Ivermectin for COVID-19: real-time meta analysis of 64 studies

Covid Analysis, **Oct 29, 2021**, Version 140 — GMK response updates [BBC, GMK response]

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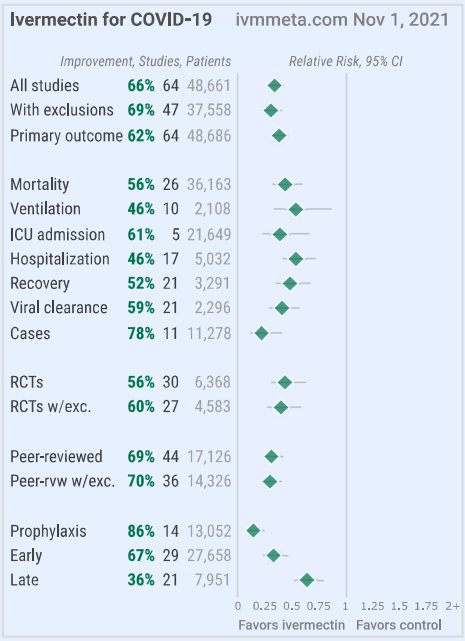
- Meta analysis using the most serious outcome reported shows 67% [53-76%] and 86% [75-92%] improvement for early treatment and prophylaxis, with similar results after exclusion based sensitivity analysis (which excludes all of the GMK/BBC team studies), with primary outcomes, and after restriction to peer-reviewed studies or Randomized Controlled Trials.
- Statistically significant improvements are seen for mortality, ventilation, ICU admission, hospitalization, recovery, cases, and viral clearance. All remain statistically significant after exclusions. 31 studies show statistically significant improvements in isolation.
- Results are very robust — in worst case exclusion sensitivity analysis 53 of 64 studies must be excluded to avoid finding statistically significant efficacy.

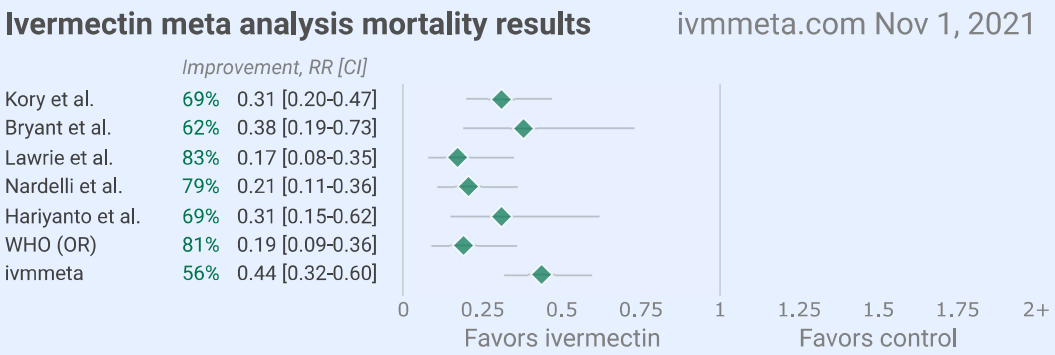


- **While many treatments have some level of efficacy, they do not replace vaccines and other measures to avoid infection. Only 25% of ivermectin studies show zero events in the treatment arm.**
- Multiple treatments are typically used in combination, and other treatments could be more effective, including monoclonal antibodies which may be available in countries not recommending ivermectin (sotrovimab, casirivimab/imdevimab, and bamlanivimab/etesevimab).
- Elimination of COVID-19 is a race against viral evolution. No treatment, vaccine, or intervention is 100% available and effective for all variants. All practical, effective, and safe means should be used, including treatments, as supported by Pfizer ***[Pfizer, TrialSiteNews]***. Denying the efficacy of treatments increases the risk of COVID-19 becoming endemic; and increases mortality, morbidity, and collateral damage.

	Studies	*Prophylaxis*	*Early treatment*	*Late treatment*	*Patients*
All studies	64	**86%** [75-92%]	**67%** [53-76%]	**36%** [21-48%]	48,661
Peer-reviewed	44	**86%** [74-93%]	**71%** [54-82%]	**38%** [16-55%]	17,126
With GMK/BBC exclusions	47	**84%** [69-91%]	**73%** [63-80%]	**45%** [22-61%]	37,558
Randomized Controlled Trials	30	**84%** [25-96%]	**63%** [44-75%]	**20%** [-6-39%]	6,368

Percentage improvement with ivermectin treatment

- There is evidence of a negative publication bias, and the probability that an ineffective treatment generated results as positive as the 64 studies is estimated to be 1 in 222 billion.
- Over 20 countries have adopted ivermectin for COVID-19. The evidence base is much larger and has much lower conflict of interest than typically used to approve drugs.
- All data to reproduce this paper and sources are in the appendix. See ***[Bryant, Hariyanto, Kory, Lawrie, Nardelli]*** for other meta analyses with similar results confirming efficacy.



Evidence base used for other COVID-19 approvals			
Medication	Studies	Patients	Improvement
Budesonide (UK)	1	1,779	17%
Remdesivir (USA EUA)	1	1,063	31%
Casirivimab/i.. (USA EUA)	1	799	66%
Ivermectin evidence	64	48,637	66% [57-73%]


Ivermectin COVID-19 early treatment and prophylaxis studies
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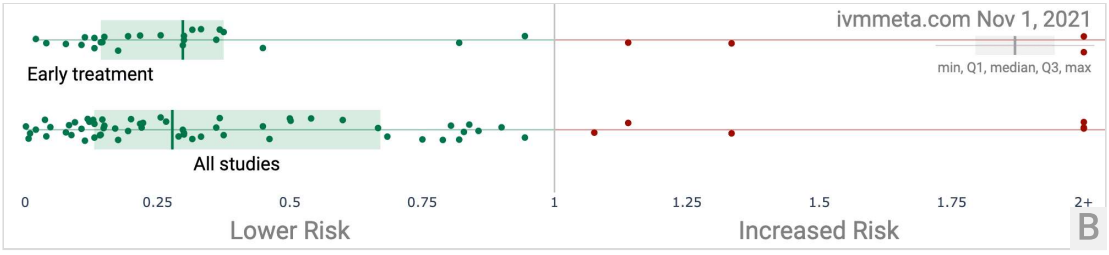
Improvement, RR [CI]
Treatment
Control
Dose (4d)
Chowdhury (RCT) 81% 0.19 [0.01-3.96] hosp. 0/60 2/56 14mg OT1 CT2
Espitia-Hernandez 70% 0.30 [0.16-0.55] recov. time 28 (n) 7 (n) 12mg CT2
Carvallo 85% 0.15 [0.02-1.28] death 1/32 3/14 36mg CT2
Mahmud (DB RCT) 86% 0.14 [0.01-2.75] death 0/183 3/183 12mg CT2
Szente Fonseca -14% 1.14 [0.75-1.66] hosp. 340 (n) 377 (n) 24mg
Cadegiani 78% 0.22 [0.01-4.48] death 0/110 2/137 42mg CT2
Ahmed (DB RCT) 85% 0.15 [0.01-2.70] symptoms 0/17 3/19 48mg
Chaccour (DB RCT) 96% 0.04 [0.00-1.01] symptoms 12 (n) 12 (n) 28mg
Ghauri 98% 0.02 [0.00-0.20] symptoms 37 (n) 53 (n) 48mg
Babalola (DB RCT) 64% 0.36 [0.10-1.27] viral+ 40 (n) 20 (n) 24mg OT1
Ravikirti (DB RCT) 89% 0.11 [0.01-2.05] death 0/55 4/57 24mg
Bukhari (RCT) 82% 0.18 [0.07-0.46] viral+ 4/41 25/45 12mg
Mohan (DB RCT) 62% 0.38 [0.08-1.75] no recov. 2/40 6/45 28mg
Biber (DB RCT) 70% 0.30 [0.03-2.76] hosp. 1/47 3/42 36mg
Elalfy 87% 0.13 [0.06-0.27] viral+ 7/62 44/51 36mg CT2
López-Me.. (DB RCT) 67% 0.33 [0.01-8.11] death 0/200 1/198 84mg
Roy 6% 0.94 [0.52-1.93] recov. time 14 (n) 15 (n) n/a CT2
Chahla (CLUS. RCT) 87% 0.13 [0.03-0.54] no disch. 2/110 20/144 24mg
Mourya 89% 0.11 [0.05-0.25] viral+ 5/50 47/50 48mg
Loue (QR) 70% 0.30 [0.04-2.20] death 1/10 5/15 14mg
Merino (QR) 74% 0.26 [0.11-0.57] hosp. population-based cohort 24mg
Faisal (RCT) 68% 0.32 [0.14-0.72] no recov. 6/50 19/50 48mg
Aref (RCT) 63% 0.37 [0.22-0.61] recov. time 57 (n) 57 (n) n/a
Krolewiecki (RCT) -152% 2.52 [0.11-58.1] ventilation 1/27 0/14 168mg
Vallejos (DB RCT) -33% 1.33 [0.30-5.72] death 4/250 3/251 24mg
Together.. (DB RCT) 18% 0.82 [0.44-1.52] death 18/677 22/678 84mg
Buonfrate (DB RCT) -600% 7.00 [0.39-126] hosp. 4/58 0/29 336mg
Mayer 55% 0.45 [0.32-0.63] death 3,266 (n) 17,966 (n) 151mg
Borody 92% 0.08 [0.01-0.79] death 0/600 6/600 96mg CT2 SC4
Early treatment 67% 0.33 [0.24-0.47] 56/6,473 218/21,185
67% improvement
Tau² = 0.38; I² = 62.8%
Improvement, RR [CI]
Treatment
Control
Dose (1m)
Shouman (RCT) 91% 0.09 [0.03-0.23] symp. case 15/203 59/101 36mg
Carvallo 96% 0.04 [0.00-0.63] cases 0/131 11/98 14mg CT2
Behera 54% 0.46 [0.29-0.71] cases 41/117 145/255 42mg
Carvallo 100% 0.00 [0.00-0.02] cases 0/788 237/407 48mg CT2
Hellwig (ECO.) 78% 0.22 [0.05-0.89] cases ecological 14mg
Bernigaud 99% 0.01 [0.00-0.10] death 0/69 150/3,062 84mg
Alam 91% 0.09 [0.04-0.25] cases 4/58 44/60 12mg
Vallejos 73% 0.27 [0.15-0.48] cases 13/389 61/486 48mg MD3
Chahla (RCT) 95% 0.05 [0.00-0.80] m/s case 0/117 10/117 48mg CT2
Behera 83% 0.17 [0.12-0.23] cases 45/2,199 133/1,147 42mg
Tanioka (ECO.) 88% 0.12 [0.03-0.51] death ecological 14mg
Seet (CLUS. RCT) 50% 0.50 [0.33-0.76] symp. case 32/617 64/619 12mg OT1
Morgenstern (PSM) 80% 0.20 [0.01-4.15] hosp. 0/271 2/271 56mg
Mondal 88% 0.12 [0.01-0.55] symp. case 128 (n) 1,342 (n) n/a
Prophylaxis 86% 0.14 [0.08-0.25] 150/5,087 916/7,965
86% improvement
Tau² = 0.59; I² = 83.9%
All studies 75% 0.25 [0.18-0.33] 206/11,560 1,134/29,150
75% improvement
1 OT: ivermectin vs. other treatment
2 CT: study uses combined treatment
3 MD: minimal detail available currently
4 SC: study uses synthetic control arm
Tau² = 0.48; I² = 75.3%; Z = 9.21
Effect extraction pre-specified, see appendix
0 0.25 0.5 0.75 1 1.25 1.5 1.75
Favors ivermectin
Favors contro
A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min, Q1, median, Q3, max
Early treatment
All studies
0 0.25 0.5 0.75 1 1.25 1.5 1.75 2+
Lower Risk
Increased Risk
B

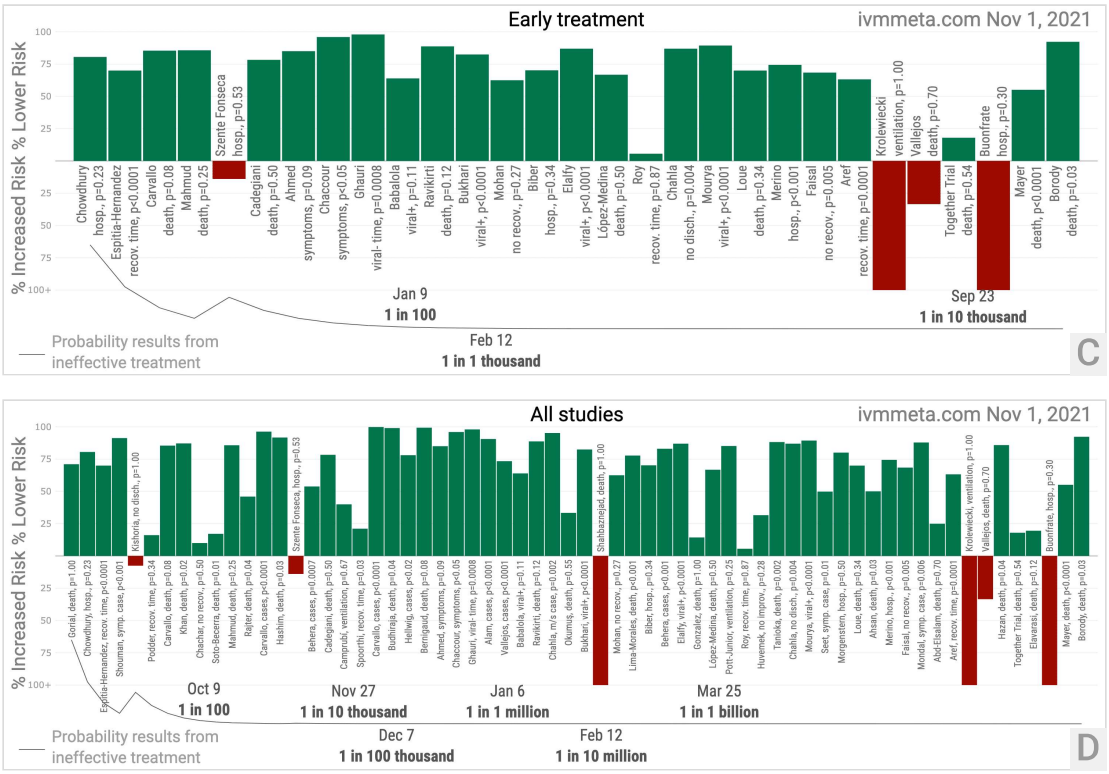

Figure 1. *A. Random effects meta-analysis excluding late treatment. This plot shows pooled effects, analysis for individual outcomes is below, and more details on pooled effects can be found in the heterogeneity section. Effect extraction is pre-specified, using the most serious outcome reported. Simplified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

Introduction

We analyze all significant studies concerning the use of ivermectin for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random effects meta-analysis results for all studies, for studies within each treatment stage, for mortality results, for COVID-19 case results, for viral clearance results, for peer-reviewed studies, for Randomized Controlled Trials (RCTs), and after exclusions.

