vary.</p> | <p>risk of death, 85.7% lower, RR 0.14, $p = 0.25$, treatment 0 of 183 (0.0%), control 3 of 183 (1.6%), continuity correction due to zero event (with reciprocal of the contrasting arm).</p> |
| | <p>risk of disease progression, 57.0% lower, RR 0.43, $p < 0.001$, treatment 16 of 183 (8.7%), control 32 of 180 (17.8%), adjusted per study, Cox regression.</p> |
| | <p>risk of no recovery, 94.0% lower, RR 0.06, $p < 0.001$, treatment 72 of 183 (39.3%), control 100 of 180 (55.6%), adjusted per study, day 7, Cox regression.</p> |
| | <p>risk of no recovery, 38.5% lower, RR 0.61, $p = 0.005$, treatment 40 of 183 (21.9%), control 64 of 180 (35.6%), day 11.</p> |
| | <p>risk of no recovery, 96.0% lower, RR 0.04, $p < 0.001$, treatment 42 of 183 (23.0%), control 67 of 180 (37.2%), adjusted per study, day 12, Cox regression.</p> |
| | <p>time to recovery, 27.0% lower, RR 0.73, $p = 0.003$, treatment 183, control 180, Cox regression.</p> |
| | <p>risk of no virological cure, 39.0% lower, RR 0.61, $p = 0.002$, treatment 14 of 183 (7.7%), control 36 of 180 (20.0%), adjusted per study, Cox regression.</p> |
| <p>[Merino], 5/3/2021, retrospective quasi-randomized (patients receiving kit), population-based cohort, Mexico, North America, preprint, 7 authors, dosage 6mg bid days 1-2.</p> | <p>risk of hospitalization, 74.4% lower, RR 0.26, $p < 0.001$, model 7, same time period, patients receiving kit.</p> |
| | <p>risk of hospitalization, 68.4% lower, RR 0.32, $p < 0.001$, model 1, different time periods, administrative rule.</p> |
| <p>[Mohan], 2/2/2021, Double Blind Randomized Controlled Trial, India, South Asia, preprint, 27 authors, dosage</p> | <p>risk of no discharge at day 14, 62.5% lower, RR 0.38, $p = 0.27$, treatment 2 of 40 (5.0%), control 6 of 45 (13.3%), ivermectin 24mg.</p> |

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| <p>400µg/kg single dose, 200µg/kg also tested.</p> | <p>risk of no discharge at day 14, 43.8% lower, RR 0.56, $p = 0.49$, treatment 3 of 40 (7.5%), control 6 of 45 (13.3%), ivermectin 12mg.</p> <p>risk of no virological cure, 10.3% lower, RR 0.90, $p = 0.65$, treatment 20 of 36 (55.6%), control 26 of 42 (61.9%), ivermectin 24mg, day 7.</p> <p>risk of no virological cure, 3.2% higher, RR 1.03, $p = 1.00$, treatment 23 of 36 (63.9%), control 26 of 42 (61.9%), ivermectin 12mg, day 7.</p> <p>risk of no virological cure, 23.8% lower, RR 0.76, $p = 0.18$, treatment 21 of 40 (52.5%), control 31 of 45 (68.9%), ivermectin 24mg, day 5.</p> <p>risk of no virological cure, 5.6% lower, RR 0.94, $p = 0.82$, treatment 26 of 40 (65.0%), control 31 of 45 (68.9%), ivermectin 12mg, day 5.</p> |
| <p>[Mourya], 4/1/2021, retrospective, India, South Asia, peer-reviewed, 5 authors, dosage 12mg days 1-7.</p> | <p>risk of no virological cure, 89.4% lower, RR 0.11, $p < 0.001$, treatment 5 of 50 (10.0%), control 47 of 50 (94.0%).</p> |
| <p>[Ravikirti], 1/9/2021, Double Blind Randomized Controlled Trial, India, South Asia, peer-reviewed, 11 authors, dosage 12mg days 1, 2.</p> | <p>risk of death, 88.7% lower, RR 0.11, $p = 0.12$, treatment 0 of 55 (0.0%), control 4 of 57 (7.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).</p> <p>risk of mechanical ventilation, 79.3% lower, RR 0.21, $p = 0.10$, treatment 1 of 55 (1.8%), control 5 of 57 (8.8%).</p> <p>risk of ICU admission, 13.6% lower, RR 0.86, $p = 0.80$, treatment 5 of 55 (9.1%), control 6 of 57 (10.5%).</p> <p>risk of no virological cure, 11.6% higher, RR 1.12, $p = 0.35$, treatment 42 of 55 (76.4%), control 39 of 57 (68.4%).</p> |
| <p>[Roy], 3/12/2021, retrospective, database analysis, India, South Asia, preprint, 5 authors, dosage not specified, this trial uses multiple treatments in the treatment arm (combined with doxycycline) - results of individual treatments may vary.</p> | <p>relative time to clinical response of wellbeing, 5.6% lower, relative time 0.94, $p = 0.87$, treatment 14, control 15.</p> |

