

Ivermectin for COVID-19: real-time meta analysis of 56 studies

Covid Analysis, Nov 26, 2020 (Version 83, May 18, 2021 — Merck analysis)

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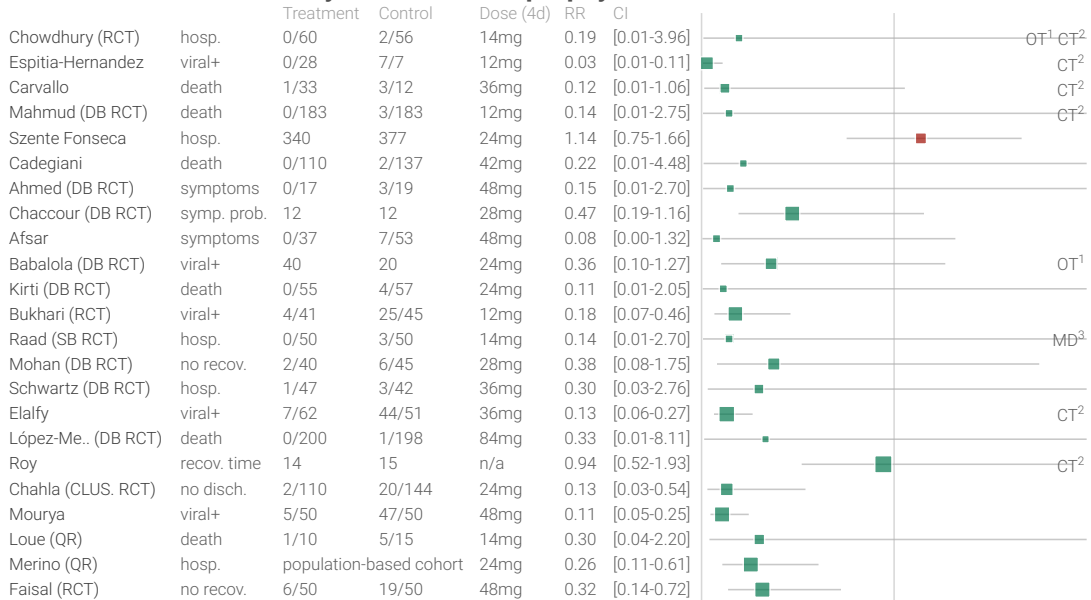
- 97% of 37 early treatment and prophylaxis studies report positive effects (95% of all 56 studies). 26 studies show statistically significant improvements in isolation.
- Random effects meta-analysis with pooled effects using the most serious outcome reported shows 78% and 85% improvement for early treatment and prophylaxis (RR 0.22 [0.12-0.39] and 0.15 [0.09-0.25]). Results are similar after exclusion based sensitivity analysis: 80% and 87% (RR 0.20 [0.14-0.28] and 0.13 [0.07-0.25]), and after restriction to 30 peer-reviewed studies: 80% and 88% (RR 0.20 [0.12-0.35] and 0.12 [0.05-0.30]).
- 81% and 96% lower mortality is observed for early treatment and prophylaxis (RR 0.19 [0.07-0.54] and 0.04 [0.00-0.58]). Statistically significant improvements are seen for mortality, ventilation, hospitalization, cases, and viral clearance.
- 100% of the 17 Randomized Controlled Trials (RCTs) for early treatment and prophylaxis report positive effects, with an estimated improvement of 73% and 83% respectively (RR 0.27 [0.18-0.41] and 0.17 [0.05-0.61]), and 93% of all 28 RCTs.
- The probability that an ineffective treatment generated results as positive as the 56 studies to date is estimated to be 1 in 2 trillion ($p = 0.00000000000041$).
- Heterogeneity arises from many factors including treatment delay, patient population, the effect measured, variants, and treatment regimens. The consistency of positive results across a wide variety of cases is remarkable. Heterogeneity is low in specific cases, for example early treatment mortality.
- 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. Multiple approaches are required to protect everyone from all existing and future variants.
- Many studies do not specify administration, or specify fasting. Administration with food may significantly increase plasma and tissue concentration.
- All data to reproduce this paper and the sources are in the appendix. See [Bryant, Hill, Kory, Lawrie, Nardelli] for other meta analyses, all with similar results confirming effectiveness.

	<i>Improvement</i>	<i>Studies</i>	<i>Authors</i>	<i>Patients</i>
<u>Early treatment</u>	78% [61-88%]	23	212	3,227
<u>Late treatment</u>	46% [28-60%]	19	149	6,431
<u>Prophylaxis</u>	85% [75-91%]	14	108	8,789
<u>Mortality</u>	74% [56-85%]	20	179	7,361
<u>RCTs only</u>	66% [50-76%]	28	270	4,997
<u>All studies</u>	72% [64-79%]	56	469	18,447

Evidence base used for other COVID-19 approvals			
Medication	Studies	Patients	Improvement
Budesonide (UK)	1	1,779	17%
Remdesivir (USA)	1	1,063	31%
Casiri/imdevimab (USA)	1	799	66%
Ivermectin evidence	56	18,447	72% [64-79%]

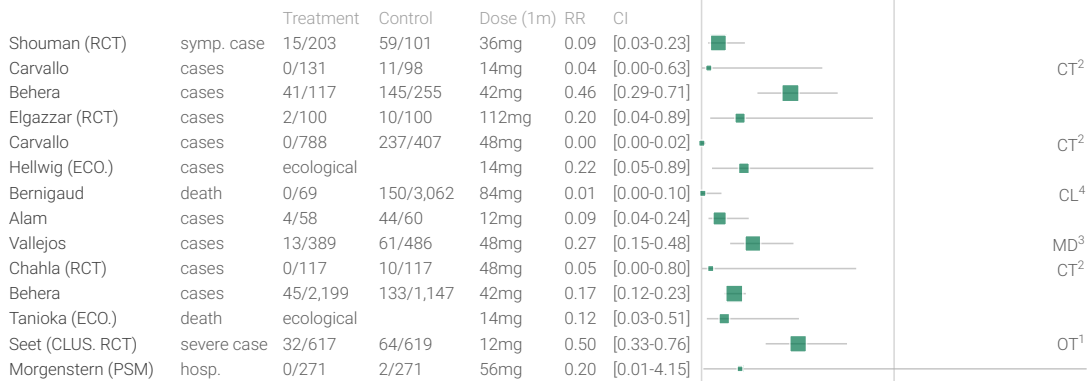
Ivermectin COVID-19 early treatment and prophylaxis studies

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Early treatment 29/1,589 204/1,638 0.22 [0.12-0.39] **78% improvement**

Tau² = 1.18; I² = 82.6%



Prophylaxis 152/5,059 926/3,730 0.15 [0.09-0.25] **85% improvement**

Tau² = 0.58; I² = 83.8%

All studies 181/6,648 1,130/5,368 0.18 [0.12-0.27] **82% improvement**

¹ OT: ivermectin vs. other treatment
² CT: study uses combined treatment
³ MD: minimal detail available currently
⁴ CL: control group size limited in totals
 Tau² = 0.97; I² = 89.5%; Z = 8.12 (p < 0.0001)

0 0.25 0.5 0.75 1 1.25 1.5 1.75 2+
 Lower Risk Increased Risk

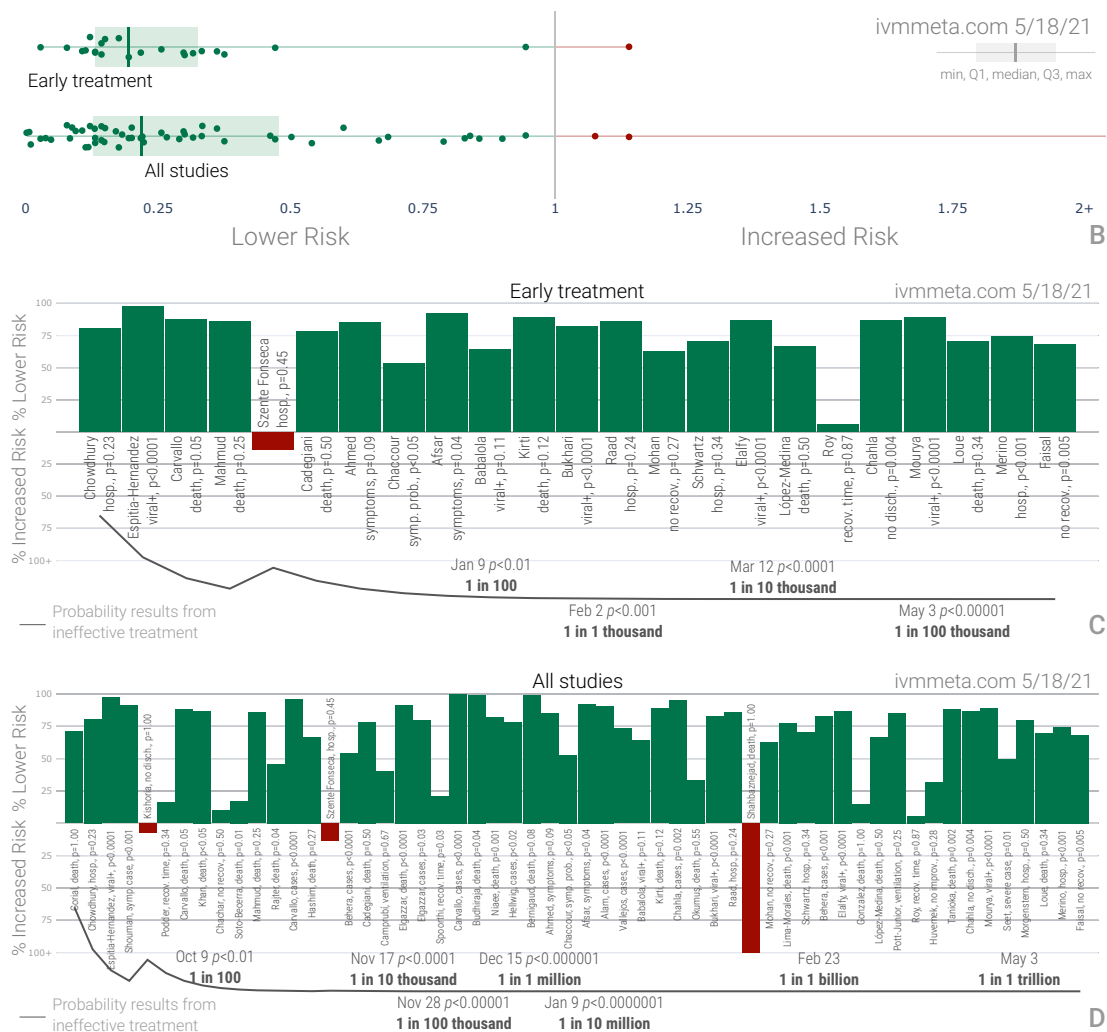


Figure 1. A. Random effects meta-analysis excluding late treatment. This plot shows pooled effects, analysis for individual outcomes is below, and more details on pooled effects can be found in the heterogeneity section. Simplified dosages are shown for comparison, these are the total dose in the first four days for treatment, and the monthly dose for prophylaxis, for a 70kg person. For full details 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.