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

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

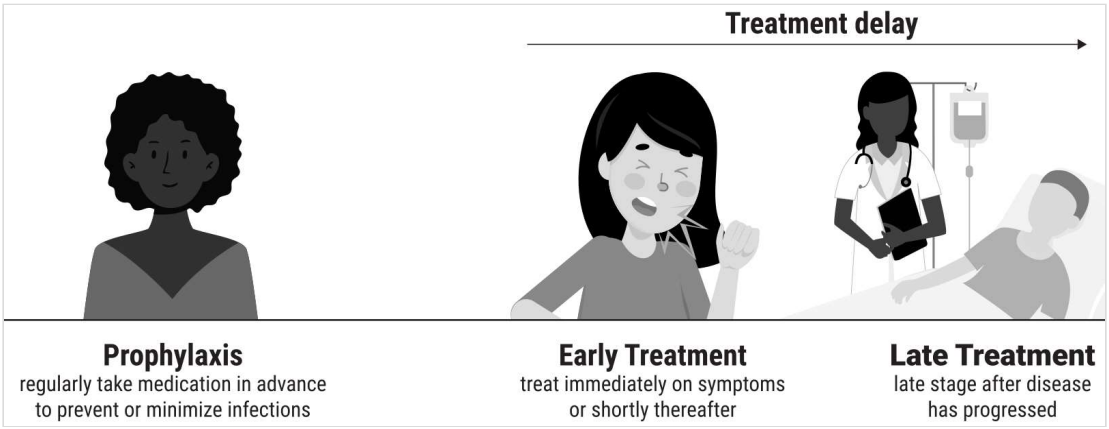

Figure 2. *Treatment stages.*

Results

Figure 3, 4, and 5 show results by treatment stage. Figure 6, 7, 8, 9, 10, 11, 12, and 13 show forest plots for a random effects meta-analysis of all studies with pooled effects, and for studies reporting mortality results, ICU admission, mechanical ventilation, hospitalization, recovery, COVID-19 cases, and viral clearance results only. Figure 14 shows results for peer reviewed trials only, and the supplementary data contains peer reviewed and individual outcome results after exclusions. 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	25	29	86.2%	1 in 19 thousand	**67%** improvement RR 0.33 [0.24-0.47] p < 0.0001
Late treatment	19	21	**90.5%**	1 in 9 thousand	36% improvement RR 0.64 [0.52-0.79] p < 0.0001
Prophylaxis	14	14	**100%**	1 in 16 thousand	**86%** improvement RR 0.14 [0.08-0.25] p < 0.0001
All studies	58	64	**90.6%**	1 in 222 billion	**66%** improvement RR 0.34 [0.27-0.43] p < 0.0001

Table 1. *Results by treatment stage.*

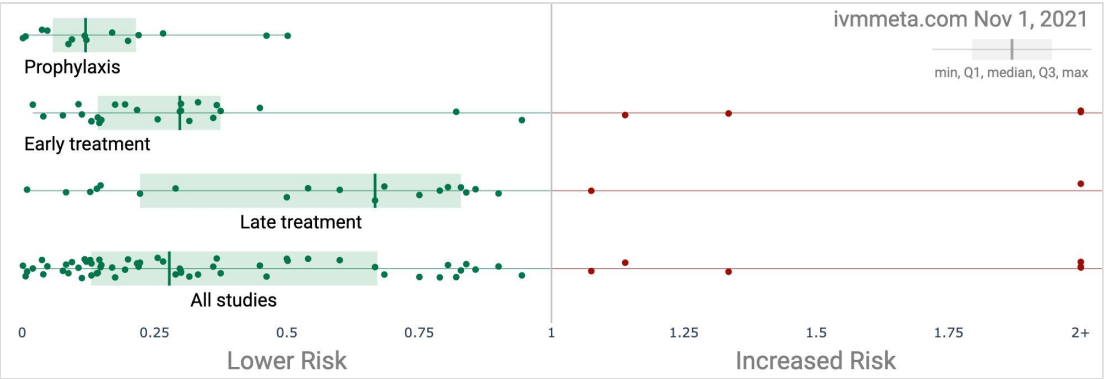

Figure 3. *Results by treatment stage.*

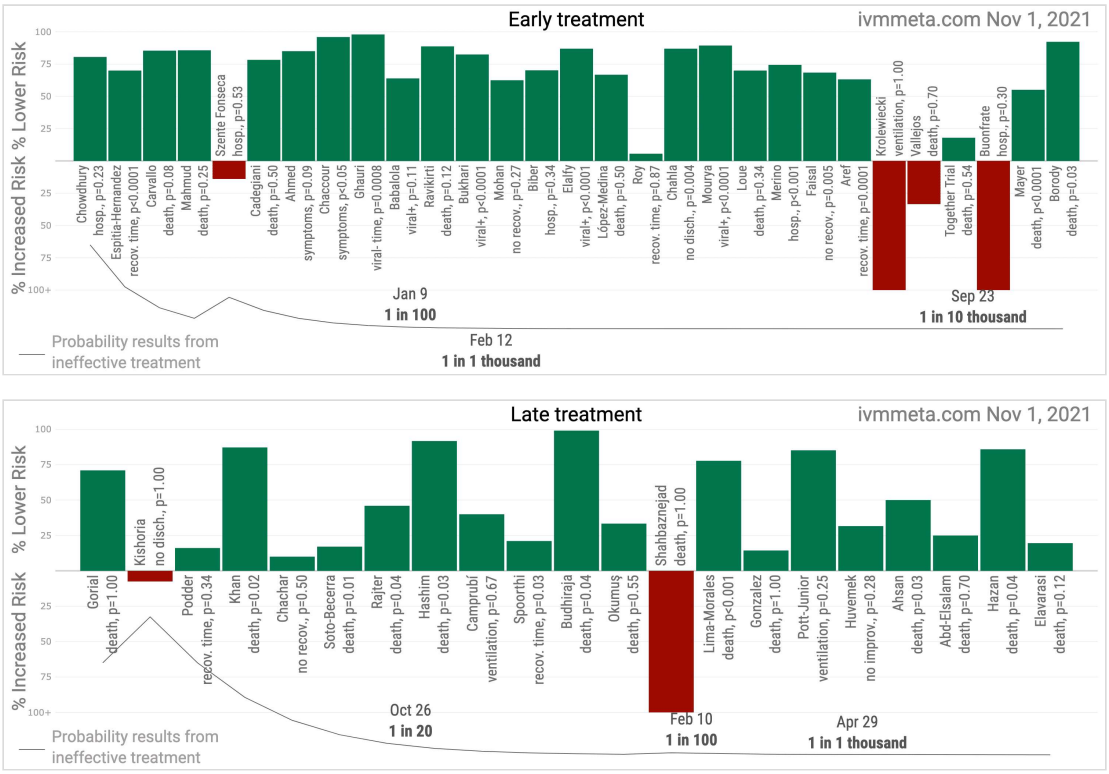

Figure 4. *Chronological history of early and late treatment results, with the probability that the observed frequency of positive results occurred due to random chance from an ineffective treatment.*

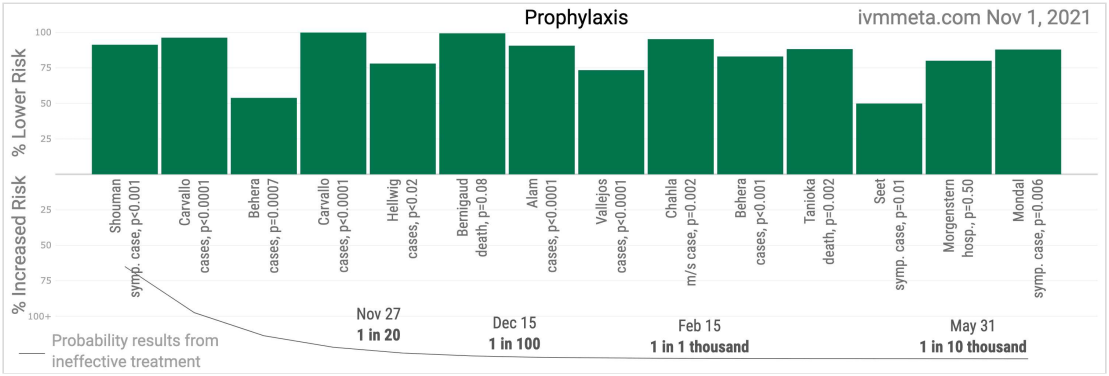

Figure 5. *Chronological history of prophylaxis results.*

All 64 ivermectin COVID-19 studies

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	Improvement, RR [CI]			Treatment	Control	Dose (4d)
Chowdhury (RCT)	81%	0.19 [0.01-3.96]	hosp.	0/60	2/56	14mg
Espitia-Hernandez	70%	0.30 [0.16-0.55]	recov. time	28 (n)	7 (n)	12mg
Carvallo	85%	0.15 [0.02-1.28]	death	1/32	3/14	36mg
Mahmud (DB RCT)	86%	0.14 [0.01-2.75]	death	0/183	3/183	12mg
Szente Fonseca	-14%	1.14 [0.75-1.66]	hosp.	340 (n)	377 (n)	24mg
Cadegiani	78%	0.22 [0.01-4.48]	death	0/110	2/137	42mg
Ahmed (DB RCT)	85%	0.15 [0.01-2.70]	symptoms	0/17	3/19	48mg
Chaccour (DB RCT)	96%	0.04 [0.00-1.01]	symptoms	12 (n)	12 (n)	28mg
Ghauri	98%	0.02 [0.00-0.20]	symptoms	37 (n)	53 (n)	48mg
Babalola (DB RCT)	64%	0.36 [0.10-1.27]	viral+	40 (n)	20 (n)	24mg
Ravikirti (DB RCT)	89%	0.11 [0.01-2.05]	death	0/55	4/57	24mg
Bukhari (RCT)	82%	0.18 [0.07-0.46]	viral+	4/41	25/45	12mg
Mohan (DB RCT)	62%	0.38 [0.08-1.75]	no recov.	2/40	6/45	28mg
Biber (DB RCT)	70%	0.30 [0.03-2.76]	hosp.	1/47	3/42	36mg
Elalfy	87%	0.13 [0.06-0.27]	viral+	7/62	44/51	36mg
López-Me.. (DB RCT)	67%	0.33 [0.01-8.11]	death	0/200	1/198	84mg
Roy	6%	0.94 [0.52-1.93]	recov. time	14 (n)	15 (n)	n/a
Chahla (CLUS. RCT)	87%	0.13 [0.03-0.54]	no disch.	2/110	20/144	24mg
Mourya	89%	0.11 [0.05-0.25]	viral+	5/50	47/50	48mg
Loue (QR)	70%	0.30 [0.04-2.20]	death	1/10	5/15	14mg
Merino (QR)	74%	0.26 [0.11-0.57]	hosp.	population-based cohort		24mg
Faisal (RCT)	68%	0.32 [0.14-0.72]	no recov.	6/50	19/50	48mg
Aref (RCT)	63%	0.37 [0.22-0.61]	recov. time	57 (n)	57 (n)	n/a
Krolewiecki (RCT)	-152%	2.52 [0.11-58.1]	ventilation	1/27	0/14	168mg
Vallejos (DB RCT)	-33%	1.33 [0.30-5.72]	death	4/250	3/251	24mg
Together.. (DB RCT)	18%	0.82 [0.44-1.52]	death	18/677	22/678	84mg
Buonfrate (DB RCT)	-600%	7.00 [0.39-126]	hosp.	4/58	0/29	336mg
Mayer	55%	0.45 [0.32-0.63]	death	3,266 (n)	17,966 (n)	151mg
Borody	92%	0.08 [0.01-0.79]	death	0/600	6/600	96mg
Early treatment	67%	0.33 [0.24-0.47]		56/6,473	218/21,185	

$Tau^2 = 0.38$; $I^2 = 62.8\%$

67% improvement

	Improvement, RR [CI]			Treatment	Control	Dose (4d)
Gorial	71%	0.29 [0.01-5.76]	death	0/16	2/71	14mg
Kishoria (RCT)	-8%	1.08 [0.57-2.02]	no disch.	11/19	7/13	12mg
Podder (RCT)	16%	0.84 [0.55-1.12]	recov. time	32 (n)	30 (n)	14mg
Khan	87%	0.13 [0.02-1.00]	death	1/115	9/133	12mg
Chachar (RCT)	10%	0.90 [0.44-1.83]	no recov.	9/25	10/25	36mg
Soto-Becerra	17%	0.83 [0.71-0.97]	death	92/203	1,438/2,630	14mg
Rajter (PSM)	46%	0.54 [0.27-0.99]	death	13/98	24/98	14mg
Hashim (SB RCT)	92%	0.08 [0.00-1.44]	death	0/59	6/70	28mg
Camprubí	40%	0.60 [0.18-2.01]	ventilation	3/13	5/13	14mg
Spoorthi	21%	0.79 [0.64-0.98]	recov. time	50 (n)	50 (n)	n/a
Budhiraja	99%	0.01 [0.00-0.15]	death	0/34	103/942	n/a
Okumuş (DB RCT)	33%	0.67 [0.27-1.64]	death	6/30	9/30	56mg
Shahbazn.. (DB RCT)	-197%	2.97 [0.13-70.5]	death	1/35	0/34	14mg
Lima-Morales	78%	0.22 [0.12-0.41]	death	15/481	52/287	12mg
Gonzalez (DB RCT)	14%	0.86 [0.29-2.56]	death	5/36	6/37	12mg
Pott-Junior (RCT)	85%	0.15 [0.01-1.93]	ventilation	1/27	1/4	14mg
Huvemek (DB RCT)	32%	0.68 [0.38-1.23]	no improv.	13/50	19/50	84mg
Ahsan	50%	0.50 [0.28-0.90]	death	17/110	17/55	21mg
Abd-Elsalam (RCT)	25%	0.75 [0.17-3.06]	death	3/82	4/82	36mg
Hazan	86%	0.14 [0.01-2.19]	death	0/24	synthetic	24mg
Elavarasi	20%	0.80 [0.61-1.06]	death	48/283	311/1,475	n/a
Late treatment	36%	0.64 [0.52-0.79]		238/1,822	2,023/6,129	

$Tau^2 = 0.08$; $I^2 = 54.8\%$

36% improvement

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

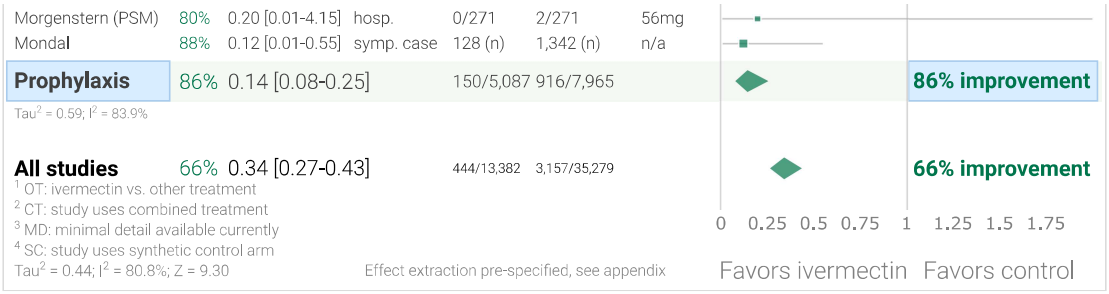


Figure 6. *Random effects meta-analysis for all studies. This plot shows pooled effects, analysis for individual outcomes is below, and more details on pooled effects can be found in the heterogeneity section. Effect extraction is pre-specified, using the most serious outcome reported. Simplified dosages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