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| <p><i>[Samaha]</i>, 1/16/2021, Randomized Controlled Trial, Lebanon, Middle East, peer-reviewed, 16 authors, dosage 12mg single dose, 45–64kg, 65–84kg, and >85kg patients received 9mg, 12mg, or 150µg/kg respectively.</p> | <p>risk of hospitalization, 85.7% lower, RR 0.14, $p = 0.24$, treatment 0 of 50 (0.0%), control 3 of 50 (6.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).</p> |
| | <p>risk of fever at day 3, 90.9% lower, RR 0.09, $p = 0.004$, treatment 1 of 50 (2.0%), control 11 of 50 (22.0%).</p> |
| <p><i>[Szente Fonseca]</i>, 10/31/2020, retrospective, Brazil, South America, peer-reviewed, mean age 50.6, 10 authors, dosage 12mg days 1-2.</p> | <p>risk of hospitalization, 13.9% higher, RR 1.14, $p = 0.45$, treatment 340, control 377, adjusted per study, odds ratio converted to relative risk, control prevalence approximated with overall prevalence.</p> |
| <p><i>[Together Trial]</i>, 8/6/2021, Double Blind Randomized Controlled Trial, Brazil, South America, preprint, 1 author, dosage 400µg/kg days 1-3.</p> | <p>risk of death, 18.0% lower, RR 0.82, $p = 0.54$, treatment 18 of 677 (2.7%), control 22 of 678 (3.2%).</p> |
| | <p>extended ER observation or hospitalization, 9.0% lower, RR 0.91, $p = 0.51$, treatment 86 of 677 (12.7%), control 95 of 678 (14.0%).</p> |
| <p><i>[Vallejos (B)]</i>, 7/2/2021, Double Blind Randomized Controlled Trial, Argentina, South America, peer-reviewed, 29 authors, dosage 12mg days 1-2, <80kg 12mg, 80-110kg 18mg, >110kg 24mg.</p> | <p>risk of death, 33.5% higher, RR 1.33, $p = 0.70$, treatment 4 of 250 (1.6%), control 3 of 251 (1.2%), odds ratio converted to relative risk.</p> |
| | <p>risk of mechanical ventilation, 33.5% higher, RR 1.33, $p = 0.70$, treatment 4 of 250 (1.6%), control 3 of 251 (1.2%), odds ratio converted to relative risk.</p> |
| | <p>risk of hospitalization, 33.0% lower, RR 0.67, $p = 0.23$, treatment 14 of 250 (5.6%), control 21 of 251 (8.4%), odds ratio converted to relative risk.</p> |
| | <p>risk of no virological cure, 5.0% higher, RR 1.05, $p = 0.55$, treatment 137 of 250 (54.8%), control 131 of 251 (52.2%), odds ratio converted to relative risk, day 3.</p> |
| | <p>risk of no virological cure, 26.8% higher, RR 1.27, $p = 0.29$, treatment 38 of 250 (15.2%), control 30 of 251 (12.0%), odds ratio converted to relative risk, day 12.</p> |