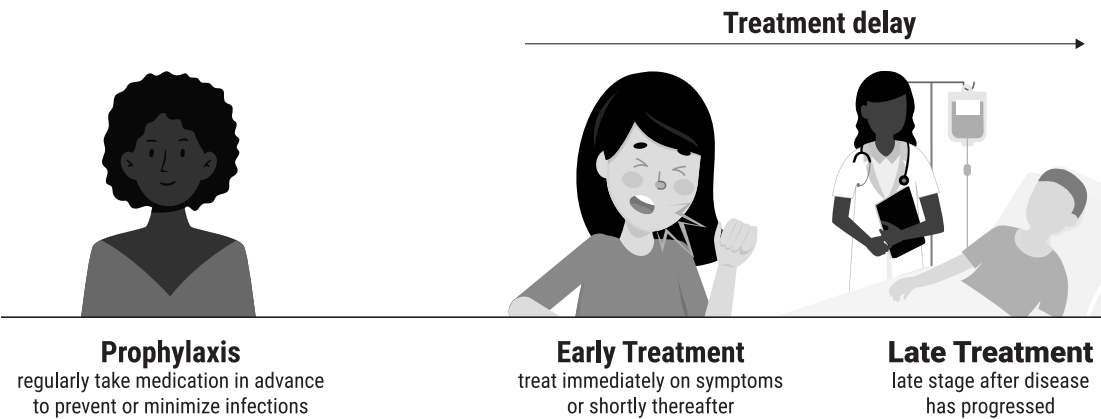


Figure 2. Treatment stages.

Results

Figure 3, 4, and 5 show results by treatment stage. Figure 6, 7, 8, 9, 10, 11, and 12 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, COVID-19 cases, and viral clearance results only. Figure 13 shows results for peer reviewed trials only. 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	22	23	95.7%	0.0000029 1 in 350 thousand	78% improvement RR 0.22 [0.12-0.39] p < 0.0001
Late treatment	17	19	89.5%	0.00036 1 in 3 thousand	46% improvement RR 0.54 [0.40-0.72] p < 0.0001
Prophylaxis	14	14	100%	0.000061 1 in 16 thousand	85% improvement RR 0.15 [0.09-0.25] p < 0.0001
All studies	53	56	94.6%	0.00000000000041 1 in 2 trillion	72% improvement RR 0.28 [0.21-0.36] p < 0.0001

Table 1. Results by treatment stage.

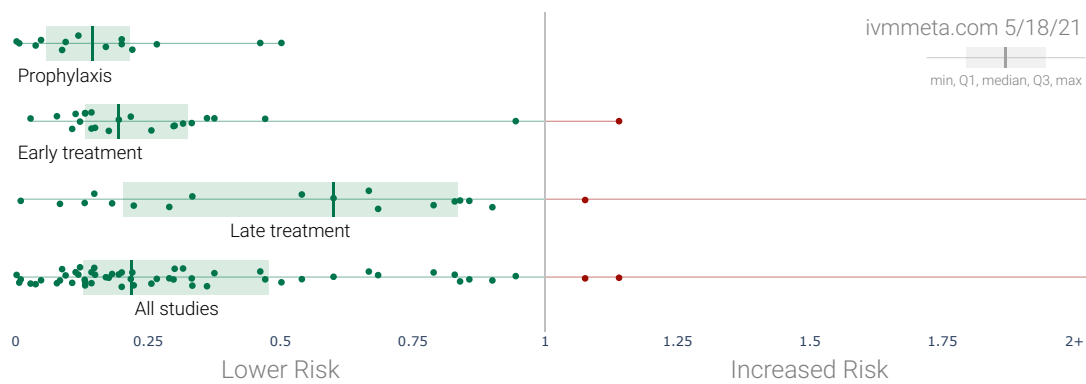


Figure 3. Results by treatment stage.

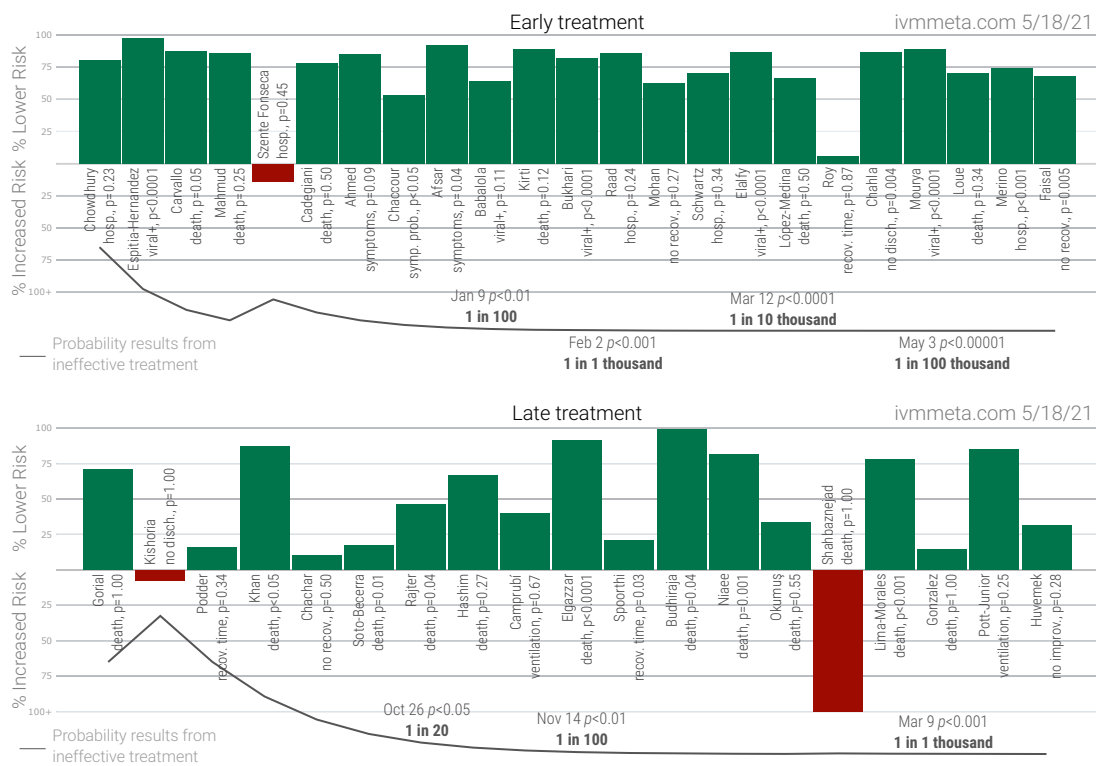


Figure 4. Chronological history of early and late treatment results, with the probability that the observed frequency of positive results occurred due to random chance from an ineffective treatment.