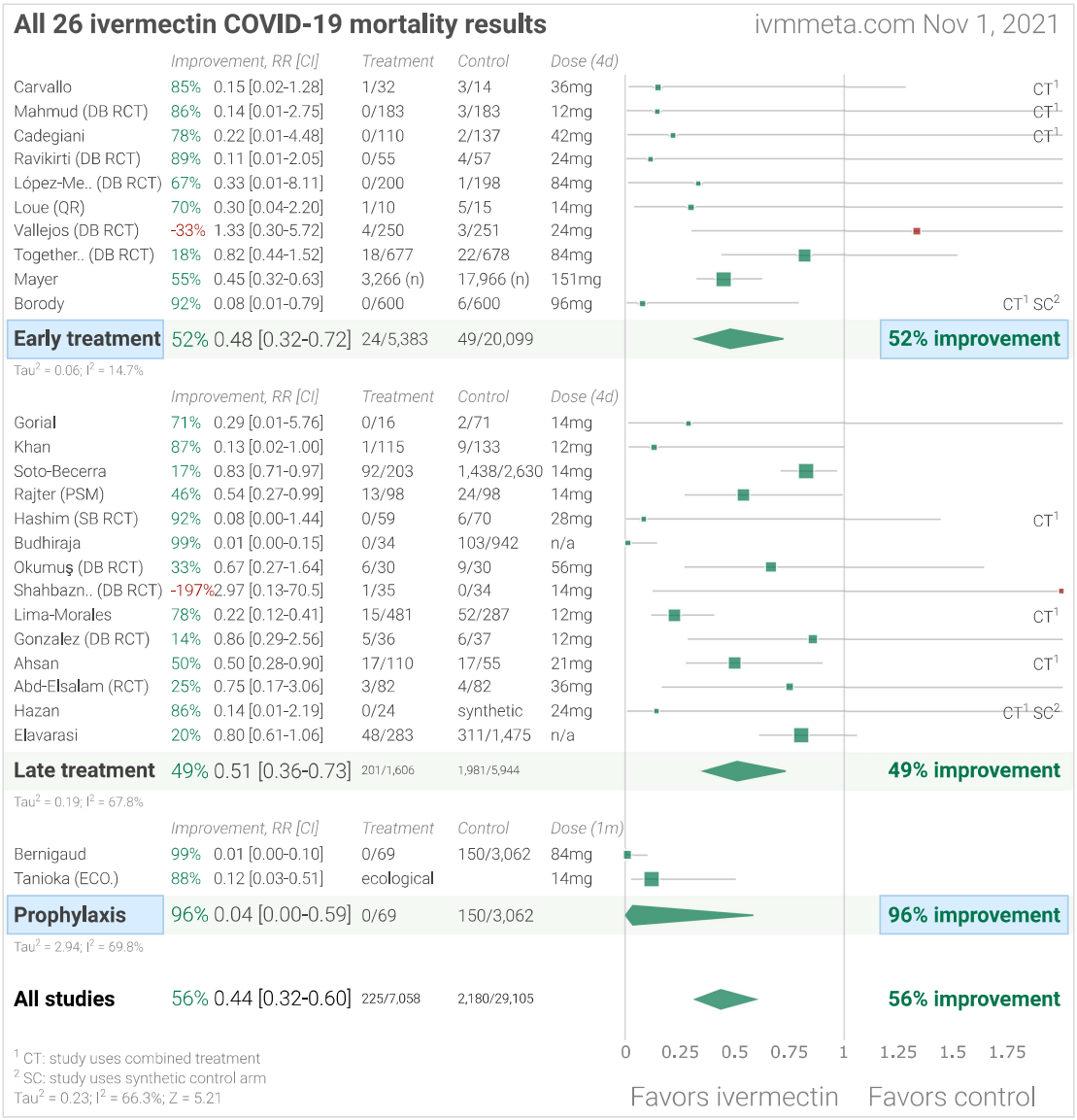


Figure 7. *Random effects meta-analysis for mortality.*

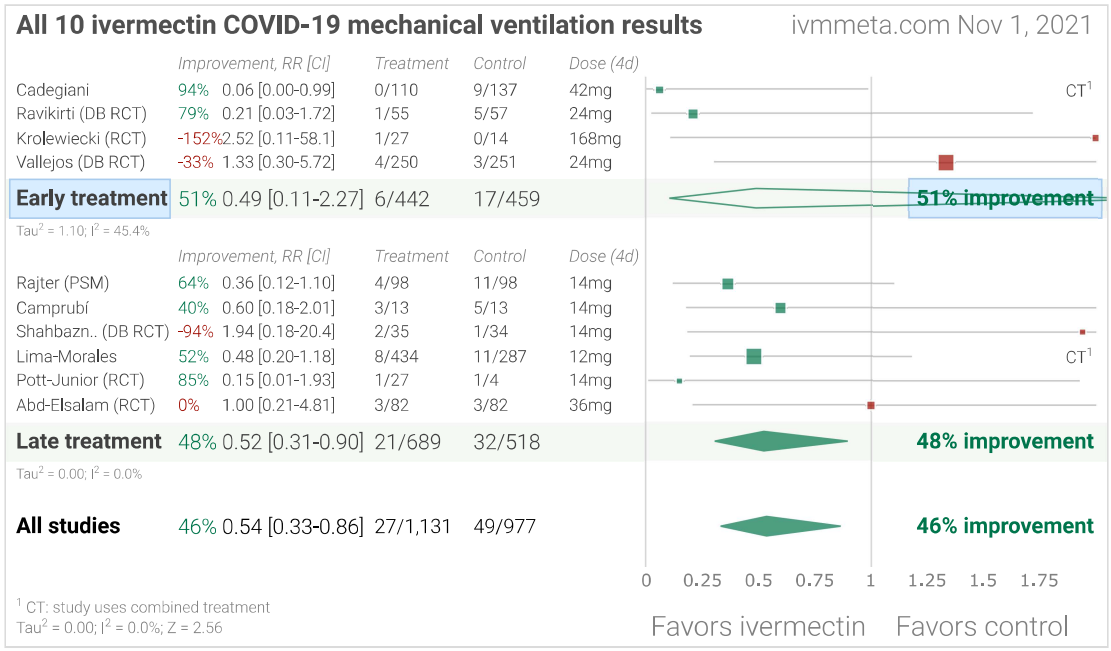


Figure 8. *Random effects meta-analysis for mechanical ventilation.*

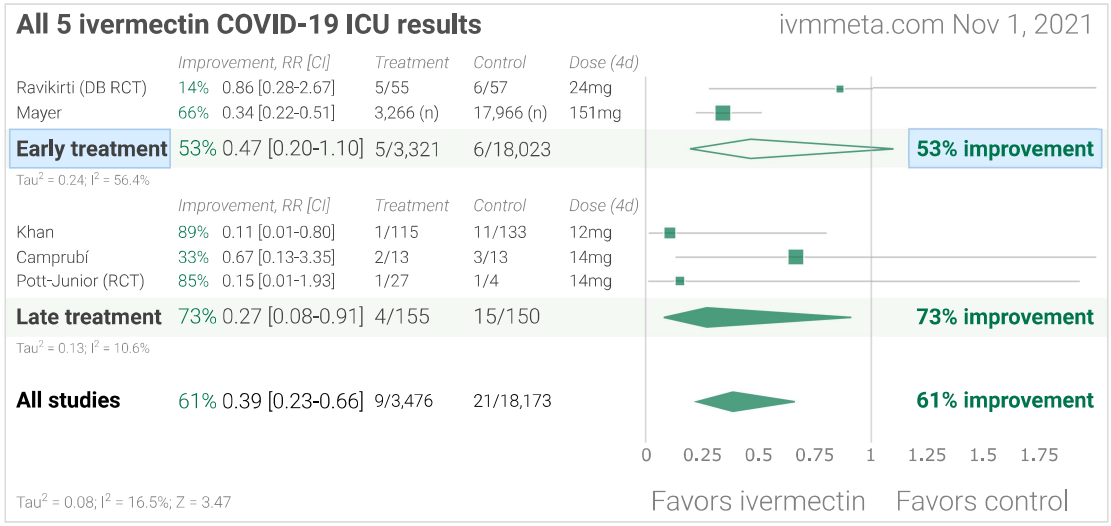


Figure 9. *Random effects meta-analysis for ICU admission.*

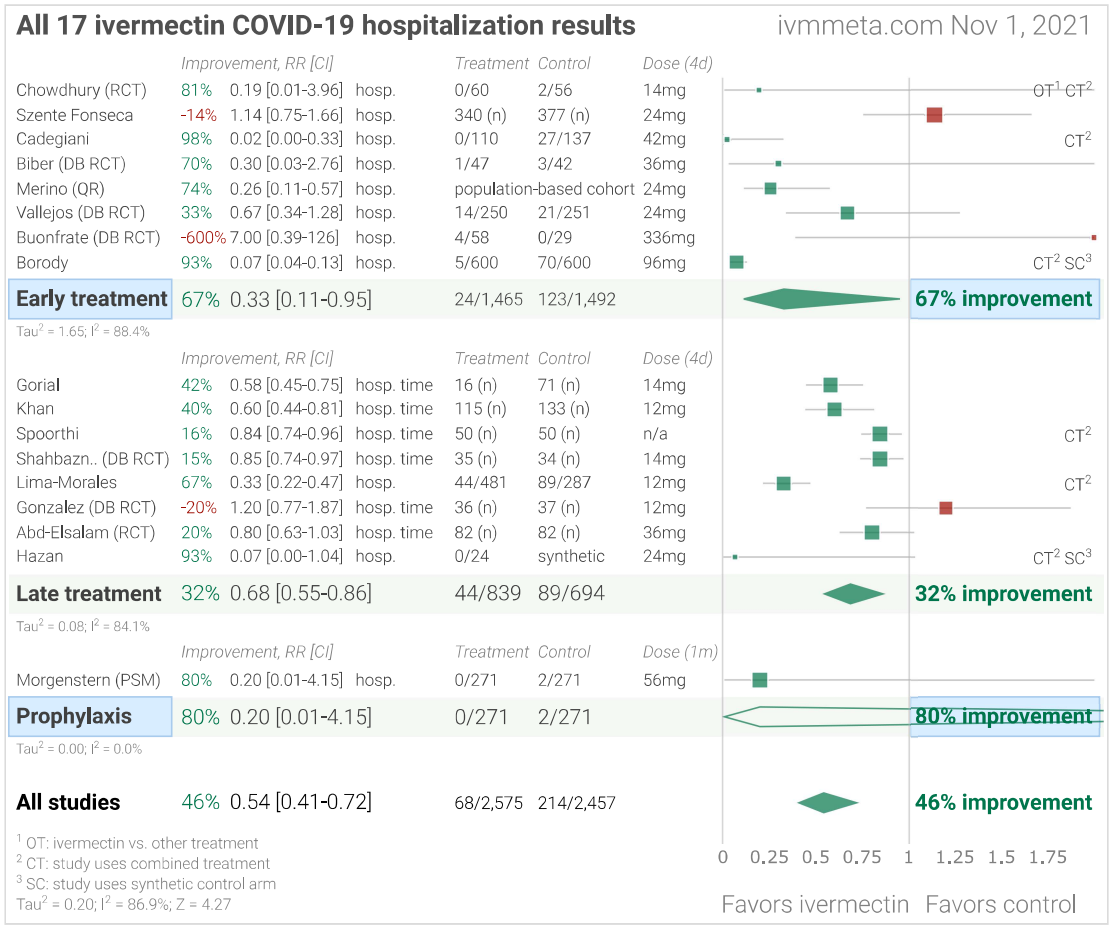


Figure 10. *Random effects meta-analysis for hospitalization.*

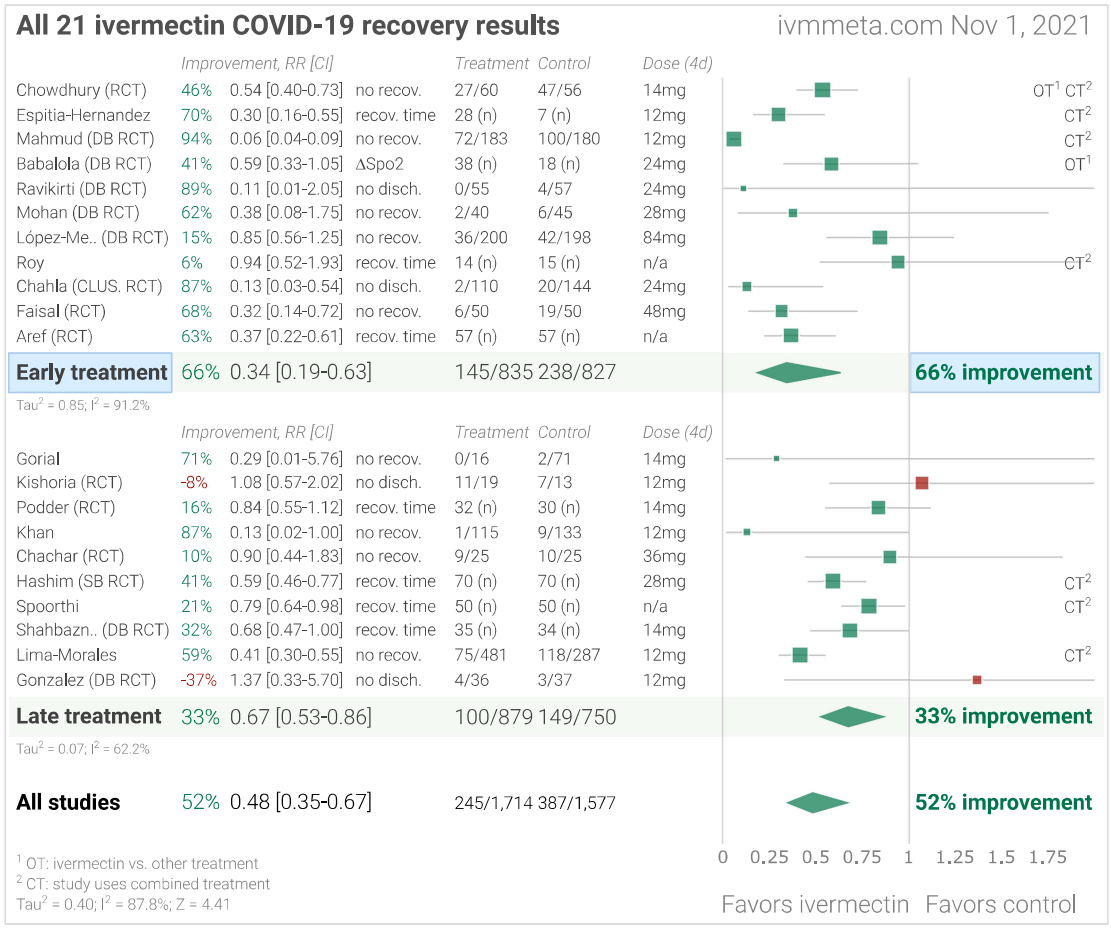


Figure 11. *Random effects meta-analysis for recovery results only.*

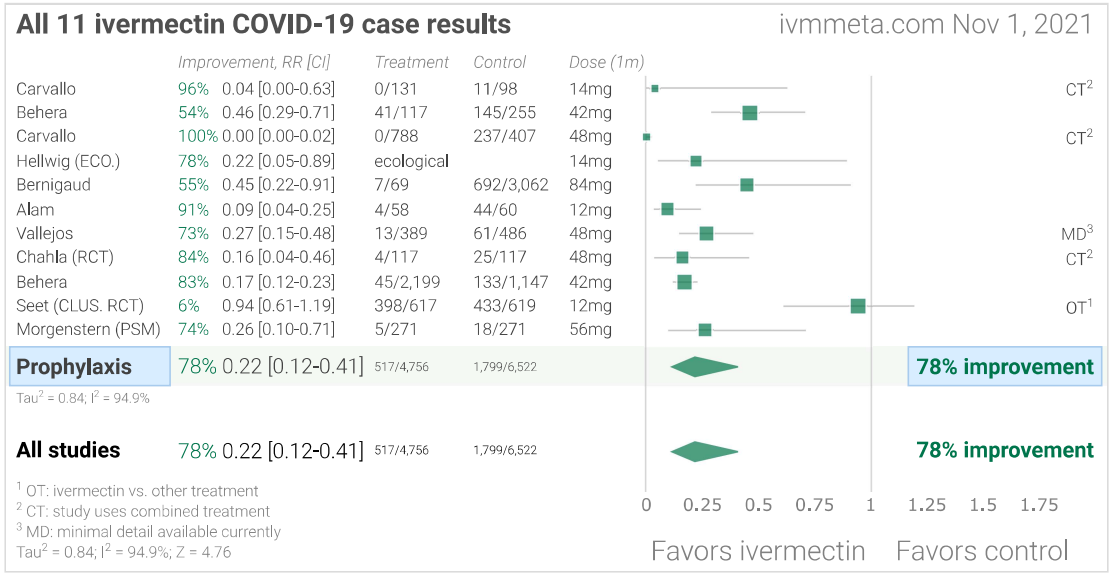


Figure 12. *Random effects meta-analysis for COVID-19 case results.*

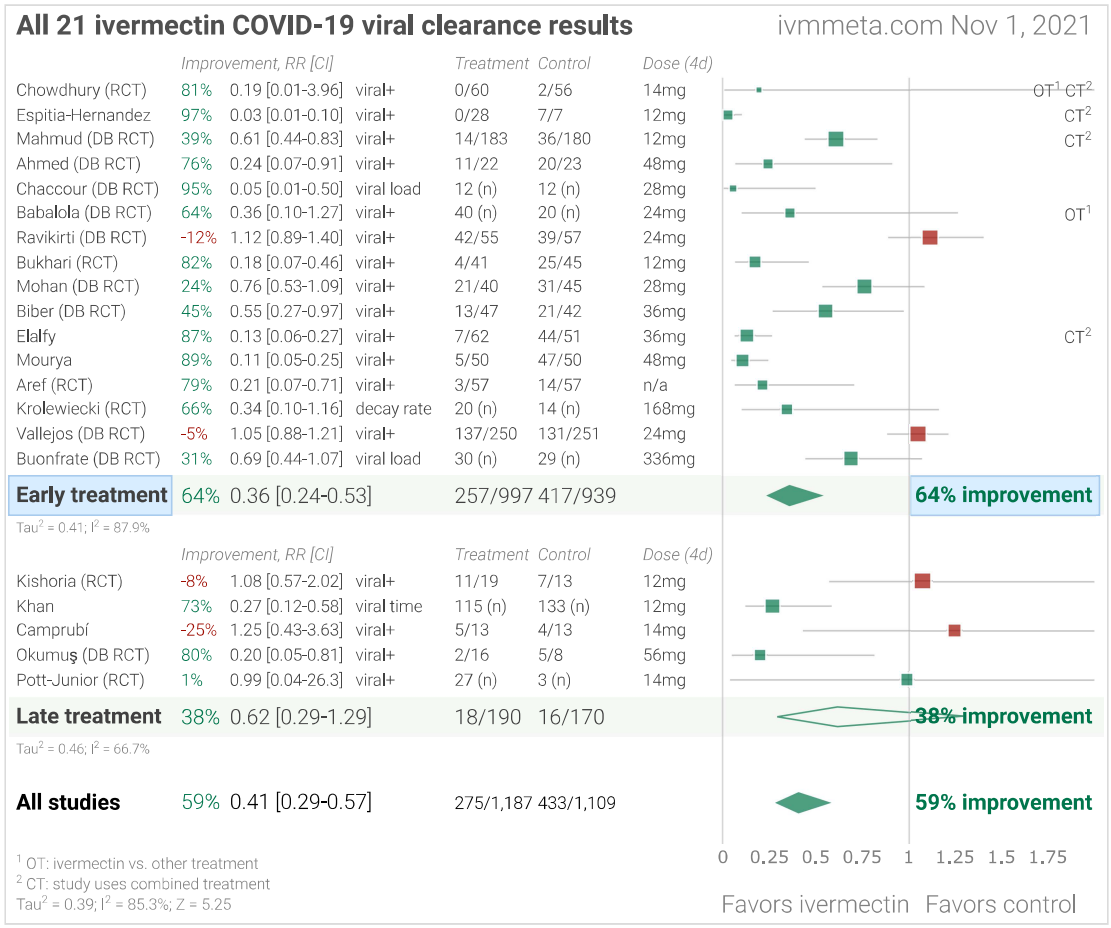


Figure 13. *Random effects meta-analysis for viral clearance.*

Figure 14. *Random effects meta-analysis for peer reviewed trials. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.*

Randomized Controlled Trials (RCTs)

Results restricted to Randomized Controlled Trials (RCTs) are shown in Figure 15, 16, 17, and 18, and Table 2. The supplementary data contains RCT results after exclusions.

RCTs have a bias against finding an effect for interventions that are widely available — patients that believe they need the intervention are more likely to decline participation and take the intervention. This is illustrated with the extreme example of an RCT showing no significant differences for use of a parachute when jumping from a plane *[Yeh]*. RCTs for ivermectin are more likely to enroll low-risk participants that do not need treatment to recover, making the results less applicable to clinical practice. This bias is likely to be greater for widely known treatments such as ivermectin. The bias may also be greater in locations where ivermectin is more easily obtained. Note that this bias does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable.

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]*.

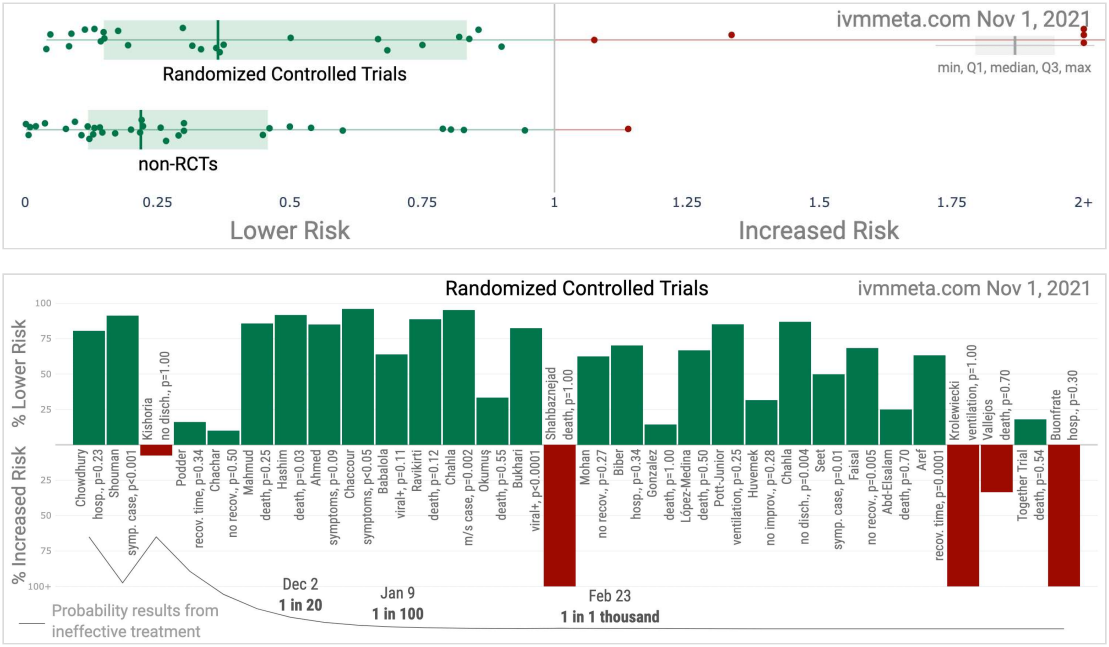


Figure 15. *Randomized Controlled Trials. The distribution of results for RCTs is similar to the distribution for all other studies.*

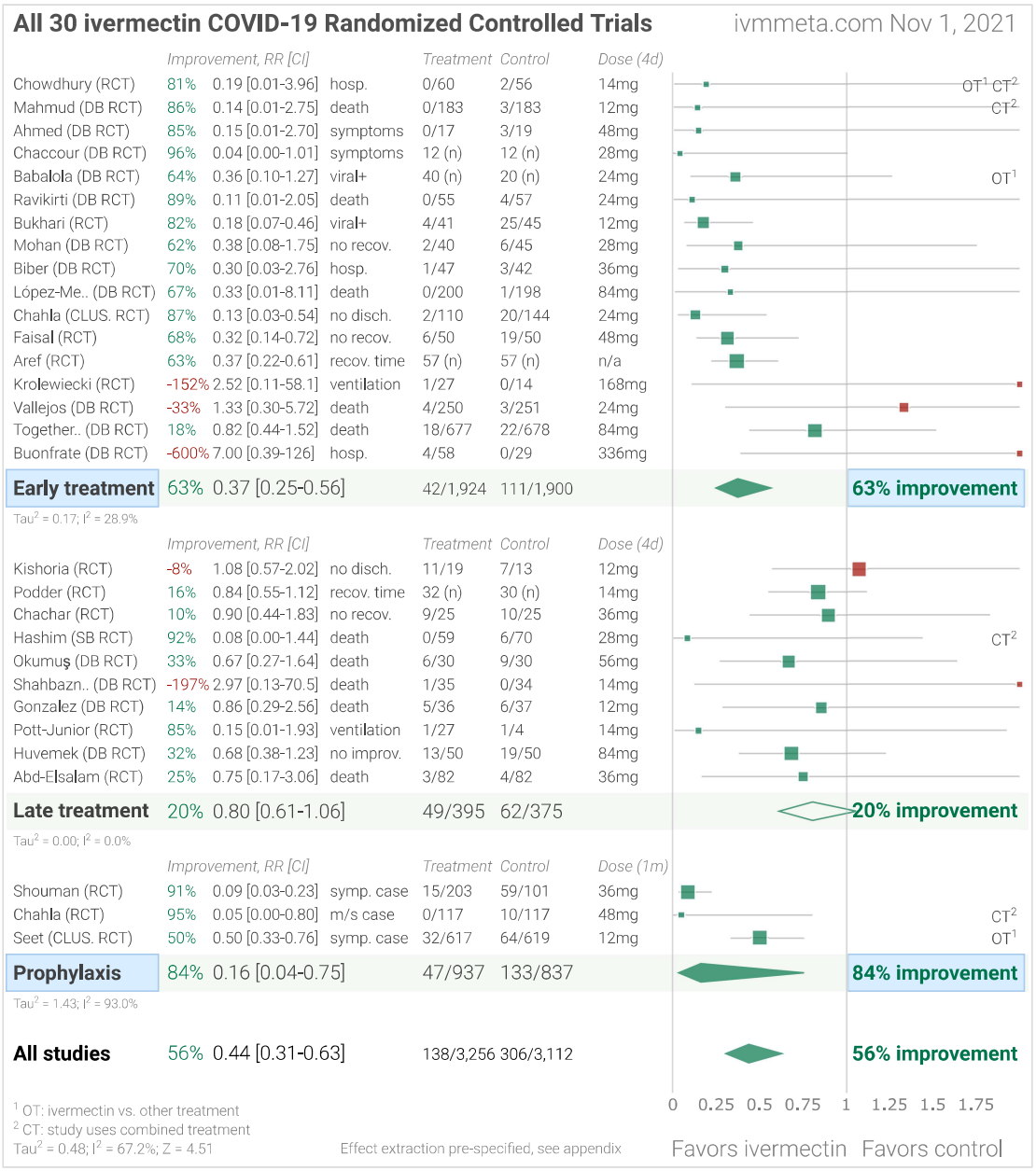


Figure 16. *Random effects meta-analysis for Randomized Controlled Trials only. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.*

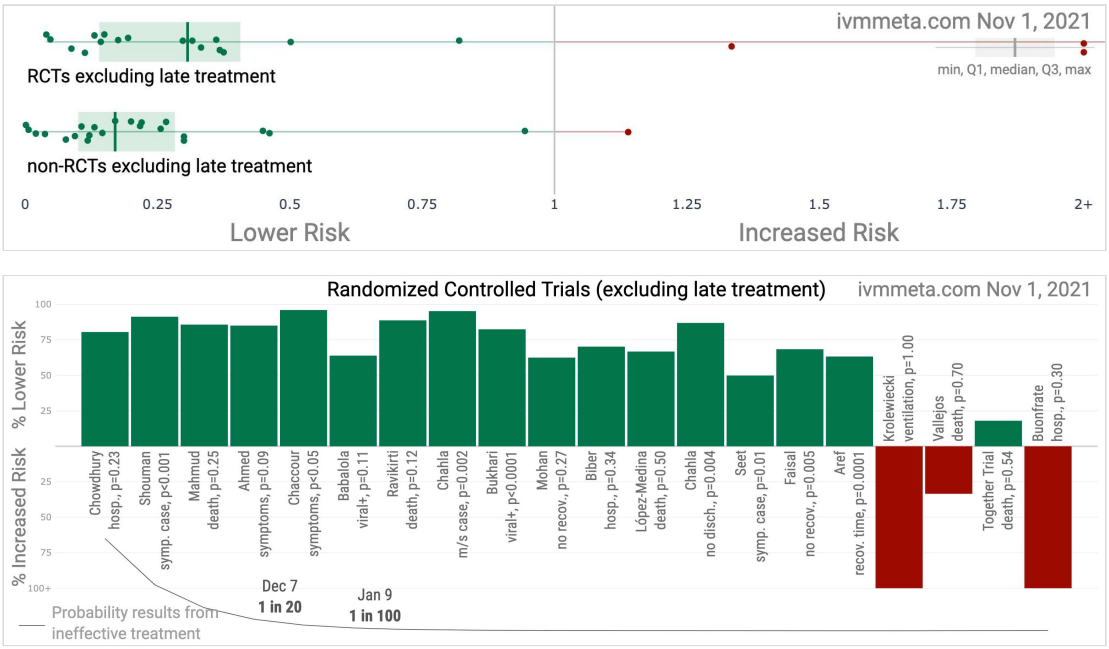


Figure 18. *RCTs excluding late treatment.*

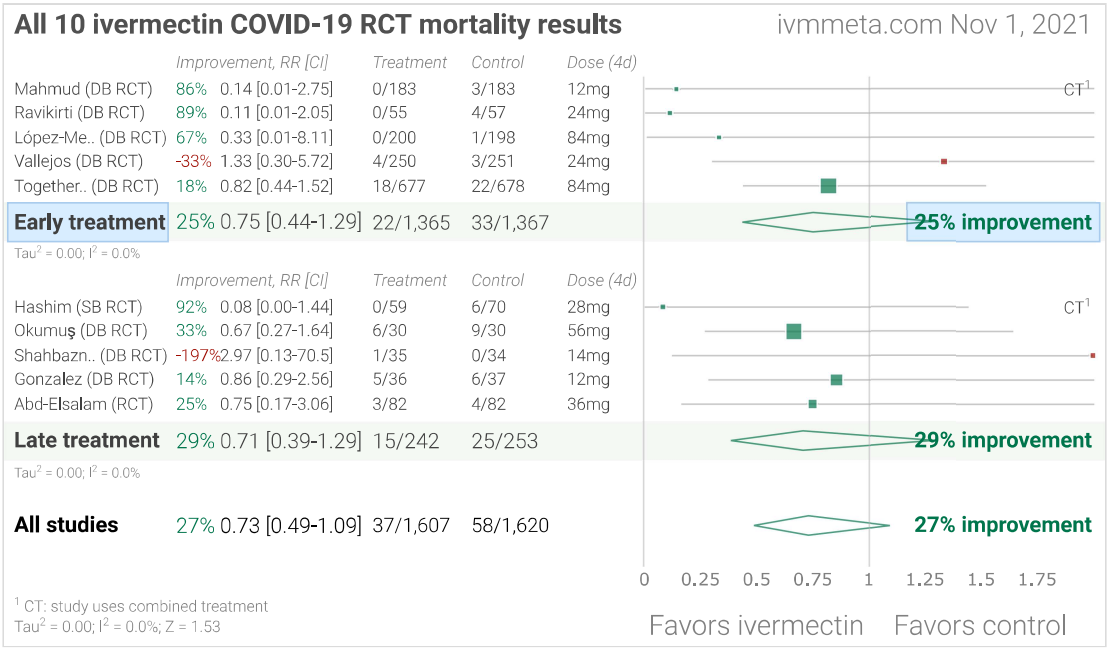


Figure 17. *Random effects meta-analysis for Randomized Controlled Trial mortality results only.*

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	25	30	83.3%	1 in 6 thousand	**56%** improvement RR 0.44 [0.31-0.63] p < 0.0001
