Ivermectin is effective for COVID-19: meta analysis of 26 studies

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- Ivermectin is effective for COVID-19. 100% of studies report positive effects. The probability that an ineffective treatment generated results as positive as the 26 studies to date is estimated to be 1 in 67 million (p = 0.000000015).
- Early treatment is most successful, with an estimated reduction of 87% in the effect measured using a random effects meta-analysis, RR 0.13 [0.04-0.40].
- 100% of the 10 Randomized Controlled Trials (RCTs) report positive effects, with an estimated reduction of 74% in the effect measured using a random effects meta-analysis, RR 0.26 [0.12-0.56].

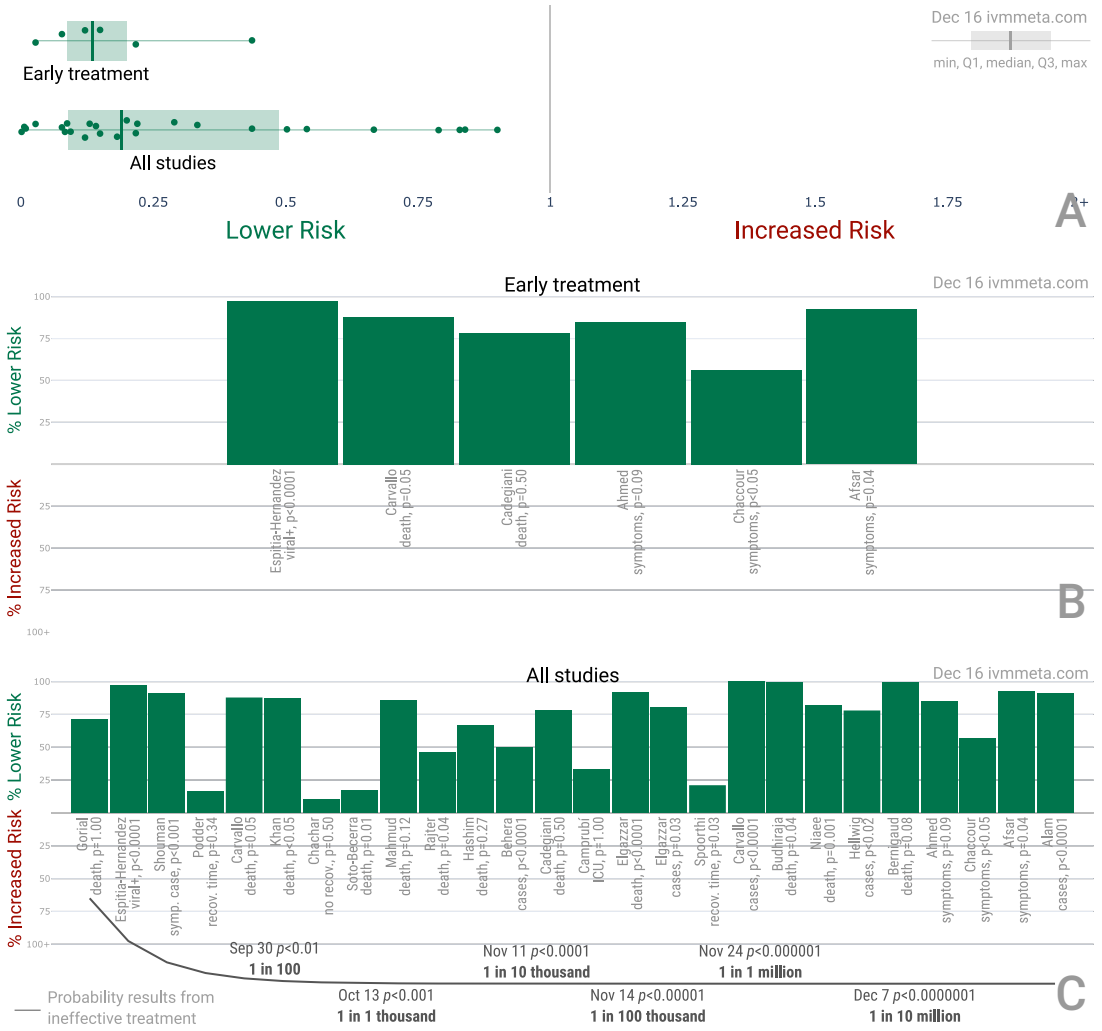

Figure 1. *A. Scatter plot showing the distribution of effects reported in early treatment studies and in all studies (the vertical lines and shaded boxes show the median and interquartile range). Early treatment is more effective.* ***B and C.*** *Study results ordered by date, with the line showing 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), PRISMA answers, statistical methods, and individual study results are detailed in Appendix 1. We present random-effects meta-analysis results for all studies, for studies within each treatment stage, for mortality results only, and for Randomized Controlled Trials (RCTs) only.