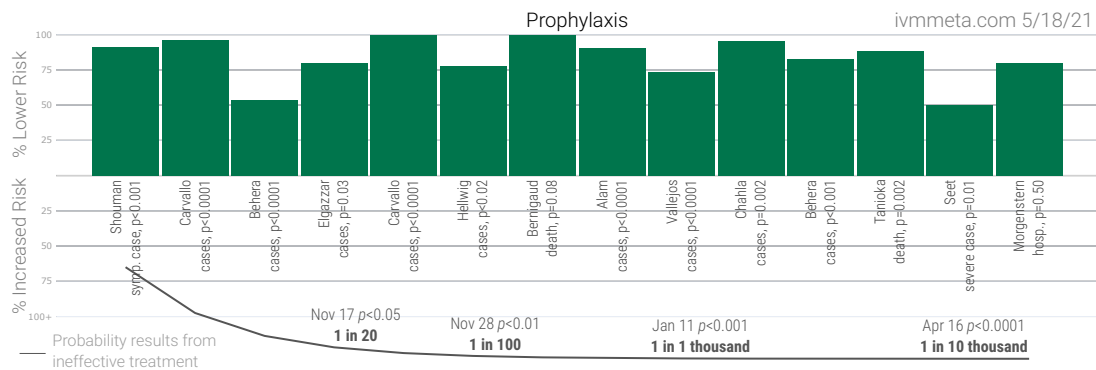
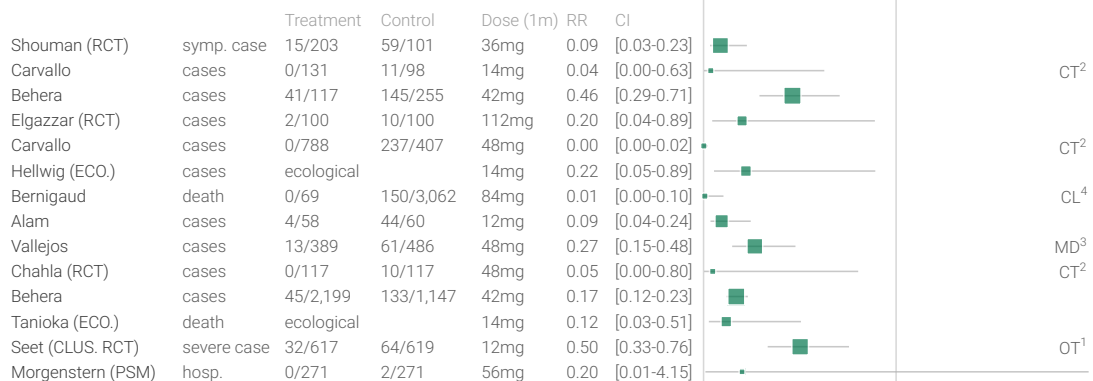
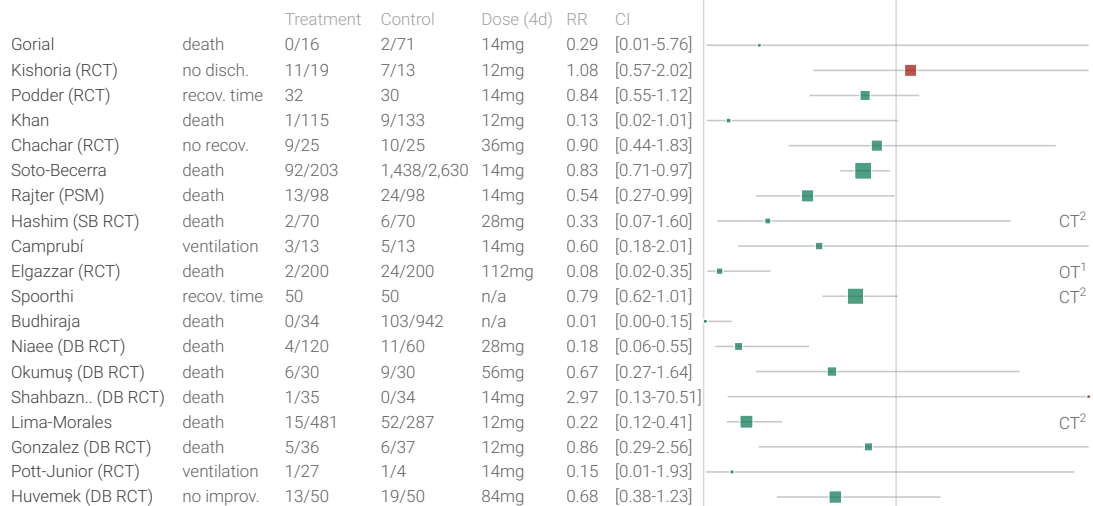
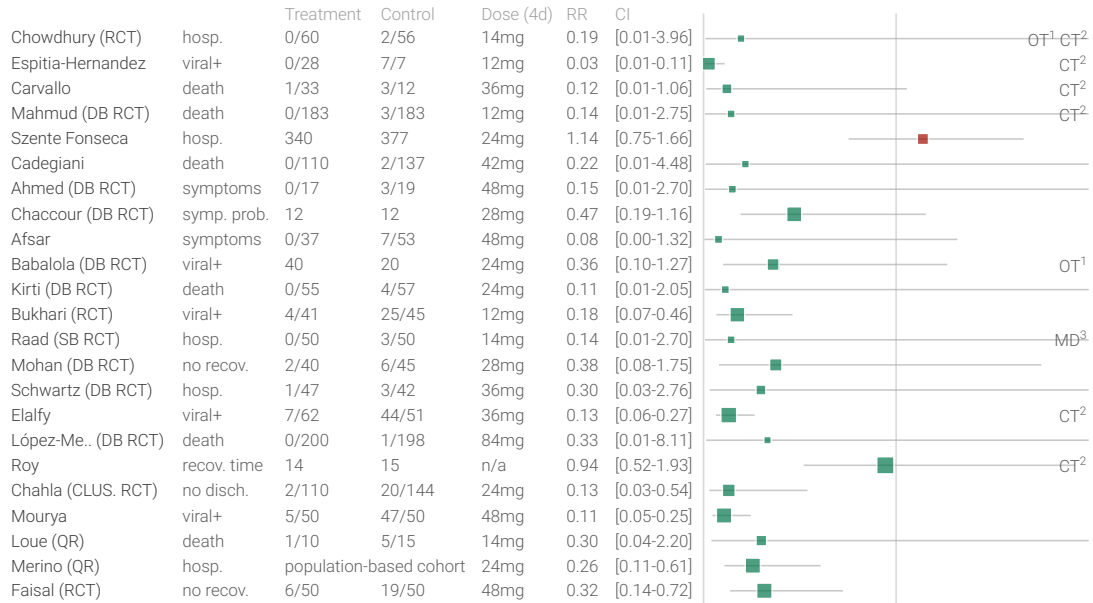


Figure 5. Chronological history of prophylaxis results.

All 56 ivermectin COVID-19 studies

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All studies 359/8,302 2,856/10,145 0.28 [0.21-0.36] **72% improvement**

¹ OT: ivermectin vs. other treatment

² CT: study uses combined treatment
³ MD: minimal detail available currently
⁴ CL: control group size limited in totals
 Tau² = 0.52; I² = 86.4%; Z = 9.63 (p < 0.0001)

0 0.25 0.5 0.75 1 1.25 1.5 1.75 2+
 Lower Risk Increased Risk

Figure 6. Random effects meta-analysis for all studies.

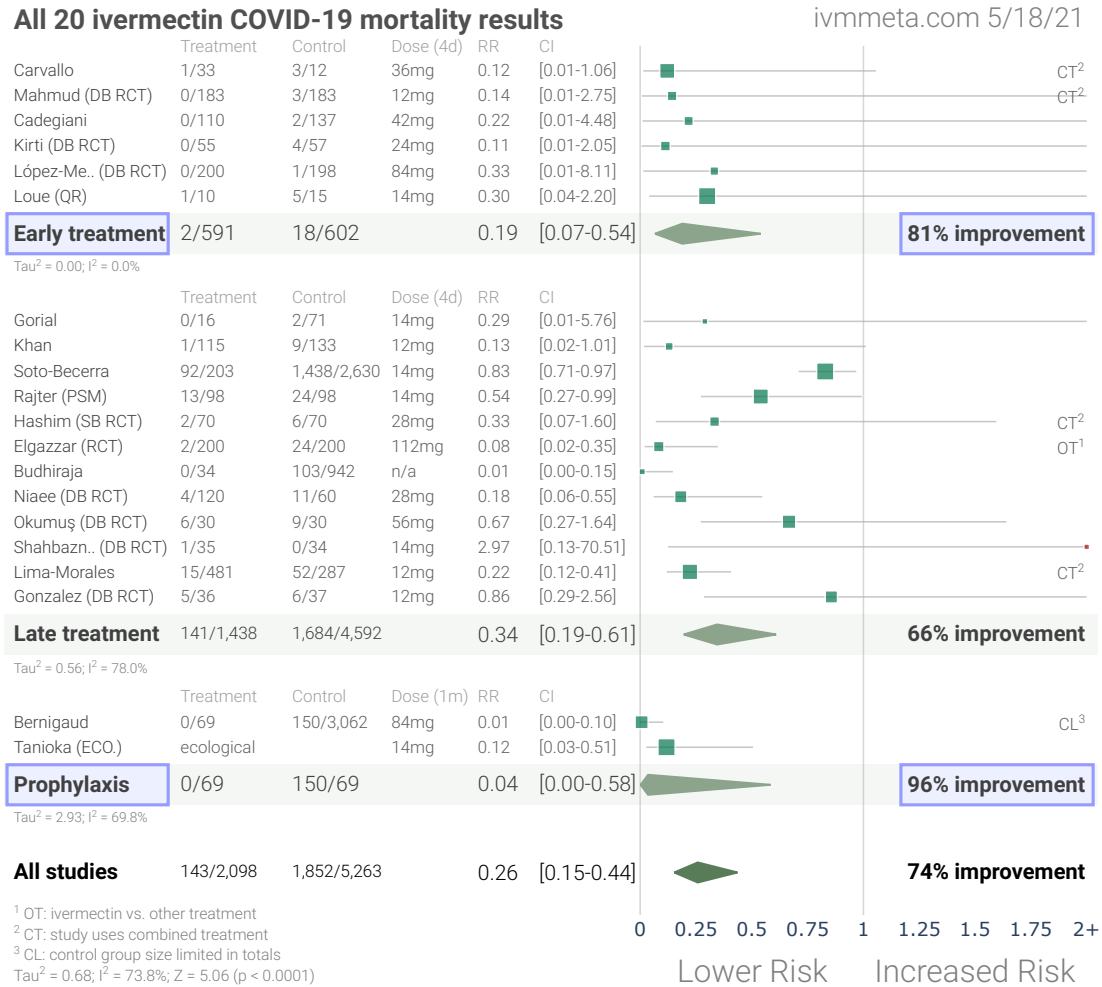


Figure 7. Random effects meta-analysis for mortality results only.

All 6 ivermectin COVID-19 mechanical ventilation results

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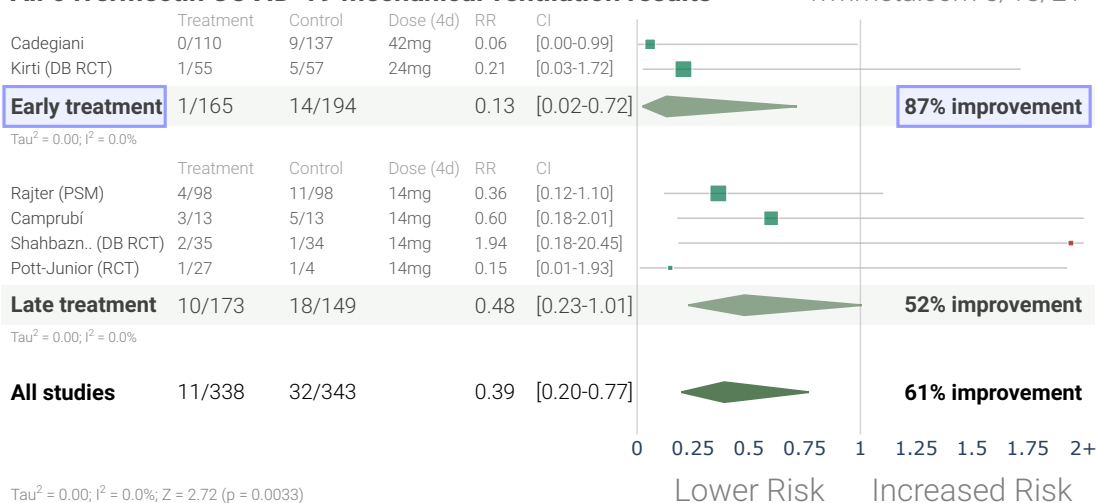


Figure 8. Random effects meta-analysis for mechanical ventilation results only.