Randomized Controlled Trials (excluding late treatment)	17	20	85.0%	1 in 776	**69%** improvement RR 0.31 [0.19-0.50] p < 0.0001

Table 2. *Summary of RCT results.*

Exclusions

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

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

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

also little room for improvement - 58% recovered within the first 2 days to "not hospitalized and no limitation of activities" or better. There was only one death (in the control arm). This study also gave ivermectin to the control arm for 38 patients and it is unknown if the full extent of the error was identified, or if there were additional undiscovered errors. The side effect data reported in this trial raises major concerns, with more side effects reported in the placebo arm, suggesting that more placebo patients may have received treatment. Ivermectin was widely used in the population and available OTC at the time of the study. The study protocol allows other treatments but does not report on usage. The name of the study drug was concealed by refering 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 signficance is the low number of events in a low risk population where most recover quickly without treatment.

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

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

Summarizing, the studies excluded are as follows, and the resulting forest plot is shown in Figure 19. The supplementary data shows results after restrictions and exclusions.

[Ahsan], unadjusted results with no group details.

[Borody], preliminary report with minimal details.

[Cadegiani], control group retrospectively obtained from untreated patients in the same population.

[Carvallo], concern about potential data issues.

[Carvallo (B)], concern about potential data issues.

[Carvallo (C)], minimal details of groups provided.

[Elavarasi], unadjusted results with no group details.

[Hazan], study uses a synthetic control arm.

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

[Kishoria], excessive unadjusted differences between groups.

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

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

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

[Szente Fonseca], result is likely affected by collinearity across treatments in the model.

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

[Together Trial], preliminary report with minimal details.

[Vallejos], detail too minimal.