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 >= *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. Pre-Exposure Prophylaxis (PrEP) refers to regularly taking medication before being infected, in order to prevent or minimize infection. In Post-Exposure Prophylaxis (PEP), medication is taken after exposure but before symptoms appear. Early Treatment refers to treatment immediately or soon after symptoms appear, while Late Treatment refers to more delayed treatment.

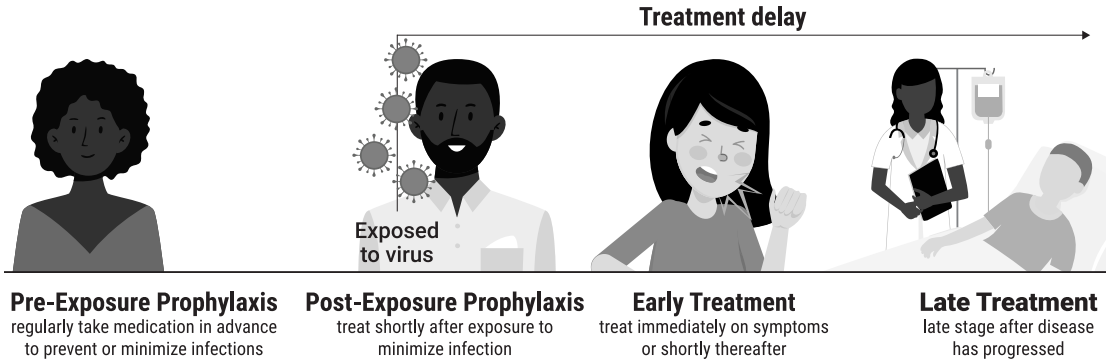

Figure 2. *Treatment stages.*

Results

Figure 3, Figure 4 and Table 1 show results by treatment stage. Figure 5 and Figure 6 show forest plots for a random effects meta-analysis of all studies and for mortality results only.

Treatment time	Number of studies reporting positive results	Total number of studies	Percentage of studies reporting positive results	Probability of an equal or greater percentage of positive results from an ineffective treatment	Random effects meta-analysis results
Early treatment	6	6	**100%**	0.016 1 in 64	**87%** improvement RR 0.13 [0.04-0.40] p = 0.00052
Late treatment	13	13	**100%**	**0.00012** 1 in 8 thousand	48% improvement RR 0.52 [0.36-0.74] p = 0.0003
Pre-Exposure Prophylaxis	5	5	**100%**	0.031 1 in 32	**96%** improvement RR 0.04 [0.01-0.31] p = 0.0021
Post-Exposure Prophylaxis	2	2	**100%**	0.25 1 in 4	**90%** improvement RR 0.10 [0.06-0.17] p < 0.0001
All studies	26	26	**100%**	**0.000000015** 1 in 67 million	**77%** improvement RR 0.23 [0.15-0.35] p < 0.0001