All 4 ivermectin COVID-19 ICU results

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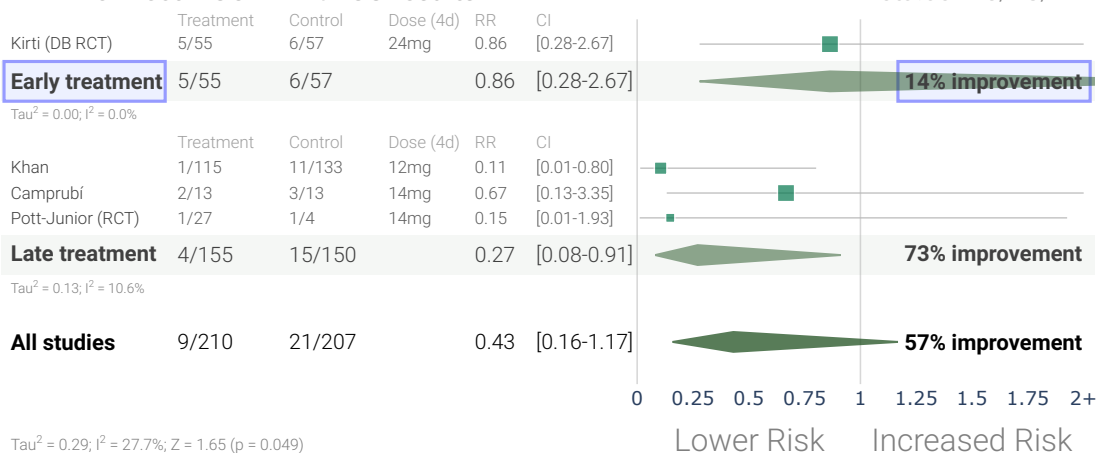


Figure 9. Random effects meta-analysis for ICU admission results only.

All 11 ivermectin COVID-19 hospitalization results

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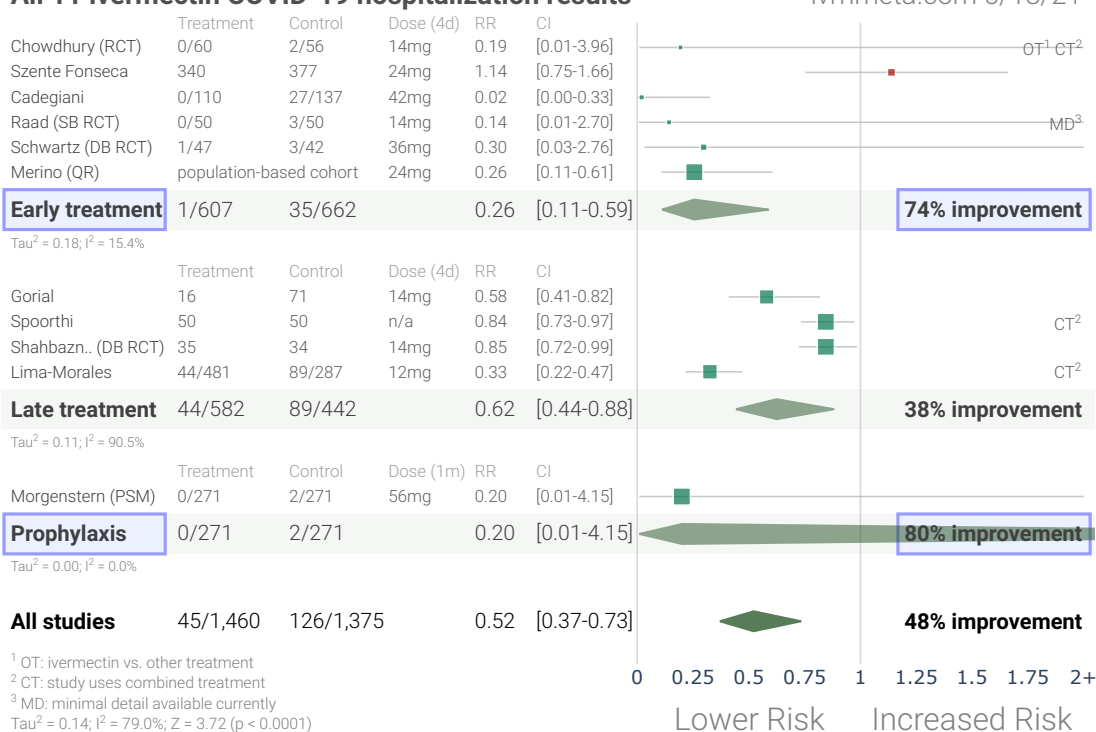


Figure 10. Random effects meta-analysis for hospitalization results only.

All 12 ivermectin COVID-19 case results

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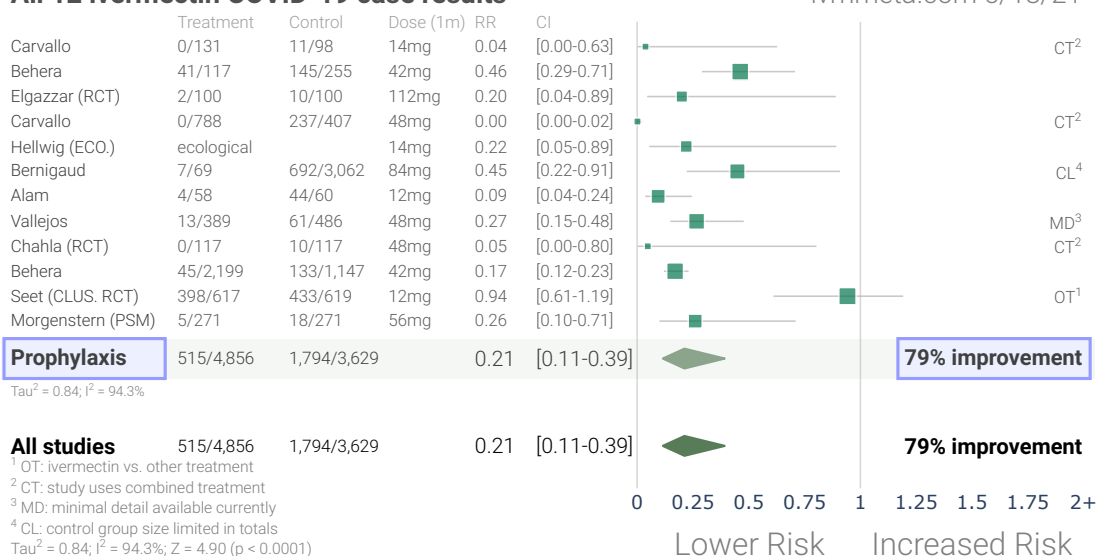


Figure 11. Random effects meta-analysis for COVID-19 case results only.

All 15 ivermectin COVID-19 viral clearance results

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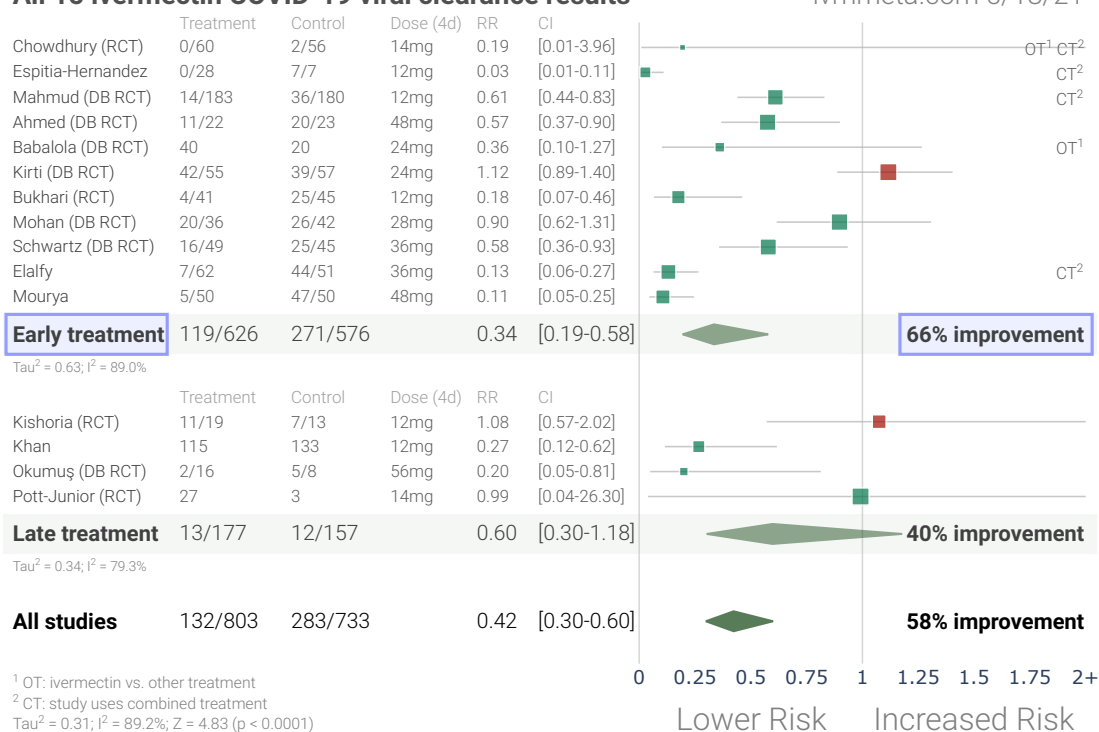


Figure 12. Random effects meta-analysis for viral clearance results only.