Late treatment

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

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| <p><i>[Abd-El salam]</i>, 6/2/2021, Randomized Controlled Trial, Egypt, Africa, peer-reviewed, 16 authors, dosage 12mg days 1-3.</p> | <p>risk of death, 25.0% lower, RR 0.75, $p = 0.70$, treatment 3 of 82 (3.7%), control 4 of 82 (4.9%), odds ratio converted to relative risk, logistic regression.</p> |
| | <p>risk of mechanical ventilation, no change, RR 1.00, $p = 1.00$, treatment 3 of 82 (3.7%), control 3 of 82 (3.7%).</p> |
| | <p>hospitalization time, 19.6% lower, relative time 0.80, $p = 0.09$, treatment 82, control 82.</p> |
| <p><i>[Ahsan]</i>, 4/29/2021, retrospective, Pakistan, South Asia, peer-reviewed, 10 authors, dosage 150µg/kg days 1-2, 150-200µg/kg, this trial uses multiple treatments in the treatment arm (combined with doxycycline) - results of individual treatments may vary.</p> | <p>risk of death, 50.0% lower, RR 0.50, $p = 0.03$, treatment 17 of 110 (15.5%), control 17 of 55 (30.9%).</p> |
| <p><i>[Budhiraja]</i>, 11/18/2020, retrospective, India, South Asia, preprint, 12 authors, dosage not specified.</p> | <p>risk of death, 99.1% lower, RR 0.009, $p = 0.04$, treatment 0 of 34 (0.0%), control 103 of 942 (10.9%), continuity correction due to zero event (with reciprocal of the contrasting arm).</p> |
| <p><i>[Camprubi]</i>, 11/11/2020, retrospective, Spain, Europe, peer-reviewed, 9 authors, dosage 200µg/kg single dose.</p> | <p>risk of mechanical ventilation, 40.0% lower, RR 0.60, $p = 0.67$, treatment 3 of 13 (23.1%), control 5 of 13 (38.5%).</p> |
| | <p>risk of ICU admission, 33.3% lower, RR 0.67, $p = 1.00$, treatment 2 of 13 (15.4%), control 3 of 13 (23.1%), ICU at day 8.</p> |
| | <p>risk of no improvement at day 8, 33.3% higher, RR 1.33, $p = 1.00$, treatment 4 of 13 (30.8%), control 3 of 13 (23.1%).</p> |
| <p><i>[Chachar]</i>, 9/30/2020, Randomized Controlled Trial, India, South Asia, peer-reviewed, 6 authors, dosage 36mg, 12mg stat, 12mg after 12 hours, 12mg after 24 hours.</p> | <p>risk of no recovery at day 7, 10.0% lower, RR 0.90, $p = 0.50$, treatment 9 of 25 (36.0%), control 10 of 25 (40.0%).</p> |
| <p><i>[Elavarasi]</i>, 8/12/2021, retrospective, India, South Asia, preprint, 26 authors, dosage not specified.</p> | <p>risk of death, 19.6% lower, RR 0.80, $p = 0.12$, treatment 48 of 283 (17.0%), control 311 of 1475 (21.1%), unadjusted.</p> |
| <p><i>[Gonzalez]</i>, 2/23/2021, Double Blind Randomized Controlled Trial, Mexico,</p> | <p>risk of death, 14.4% lower, RR 0.86, $p = 1.00$, treatment 5 of 36 (13.9%), control 6 of 37 (16.2%).</p> |