Table 1. *Results by treatment stage.*

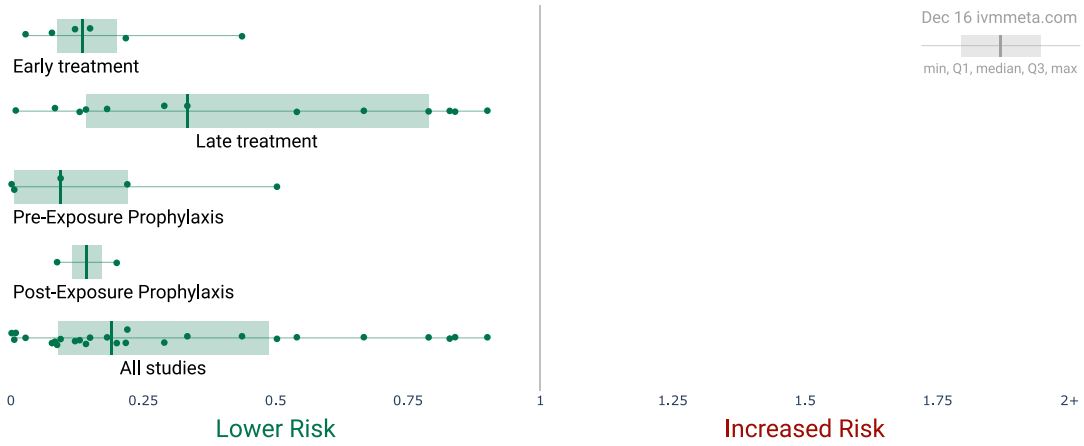

Figure 3. *Results by treatment stage.*

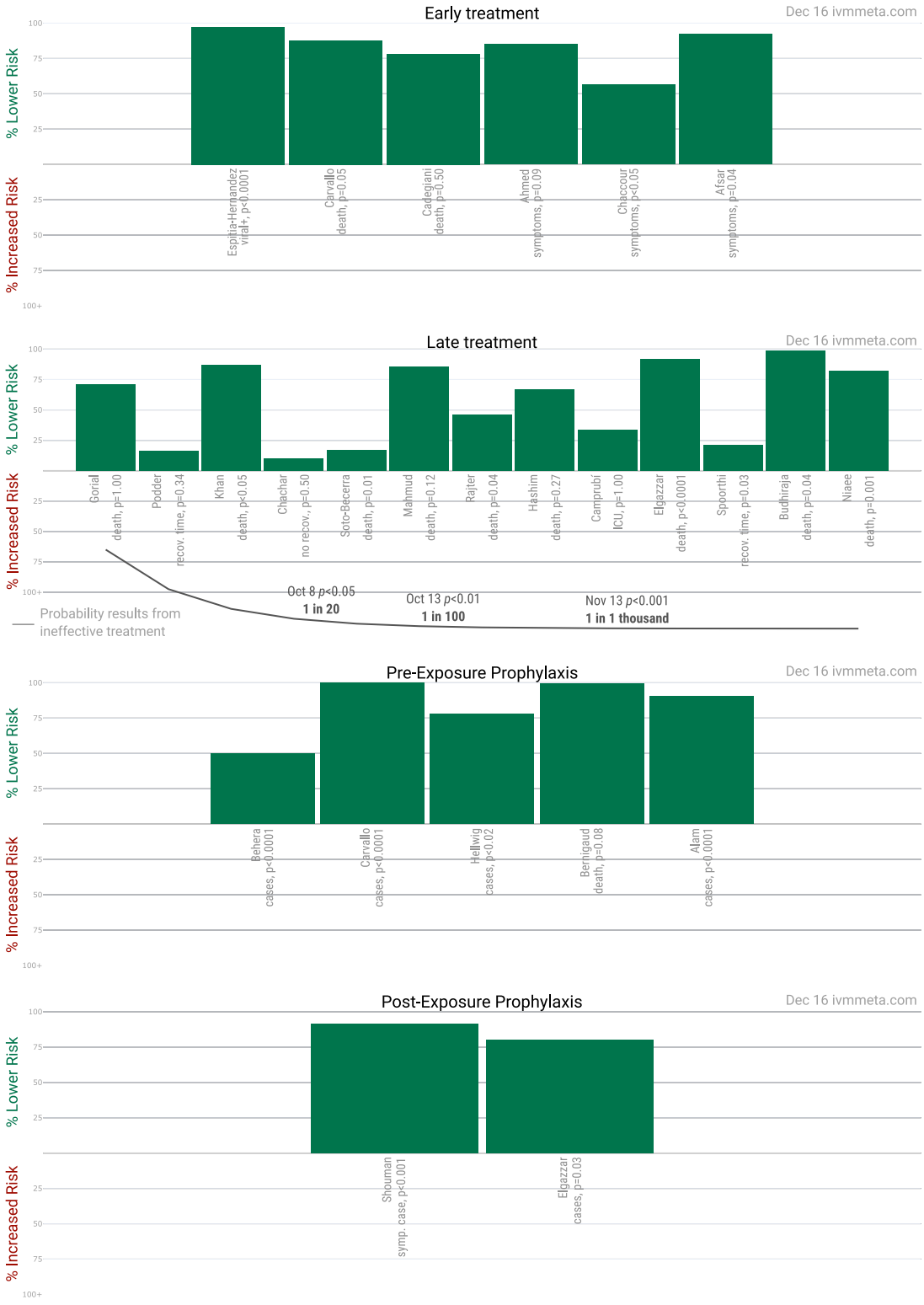

Figure 4. *Results by treatment stage. Study results are ordered by date, with the line showing the probability that the observed frequency of positive results occurred due to random chance from an ineffective treatment.*