All 30 ivermectin COVID-19 peer reviewed trials

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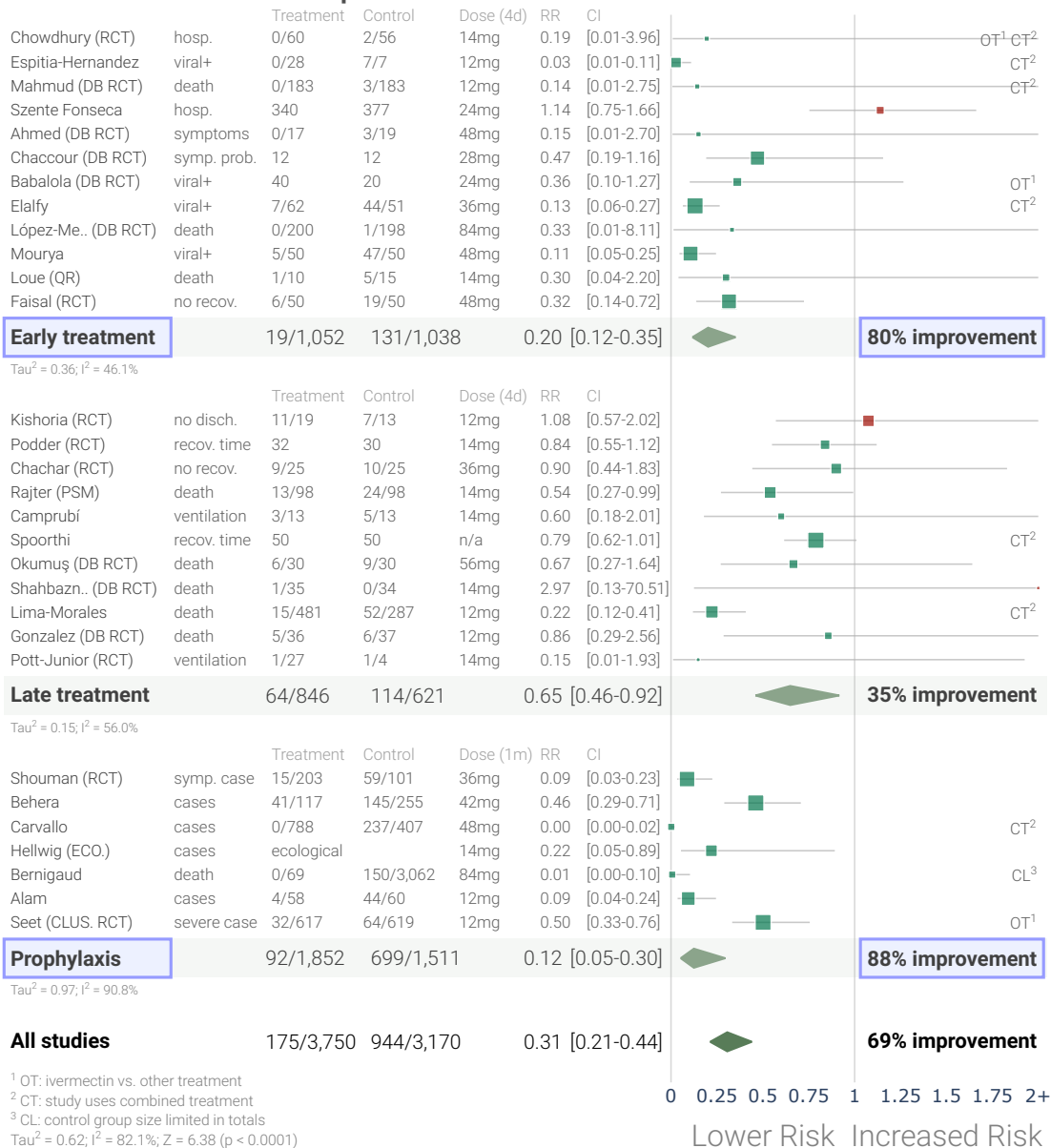


Figure 13. Random effects meta-analysis for peer reviewed trials only.

Randomized Controlled Trials (RCTs)

Results restricted to Randomized Controlled Trials (RCTs) are shown in Figure 14, 15, 16, and 17, 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].

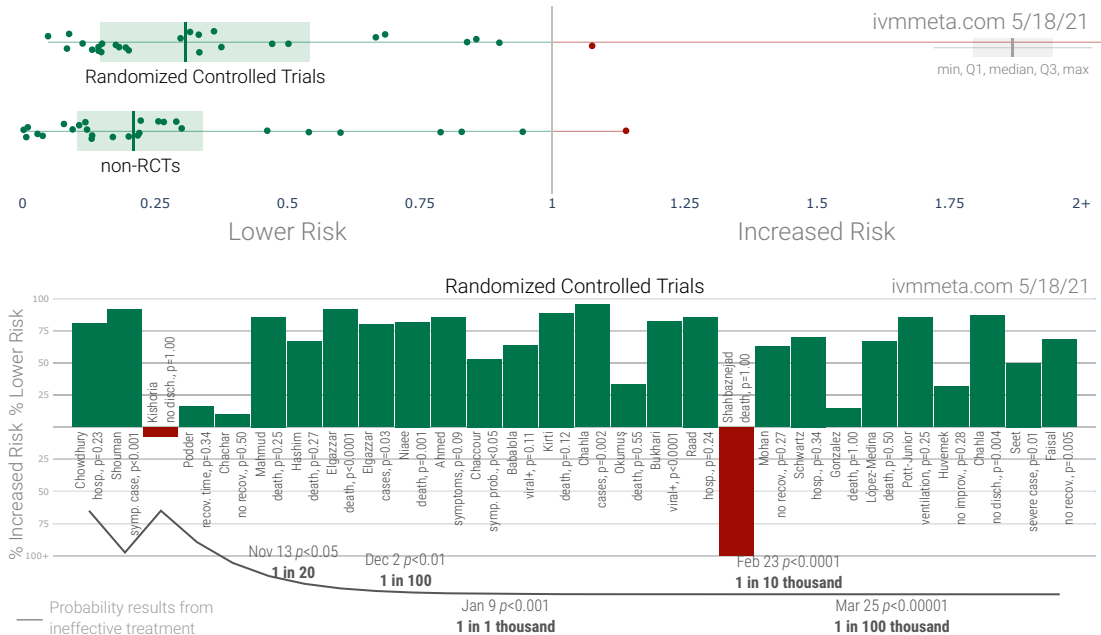


Figure 14. Randomized Controlled Trials. The distribution of results for RCTs is similar to the distribution for all other studies.

All 28 ivermectin COVID-19 Randomized Controlled Trials

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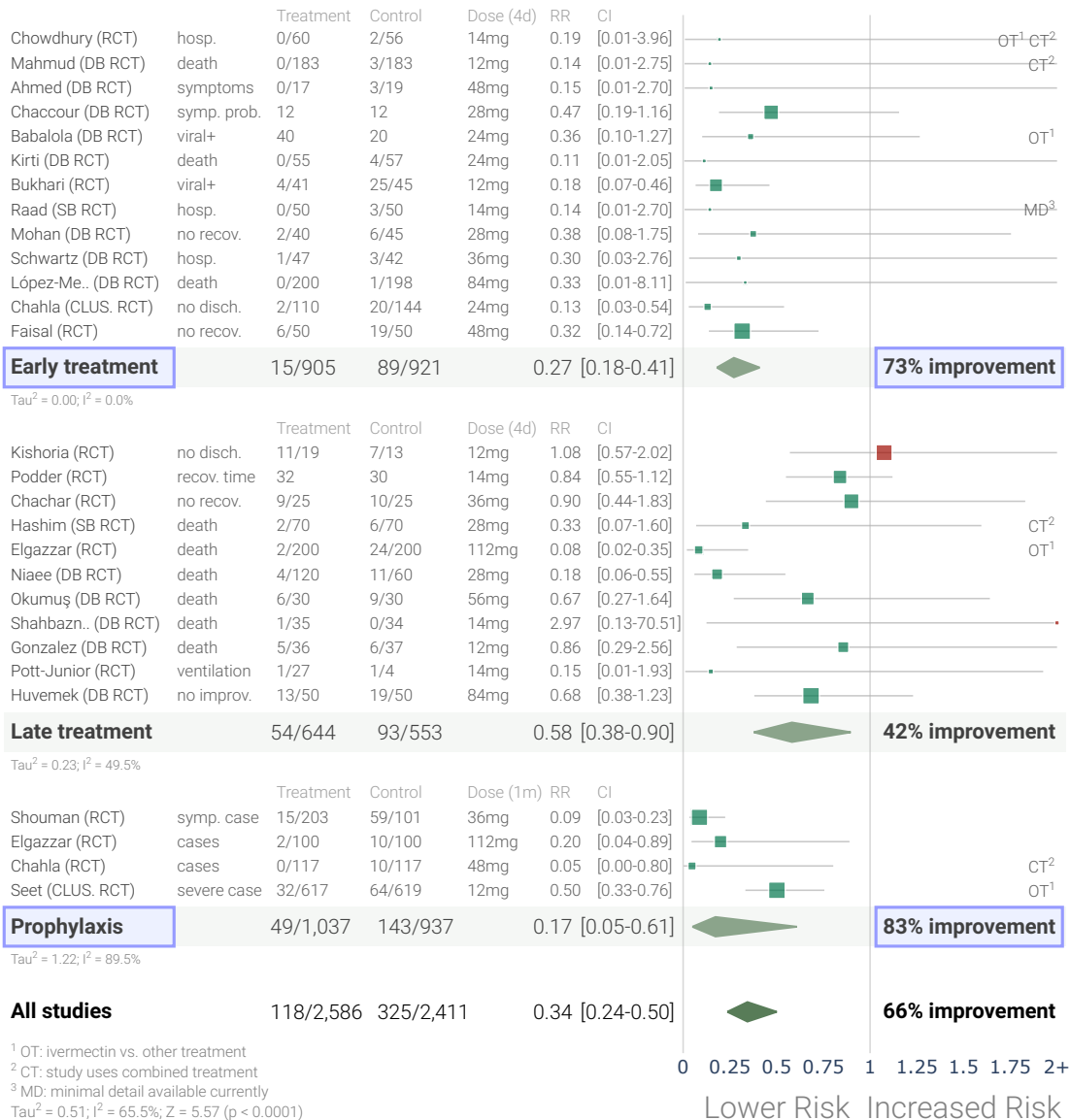


Figure 15. Random effects meta-analysis for Randomized Controlled Trials only.