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| North America, preprint, mean age 53.8, 13 authors, dosage 12mg single dose, 18mg for patients >80kg. | risk of respiratory deterioration or death, 8.6% lower, RR 0.91, $p = 1.00$, treatment 8 of 36 (22.2%), control 9 of 37 (24.3%). |
| | risk of no hospital discharge, 37.0% higher, RR 1.37, $p = 0.71$, treatment 4 of 36 (11.1%), control 3 of 37 (8.1%). |
| <i>[Gorial]</i> , 7/8/2020, retrospective, Iraq, Middle East, preprint, 9 authors, dosage 200µg/kg single dose. | risk of death, 71.0% lower, RR 0.29, $p = 1.00$, treatment 0 of 16 (0.0%), control 2 of 71 (2.8%), continuity correction due to zero event (with reciprocal of the contrasting arm). |
| | hospitalization time, 42.0% lower, relative time 0.58, $p < 0.001$, treatment 16, control 71. |
| <i>[Hashim]</i> , 10/26/2020, Single Blind Randomized Controlled Trial, Iraq, Middle East, peer-reviewed, 7 authors, dosage 200µg/kg days 1-2, some patients received a third dose on day 8, this trial uses multiple treatments in the treatment arm (combined with doxycycline) - results of individual treatments may vary. | risk of death, 91.7% lower, RR 0.08, $p = 0.03$, treatment 0 of 59 (0.0%), control 6 of 70 (8.6%), continuity correction due to zero event (with reciprocal of the contrasting arm), excluding non-randomized critical patients. |
| | risk of death, 67.1% lower, RR 0.33, $p = 0.16$, treatment 2 of 70 (2.9%), control 6 of 70 (8.6%), odds ratio converted to relative risk, including critical patients which were always allocated to treatment. |
| | risk of disease progression, 83.1% lower, RR 0.17, $p = 0.07$, treatment 1 of 59 (1.7%), control 7 of 70 (10.0%), excluding non-randomized critical patients. |
| | risk of disease progression, 57.4% lower, RR 0.43, $p = 0.20$, treatment 3 of 70 (4.3%), control 7 of 70 (10.0%), odds ratio converted to relative risk, including critical patients which were always allocated to treatment. |
| | recovery time, 40.7% lower, relative time 0.59, $p < 0.001$, treatment 70, control 70. |
| <i>[Hazan]</i> , 7/7/2021, retrospective, USA, North America, preprint, 7 authors, dosage 12mg days 1, 4, 8, this trial uses multiple treatments in the treatment arm | risk of death, 85.9% lower, RR 0.14, $p = 0.04$, continuity correction due to zero event (with reciprocal of the contrasting arm). |
| | risk of hospitalization, 93.3% lower, RR 0.07, $p = 0.001$, continuity correction due to zero event (with |