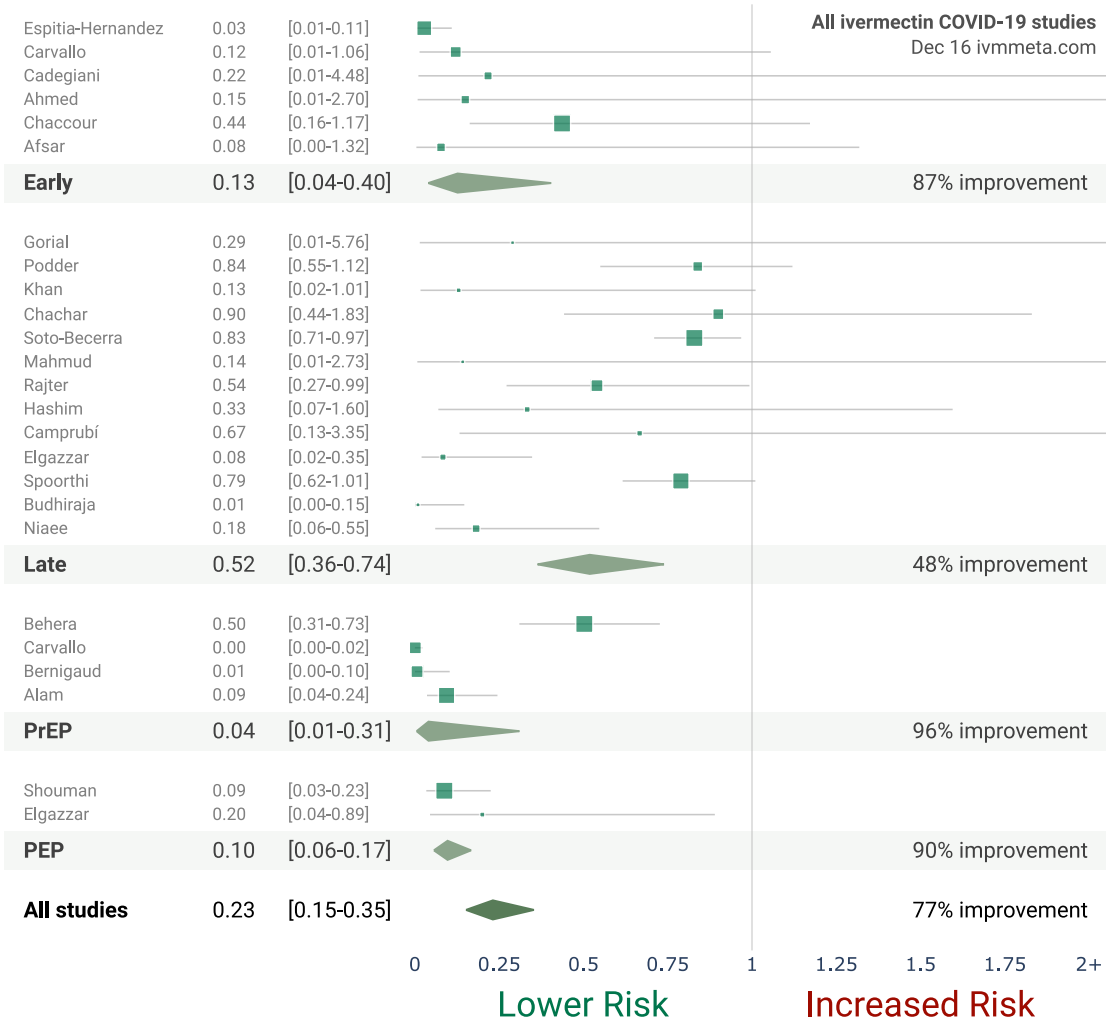

Figure 5. *Forest plot (random effects model).*

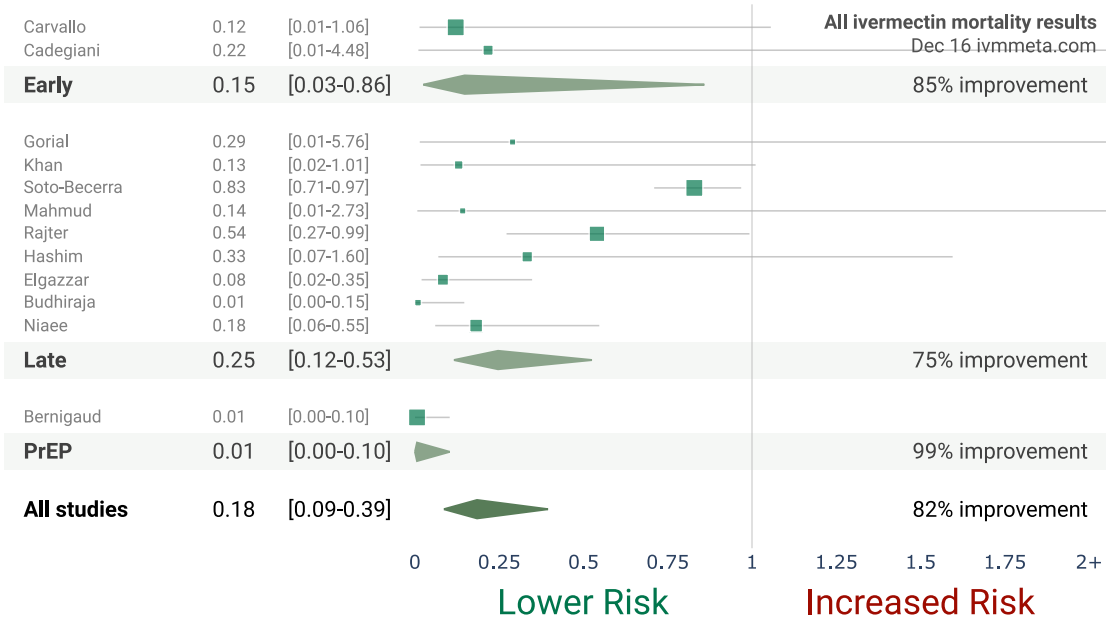

Figure 6. *Forest plot (random effects model) for mortality results only.*

Randomized Controlled Trials (RCTs)