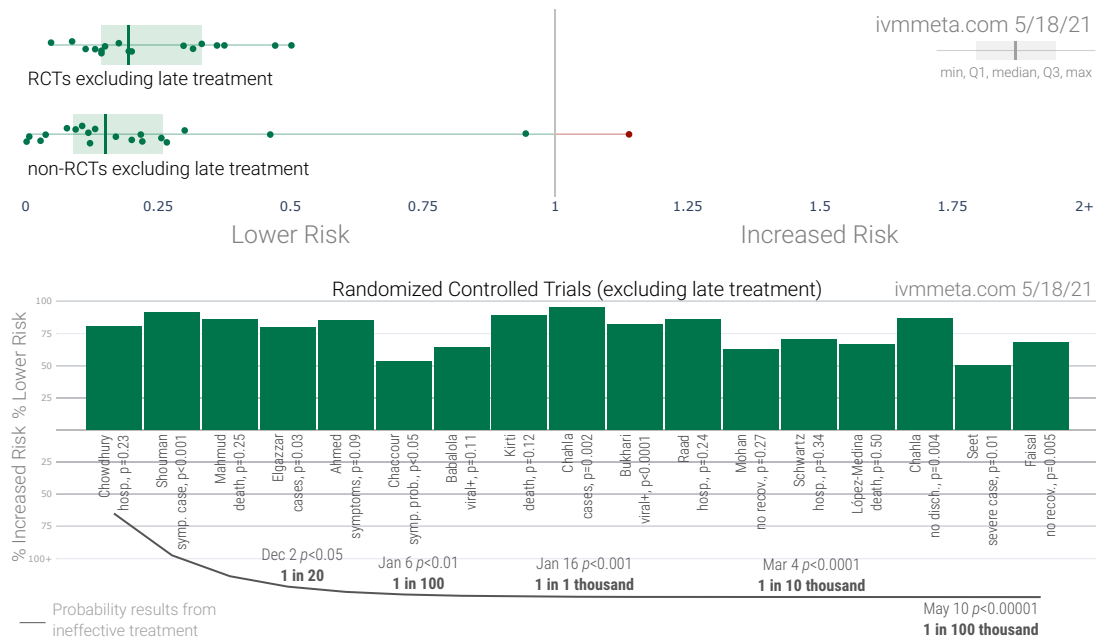


Figure 17. RCTs excluding late treatment.

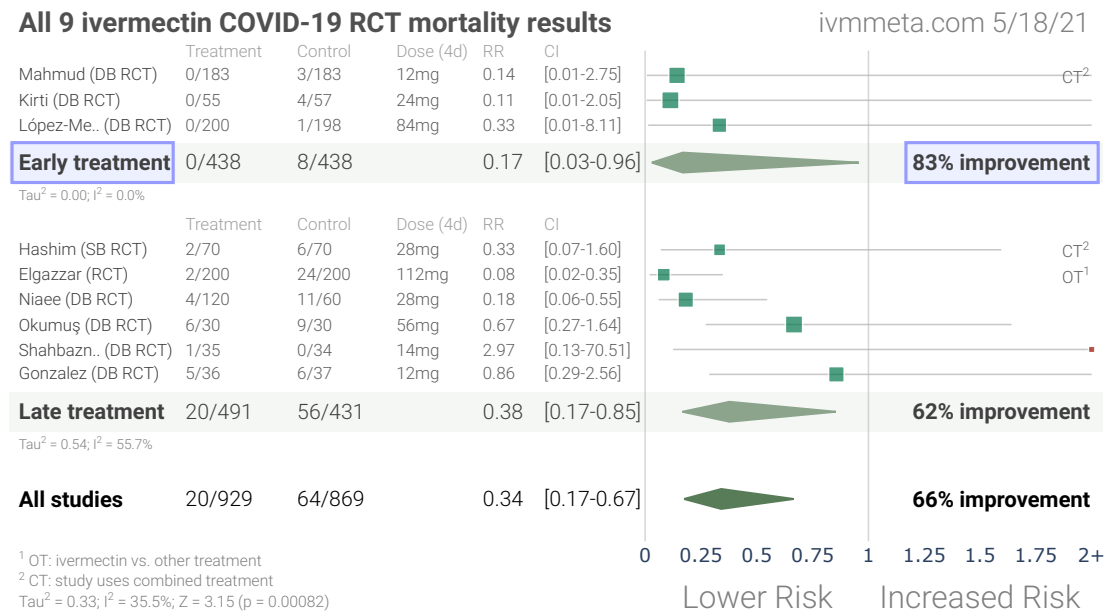


Figure 16. Random effects meta-analysis for Randomized Controlled Trial mortality results only.

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	26	28	92.9%	0.0000015 1 in 660 thousand	66% improvement RR 0.34 [0.24-0.50] p < 0.0001
Randomized Controlled Trials (excluding late treatment)	17	17	100%	0.0000076 1 in 131 thousand	77% improvement RR 0.23 [0.14-0.37] 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 is 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 (for example, lack of blinding for an objective mortality outcome, or certain specifics of randomization with a very large effect size). However, these approaches are also valuable when done well and other groups have used them [Bryant, Hill, Lawrie], with similar results confirming efficacy.

[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.

[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. [Krolewiecki] show a concentration dependent antiviral activity of ivermectin whereby the viral decay rate for patients with ivermectin >160ng/mL was $0.64 \log_{10}$ copies/reaction/day versus 0.13 for control. However, they do not provide the results for the entire treatment group vs. control. [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. Results for [Raad] are available in [Hill], however no paper is currently available.

Summarizing, the studies excluded are as follows, and the resulting forest plot is shown in Figure 18.

[Carvalho], control group formed from cases in the same hospital not in the study.

[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.

[Raad], detail too minimal.

[*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.

[*Vallejos*], detail too minimal.

All 47 ivermectin COVID-19 studies with exclusions

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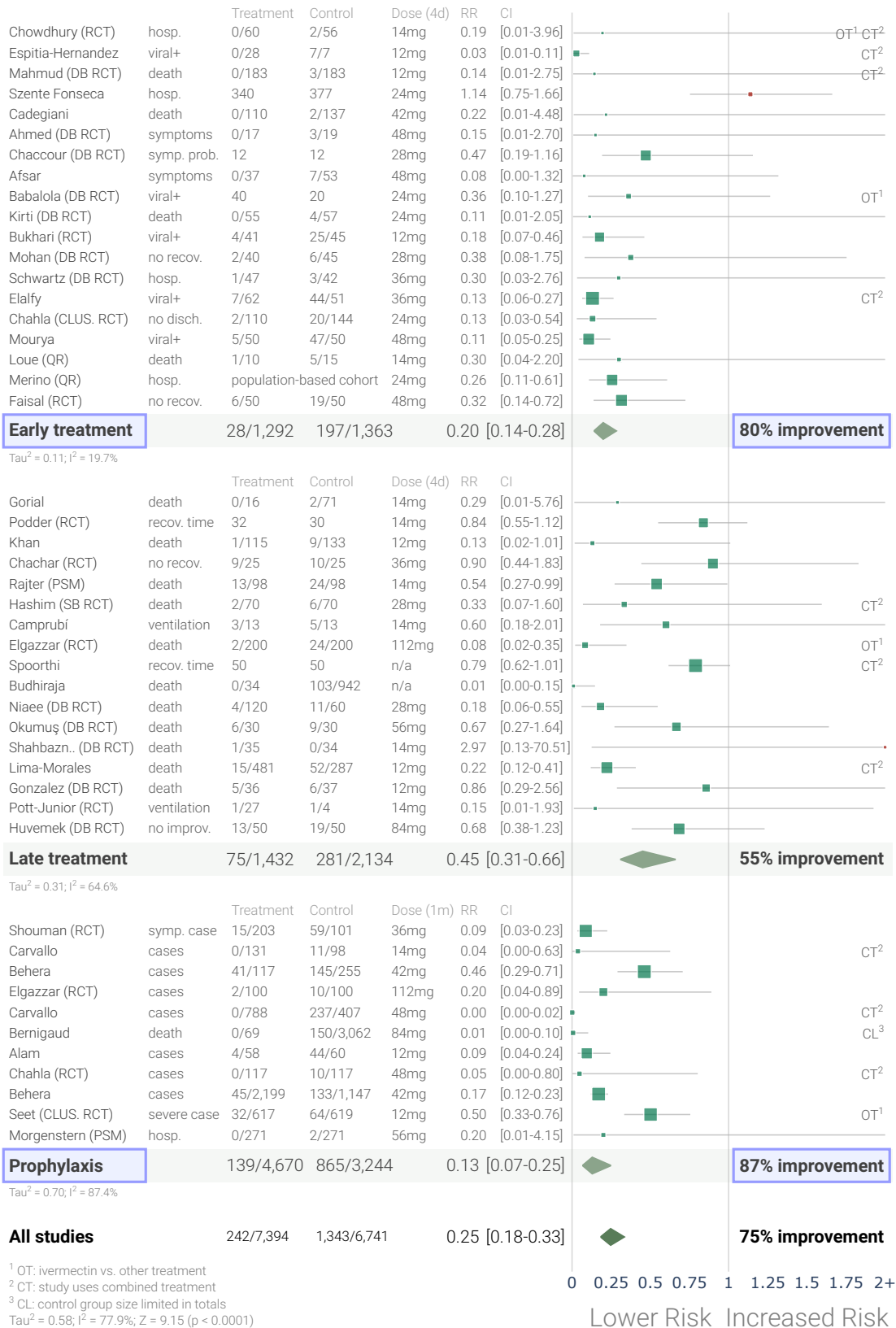


Figure 18. Random effects meta-analysis excluding studies with significant issues.

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 19 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].

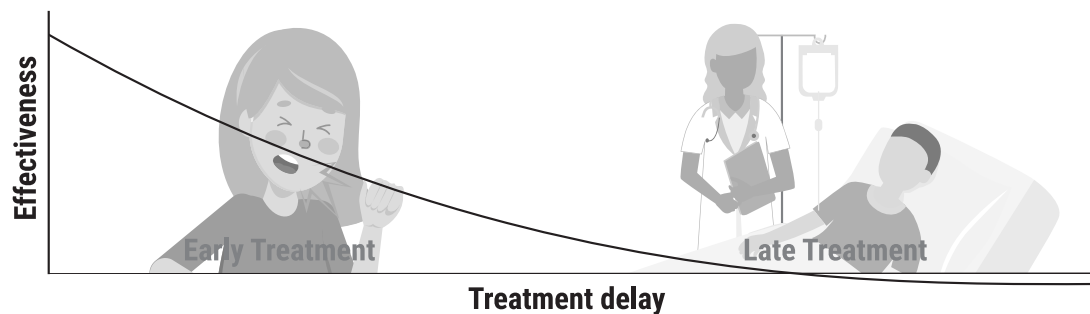


Figure 19. Effectiveness may depend critically on treatment delay.

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 20: 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.