Figure 19. *Random effects meta-analysis excluding studies with significant issues. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.*

Heterogeneity

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

Treatment delay. The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Figure 20 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]*.

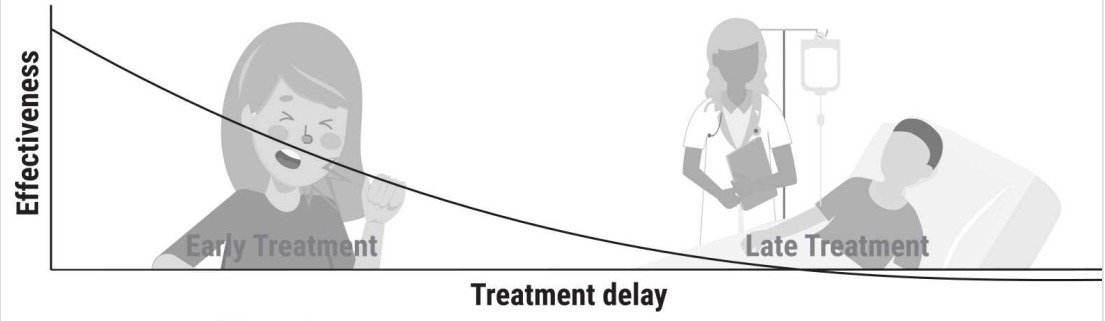


Figure 20. *Effectiveness may depend critically on treatment delay.*

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 *[Babalola]*. Method of administration may also be critical. *[Guzzo]* show that the plasma concentration of ivermectin is much higher when administered with food (Figure 21: 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.

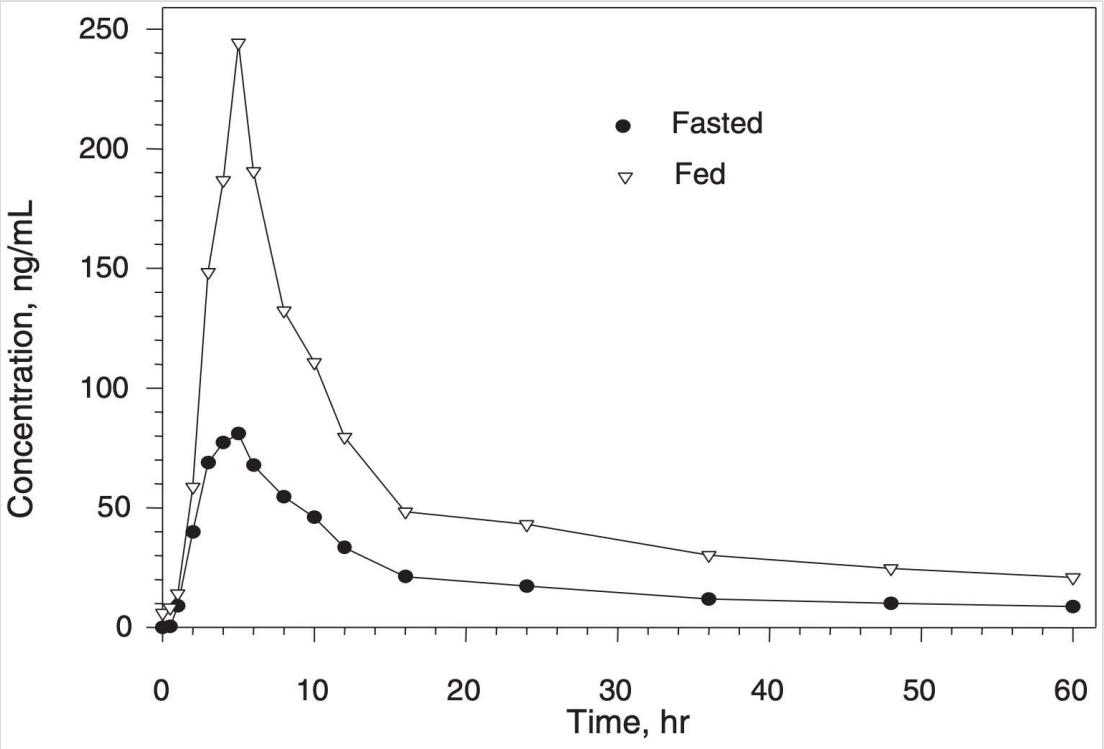


Figure 21. *Mean plasma concentration (ng/ml) profiles of ivermectin following single oral doses of 30mg (fed and fasted administration), from* ***[Guzzo]****.*

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 64 studies to date is estimated to be 1 in 222 billion. This result benefits from the fact that ivermectin shows some degree of efficacy for COVID-19 in a wide variety of cases. It also likely benefits from the fact that relatively few ivermectin trials to date have been designed in a way that favors poor results. However, more trials designed in this way are expected, for example the TOGETHER trial is testing ivermectin in locations known to

have a high degree of self-medication and using low doses compared to current clinical recommendations as updated for current variants. As with a companion trial, this trial may also include very low-risk patients, include relatively late treatment while identifying as an early treatment trial, and use an active placebo (vitamin C). While we present results for all studies in this paper, the individual outcome and treatment time analyses are more relevant for specific use cases.

Discussion

Publication bias. Publishing is often biased towards positive results, which we would need to adjust for when analyzing the percentage of positive results. For ivermectin, there is currently not enough data to evaluate publication bias with high confidence. One method to evaluate bias is to compare prospective vs. retrospective studies. Prospective studies are likely to be published regardless of the result, while retrospective studies are more likely to exhibit bias. For example, researchers may perform preliminary analysis with minimal effort and the results may influence their decision to continue. Retrospective studies also provide more opportunities for the specifics of data extraction and adjustments to influence results. Figure 22 shows a scatter plot of results for prospective and retrospective studies. The median effect size for prospective studies is 69% improvement, compared to 74% for retrospective studies, showing no significant difference. ***[Bryant]*** also perform a funnel plot analysis, which they found did not suggest evidence of publication bias. We note that there is extreme attention from many people towards locating any missing or unpublished negative trials — if they existed it would likely be known. Negative studies are submitted to us by multiple people immediately on publication. On the other hand, there is substantial evidence that journals are delaying the publication of positive studies, for example by accepting a paper for review, holding it for some time, and then rejecting it without review ***[Jerusalem Post, Kory (B)]***. One group performed prophylaxis and early treatment trials, with only the less positive study being formally published to date ***[Vallejos, Vallejos (B)]***, suggesting a negative publication bias.

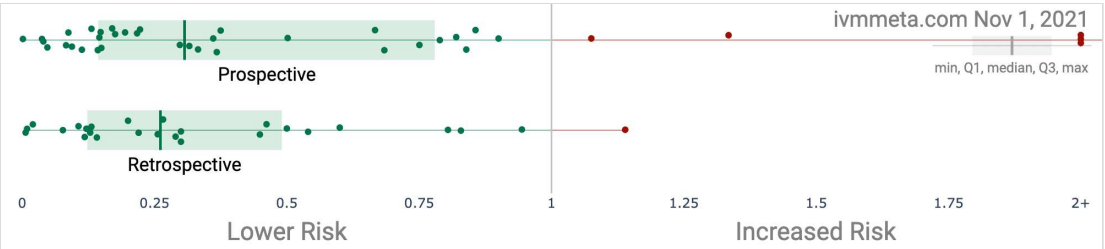


Figure 22. *Prospective vs. retrospective studies.*

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.

In Vitro* evidence on required concentration.** Some people claim that ***[Caly] shows that therapeutic concentrations are not easily reached in humans. This is incorrect. The authors explain why their *in vitro* study cannot be used to determine the effective dose *in vivo*, and state that the concentration required is very unlikely to be an issue ***[Wagstaff]***. The study used monkey kidney cells (the only choice at the time of the experiments), which lack adaptive immune responses and do not produce interferon. Authors also note that ivermectin accumulates in lung and other tissues, that

subsequent experiments with lung cells show many times greater concentrations, and that the average lung concentration shown in modeling studies exceeds the effective level shown in their research. Authors note that ivermectin works with the immune system and a 1:1 ratio of drug to virus is unlikely to be required. In *[Bray]*, author reply that "ivermectin's key direct target in mammalian cells is a not a viral component, but a host protein important in intracellular transport; the fact that it is a host-directed agent (HDA) is almost certainly the basis of its broad-spectrum activity against a number of different RNA viruses in vitro. The way a HDA can reduce viral load is by inhibiting a key cellular process that the virus hijacks to enhance infection by suppressing the host antiviral response. Reducing viral load by even a modest amount by using a HDA at low dose early in infection can be the key to enabling the body's immune system to begin to mount the full antiviral response before the infection takes control." In further research, authors note that they find efficacy for prophylactic use, and that smaller repeated doses are more efffective than a single larger dose *[Wagstaff]*.

Conflicts of interest. Pharmaceutical drug trials often have conflicts of interest whereby sponsors or trial staff have a financial interest in the outcome being positive. Ivermectin for COVID-19 lacks this because it is off-patent, has many manufacturers, and is very low cost. In contrast, most COVID-19 ivermectin trials have been run by physicians on the front lines with the primary interest of finding the best methods to save human lives and minimize the collateral damage caused by COVID-19. While pharmaceutical companies are careful to run trials under optimal conditions (for example, restricting patients to those most likely to benefit, only including patients that can be treated soon after onset when necessary, ensuring accurate dosing), many ivermectin trials do not represent the optimal conditions for efficacy.

Two ivermectin trials to date involve very large financial conflicts of interest *[López-Medina, Together Trial]* — companies closely involved with the trial or organizers stand to lose billions of dollars if ivermectin efficacy becomes more widely known. The design of these trials favors producing a null outcome as detailed in *[López-Medina, Together Trial]*. Note that biasing an RCT to produce a false positive result is difficult (suppressing adverse events is relatively easy *[Evans]*), but biasing a trial to produce a false negative result is very easy — for example, in a trial of an antiviral that works within the first 24 hours of symptom onset, trial organizers only need to avoid treating people within the first 24 hours; or with a disease like COVID-19, organizers only need to select a low-risk population where most people recover quickly without treatment. We note that, even under the very suboptimal designs, these trials produced positive results, although without statistical significance.

Designed to fail. Additional upcoming trials including ACTIV-6, COVID-OUT, and PRINCIPLE have been designed in a way that favors finding no effect, with a number of methods including late treatment, selecting low-risk patients, fasting administration, very high conflict of interest medication sourcing, and dosing below current clinical practice. For discussion see *[Goodkin]*.

If these trials provide results for high-risk patients stratified by treatment delay, including patients treated within 1, 2, and 3 days of symptom onset (including any shipping delay), they may be informative even with limited dosing.

Early/late vs. mild/moderate/severe. Some analyses classify treatment based on early/late administration (as we do here), while others distinguish between mild/moderate/severe cases. We note that viral load does not indicate degree of symptoms — for example patients may have a high viral load while being asymptomatic. With regard to treatments that have antiviral properties, timing of treatment is critical — late administration may be less helpful regardless of severity.

Study notes. 3 of the 64 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. 16 of 64 studies combine treatments, for example ivermectin + doxycycline. The results of ivermectin alone may differ. 4 of 30 RCTs use combined treatment, three with doxycycline, and one with iota-carrageenan. 1 of 64 studies currently have minimal published details available.

Meta analyses. 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, Kory, Lawrie]***. Figure 23 shows a comparison of mortality results across meta analyses. ***[Kory]*** also review epidemiological data and provide suggested treatment regimens.

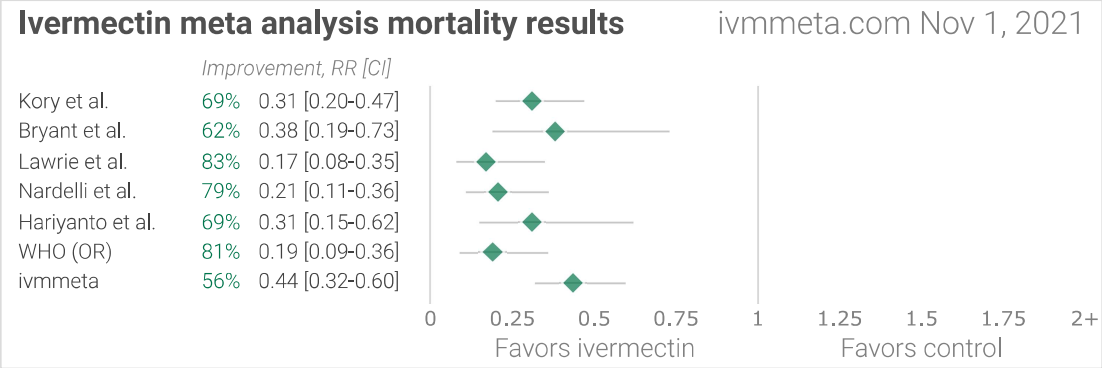


Figure 23. *Comparison of mortality results from different meta analyses. OR converted to RR for* ***[Kory, Nardelli]****. OR displayed for* ***[WHO]****. WHO provides two results, one based on 5 studies and one based on 7, with no explanation for the difference. The result based on 7 studies is shown here, for which the details required to calculate the RR are not provided.*

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

Indication	*Studies*	*Patients*	*Status*
Strongyloidiasis ***[Kory (C)]***	5	591	Approved
Scabies ***[Kory (C)]***	10	852	Approved
COVID-19	64	48,637	Pending
COVID-19 RCTs	30	6,368	

Table 3. *WHO ivermectin approval status.*

Medication	*Studies*	*Patients*	*Improvement*	*Status*
Budesonide (UK)	1	1,779	17%	Approved
Remdesivir (USA)	1	1,063	31%	Approved
Casiri/imdevimab (USA)	1	799	66%	Approved
Ivermectin evidence	64	48,637	66% [57-73%]	Pending

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

	Ibuprofen	*Ivermectin (for scabies)*	*Ivermectin (for COVID-19)*
Lives saved	0	0	>500,000
Deaths per year	~450	<1	<1
CDC recommended	Yes	Yes	No
Based on	0 RCTs	10 RCTs 852 patients	30 RCTs 6,368 patients

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

WHO, Merck, FDA

WHO Analysis

WHO updated their treatment recommendations on 3/30/2021 ***[WHO]***. For ivermectin they reported a mortality odds ratio of 0.19 [0.09-0.36] based on 7 studies with 1,419 patients. They do not specify which trials they included. The report is inconsistent, with a forest plot that only shows 4 studies with mortality results. WHO's recommendation has not been updated for 216 days.

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

- Of the 64 studies (30 RCTs), they only included 16.
- They excluded all 14 prophylaxis studies (3 RCTs).
- There was no protocol for data exclusion.
- Trials included in the original UNITAID search protocol 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 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, along with individual studies ***[Babalola]***.
- 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 Collaboraton 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 222 billion. 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 64 studies by 627 scientists with 48,637 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 recommended against ivermectin ***[Merck]***, however this recommendation has not been updated for 270 days.

They stated that there is *"no scientific basis for a potential therapeutic effect against COVID-19 from pre-clinical studies"*. This is contradicted by many papers and studies, including ***[Arévalo, Bello, Choudhury, de Melo, DiNicolantonio, DiNicolantonio (B), Errecalde, Eweas, Francés-Monerris, Heidary, Jans, Jeffreys, Kalfas, Kory, Lehrer, Li, Mody, Mountain Valley MD, Qureshi, Saha, Surnar, Udofia, Wehbe, Yesilbag, Zaidi, 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 ***[Alam, Aref, Babalola, Behera, Behera (B), Bernigaud, Budhiraja, Bukhari, Chaccour, Chahla, Chahla (B), Chowdhury, Elalfy, Espitia-Hernandez, Faisal, Ghauri, Hashim, Huvemek, Khan, Lima-Morales, Loue, Mahmud, Mayer, Merino, Mohan, Mondal, Morgenstern, Mourya, Okumuş, Ravikirti, Seet]***.

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

Merck has a number of conflicts of interest:

- Merck has committed to give ivermectin away for free *"as much as needed, for as long as needed"* in the Mectizan® Donation Program ***[Merck (B)]***, to help eliminate river blindness.

- Merck has their own new COVID-19 treatments MK-7110 (formerly CD24Fc) ***[Adams]*** and Molnupiravir (MK-4482) ***[Merck (C), Wikipedia]***. Merck has a ~$US1.2B agreement to supply molnupiravir to the US government, if it receives EUA or approval ***[Khan (B)]***. Over $US10B in near-term orders are expected if approved ***[Genetic Engineering and Biotechnology News]***.