RCTs are very valuable and minimize potential bias, however they are neither necessary or sufficient. *[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. Limitations in an RCT can easily outweigh the benefits, for example excessive dosages, excessive treatment delays, or Internet survey bias could easily have a greater effect on results. Ethical issues may prevent running RCTs for known effective treatments. For more on the problems with RCTs see *[Deaton, Nichol]*. Results restricted to RCTs are shown in Figure 7, Figure 8, Figure 9, and Table 2.

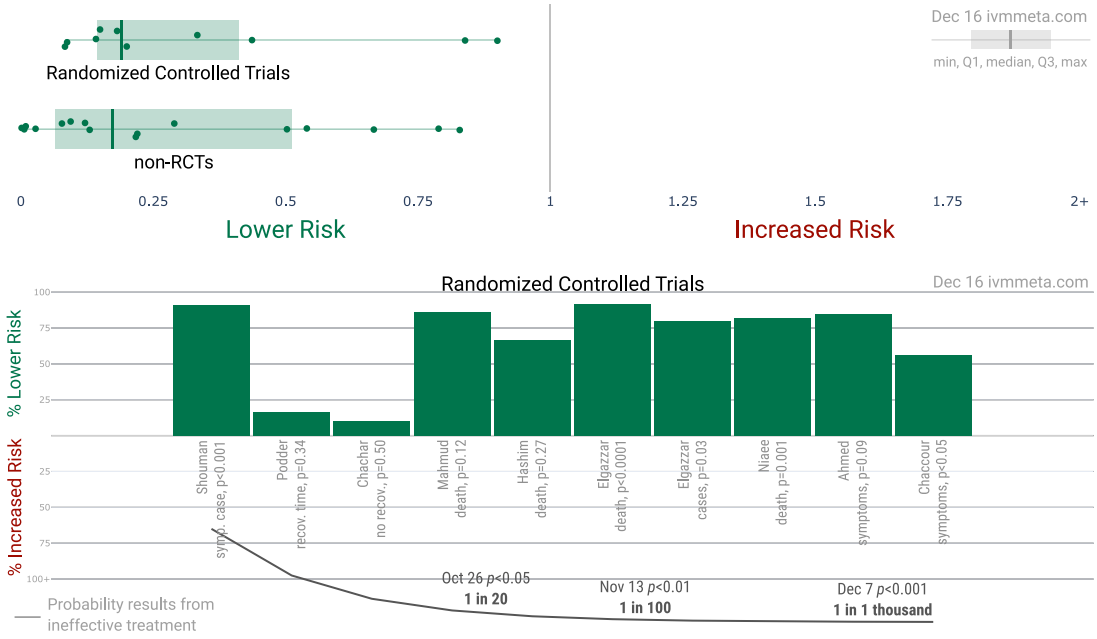

Figure 7. *Randomized Controlled Trials. The distribution of results for RCTs is similar to the distribution for all other studies.*