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| <p>(combined with doxycycline, zinc, vitamin D, vitamin C) - results of individual treatments may vary.</p> | <p>reciprocal of the contrasting arm).</p> |
| <p><i>[Huvemek]</i>, 3/25/2021, Double Blind Randomized Controlled Trial, Bulgaria, Europe, preprint, 1 author, dosage 400µg/kg days 1-3.</p> | <p>risk of no improvement, 31.6% lower, RR 0.68, $p = 0.28$, treatment 13 of 50 (26.0%), control 19 of 50 (38.0%), day 7, patients with improvement on WHO scale.</p> |
| | <p>risk of no improvement, 34.5% lower, RR 0.66, $p = 0.07$, treatment 19 of 50 (38.0%), control 29 of 50 (58.0%), day 4, patients with improvement on WHO scale.</p> |
| <p><i>[Khan]</i>, 9/24/2020, retrospective, Bangladesh, South Asia, preprint, median age 35.0, 8 authors, dosage 12mg single dose.</p> | <p>risk of death, 87.0% lower, RR 0.13, $p < 0.05$, treatment 1 of 115 (0.9%), control 9 of 133 (6.8%).</p> |
| | <p>risk of ICU admission, 89.5% lower, RR 0.11, $p = 0.007$, treatment 1 of 115 (0.9%), control 11 of 133 (8.3%).</p> |
| | <p>time to viral-, 73.3% lower, relative time 0.27, $p < 0.001$, treatment 115, control 133.</p> |
| <p><i>[Kishoria]</i>, 8/31/2020, Randomized Controlled Trial, India, South Asia, peer-reviewed, 7 authors, dosage 12mg single dose.</p> | <p>risk of no hospital discharge, 7.5% higher, RR 1.08, $p = 1.00$, treatment 11 of 19 (57.9%), control 7 of 13 (53.8%).</p> |
| | <p>risk of no virological cure, 7.5% higher, RR 1.08, $p = 1.00$, treatment 11 of 19 (57.9%), control 7 of 13 (53.8%), day 3.</p> |
| | <p>risk of no virological cure, 220.0% higher, RR 3.20, $p = 0.45$, treatment 1 of 5 (20.0%), control 0 of 6 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 5.</p> |
| <p><i>[Lima-Morales]</i>, 2/10/2021, prospective, Mexico, North America, peer-reviewed, 9 authors, dosage 12mg single dose, this trial uses multiple treatments in the treatment arm (combined with azithromycin, montelukast, and aspirin) - results of individual treatments may vary.</p> | <p>risk of death, 77.7% lower, RR 0.22, $p < 0.001$, treatment 15 of 481 (3.1%), control 52 of 287 (18.1%), adjusted per study, odds ratio converted to relative risk, multivariate.</p> |
| | <p>risk of hospitalization, 67.4% lower, RR 0.33, $p < 0.001$, treatment 44 of 481 (9.1%), control 89 of 287 (31.0%), adjusted per study, odds ratio converted to relative risk, multivariate.</p> |
| | <p>risk of no recovery, 58.6% lower, RR 0.41, $p < 0.001$, treatment 75 of 481 (15.6%), control 118 of</p> |