- Ivermectin is off-patent, there are many manufacturers, and Merck is unlikely to be able to compete with low cost manufacturers.

- Promoting the use of low cost off-patent medications compared to new products may be undesirable to some shareholders.
- Japan requested Merck conduct clinical trials early in the pandemic and they declined. Merck may be reluctant to admit this mistake ***[Yagisawa]***.

For other concerns regarding Merck's statement and prior actions related to Vioxx, see ***[Scheim]***.

FDA Analysis

The US FDA recommended against ivermectin on March 5, 2021, however they stated that *"The FDA has not reviewed data to support use of ivermectin in COVID-19 patients to treat or to prevent COVID-19"*. There is still no indication that the FDA has reviewed the clinical trials 241 days later.

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

They state that *"Ivermectin is not an anti-viral"*, however many studies contradict this ***[Ahmed, Aref, Babalola, Biber, Bukhari, Buonfrate, Caly, Chowdhury, Elalfy, Espitia-Hernandez, Khan, Mahmud, Mohan, Mourya, Okumuş]***, including 10 RCTs.

They note that *"some initial research is underway"*, however there had been many studies completed and published prior to the FDA recommendation ***[Ahmed, Alam, Babalola, Behera, Bernigaud, Biber, Budhiraja, Bukhari, Cadegiani, Camprubí, Carvallo (C), Chaccour, Chachar, Chahla (B), Chowdhury, Elalfy, Espitia-Hernandez, Ghauri, Gonzalez, Gorial, Hashim, Hellwig, Khan, Lima-Morales, López-Medina, Mahmud, Mohan, Okumuş, Podder, Rajter, Ravikirti, Shouman, Spoorthi]***, including 17 RCTs.

Sep 3, 2021: The FDA revised their statement slightly. They removed the false claim that invermectin is not an antiviral, and they removed the statement that they have not reviewed the data. However, there is still nothing to indicate that they have reviewed the clinical trials. Indeed, they state "currently available data do not show ivermectin is effective against COVID-19" and "ivermectin has not been shown to be safe or effective for these indications", which are both false.

Conclusion

Ivermectin is an effective treatment for COVID-19. Treatment is more effective when used early. Meta analysis using the most serious outcome reported shows 67% [53-76%] and 86% [75-92%] improvement for early treatment and prophylaxis, with similar results after exclusion based sensitivity analysis (which excludes all of the GMK/BBC team studies), with primary outcomes, and after restriction to peer-reviewed studies or Randomized Controlled Trials. Statistically significant improvements are seen for mortality, ventilation, ICU admission, hospitalization, recovery, cases,

and viral clearance. All remain statistically significant after exclusions. 31 studies show statistically significant improvements in isolation. Results are very robust — in worst case exclusion sensitivity analysis 53 of 64 studies must be excluded to avoid finding statistically significant efficacy.

Responses

Inconclusive meta analyses. *[Popp, Roman]* provide meta analyses that show positive effects without reaching statistical significance. The primary methods used that result in a lack of statistical significance are the exclusion of the majority of the evidence base, and division of the remaining subset. For more details see the study notes.

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

How should the result be interpreted when pooling effects? In the pooled analysis, the result is a weighted average of the improvement in the most serious outcome reported. The specific analyses should be used for specific outcomes. Note that a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, etc. Note that we have to consider all information to create the most accurate prediction of efficacy. While there are more sophisticated ways to combine all of the information, the advantage of the method used here is simplicity and transparency. Note that the highly significant results observed are without incorporating additional information that would further increase confidence, such as the treatment delay-response relationship.

Primary outcome analysis. We use fixed pre-specified effect extraction to avoid bias and to focus on the most clinically relevant results. For comparison, we have also performed analysis using the primary outcome of studies (shown in the supplementary data), with results showing similar effect sizes. Prophylaxis results are very similar with 100% (14 of 14) positive effects. Early treatment shows 97% (28 of 29) positive effects, improved due to the very small event count negative serious outcomes in Krolewiecki, Vallejos, and Buonfrate no longer having priority. Late treatment shows 76% (16 of 21) positive effects, reduced slightly, primarily due to viral clearance results being the primary outcome in some studies, and viral clearance being less successful with late treatment. Overall, the primary outcome analysis shows 91% (58 of 64) positive effects, which is currently identical to the results of the main protocol analysis.

Elgazzar. This study was withdrawn and was removed from this analysis on the same day. There was no significant change (excluding 1 of 67 studies has very little effect, and the exclusion actually improves the treatment delay-response relationship).

Samaha. This study was removed from this analysis within an hour of notification that it was pending retraction. There was no significant change in the results, and the exclusion improves the dose-response relationship.

Carvallo. Concerns have been raised about *[Carvallo]*. There appears to be some valid concerns with potential data issues, and this study is excluded in the exclusion analysis. There is no significant change in results, with only a minor reduction in prophylaxis efficacy to 84% [69-91%]. However, it is difficult to trust information from the personality reporting the concerns. The author suggests that the study may not have happened at all, claiming for example that the team could not have afforded the medications without funding, and that a busy clinician would not have enough time. However, with just basic checks, the author would know that a drug company has confirmed donating the medications, that they confirmed authorization for the study was received, that the main hospital for the study requested additional supplies, and that the hospital confirmed ethics committee approval. For additional details see *[O'Reilly]*. We also note that the combined treatment in this study has been independently shown to be effective, and the complementary mechanisms of action support improved efficacy of the combination *[Figueroa]*.

BBC response. A BBC article raises questions due to data issues in some studies, based on an analysis from a team of researchers. One of the researchers reports that data in some trials could have been manipulated, while noting that human error can not be ruled out. Others in the team directly accuse authors of malfeasance. Regardless of the cause, concern over these studies is valid. Currently, 2 studies have been retracted and two more have been reported as pending retraction (neither of these papers has been retracted to date, and the journal for one of them has indicated that no retraction is pending). None of these studies are in our analysis.

Existence of some lower quality studies is typical in large evidence bases. The percentage of studies with issues is not greater than reported averages, and is not close to removing evidence of efficacy (and may actually improve evidence as detailed below). We performed an absolute worst case sensitivity analysis, where positive studies are excluded in order of the effect size, with the largest effect first. **83%, or 53 of 64 studies must be excluded to avoid finding statistically significant efficacy (this is in addition to the four papers not in this analysis).**

The summary statistics from meta analysis necessarily obscure most of the information in the evidence base. For those that have read all of the research, knowledge of efficacy is supported by extensive additional information, including for example relationships between outcomes within a study, dose-response relationships within and across studies, treatment delay-efficacy relationships within and across studies, variant-efficacy relationships, etc. Notably, removal of Elgazzar, Samaha, and Niaee improve the treatment delay-efficacy and dose-response relationships and may further increase confidence when considering all information.

Concerns about *[Cadegiani, Carvallo, Carvallo (B), Carvallo (C)]* have also been reported. All of these studies are excluded in our exclusion analysis.

	Studies	*Prophylaxis*	*Early treatment*	*Late treatment*	*Patients*
With GMK/BBC exclusions	47	84% [69-91%]	73% [63-80%]	45% [22-61%]	37,558

Percentage improvement with ivermectin treatment after exclusion of all studies reported by this team

We note that, while malfeasance cannot be ruled out, reported concerns may also be caused by typos, data collection errors not affecting analyzed outcomes, and expected results from multiple tests. Authors, without any prior registration or statistical analysis plan, perform thousands of statistical tests across data in the studies and report results without correcting for multiple tests. For example, reporting the occurrence of a 1 in 1,000 event as evidence of randomization failure, while performing more than this number of tests across studies.

This group often dismisses studies based on an arbitrary statistical significance threshold for a specific outcome, a misunderstanding of statistics ***[Amrhein]***, and indefensible as a pre-filter in meta analysis.

This group has made many claims unsupported by the data. For Niaee, one author claimed the study *"made a HUGE difference"*. It has no effect on early treatment or prophylaxis. For late treatment, which is not recommended, the change was relatively minor. For Elgazzar, the author claimed that it could be *"the most consequential medical fraud ever committed"*. There was almost no difference in our analysis after removing this paper (excluding 1 of 67 studies has very little effect, and the exclusion actually improves the treatment delay-response relationship).

Statements by the group suggest significant bias. The main author first referred to ivermectin as "something else to debunk" in December 2020, and later as a "horse dewormer". Another group member has called for charging scientists that recommend vitamin D with *"crimes against humanity"*.

The group has made claims about all ivermectin evidence based on the existence of some studies with issues. It is inappropriate to generalize about the entire group of 627 scientists and researchers based on the mistakes or actions of a few individuals.

This group has focused on finding issues in papers reporting large positive effects, which introduces a significant bias. Notably, the few studies that contribute most to minimizing the effects in meta analysis include studies with very high conflicts of interest and many reported protocol violations and data issues, however this group disregards all of these issues.

The article claims *"The largest and highest quality ivermectin study published so far is the Together trial"* which *"found no benefit"*, however this study has not been published, is one of the lowest quality trials with many documented design, execution, and analysis issues, has extremely high conflicts of interest, there is a history of inaccurate reporting prior to publication for a previous treatment in the same trial, and the trial actually reported 18% lower mortality (not statistically significant).

The article reports that 26 studies were examined, however there are 67 studies, authors have not reported their results for all 26, and have not even provided a list of the 26 studies.

The group has an excessive focus on RCTs, which have a fundamental bias against finding an effect for interventions like ivermectin that are widely known and easily available — patients that believe they need treatment are more likely to decline participation and take the treatment ***[Yeh]*** (this does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable and unfamiliar).

The main author of the group is also against vitamin D. Of the 52 vitamin D COVID-19 treatment studies, author suggests only one trial is worth looking at ***[Murai]***. This gives us a simple case to examine potential bias. ***[Murai]*** is a small trial providing no statistically significant effects (mortality $p = 0.43$, other outcomes are positive while also not significant). Author acknowledges that the trial is too small for a conclusion. More importantly, this trial provides no information about whether vitamin D reduces the risk of a serious COVID-19 case, because the patients in this trial already had a serious COVID-19 case (90% already on oxygen treatment at baseline). Author does not mention this. The trial also has poorly matched arms in terms of gender, ethnicity, hypertension, diabetes, and baseline ventilation, all favoring the control group. Further, this study uses an inappropriate form of vitamin D — cholecalciferol. In reality physicians would use calcifediol or calcitriol with late stage treatment, because they avoid a very long delay for conversion. We are unaware of a reason to use cholecalciferol in this case (other than to produce a null result). In summary, author's chosen study is the study providing the least useful information from the 52 vitamin D treatment studies to date, suggesting biased analysis.

We fully support this team's effort to clean up the evidence base. This is extremely valuable and improves the integrity of the evidence base (and the accuracy if done equally for all studies). We hope this or other teams can do the same for all treatments. However the analysis plan should be published, details of all tests should be provided, results should be corrected for multiple testing, results for all studies and tests should be provided, and equal attention should be given to studies with non-statistically significant results, especially those with major reported data issues that have been disregarded by this team (for example data suggesting substantial protocol violations including confounding by time in ***[Together Trial]*** and control arm use of treatments in ***[López-Medina]***).

For coverage of other errors in the BBC article, and illumination of the stark contrast between Dr. Lawrie's response to the BBC before publication and what they chose to report, see ***[BiRD Group, Campbell, Elijah, Lawrie (B)]***.

More details can be found in the following response regarding the main author of this group.

GMK response. An influential anti-treatment Twitter personality, journalist, and student epidemiologist has made a number of incorrect, misleading, hyperbolic, and unsupported statements. This author is notable in that they are perhaps the only person that claims to have read more than about half of the studies, but does not find the evidence to be positive. However, their opinion appears to have been formed before reading any of the studies — they first referred to ivermectin as "something else to debunk". We note that the author has made very valuable contributions identifying significant issues with some studies, which has helped to improve the quality of the ivermectin evidence base, and has improved the dose-response and treatment delay-response relationships.

Author has been paid for writing anti-treatment articles, and has also referred to ivermectin as a "horse dewormer". Author reports having family members that have died of COVID-19, and may be biased against acknowledging errors in treatment advice. If the author continues to deny effective treatments, we encourage them to at least direct readers to government-approved treatments, for which there are several in the author's country, and many more in other countries (including ivermectin). While approved treatments in a specific country may not be as effective (or as inexpensive) as current evidence-based protocols combining multiple treatments, they are better than no recommendation.

Author's attempt to discredit ivermectin research centers on the fundamentally false assertion that excluding a small number of lower quality trials results in a negative outcome. It should be clear from the forest plot that this is not possible, but we can be more specific. We perform an absolute worst case sensitivity analysis, where positive studies are excluded in order of the effect size, with the largest effect first. How many studies do we need to exclude before the meta analysis RR has a confidence interval exceeding 1.0? **83%, or 53 of 64 studies must be excluded to avoid finding statistically significant efficacy.** As with all data in this paper, this analysis will automatically update as the evidence base evolves. Also note that this is after exclusion of withdrawn papers - one has never been in this analysis, the second was removed on the same day it was withdrawn, and the other two were removed in advance of retraction based on author's notification that retraction is pending (neither of these papers has actually been retracted, and the journal for Niaee et al. has reported that no retraction is pending).

Author claims that we include several papers that are already excluded in the 10 exclusion analyses.

Author claims that there is a greater percentage of low quality studies for ivermectin and COVID-19 compared to other treatments. This is unsupported for such a large evidence base, and does not match previous studies.

Author often makes a basic error by equating positive effects that are not statistically significant at a specific level with "no effect", a misunderstanding of statistics ***[Amrhein]***. For example, if a study reports 50% improvement with a *p* value of 0.1, we cannot say that the study shows the treatment is ineffective, or in the words of the author shows "no benefit at all". Author repeatedly makes false claims in this way.

Author appears to favor pharmaceutical company affiliated/operated trials. For example, the author has no problem with the lack of IPD for many pharmaceutical affiliated COVID-19 trials that support the author's treatment positions, yet considers the lack of IPD in a positive ivermectin trial to be problematic. Author believes the pharmaceutical affiliated Together Trial is the highest quality trial so far, yet not only is there no IPD currently available, there is no preprint, the trial has many documented design, execution, and analysis issues, has extremely high conflicts of interest, and there is a history of inaccurate reporting prior to publication for a previous treatment in the same trial.

Author has an unwarranted focus on a specific outcome (mortality) and a specific subset of trials (RCTs). Other outcomes are also important — accelerating viral clearance, and reducing cases, hospitalization, ICU admission, ventilation, etc. are all very valuable, for example reducing serious "long COVID" problems, reducing transmission of the virus, and reducing the burden on the healthcare system. These outcomes are also likely to correlate with reduced mortality among larger or higher-risk populations. We note that there is extensive evidence for the mortality outcome when not restricting to RCTs. RCTs have mostly been run with relatively low risk populations where mortality is low, leading to limited statistical significance. However RCTs are inherently biased towards low mortality and towards not finding an effect in this case — ivermectin is well-known to be beneficial for COVID-19 and is easily available, therefore participants that believe they may be at serious risk are more likely to decline participation in the RCT and take the recommended medications. Patients that do choose to participate are also more likely to have low adherence. This bias of RCTs is likely to be even larger in locations where ivermectin is widely used in the community and very easily obtained, which correlates with the observed RCT results.

Author suggests that we have chosen the wrong outcome in some cases. While mistakes are possible, for example we corrected errors with Espitia-Hernandez et al. and Jain et al., the claims made suggest that the author has not read the studies and/or our protocol carefully. Details are below. We note that the author disregards the existence of the individual outcome analyses and the primary outcome analysis.

The author's other errors are as follows. None of these have been corrected over two months later. They are all still live, highly-ranked in search results, and highly influential.