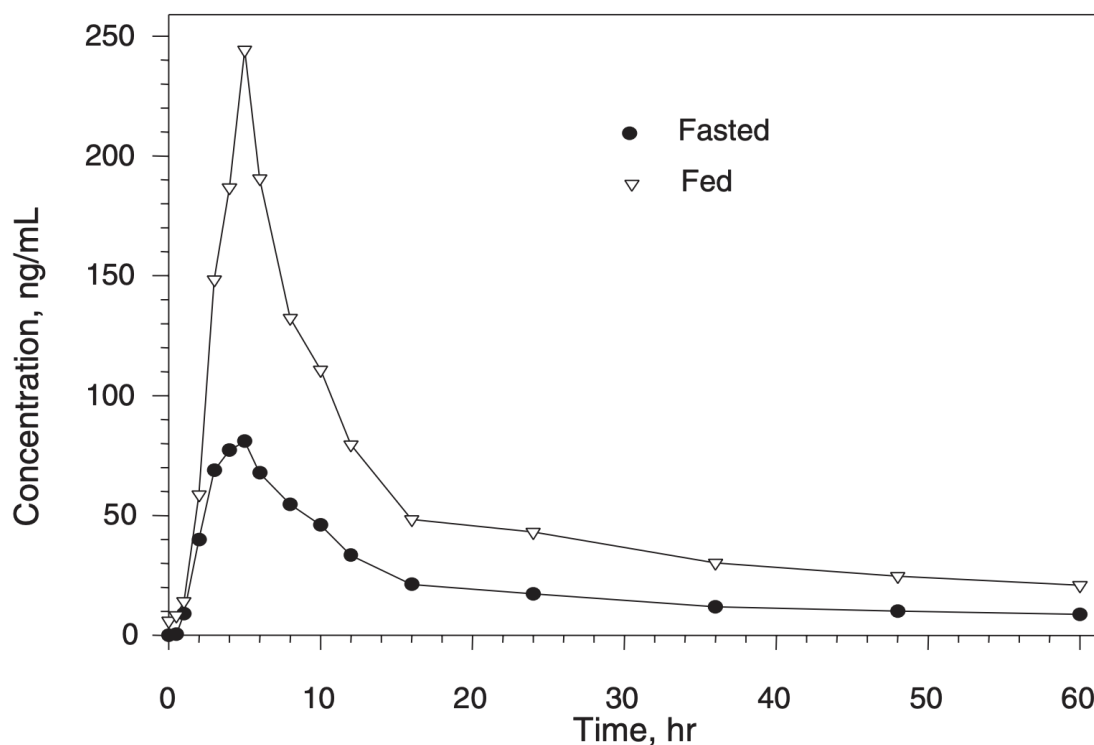


Figure 20. Mean plasma concentration (ng/ml) profiles of ivermectin following single oral doses of 30mg (fed and fasted administration), from [Guzzo].

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 56 studies to date is estimated to be 1 in 2 trillion ($p = 0.00000000000041$). 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

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 21 shows a scatter plot of results for prospective and retrospective studies. The median effect size for prospective studies is 79% 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.

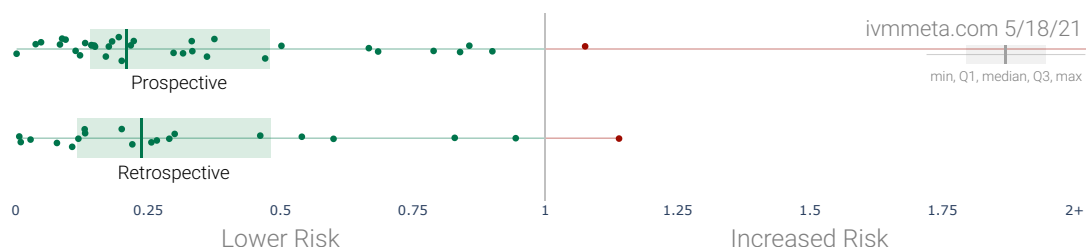


Figure 21. Prospective vs. retrospective studies.

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.

4 of the 56 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. 12 of 56 studies combine treatments, for example ivermectin + doxycycline. The results of ivermectin alone may differ. 4 of 28 RCTs use combined treatment, three with doxycycline, and one with iota-carrageenan. 2 of 56 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 22 shows a comparison of mortality results across meta analyses. [Kory] also review epidemiological data and provide suggested treatment regimens.

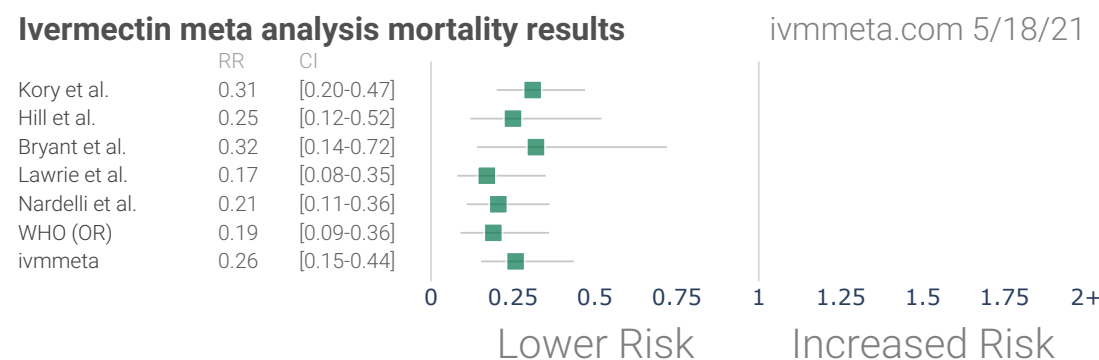


Figure 22. Comparison of mortality results from different meta analyses. OR converted to RR for [Kory, Nardelli]. OR displayed for [WHO] (they do not provide the details required to calculate the RR).

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.

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>	56	18,447	72% [64-79%]	Pending

Table 3. Evidence base used for other COVID-19 approvals compared with the ivermectin evidence base.

Indication	Studies	Patients	Status
Scabies [Kory (B)]	10	852	Approved
Strongyloidiasis [Kory (B)]	5	591	Approved
COVID-19	56	18,447	Pending
COVID-19 RCTs	28	4,997	

Table 4. WHO ivermectin approval status.

	Ibuprofen	Ivermectin for scabies	Ivermectin for COVID-19
Deaths per year	~450	<1	<1
Lives saved	0	0	>500,000
CDC recommended for COVID-19	Yes	Yes	No
Based on	0 RCTs	10 RCTs, 852 patients	28 RCTs, 4,997 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.

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

- Of the 56 studies (28 RCTs), they only included 16.
- They excluded all 14 prophylaxis studies (4 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 2 trillion ($p = 0.000000000000041$). 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 56 studies by 469 scientists with 18,447 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 [Rochwerg].

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 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, Qureshi, Saha, Surnar, Udofia, Wehbe, Yesilbag, Zatloukal].

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, Babalola, Behera, Behera (B), Bernigaud, Budhiraja, Bukhari, Cadegiani, Carvalho (B), Carvalho (C), Chaccour, Chahla, Chahla (B), Chowdhury, Elalfy, Elgazzar, Elgazzar (B), Espitia-Hernandez, Faisal, Hashim, Huvenek, Khan, Kirti, Lima-Morales, Loue, Mahmud, Merino, Mohan, Morgenstern, Mourya, Niaee, Okumuş, 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 [Afsar, Ahmed, Babalola, Behera (B), Bhattacharya, Bukhari, Camprubí, Carvallo, Chaccour, Chahla (B), Chowdhury, Elalfy, Elgazzar, Espitia-Hernandez, Gorial, Huvemek, Khan, Kishoria, Lima-Morales, Loue, López-Medina, Mahmud, Mohan, Morgenstern, Mourya, Niaee, Okumuş, Pott-Junior, Schwartz, Seet, Shahbaznejad, Shouman, Spoorthi, Szente Fonseca].

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], to help eliminate river blindness.
- Merck has their own new COVID-19 treatments MK-7110 (formerly CD24Fc) [Adams] and Molnupiravir (MK-4482) [Wikipedia].
- Ivermectin is off-patent, there are many manufactureres, 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].

Conclusion

Ivermectin is an effective treatment for COVID-19. The probability that an ineffective treatment generated results as positive as the 56 studies to date is estimated to be 1 in 2 trillion ($p = 0.000000000000041$). As expected for an effective treatment, early treatment is more successful, with an estimated reduction of 78% in the effect measured using random effects meta-analysis (RR 0.22 [0.12-0.39]). 81% and 96% lower mortality is observed for early treatment and prophylaxis (RR 0.19 [0.07-0.54] and 0.04 [0.00-0.58]). Statistically significant improvements are seen for mortality, ventilation, hospitalization, cases, and viral clearance. The consistency of positive results across a wide variety of heterogeneous studies is remarkable, with 95% of the 56 studies reporting positive effects (26 statistically significant in isolation).

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 [Carvallo (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 [Kirti]. 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 [Raad, 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 [Schwartz].

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 [Okumus] 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 (B)].

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 [Schwartz] 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 [Okumus] 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.

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 an effect compared to 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 (this does not result in the exclusion of any studies – the next most serious outcome is used). 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 (3.9.1) with scipy (1.6.3), pythonmeta (1.23), numpy (1.20.2), 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].

Due to the much larger size of the control group in *[Bernigaud]*, we limit the size of the control group to be the same as the treatment group for calculation of the number of patients.

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.