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| | 287 (41.1%), adjusted per study, odds ratio converted to relative risk, recovery at day 14 after symptoms, multivariate. |
| <p>[Niaee], 11/24/2020, Double Blind Randomized Controlled Trial, Iran, Middle East, peer-reviewed, mean age 56.0, 14 authors, dosage 400µg/kg single dose, dose varies in different groups.</p> | <p>risk of death, 81.8% lower, RR 0.18, $p = 0.001$, treatment 4 of 120 (3.3%), control 11 of 60 (18.3%), All IVM vs. all control.</p> |
| | <p>risk of death, 94.3% lower, RR 0.06, $p = 0.01$, treatment 0 of 30 (0.0%), control 11 of 60 (18.3%), continuity correction due to zero event (with reciprocal of the contrasting arm), IVM single dose 200mcg/kg vs. all control.</p> |
| | <p>risk of death, 45.5% lower, RR 0.55, $p = 0.37$, treatment 3 of 30 (10.0%), control 11 of 60 (18.3%), IVM three dose 200mcg/kg vs. all control.</p> |
| | <p>risk of death, 94.3% lower, RR 0.06, $p = 0.01$, treatment 0 of 30 (0.0%), control 11 of 60 (18.3%), continuity correction due to zero event (with reciprocal of the contrasting arm), IVM single dose 400mcg/kg vs. all control.</p> |
| | <p>risk of death, 81.8% lower, RR 0.18, $p = 0.06$, treatment 1 of 30 (3.3%), control 11 of 60 (18.3%), IVM three dose 400/200/200mcg/kg vs. all control.</p> |
| <p>[Okumuş], 1/12/2021, Double Blind Randomized Controlled Trial, Turkey, Europe, peer-reviewed, 15 authors, dosage 200µg/kg days 1-5, 36-50kg - 9mg, 51-65kg - 12mg, 66-79kg - 15mg, >80kg 200µg/kg.</p> | <p>risk of death, 33.3% lower, RR 0.67, $p = 0.55$, treatment 6 of 30 (20.0%), control 9 of 30 (30.0%).</p> |
| | <p>risk of no improvement at day 10, 42.9% lower, RR 0.57, $p = 0.18$, treatment 8 of 30 (26.7%), control 14 of 30 (46.7%).</p> |
| | <p>risk of no improvement at day 5, 15.8% lower, RR 0.84, $p = 0.60$, treatment 16 of 30 (53.3%), control 19 of 30 (63.3%).</p> |
| | <p>risk of no virological cure, 80.0% lower, RR 0.20, $p = 0.02$, treatment 2 of 16 (12.5%), control 5 of 8 (62.5%), day 10.</p> |
| <p>[Podder], 9/3/2020, Randomized Controlled Trial, Bangladesh, South Asia, peer-reviewed, 4 authors, dosage 200µg/kg single dose.</p> | <p>recovery time from enrollment, 16.1% lower, relative time 0.84, $p = 0.34$, treatment 32, control 30.</p> |
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| <p><i>[Pott-Junior]</i>, 3/9/2021, Randomized Controlled Trial, Brazil, South America, peer-reviewed, 10 authors, dosage 200µg/kg single dose, dose varies in three arms 100, 200, 400µg/kg.</p> | <p>risk of mechanical ventilation, 85.2% lower, RR 0.15, $p = 0.25$, treatment 1 of 27 (3.7%), control 1 of 4 (25.0%).</p> |
| | <p>risk of ICU admission, 85.2% lower, RR 0.15, $p = 0.25$, treatment 1 of 27 (3.7%), control 1 of 4 (25.0%).</p> |
| | <p>relative improvement in Ct value, 0.8% lower, RR 0.99, $p = 1.00$, treatment 27, control 3.</p> |
| | <p>risk of no virological cure, 11.1% higher, RR 1.11, $p = 1.00$, treatment 10 of 27 (37.0%), control 1 of 3 (33.3%).</p> |
| | <p>time to viral-, 16.7% lower, relative time 0.83, treatment 27, control 3.</p> |
| <p><i>[Rajter]</i>, 10/13/2020, retrospective, propensity score matching, USA, North America, peer-reviewed, 6 authors, dosage 200µg/kg single dose.</p> | <p>risk of death, 46.0% lower, RR 0.54, $p = 0.04$, treatment 13 of 98 (13.3%), control 24 of 98 (24.5%), adjusted per study, odds ratio converted to relative risk, PSM.</p> |
| | <p>risk of death, 66.9% lower, RR 0.33, $p = 0.03$, treatment 26 of 173 (15.0%), control 27 of 107 (25.2%), adjusted per study, odds ratio converted to relative risk, multivariate.</p> |
| | <p>risk of mechanical ventilation, 63.6% lower, RR 0.36, $p = 0.10$, treatment 4 of 98 (4.1%), control 11 of 98 (11.2%), matched cohort excluding intubated at baseline.</p> |
| <p><i>[Shahbaznejad]</i>, 1/19/2021, Double Blind Randomized Controlled Trial, Iran, Middle East, peer-reviewed, 8 authors, dosage 200µg/kg single dose.</p> | <p>risk of death, 197.1% higher, RR 2.97, $p = 1.00$, treatment 1 of 35 (2.9%), control 0 of 34 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), patient died within 24 hours of admission.</p> |
| | <p>risk of mechanical ventilation, 94.3% higher, RR 1.94, $p = 1.00$, treatment 2 of 35 (5.7%), control 1 of 34 (2.9%).</p> |
| | <p>recovery time, 31.6% lower, relative time 0.68, $p = 0.05$, treatment 35, control 34, duration of dsypnea.</p> |
| | <p>recovery time, 19.2% lower, relative time 0.81, $p = 0.02$, treatment 35, control 34, duration of all</p> |