- that excluding Elgazzar et al. completely changes the results and could be *"the most consequential medical fraud ever committed"*. Excluding 1 of 67 studies has very little effect, and the exclusion improves the treatment delay-response relationship.
- that Niaee et al. *"made a HUGE difference"*. It has no effect on early treatment or prophylaxis. For late treatment, which is not recommended, the change was relatively minor, and the exclusion improves the treatment delay-response relationship.
- making basic errors suggesting very superficial reading of studies, for example claiming the RR in Szente Fonseca is the risk of being treated
- making basic errors suggesting very superficial reading of this paper, for example claiming that a result for prophylaxis studies is based on the number of patients from all studies
- equating a high degree of COVID-19 in a country partially adopting a treatment with a lack of efficacy, disregarding obvious confounding such as heavily affected areas being more likely to adopt treatment (analysis of results in regions or time periods adopting treatment, while not equivalent to controlled studies, is more informative and shows efficacy ***[Chamie-Quintero, Chamie-Quintero (B), Merino, Ontai]***)
- confusing heterogeneity due to dose, treatment delay, etc. and due to bias
- disregarding treatment delay to dilute or obscure effects by including late treatment (author has also used this method with other treatments)
- disregarding the existence of specific outcome analyses, RCT analysis, and exclusion-based sensitivity analysis
- suggesting that efficacy over longer periods is not possible because ivermectin has a half-life of "about a day". Author disregards known efficacy for other conditions over much longer periods, and mischaracterizes the half-life. Antiparasitic efficacy can persist for several months after a single dose ***[Canga]***. Plasma half-life is longer in some studies, and significant plasma concentration can persist for over 2 weeks in some patients ***[Muñoz]***. More importantly, ivermectin is highly lipophilic and may accumulate in the lung and other tissues where concentrations may be many times higher ***[Chaccour (B), Chiu]***.
- misunderstanding funnel plot analysis and explanations other than selective reporting (and providing no evidence of unreported negative studies, while there is substantial evidence of difficulty publishing positive studies ***[Jerusalem Post, Kory (B)]***)
- suggesting that it is impossible to combine evidence from mortality and hospitalization (for example), but combining late treatment and early treatment in order to obscure efficacy (if a treatment reduces disease severity requiring hospitalization, reduced mortality in at-risk populations logically follows, whereas lack of efficacy several days after onset can not be extrapolated to early treatment — treatments for a viral infection are often less effective when delayed)

- making serious claims about individual studies without contacting authors (for example claiming patients were excluded for reaching the endpoint too quickly, whereas authors report exclusions due to baseline negative status)
- author is unaware of different variants, suggesting that results should be identical for treatment at a given delay, even when the predominant variants have markedly different peak viral load, time to peak viral load ***[Faria, Karita, Nonaka]***, and mortality (for example Gamma vs. non-Gamma aHR 4.73 [1.15-19.41] ***[Zavascki]***)

The cases where author suggests we have chosen the wrong outcome indicate that the author has not read the studies and/or our protocol carefully:

- suggesting that the risk of a good outcome should be selectively used instead of the risk of a bad outcome (author would like to do this when it reduces the effect size). This would be like using the risk of surviving instead of the risk of death. 99% survival may only be a 4% improvement over 95% survival, but most people would appreciate the 80% lower risk of death.
- suggesting that hospitalization time should be used for symptomatic recovery in a study where discharge is based on viral clearance (and only tested weekly).
- suggesting that a specific symptom such as cough should be used (author would prefer a less positive result for the study)
- suggesting that viral load is more important than symptomatic results
- suggesting that mortality should be used in populations with zero mortality (for low-risk populations with no mortality, reduction in mortality is not possible, this does not mean a reduction in hospitalization, for example, is not valuable)
- suggesting that unadjusted results should be used in a study where the adjustments clearly make a significant difference (author wants to cherry-pick unadjusted cough results)
- suggesting that, for example, in a study of viral load where all patients recover, it is not valuable if treated patients recover faster (or are less likely to transmit the virus to others)
- suggesting that study selected outcomes should have priority rather than using a consistent pre-specified protocol, disregarding the added bias and the fact that this actually improves results for ivermectin (for example the very small event count negative serious outcomes in Krolewiecki, Vallejos, and Buonfrate would no longer have priority)
- suggesting that cough is a more important symptom than low SpO_2 or fever. Cough can persist for a long time after more serious symptoms resolve, and persistent cough may be caused by many conditions.
- suggesting that combined low dose treatment results should be used in a study that had a combined ivermectin/doxycycline arm (single dose ivermectin, 5 days doxycline) and an ivermectin arm with treatment for 5 days

We note that this personality has an extensive history of incorrect advice, including for example:

- claiming that flu is more dangerous than COVID-19
- claiming that SARS-CoV-2 is not airborne
- claiming that it's impossible to improve immune system functioning

- even believing and propagating a made up story that claimed ivermectin overdose was causing gunshot victims to wait at an ER

Author has taken a public position against early treatments for COVID-19 since at least July 2020. Given this longstanding and influential negative position, they may tend to view information with a negative filter and confirmation bias, and may be reluctant to admit errors. They acknowledge not having read all of the studies (and appear to have very superficially read others). They submitted zero feedback to us, suggesting that they know their comments are incorrect or that they have a motivation other than correcting errors. Author claims that they could not contact us, however there are over 50 feedback links throughout this article. We also note that the author is not open to critical feedback and routinely blocks Twitter users correcting mistakes or expressing anything critical on their feed. Reports suggest that the author also pre-emptively blocks people that follow other users that have reported on the author's errors, even when there has been no previous interaction with the author.

The author is also against vitamin D. Of the 52 vitamin D COVID-19 treatment studies, author suggests only one trial is worth looking at ***[Murai]***. This gives us a simple case to examine potential bias. ***[Murai]*** is a small trial providing no statistically significant effects (mortality p = 0.43, other outcomes are positive while also not significant). Author acknowledges that the trial is too small for a conclusion. More importantly, this trial provides no information about whether vitamin D reduces the risk of a serious COVID-19 case, because the patients in this trial already had a serious COVID-19 case (90% already on oxygen treatment at baseline). Author does not mention this. The trial also has poorly matched arms in terms of gender, ethnicity, hypertension, diabetes, and baseline ventilation, all favoring the control group. Further, this study uses an inappropriate form of vitamin D — cholecalciferol. In reality physicians would use calcifediol or calcitriol with late stage treatment, because they avoid a very long delay for conversion. We are unaware of a reason to use cholecalciferol in this case (other than to produce a null result). In summary, author's chosen study is the study providing the least useful information from the 52 studies to date, suggesting biased analysis.

Based on many comments, author appears to focus on superficial criteria such as typesetting and quality of writing. While many of the studies have been performed by non-native English speakers with minimal budgets, this does not imply the researchers are less reliable. Indeed, the author is highly critical of the program used to create a graph, for example, but is unable to see flaws in high budget high conflict of interest trials, even when they prompt >100 scientists to write an open letter requesting retraction ***[Open Letter]***.

Two months later, the author has still not contacted us, and has only made content-free comments on Twitter such as calling us "sh*tty". Other individuals pointing out errors with detailed and careful feedback get similar treatment, such as being called a "d*ckhead" (and being blocked).

More details can be found in the BBC response.

AT response. A technology blog published an article with incorrect and unsupported claims. The article refers to c19ivermectin.com (which is only a database of ivermectin research), but makes comments about this analysis. Most of the comments in this article are already addressed above.

Author correctly notes that the majority of results are positive and that no matter how you slice the data, the results are positive, but appears to dismiss the obvious reason without examining the evidence.

Author believes that because other effective treatments exist, and because we have also covered those, there must be a positive bias. For ivermectin though, we find evidence of a negative publication bias, and despite enormous worlwide attention, there is no evidence of missing negative trials, while there is substantial evidence of positive trials being delayed by editors(journals fast track null results, while holding positive trials and later returning them without review). We also note that many of the effective treatments are adopted by governments worldwide, including several in the author's country. Appoved treatments include sotrovimab, casirivimab, imdevimab, bamlanivimab, etesevimab, budesonide, favipiravir, and convalescent plasma (although not showing efficacy in our analysis), others have already been purchased pending approval or are not yet available (molnupiravir, proxalutamide), and others are widely accepted to be helpful, including in the author's country, despite gaining minimal attention from authorities (vitamin D, vitamin C) ***[Miller]***.

Author finds the heterogeneity in dosage, treatment time, etc. concerning. This heterogeneity is beneficial and gives us much more information on the situations where treatment is effective, and the optimal dosage. Results from a single study only apply to the conditions of that study and cannot be extrapolated to other conditions — author makes this mistake claiming another treatment is ineffective based on definitive evidence, but that evidence only applies to very late treatment in a very sick population with excessive dosage — not the optimal use of an antiviral for COVID-19. While we cannot use the larger evidence base to predict a specific situation, e.g., mortality in high risk patients with specific treatment delay and dosing, we can use the larger evidence base as evidence for/against efficacy, and many subgroup analyses have sufficient evidence for more specific cases.

Author refers to the withdrawn Elgazzar study (removed from this analysis on the same day) as a major development, however there was no significant change. Excluding 1 of 67 studies has very little effect, and the exclusion actually improves the treatment delay-response relationship. 53 of 64 studies need to be excluded to avoid finding statistically significant efficacy in a worst case sensitivity analysis.

Author is concerned that some studies use combined treatment, however 48 do not use combined treatment, and most of the additions are treatments independently known to not have significant efficacy alone.

We also note that the author has never contacted us.

Study Notes

Together Trial

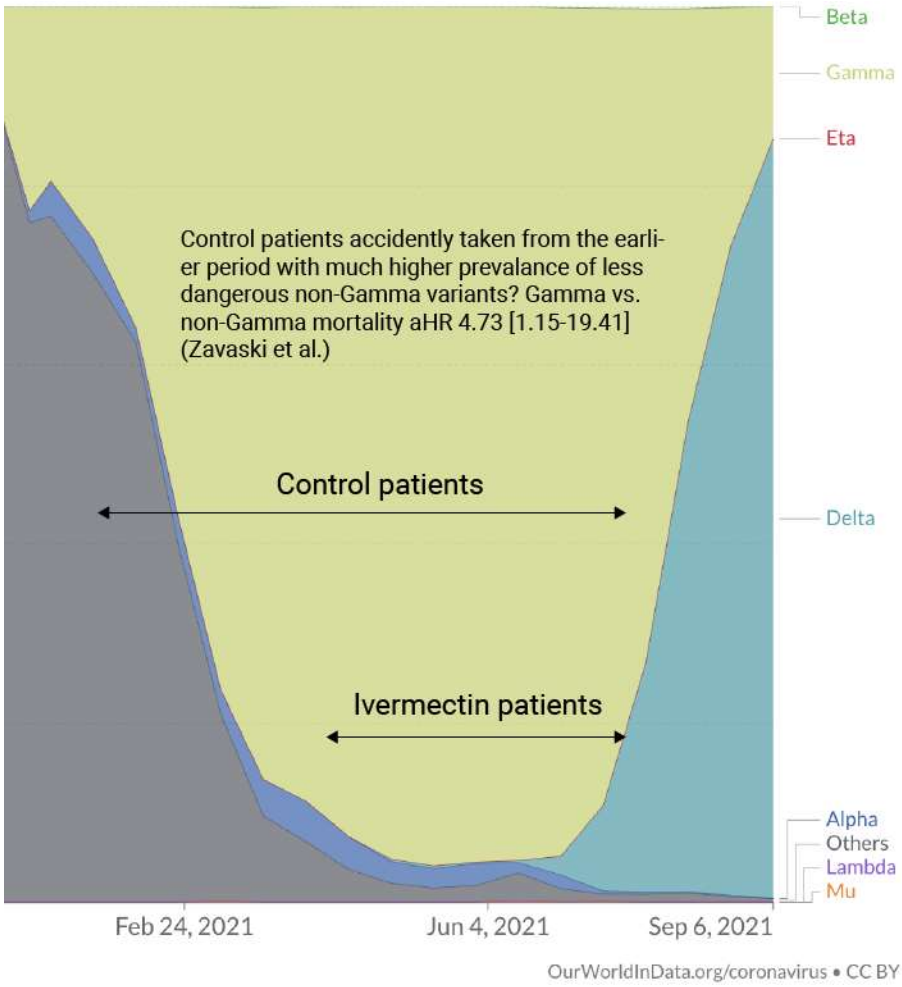
Minimal information about the Together Trial is currently available. They released partial results in a presentation, but have not released the preprint yet. The preprint for the fluvoxamine arm, concluded at the same time, was released August 23, 2021.

The same trial's results for a previous treatment were initially reported as RR 1.0 [0.45-2.21] ***[ajtmh.org]***, while the final paper reported something very different — RR 0.76 [0.30-1.88] ***[jamanetwork.com]***.

The trial randomization chart does not match the protocol, suggesting major problems and indicating substantial confounding by time. For example, trial week 43, the first week for 3 dose ivermectin, shows ~3x patients assigned to ivermectin vs. placebo ***[reddit.com]***. Treatment efficacy

can vary significantly over time, for example due to overall improvement in protocols, changes in the distribution of variants, or changes in public awareness and treatment delays. ***[Zavascki]*** show dramatically higher mortality for Gamma vs non-Gamma variants (28 day mortality from symptom onset aHR 4.73 [1.15-19.41]), and the prevalence of the Gamma variant varied dramatically throughout the trial ***[ourworldindata.org]***. This introduces confounding by time, which is common in COVID-19 retrospective studies and has often obscured efficacy (many retrospectives have more patients in the treatment group earlier in time when overall treatment protocols were significantly worse).

According to this analysis ***[reddit.com]***, the total number of patients for the ivermectin and placebo groups do not appear to match the totals in the presentation (the numbers for the fluvoxamine arm match) — reaching the number reported for ivermectin would require including some of the patients assigned to single dose ivermectin. Reaching the placebo number requires including placebo patients from the much earlier ivermectin single dose period, and from the early two week period when zero ivermectin patients were assigned. If these earlier participants were accidently included in the control group, this would dramatically change the results in favor of the control group according to the changes in Gamma variant prevalence.



Treatment delay is currently unknown, however the protocol allows very late inclusion and a companion trial reported mostly late treatment. Overall mortality is high for 18+ outpatients. Results may be impacted by late treatment, poor SOC, and may be specific to local variants ***[Faria, Nonaka, Sabino]***. Treatment was administered on an empty stomach, greatly reducing expected tissue

concentration *[Guzzo]* and making the effective dose about 1/5th of current clinical practice. The trial was conducted in Minas Gerais, Brazil which had substantial community use of ivermectin *[otempo.com.br]*, and prior use of ivermectin is not listed in the excluson criteria.

Time from symptom onset to randomization is specified as within 7 days. However the schedule of study activities specifies treatment administration only one day after randomization, suggesting that treatment was delayed an additional day for all patients.

This trial uses a soft primary outcome, easily subject to bias and event inflation in both arms (e.g., observe >6 hours independent of indication). There is also an unusual inclusion criteria: "patients with expected hospital stays of <= 5 days". This is similar to "patients less likely to need treatment beyond SOC to recover", and would make it very easy to reduce the effect seen. This is not in either of the published protocols.

The trial took place in an area of Brazil where the Gamma variant was prominent. Brazilian clinicians report that this variant is much more virulent, and that significantly higher dosage and/or earlier treatment is required, as may be expected for variants where the peak viral load is significantly higher and/or reached earlier *[Faria, Nonaka]*.

RCTs have a fundamental bias against finding an effect for interventions that are widely available — patients that believe they need treatment are more likely to decline participation and take the intervention *[Yeh]*, i.e. RCTs are more likely to enroll low-risk participants that do not need treatment to recover (this does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable). This trial was run in a community where ivermectin is widely known and used.

Trial design, analysis, and presentation, along with previous public and private statements suggest investigator bias. Design: including very late treatment, additional day before administration, operation in a region with high community use, specifying administration on an empty stomach, limiting treatment to 3 days, using soft inclusion criterion and a soft primary outcome, easily subject to bias. Analysis: authors perform analysis excluding events very shortly after randomization for fluvoxamine but not ivermectin, and report viral load results for fluvoxamine but not ivermectin. Presentation: falsely describing positive but not statistically significant effects as "no effect, what so ever" *[Amrhein, odysee.com]*. Prior statements: *[odysee.com]*.

López-Medina et al.

An open letter, signed by >100 physicians, concluding this study is fatally flawed can be found at *[jamaletter.com]*.