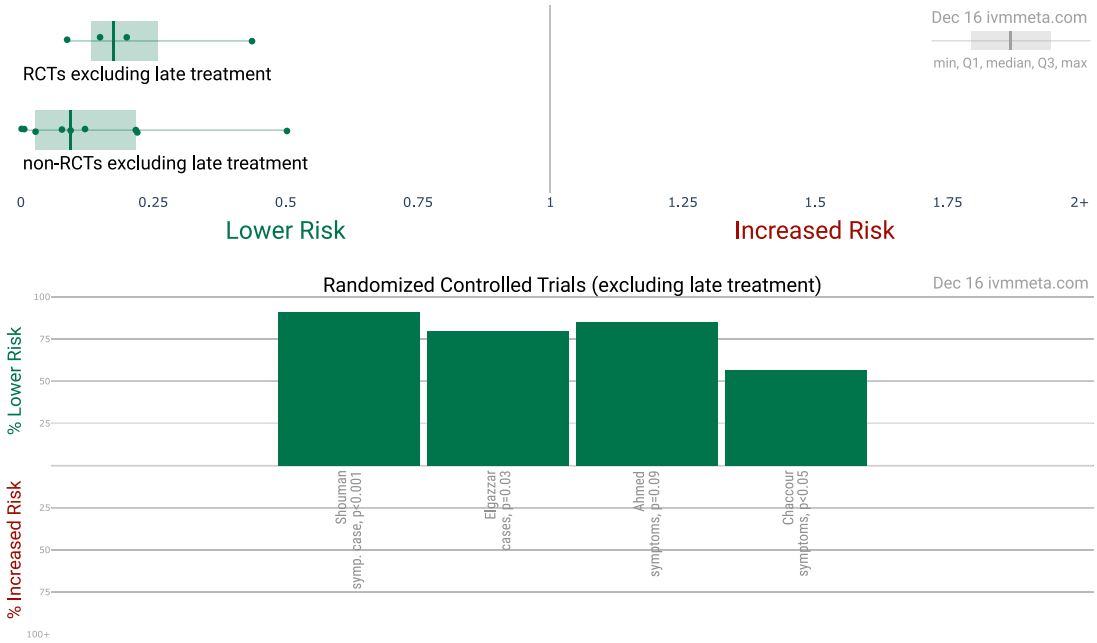

Figure 8. *RCTs excluding late treatment.*

Treatment time	Number of studies reporting positive results	Total number of studies	Percentage of studies reporting positive results	Probability of an equal or greater percentage of positive results from an ineffective treatment	Random effects meta-analysis results
Randomized Controlled Trials	10	10	**100%**	**0.00098** 1 in 1 thousand	**74%** improvement RR 0.26 [0.12-0.56] p = 0.00053

Table 2. *Summary of RCT results.*

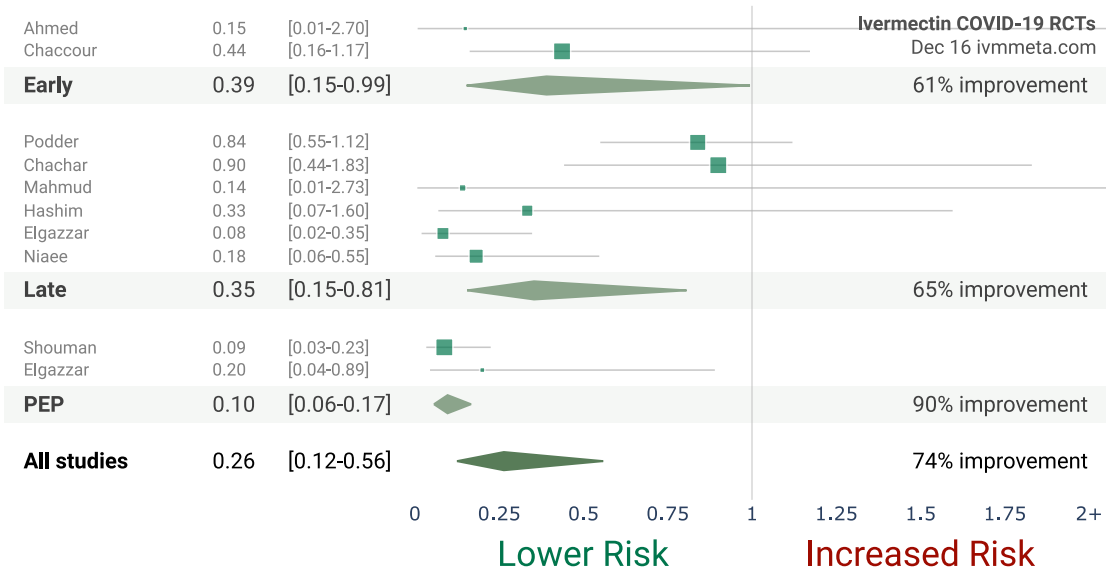

Figure 9. *Forest plot (random effects model) for Randomized Controlled Trials only.*

Discussion

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 look at 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. While some effects are not statistically significant when considered alone, currently all ivermectin studies report positive effects. We note that 15 of the 26 studies are prospective studies.

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 note that the positive results are relatively insensitive to potential selection criteria, effect extraction rules, and/or bias evaluation.

Conclusion

Ivermectin is an effective treatment for COVID-19. The probability that an ineffective treatment generated results as positive as the 26 studies to date is estimated to be 1 in 67 million (p = 0.000000015). Early treatment is most successful, with an estimated reduction of 87% in the effect measured using a random effects meta-analysis, RR 0.13 [0.04-0.40].

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.

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]*.

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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 both positive and negative 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. All studies regarding the use of ivermectin for COVID-19 that report an effect compared to a control group are included in the main analysis. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in 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. Clinical outcome is considered more important than PCR testing status. For PCR results reported at multiple times, preference is given to results mid-recovery (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 are 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 (3.9.0) with scipy (1.5.4), pythonmeta (1.11), numpy (1.19.4), statsmodels (0.12.1), and plotly (4.14.1). 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). 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 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**]*.

A summary of study results is below. It is easy to propose excluding certain papers for various reasons. To avoid potential bias in evaluation we currently include all studies.

Please submit updates and corrections with the form at https://ivmmeta.com/.