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| | symptoms. |
| | hospitalization time, 15.5% lower, relative time 0.85, $p = 0.02$, treatment 35, control 34. |
| [Soto-Becerra], 10/8/2020, retrospective, database analysis, Peru, South America, preprint, median age 59.4, 4 authors, dosage 200µg/kg single dose. | risk of death, 17.1% lower, RR 0.83, $p = 0.01$, treatment 92 of 203 (45.3%), control 1438 of 2630 (54.7%), IVM vs. control day 43 (last day available) weighted KM from figure 3, per the pre-specified rules, the last available day mortality results have priority. |
| | risk of death, 39.0% higher, RR 1.39, $p = 0.16$, treatment 47 of 203 (23.2%), control 401 of 2630 (15.2%), adjusted per study, day 30, Table 2, IVM wHR. |
| [Spoorthi], 11/14/2020, prospective, India, South Asia, peer-reviewed, 2 authors, dosage not specified, this trial uses multiple treatments in the treatment arm (combined with doxycycline) - results of individual treatments may vary. | recovery time, 21.1% lower, relative time 0.79, $p = 0.03$, treatment 50, control 50. |
| | hospitalization time, 15.5% lower, relative time 0.84, $p = 0.01$, treatment 50, control 50. |

Prophylaxis

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

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| [Alam], 12/15/2020, prospective, Bangladesh, South Asia, peer-reviewed, 13 authors, dosage 12mg monthly. | risk of COVID-19 case, 90.6% lower, RR 0.09, $p < 0.001$, treatment 4 of 58 (6.9%), control 44 of 60 (73.3%). |
| [Behera (B)], 2/15/2021, prospective, India, South Asia, peer-reviewed, 14 authors, dosage 300µg/kg days 1, 4. | risk of COVID-19 case, 83.0% lower, RR 0.17, $p < 0.001$, treatment 45 of 2199 (2.0%), control 133 of 1147 (11.6%), two doses. |
| | risk of COVID-19 case, 4.0% higher, RR 1.04, $p = 0.85$, treatment 23 of 186 (12.4%), control 133 of 1147 (11.6%), patients only receiving the first dose. |
| [Behera], 11/3/2020, retrospective, India, South Asia, peer-reviewed, 13 authors, dosage 300µg/kg days 1, 4. | risk of COVID-19 case, 53.8% lower, RR 0.46, $p < 0.001$, treatment 41 of 117 (35.0%), control 145 of 255 (56.9%), adjusted per study, odds ratio converted to relative risk, model 2 2+ doses conditional logistic regression. |

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| | risk of COVID-19 case, 44.5% lower, RR 0.56, $p < 0.001$, treatment 41 of 117 (35.0%), control 145 of 255 (56.9%), odds ratio converted to relative risk, matched pair analysis. |
| [Bernigaud], 11/28/2020, retrospective, France, Europe, peer-reviewed, 12 authors, dosage 200µg/kg days 1, 8, 15, 400µg/kg days 1, 8, 15, two different dosages. | risk of death, 99.4% lower, RR 0.006, $p = 0.08$, treatment 0 of 69 (0.0%), control 150 of 3062 (4.9%), continuity correction due to zero event (with reciprocal of the contrasting arm). |
| | risk of COVID-19 case, 55.1% lower, RR 0.45, $p = 0.01$, treatment 7 of 69 (10.1%), control 692 of 3062 (22.6%). |
| [Carvalho (C)], 11/17/2020, prospective, Argentina, South America, peer-reviewed, 4 authors, dosage 12mg weekly, this trial uses multiple treatments in the treatment arm (combined with iota-carrageenan) - results of individual treatments may vary. | risk of COVID-19 case, 99.9% lower, RR 0.001, $p < 0.001$, treatment 0 of 788 (0.0%), control 237 of 407 (58.2%), continuity correction due to zero event (with reciprocal of the contrasting arm). |
| [Carvalho (B)], 10/19/2020, prospective, Argentina, South America, preprint, 1 author, dosage 1mg days 1-14, this trial uses multiple treatments in the treatment arm (combined with iota-carrageenan) - results of individual treatments may vary. | risk of COVID-19 case, 96.3% lower, RR 0.04, $p < 0.001$, treatment 0 of 131 (0.0%), control 11 of 98 (11.2%), continuity correction due to zero event (with reciprocal of the contrasting arm). |
| [Chahla (B)], 1/11/2021, Randomized Controlled Trial, Argentina, South America, preprint, 1 author, dosage 12mg weekly, this trial uses multiple treatments in the treatment arm (combined with iota-carrageenan) - results of individual treatments may vary. | risk of moderate/severe case, 95.2% lower, RR 0.05, $p = 0.002$, treatment 0 of 117 (0.0%), control 10 of 117 (8.5%), continuity correction due to zero event (with reciprocal of the contrasting arm), moderate/severe COVID-19. |
| | risk of COVID-19 case, 84.0% lower, RR 0.16, $p < 0.001$, treatment 4 of 117 (3.4%), control 25 of 117 (21.4%), adjusted per study, odds ratio converted to relative risk, all cases. |
| | risk of COVID-19 case, 84.0% lower, RR 0.16, $p < 0.001$, treatment 4 of 117 (3.4%), control 25 of 117 (21.4%), all cases. |
| [Hellwig], 11/28/2020, retrospective, ecological study, multiple countries, multiple regions, peer-reviewed, 2 | risk of COVID-19 case, 78.0% lower, RR 0.22, $p < 0.02$, African countries, PCTI vs. no PCT, relative cases per capita. |