<i>[Afsar]</i> , 12/15/2020, retrospective, Pakistan, South Asia, preprint, 6 authors, dosage 12mg days 1-6.	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).
<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.	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.
	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.
	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.
	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.
	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.
	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.
	time to viral-, 23.6% lower, relative time 0.76, $p = 0.02$, treatment 22, control 23, ivermectin.
	time to viral-, 9.4% lower, relative time 0.91, $p = 0.27$, treatment 23, control 23, ivermectin + doxycycline.
	hospitalization time, 1.0% lower, relative time 0.99, ivermectin.
	hospitalization time, 4.1% higher, relative time

	1.04, ivermectin + doxycycline.
[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.	adjusted risk of viral+ at day 5, 63.9% lower, RR 0.36, $p = 0.11$, treatment 40, control 20, adjusted per study.
	risk of no virological cure, 58.0% lower, RR 0.42, $p = 0.01$, treatment 20, control 20, 12mg - Cox proportional hazard model.
	risk of no virological cure, 40.5% lower, RR 0.60, $p = 0.12$, treatment 20, control 20, 6mg - Cox proportional hazard model.
	time to viral-, 49.2% lower, relative time 0.51, treatment 20, control 20, 12mg.
	time to viral-, 34.4% lower, relative time 0.66, treatment 20, control 20, 6mg.
[Bukhari], 1/16/2021, Randomized Controlled Trial, Pakistan, Middle East, 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, preprint, 4 authors, dosage 200µg/kg days 1-3.	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, preprint, 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.	risk of death for hospitalized cases in study vs. cases in the same hospital not in the study, 87.9% lower, RR 0.12, $p = 0.05$, treatment 1 of 33 (3.0%), control 3 of 12 (25.0%), the only treatment death was a patient already in the ICU before treatment.
[Chaccour], 12/7/2020, Double Blind	symptom probability, 52.9% lower, RR 0.47, $p <$

Randomized Controlled Trial, Spain, Europe, peer-reviewed, 23 authors, dosage 400µg/kg single dose.	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 America, preprint, 9 authors, dosage 24mg days 1, 8, 15, 22.	risk of no discharge, 86.9% lower, RR 0.13, $p = 0.004$, treatment 2 of 110 (1.8%), control 20 of 144 (13.9%), adjusted per study, odds ratio converted to relative risk, logistic regression.
[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.	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).
	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.
	recovery time, 15.2% lower, relative time 0.85, $p = 0.07$, treatment 60, control 56.
	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).
	time to viral-, 4.3% lower, relative time 0.96, $p = 0.23$, treatment 60, control 56.
[Elalfy], 2/16/2021, retrospective, Egypt, Middle East, 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.	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.
	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.
[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.	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).
[Faisal], 5/10/2021, Randomized Controlled Trial, Pakistan, South Asia, peer-reviewed, 3 authors, dosage 12mg days 1-5.	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.
	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.
	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.
[Kirti], 1/9/2021, Double Blind Randomized Controlled Trial, India, South Asia, preprint, 11 authors, dosage 12mg days 1, 2.	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).
	risk of mechanical ventilation, 79.3% lower, RR 0.21, $p = 0.09$, treatment 1 of 55 (1.8%), control 5 of 57 (8.8%).
	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%).
	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%).
[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, Columbia, 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.
	hazard ratio for lack of resolution of symptoms, 6.5% lower, RR 0.93, $p = 0.53$, treatment 200, control 198.
	relative median time to resolution of symptoms, 16.7% lower, relative time 0.83, treatment 200, control 198.
[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.	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).
	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.
	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.
	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.
	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.
	time to recovery, 27.0% lower, RR 0.73, $p = 0.003$, treatment 183, control 180, Cox regression.
	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.
[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.	risk of hospitalization, 74.4% lower, RR 0.26, $p < 0.001$, model 7, same time period, patients receiving kit.
	risk of hospitalization, 68.4% lower, RR 0.32, $p < 0.001$, model 1, different time periods, administrative rule.
[Mohan], 2/2/2021, Double Blind Randomized Controlled Trial, India, South Asia, preprint, 27 authors, dosage 400µg/kg single dose, 200µg/kg also tested.	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.
	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.
	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.
	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.
	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.
	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.
[Mourya] , 4/1/2021, retrospective, India, South Asia, peer-reviewed, 5 authors, dosage 12mg days 1-7.	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%).
[Raad] , 1/16/2021, Single Blind Randomized Controlled Trial, Lebanon, Middle East, preprint, 1 author, dosage 200µg/kg single dose.	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).
	risk of viral load, 59.0% lower, RR 0.41, $p = 0.01$, treatment 50, control 50, percentage relative improvement in Ct value with treatment at day 3.
[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.	relative time to clinical response of wellbeing, 5.6% lower, relative time 0.94, $p = 0.87$, treatment 14, control 15.
[Schwartz] , 2/12/2021, Double Blind Randomized Controlled Trial, Israel, Middle East, preprint, 1 author, dosage 12mg days 1-3, 15mg for patients ≥ 70 kg.	risk of hospitalization, 70.2% lower, RR 0.30, $p = 0.34$, treatment 1 of 47 (2.1%), control 3 of 42 (7.1%).
	risk of no virological cure, 42.2% lower, RR 0.58, $p = 0.01$, treatment 16 of 49 (32.7%), control 25 of 45 (55.6%), adjusted per study, odds ratio converted to relative risk, multivariable logistic regression, day 6, Ct>30.
	risk of no virological cure, 70.2% lower, RR 0.30, $p = 0.02$, treatment 4 of 47 (8.5%), control 12 of 42 (28.6%), day 6, non-infectious samples (Ct>30 or non-viable culture).
	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.

	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.
	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.
	risk of no virological cure, 31.9% lower, RR 0.68, $p = 0.16$, treatment 13 of 28 (46.4%), control 15 of 22 (68.2%), day 4, Ct>30.
<i>[Szente Fonseca]</i> , 10/31/2020, retrospective, Brazil, South America, peer-reviewed, mean age 50.6, 10 authors, dosage 12mg days 1-2.	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.

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.

<i>[Budhiraja]</i> , 11/18/2020, retrospective, India, South Asia, preprint, 12 authors, dosage not specified.	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).
<i>[Camprubi]</i> , 11/11/2020, retrospective, Spain, Europe, peer-reviewed, 9 authors, dosage 200µg/kg single dose.	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%).
	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.
	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%).
<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.	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%).
<i>[Elgazzar]</i> , 11/13/2020, Randomized Controlled Trial, Egypt, Africa, preprint, 6 authors, dosage 400µg/kg days 1-4, this trial compares with another treatment - results may be better when compared to placebo.	risk of death, 91.7% lower, RR 0.08, $p < 0.001$, treatment 2 of 200 (1.0%), control 24 of 200 (12.0%).
	risk of death, 88.9% lower, RR 0.11, $p = 0.12$, treatment 0 of 100 (0.0%), control 4 of 100 (4.0%), continuity correction due to zero event (with

	reciprocal of the contrasting arm), mild/moderate COVID-19.
	risk of death, 90.0% lower, RR 0.10, $p < 0.001$, treatment 2 of 100 (2.0%), control 20 of 100 (20.0%), severe COVID-19.
[Gonzalez], 2/23/2021, Double Blind Randomized Controlled Trial, Mexico, North America, peer-reviewed, mean age 53.8, 13 authors, dosage 12mg single dose, 18mg for patients >80kg.	risk of death, 14.4% lower, RR 0.86, $p = 1.00$, treatment 5 of 36 (13.9%), control 6 of 37 (16.2%).
	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%).
[Gorial], 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.
[Hashim], 10/26/2020, Single Blind Randomized Controlled Trial, Iraq, Middle East, preprint, 6 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, 66.7% lower, RR 0.33, $p = 0.27$, treatment 2 of 70 (2.9%), control 6 of 70 (8.6%), all patients.
	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 critical patients.
[Huvemek], 3/25/2021, Double Blind Randomized Controlled Trial, Bulgaria, Europe, preprint, 1 author, dosage 400µg/kg days 1-3.	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.
	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.
[Khan], 9/24/2020, retrospective, Bangladesh, South Asia, preprint, median age 35.0, 8 authors, dosage 12mg single dose.	risk of death, 87.0% lower, RR 0.13, $p < 0.05$, treatment 1 of 115 (0.9%), control 9 of 133 (6.8%).
	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%).
	time to viral-, 73.3% lower, relative time 0.27, $p < 0.001$, treatment 115, control 133.

<p>[Kishoria], 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>[Lima-Morales], 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 287 (41.1%), adjusted per study, odds ratio converted to relative risk, recovery at day 14 after symptoms, multivariate.</p>
<p>[Niaee], 11/24/2020, Double Blind Randomized Controlled Trial, Iran, Middle East, preprint, 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>[Okumuş], 1/12/2021, Double Blind Randomized Controlled Trial, Turkey, Middle East, peer-reviewed, 15 authors,</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>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>

dosage 200µg/kg days 1-5, 36-50kg - 9mg, 51-65kg - 12mg, 66-79kg - 15mg, >80kg 200µg/kg.	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%).
	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%).
	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.
[Podder] , 9/3/2020, Randomized Controlled Trial, Bangladesh, South Asia, peer-reviewed, 4 authors, dosage 200µg/kg single dose.	recovery time from enrollment, 16.1% lower, relative time 0.84, $p = 0.34$, treatment 32, control 30.
[Pott-Junior] , 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.	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%).
	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%).
	relative improvement in Ct value, 0.8% lower, RR 0.99, $p = 1.00$, treatment 27, control 3.
	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%).
	time to viral-, 16.7% lower, relative time 0.83, treatment 27, control 3.
[Rajter] , 10/13/2020, retrospective, propensity score matching, USA, North America, peer-reviewed, 6 authors, dosage 200µg/kg single dose.	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.
	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.
	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.
[Shahbaznejad] , 1/19/2021, Double Blind Randomized Controlled Trial, Iran, Middle East, peer-reviewed, 8 authors, dosage 200µg/kg single dose.	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.

	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%).
	recovery time, 31.6% lower, relative time 0.68, $p = 0.05$, treatment 35, control 34, duration of dyspnea.
	recovery time, 19.2% lower, relative time 0.81, $p = 0.02$, treatment 35, control 34, duration of all 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.

[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, preprint, 13 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,	risk of COVID-19 case, 53.8% lower, RR 0.46, $p < 0.001$, treatment 41 of 117 (35.0%), control 145 of

dosage 300µg/kg days 1, 4.	255 (56.9%), adjusted per study, odds ratio converted to relative risk, model 2 2+ doses conditional logistic regression.
	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.
<i>[Bernigaud]</i> , 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%).
<i>[Carvalho (C)]</i> , 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).
<i>[Carvalho (B)]</i> , 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).
<i>[Chahla (B)]</i> , 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 COVID-19 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.
<i>[Elgazzar (B)]</i> , 11/13/2020, Randomized Controlled Trial, Egypt, Africa, preprint, 6 authors, dosage 400µg/kg weekly.	risk of COVID-19 case, 80.0% lower, RR 0.20, $p = 0.03$, treatment 2 of 100 (2.0%), control 10 of 100 (10.0%).
<i>[Hellwig]</i> , 11/28/2020, retrospective, ecological study, multiple countries, Africa, peer-reviewed, 2 authors, dosage	risk of COVID-19 case, 78.0% lower, RR 0.22, $p < 0.02$, African countries, PCTI vs. no PCT, relative cases per capita.

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.
[Morgenstern], 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.
[Seet], 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.
[Shouman], 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.
[Tanioka], 3/26/2021, retrospective, ecological study, multiple countries, Africa, 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.
[Vallejos], 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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