Early treatment

Only one result per study is included in calculations, as per the details above.

[*Afsar*], risk of fever at day 14, RR 0.08, $p = 0.04$.

[*Ahmed*], risk of unresolved symptoms, RR 0.15, $p = 0.09$, day 7 fever ivermectin.

[*Ahmed*], risk of unresolved symptoms, RR 0.37, $p = 0.35$, day 7 fever ivermectin + doxycycline.

[*Ahmed*], risk of no virological cure, RR 0.58, $p = 0.01$, day 7 ivermectin.

[*Ahmed*], risk of no virological cure, RR 0.80, $p = 0.28$, day 7 ivermectin + doxycycline.

[*Ahmed*], risk of no virological cure, RR 0.37, $p = 0.02$, day 14 ivermectin.

[*Ahmed*], risk of no virological cure, RR 0.64, $p = 0.24$, day 14 ivermectin + doxycycline.

[*Ahmed*], risk of no virological cure, RR 0.76, $p = 0.02$, ivermectin.

[*Ahmed*], risk of no virological cure, RR 0.91, $p = 0.27$, ivermectin + doxycycline.

[*Cadegiani*], risk of death, RR 0.22, $p = 0.50$, control group 1.

[*Cadegiani*], risk of ventilation, RR 0.06, $p = 0.005$, control group 1.

[*Cadegiani*], risk of hospitalization, RR 0.02, $p < 0.001$, control group 1.

[*Carvallo*], risk of death for hospitalized cases in study vs. cases in the same hospital not in the study, RR 0.12, $p = 0.05$.

[*Chaccour*], risk of unresolved symptoms, RR 0.44, $p < 0.05$, probability of symptoms at day 28.

[*Chaccour*], risk of viral load, RR 0.05, day 7 mid-recovery.

[*Espitia-Hernandez*], risk of viral+ at day 10, RR 0.03, $p < 0.001$.

Late treatment

Only one result per study is included in calculations, as per the details above.

[*Budhiraja*], risk of death, RR 0.009, $p = 0.04$.

[*Camprubí*], risk of ICU admission, RR 0.67, $p = 1.00$, ICU at day 8.

[*Camprubí*], risk of no improvement at day 8, RR 1.33, $p = 1.00$.

[*Chachar*], risk of no recovery at day 7, RR 0.90, $p = 0.50$.

[*Elgazzar*], risk of death, RR 0.08, $p < 0.001$, all.

[*Elgazzar*], risk of death, RR 0.11, $p = 0.12$, mild/moderate COVID-19.

[*Elgazzar*], risk of death, RR 0.10, $p < 0.001$, severe COVID-19.

[*Gorial*], risk of death, RR 0.29, $p = 1.00$.

[*Gorial*], risk of hospitalization, RR 0.58, $p < 0.001$.

[Hashim], risk of death, RR 0.33, $p = 0.27$, all patients.

[Hashim], risk of death, RR 0.08, $p = 0.03$, excluding critical patients.

[Khan], risk of death, RR 0.13, $p < 0.05$.

[Khan], risk of no virological cure, RR 0.27, $p < 0.001$.

[Mahmud], risk of death, RR 0.14, $p = 0.12$.

[Mahmud], risk of no recovery, RR 0.51, $p < 0.004$.

[Mahmud], risk of disease progression, RR 0.45, $p < 0.01$.

[Mahmud], risk of no virological cure, RR 0.58, $p < 0.001$.

[Niaee], risk of death, RR 0.18, $p = 0.001$, All IVM vs. all control.

[Niaee], risk of death, RR 0.06, $p = 0.01$, IVM single dose 200mcg/kg vs. all control.

[Niaee], risk of death, RR 0.55, $p = 0.37$, IVM three dose 200mcg/kg vs. all control.

[Niaee], risk of death, RR 0.06, $p = 0.01$, IVM single dose 400mcg/kg vs. all control.

[Niaee], risk of death, RR 0.18, $p = 0.06$, IVM three dose 400/200/200mcg/kg vs. all control.

[Podder], relative recovery time from enrollment, RR 0.84, $p = 0.34$.

[Rajter], risk of death, RR 0.54, $p = 0.04$, matched cohort.

[Soto-Becerra], risk of death, RR 0.83, $p = 0.01$, day 43 (last day available) weighted KM.

[Soto-Becerra], risk of death, RR 1.39, $p = 0.16$, day 30.

[Spoorthi], risk of no recovery, RR 0.79, $p = 0.03$.

[Spoorthi], risk of hospitalization, RR 0.84, $p = 0.01$.

Pre-Exposure Prophylaxis

Only one result per study is included in calculations, as per the details above.

[Alam], risk of COVID-19 case, RR 0.09, $p < 0.001$.

[Behera], risk of COVID-19 case, RR 0.50, $p < 0.001$, matched pair analysis.