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| authors, dosage 200µg/kg, dose varied, typically 150-200µg/kg. | risk of COVID-19 case, 80.0% lower, RR 0.20, $p < 0.001$, worldwide, PCTI vs. no PCT, relative cases per capita. |
| <i>[Mondal]</i> , 5/31/2021, retrospective, India, South Asia, peer-reviewed, 11 authors, dosage not specified. | risk of symptomatic case, 87.9% lower, RR 0.12, $p = 0.006$, treatment 128, control 1342, odds ratio converted to relative risk, multivariate logistic regression, control prevalence approximated with overall prevalence. |
| <i>[Morgenstern]</i> , 4/16/2021, retrospective, propensity score matching, Dominican Republic, Caribbean, preprint, 16 authors, dosage 200µg/kg weekly. | risk of hospitalization, 80.0% lower, RR 0.20, $p = 0.50$, treatment 0 of 271 (0.0%), control 2 of 271 (0.7%), continuity correction due to zero event (with reciprocal of the contrasting arm), PSM. |
| | risk of COVID-19 case, 74.0% lower, RR 0.26, $p = 0.008$, treatment 5 of 271 (1.8%), control 18 of 271 (6.6%), adjusted per study, PSM, multivariate Cox regression. |
| <i>[Seet]</i> , 4/14/2021, Cluster Randomized Controlled Trial, Singapore, Asia, peer-reviewed, 15 authors, dosage 12mg single dose, 200µg/kg, maximum 12mg, this trial compares with another treatment - results may be better when compared to placebo. | risk of COVID-19 severe case, 49.8% lower, RR 0.50, $p = 0.01$, treatment 32 of 617 (5.2%), control 64 of 619 (10.3%). |
| | risk of COVID-19 case, 5.8% lower, RR 0.94, $p = 0.61$, treatment 398 of 617 (64.5%), control 433 of 619 (70.0%), adjusted per study, odds ratio converted to relative risk, model 6. |
| <i>[Shouman]</i> , 8/28/2020, Randomized Controlled Trial, Egypt, Africa, peer-reviewed, 8 authors, dosage 18mg days 1, 3, dose varies depending on weight - 40-60kg: 15mg, 60-80kg: 18mg, >80kg: 24mg. | risk of symptomatic case, 91.3% lower, RR 0.09, $p < 0.001$, treatment 15 of 203 (7.4%), control 59 of 101 (58.4%), adjusted per study, multivariate. |
| | risk of COVID-19 severe case, 92.9% lower, RR 0.07, $p = 0.002$, treatment 1 of 203 (0.5%), control 7 of 101 (6.9%), unadjusted. |
| <i>[Tanioka]</i> , 3/26/2021, retrospective, ecological study, multiple countries, multiple regions, preprint, 3 authors, dosage 200µg/kg, dose varied, typically 150-200µg/kg. | risk of death, 88.2% lower, RR 0.12, $p = 0.002$, relative mean mortality per million. |
| <i>[Vallejos]</i> , 12/20/2020, retrospective, Argentina, South America, preprint, 1 author, dosage 12mg weekly. | risk of COVID-19 case, 73.4% lower, RR 0.27, $p < 0.001$, treatment 13 of 389 (3.3%), control 61 of 486 (12.6%). |

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