[Behera], risk of COVID-19 case, RR 0.47, $p < 0.001$, model 2 2+ doses aOR.

[Bernigaud], risk of death, RR 0.006, $p = 0.08$.

[Bernigaud], risk of COVID-19 case, RR 0.45, $p = 0.01$.

[Carvallo (B)], risk of COVID-19 case, RR 0.001, $p < 0.001$.

*[**Hellwig**]*, risk of COVID-19 case, RR 0.22, $p < 0.02$, African countries.

*[**Hellwig**]*, risk of COVID-19 case, RR 0.20, $p < 0.001$, worldwide.

Post-Exposure Prophylaxis

Only one result per study is included in calculations, as per the details above.

*[**Elgazzar (B)**]*, risk of COVID-19 case, RR 0.20, $p = 0.03$.

*[**Shouman**]*, risk of symptomatic case, RR 0.09, $p < 0.001$, multivariate.

Appendix 2. Analysis with 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 bias likely to alter results. The studies excluded are as follows, and the resulting forest plot is shown in Figure 10.

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

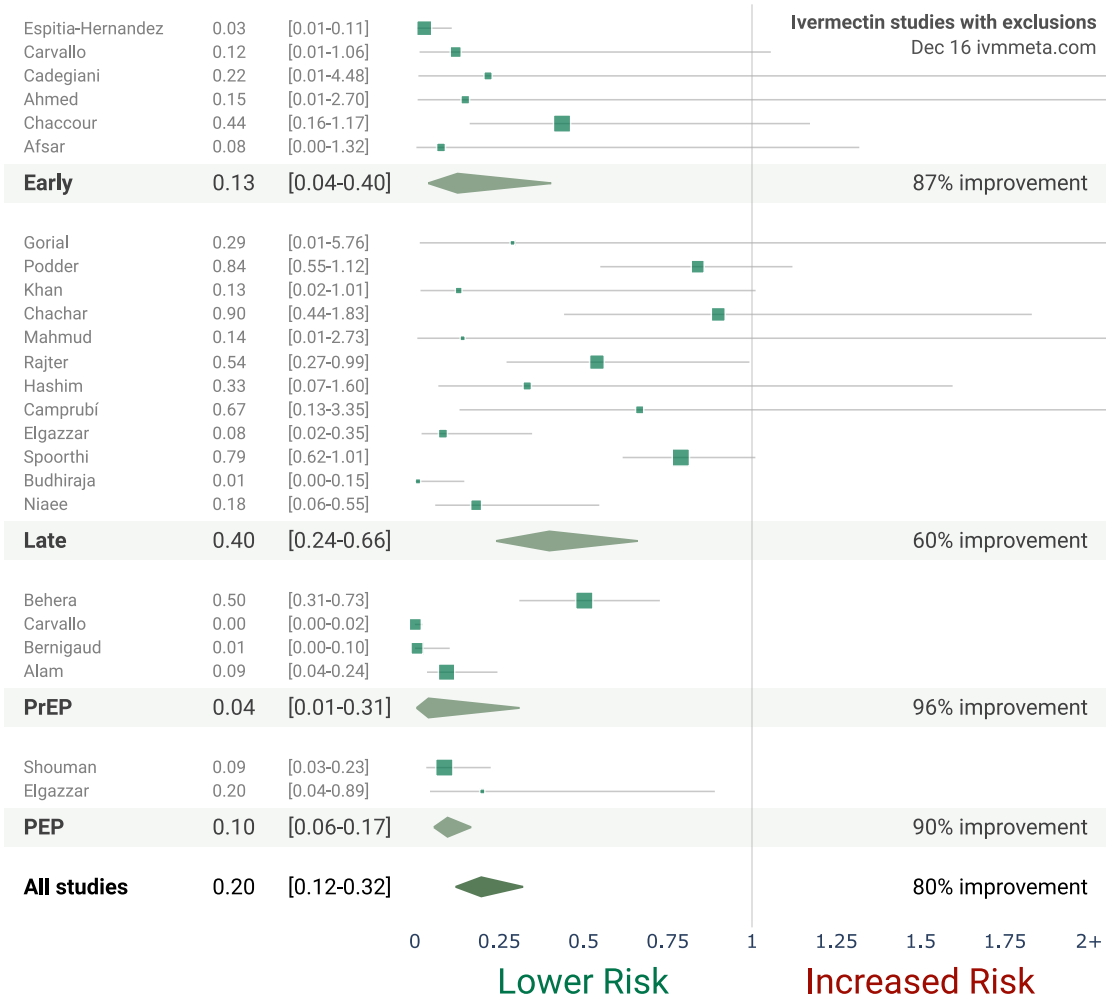

Figure 10. *Forest plot (random effects model) excluding studies with significant issues.*