This is a phone survey based RCT with low risk patients, 200 ivermectin and 198 control, showing lower mortality, lower disease progression, lower treatment escalation, and faster resolution of symptoms with treatment, without reaching statistical significance. Authors find the results of this trial alone do not support the use of ivermectin. However the effects are all positive, especially for serious outcomes which are unable to reach statistical significance with the very small number of events in the low risk population.

RCTs have a fundamental bias against finding an effect for interventions that are widely available — patients that believe they need treatment are more likely to decline participation and take the intervention *[Yeh]*, i.e., RCTs are more likely to enroll low-risk participants that do not need treatment

to recover (this does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable). This trial was run in a community where ivermectin was available OTC and very widely known and used.

With the low risk patient population, there is little room for improvement with an effective treatment - 59/57% (IVM/control) recovered within the first 2 days to either "no symptoms" or "not hospitalized and no limitation of activities"; 73/69% within 5 days. Less than 3% of all patients ever deteriorated.

The primary outcome was changed mid-trial, it was originally clinical deterioration, which is more meaningful, and shows greater benefit. The new outcome of resolution of symptoms includes "not hospitalized and no limitation of activities" as a negative outcome and is not very meaningful in terms of assessing how much treatment reduces serious outcomes. Using this measure could completely invalidate results - for example a treatment that eliminates all COVID-19 symptoms but has a temporary minor adverse event could be seen as worse.

Authors state that "preliminary reports of other randomized trials of ivermectin as treatment for COVID-19 with positive results have not yet been published in peer-reviewed journals", however there were 8 peer-reviewed RCTs with positive effects published prior to this paper(and 19 total peer-reviewed studies with positive effects).

Authors advised taking ivermectin on an empty stomach, reducing lung tissue concentration by ~2.5x ***[Guzzo]***.

76 patients were excluded due to control patients receiving ivermectin. However, there was a similar percentage of adverse events like diarrhea, nausea, and abdominal pain in both treatment and control groups. These are potential non-serious side effects of treatment and suggest that it is possible that many more control patients received some kind of treatment.

Ivermectin was widely used in the population and available OTC at the time of the study. The study protocol only excluded patients with previous ivermectin use within 5 days, however other trials often monitor effects 10+ days after the last dose ***[osf.io]***.

This study reportedly has an ethical issue whereby participants were told the study drug was "D11AX22" ***[trialsitenews.com]***. The editor-in-chief of JAMA initially offered to help with this issue, but later indicated that "JAMA does not review consent forms", however the lead author reportedly confirmed the issue ***[francesoir.fr, trialsitenews.com (B), trialsitenews.com (C)]***.

The study protocol specifically allows "the use of other treatments outside of clinical trials". The paper provides no information on what other treatments were used, but other treatments were commonly used at the time. Additionally, the control group did about 5x better than anticipated for deterioration, also suggesting that the control patients used some kind of treatment. Patients that enroll in such a study may be more likely to learn about and use other treatments, especially since they do not know if they are receiving the study medication.

The study protocol was amended 4 times. Amendments 2-4 are provided but amendment 1 is missing. Amendment 2 increased the inclusion criteria to within 7 days of onset, including more later stage patients and reducing the expected effectiveness. The trial protocol lists “the duration of supplemental oxygen” as an outcome but the results for this outcome are missing.

Grants and/or personal fees, including in some cases during the conduct of the study, were provided by Sanofi Pasteur, GlaxoSmithKline, Janssen, Merck, and Gilead. For more details see *[trialsitenews.com (D)]*.

For other confounding issues see *[osf.io (B)]* and additional issues can be found in the comments of the article *[jamanetwork.com (B)]*.

Vallejos et al.

With only 7% hospitalization, this trial is underpowered. The trial primarily includes low-risk patients that recover quickly without treatment, leaving minimal room for improvement with treatment. 74 patients had symptoms for >= 7 days and more than 25% of patients were hospitalized within 1 day (Figure S2). Among the 7 patients requiring ventilation, authors note that the earlier requirement in the ivermectin group may be due to those patients having higher severity at baseline. However, authors know the answer to this - it is unclear why it is not reported. There were more adverse events in the placebo group than the ivermectin group, suggesting a possible issue with dispensing or non-trial medication usage.

The companion prophylaxis trial *[Vallejos]*, which reported more positive results, has not yet been formally published, suggesting a negative publication bias.

Authors pre-specify multivariate analysis but do not present it, however multivariate analysis could significantly change the results. Consider for example if just a few extra patients in the ivermectin group were in severe condition based on baseline SpO2. The lower mean SpO2 in the ivermectin group, and the shorter time to ventilation, are consistent with this being the case. Additionally, there are 14% more male patients in the ivermectin group.

An extremely large percentage of patients (55%) were excluded based on ivermectin use in the last 7 days. However, ivermectin may retain efficacy much longer (for example antiparasitic activity may persist for months *[Canga]*). A significant number of patients may also misrepresent their prior and future usage — the population is clearly aware of ivermectin, and patients with progressing disease may be motivated to take it, knowing that they may be in the control group. Another report states that 12,000 patients were excluded for recent use of ivermectin *[scidev.net]*).

RCTs have a fundamental bias against finding an effect for interventions that are widely available — patients that believe they need treatment are more likely to decline participation and take the intervention *[Yeh]*, i.e., RCTs are more likely to enroll low-risk participants that do not need treatment to recover (this does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable). This trial was run in a community where ivermectin was very widely known and used.

Gonzalez et al.

Another study reports results on a larger group of patients in the same hospital, showing ivermectin mortality RR 0.81 [0.53-1.24] *[Guzman]*.

Questions have been raised about this study and the early termination of the study and discontinuation of treatments, because the hospital statistics show a dramatically lower (~75%) case fatality rate during the period of the study *[web.archive.org]* (data from *[gob.mx]*).

Date	Cases	Deaths	CFR

3/2020	2	1	50%
4/2020	4	1	25%
5/2020	**13**	**1**	**8%**
6/2020	**37**	**2**	**5%**
7/2020	**65**	**5**	**8%**
8/2020	79	23	29%
9/2020	54	12	22%
10/2020	62	21	34%
11/2020	80	26	33%
12/2020	41	13	32%

Although the data from this study is reported to be available, a researcher has been unable to obtain the data for verification *[twitter.com]*.

Popp et al.

This meta analysis is designed to exclude almost all studies. Authors select a small subset of studies, with a majority of results based on only 1 or 2 studies, showing positive (non-statistically significant) results for 8 of 9 outcomes across a total of 13 studies. 5 outcomes are based on a single study, and 4 are based on 2 studies.

Authors split up studies in order to dilute the effects and avoid statistical significance. However, we can consider the probability of 8 of 9 positive effects occurring due to chance for an ineffective treatment, which is very unlikely (0.02 with an independence assumption).

The study is entirely retrospective in the current version. The protocol is dated April 20, 2021, and the most recent study included is from March 9, 2021. The protocol was modified after publication in order to include a close to null result (Gonzalez et al. "patients discharged without respiratory deterioration or death at 28 days"), so the current protocol is dated July 28, 2021.

Authors excluded many studies by requiring results at a specific time, for example mortality, ventilation, etc. required results at exactly 28 days. Authors excluded all prophylaxis studies by requiring results at exactly 14 days.

Studies comparing with other medications were excluded, however these studies confirm efficacy of ivermectin. The only case where they could overstate the efficacy of ivermectin is if the other medication was harmful. There is some evidence of this for excessive dosage/very late stage use, however that does not apply to any of the studies here.

Studies using combined treatment were excluded, even when it is known that the other components have minimal or no effect. 3 of 4 RCTs with combined treatment use doxycycline in addition *[Butler]*. Other studies were excluded by requiring PCR confirmation.

Authors are inconsistent regarding active comparators. They state that hydroxychloroquine "does not work", yet excluded trials comparing ivermectin to a drug they hold to be inactive. On the other hand, remdesivir was an acceptable comparator, although it is considered to be effective standard of care in some locations *[Fordham]*.

Authors fail to recognize that Risk of Bias (RoB) domains such as blinding are far less important for the objective outcome of mortality.

[Fordham] summarizes several problems:

- unsupported assertions of adverse reactions to ivermectin, and the outdated claim that unsafe dosing would be needed to be effective;
- a demand for PCR or antigen testing, without analysis of reliability and not universally available even in developed countries at the start of the pandemic;
- contradictions in the exclusion criteria, including placebo and approved SoC comparators, but rejecting hydroxychloroquine, though held to be ineffective (and an approved SoC in some jurisdictions);
- inclusion of "deemed active" comparators whilst excluding "potentially active" ones;
- exclusion of combination therapies, though the norm among practising clinicians;
- the rejection of other than RCTs when the objective is a "complete evidence profile";
- arbitrary time-points for outcome measures, excluding non-compliant trials;
- fragmentation of data by location of care under varying hospitalisation criteria;
- the resulting focus on a small fraction of the available clinical evidence, with most comparisons based on single studies with no meta-analysis possible;
- a resulting inpatient mortality comparison with fewer patients than a June 2020 confounder-matched study;
- no conclusion on the headline mortality outcome, when multiple lines of evidence from elsewhere (including the WHO) point to significant mortality advantage.

Cochrane was reputable in the past, but is now controlled by pharmaceutical interests. For example, see the news related to the expulsion of founder Dr. Gøtzsche and the associated mass resignation of board members in protest *[blogs.bmj.com, bmj.com, en.x-mol.com]*. For another example of bias see *[ebm.bmj.com]*.

The BiRD group gave the following early comment: "Yesterday's Cochrane review surprisingly doesn't take a pragmatic approach comparing ivermectin versus no ivermectin, like in the majority of other existing reviews. It uses a granular approach similar to WHO's and the flawed Roman et al paper, splitting studies up and thereby diluting effects. Consequently, the uncertain conclusions add nothing to the evidence base. A further obfuscation of the evidence on ivermectin and an example of research waste. Funding conflicts of interests of the authors and of the journal concerned should be examined."

Roman et al.

This is a severely flawed meta analysis. An open letter signed by 40 physicians detailing errors and flaws, and requesting retraction, can be found at *[trialsitenews.com (E)]*. See also *[bird-group.org]*.

Authors cherry-pick to include only 4 studies reporting non-zero mortality and they initially claimed a mortality RR of 1.11 [0.16-7.65]. However, they reported incorrect values for Niaee et al., claiming an RR of 6.51 [2.18-19.45], when the correct RR for Niaee et al. is 0.18 [0.06-0.55]. After correction, their cherry-picked studies show >60% mortality reduction, however authors did not correct the conclusion.

Similarly, for viral clearance and NCT04392713, they report 20/41 treatment, 18/45 control, whereas the correct day 7 clearance numbers are 37/41 and 20/45 (sum of clearance @72hrs and @7 days), or 17/41 and 2/45 @72 hrs.

The duration of hospital stay for Niaee et al. is also incorrectly reported, showing a lower duration for the control group.

All of the errors are in one direction - incorrectly reporting lower than actual efficacy for ivermectin. Authors claim to include all RCTs excluding prophylaxis, however they only include 10 of the 24 non-prophylaxis RCTs (28 including prophylaxis at the time of publication). Authors actually reference meta analyses that do include the missing RCTs, so they should be aware of the missing RCTs.

The PubMed search strategy provided is syntactically incorrect. For additional errors, see *[pubpeer.com]*. Also see *[roundingtheearth.substack.com]*.

The authors state that they have no conflicts of interest on medRxiv, however Dr. Pasupuleti's affiliation is Cello Health, whose website *[cellohealth.com]* notes that they provide services such as "brand and portfolio commercial strategy for biotech and pharma", and that their clients are "24 of the top 25 pharmaceutical companies".

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/.

10/29: Discussion updates including GMK vitamin D analysis.

10/28: Discussion updates.

10/26: We updated the GMK response.

10/24: We added additional exclusion analyses for individual outcomes.

10/21: We added *[Borody]*.

10/19: Discussion updates.

10/18: *[Ghauri]* was updated to the journal version.

10/16: We added a summary plot for all results.

10/13: We added primary outcome analysis and additional exclusion analyses. Niaee et al. has been reported as pending retraction and has been removed. 10/27 update: the journal has reported that this is incorrect — no retraction is pending.

10/11: Discussion updates. Niaee et al. exclusion. Updates to the study notes including discussion of Vallejos et al. and additional issues in the Together Trial. Discussion of inherent bias in RCTs for widely available interventions.

10/8: Discussion updates.

10/7: Samaha et al. has been reported as pending retraction and has been removed. There was no significant change in the results.

10/4: Merck discussion updates.

9/29: We corrected a display error causing a few points to be missing in Figure 3.

9/27: We added *[Mayer]*.

9/24: We added a graph of variants over time for the Together Trial discussion and corrected outcome discussion for Popp et al.

9/22: Discussion updates.

9/20: Discussion updates.

9/18: We added *[Buonfrate]*, and updated discussion of the Together Trial.

9/17: We added study notes.

9/15: Discussion updates.

9/14: FDA discussion updates.

9/9: We added sensitivity analysis to compute the minimum number of studies that need to be excluded in order to avoid showing efficacy. Discussion updates.

9/7: Discussion updates.

9/6: We corrected *[Espitia-Hernandez]* to use the reported recovery time and added missing recovery and viral clearance results.

9/3: We updated discussion and excluded Carvallo et al. in the exclusion analysis.

8/27: We updated *[Morgenstern (B)]* with the journal version of the article.

8/26: We updated *[Mohan]* with the journal version of the article.

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

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

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

8/8: We updated discussion in the responses.

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

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

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

8/3: We added discussion in the responses section.

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

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

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

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

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

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

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

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

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

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

7/2: We updated Niaee et al. to the journal version.

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

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

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

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

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

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

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

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

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

5/26: Samaha et al. was updated to the journal version.

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

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

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

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

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

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

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

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

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

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

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

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

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

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.

5/4: We added *[Loue]*.

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

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

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.

4/26: We added notes on heterogeneity.

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

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

4/16: We added *[Morgenstern]*.

4/14: We added *[Seet]*.

4/10: We added *[Kishoria]*.

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

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

4/5: We added *[Mourya]*.

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

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

3/30: We added *[Chahla]*.

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

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

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

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

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

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

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

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

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

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.

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

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

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

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

2/18: We updated *[Babalola]* 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1/12: We added *[Okumuş]*.

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

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

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

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

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

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

1/2/2021: We added dosage information and we added the number of patients to the forest plots.

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

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

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

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

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

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

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

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

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

11/26/2020: Initial revision.

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 notification of new matches. The broad search terms result in a large volume of new studies on a daily basis which are reviewed for inclusion. All studies regarding the use of ivermectin for COVID-19 that report a comparison with a control group are included in the main analysis. Sensitivity analysis is performed, excluding studies with major issues, epidemiological studies, and studies with minimal available information. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in calculations for that study. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days are used. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms were not used (the next most serious outcome is used — no studies were excluded). For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcome is considered more important than PCR testing status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available (after most or all patients have recovered there is no room for an effective treatment to do better). If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO_2 is more important than cough. When results provide an odds ratio, we computed the relative risk when possible, or converted to a relative risk according to ***[Zhang]***. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported including propensity score matching (PSM), the PSM results are used. When needed, conversion between reported *p*-values and confidence intervals followed ***[Altman, Altman (B)]***, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 ***[Sweeting]***. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies report relative

continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.9.7) with scipy (1.7.1), pythonmeta (1.23), numpy (1.21.2), statsmodels (0.13.0), and plotly (5.3.1).

Forest plots are computed using PythonMeta ***[Deng]*** with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. 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 of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of patients contributing most to the events (for example, consider a study where most patients are treated early but late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective ***[McLean, Treanor]***.

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

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

Early treatment

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

[Ahmed], 12/2/2020, Double Blind Randomized Controlled Trial, Bangladesh, South Asia, peer-reviewed, mean age 42.0, 15 authors, dosage 12mg days 1-5, the 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%), relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 7, fever, ivermectin (5 days).
	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 (1 day) + doxycycline.
	risk of no virological cure, 75.6% lower, RR 0.24, *p* = 0.03, treatment 11 of 22 (50.0%), control 20 of 23 (87.0%), adjusted per study, day 7, ivermectin (5

	days).
	risk of no virological cure, 56.5% lower, RR 0.43, p = 0.22, treatment 16 of 23 (69.6%), control 20 of 23 (87.0%), adjusted per study, day 7, ivermectin (1 day) + doxycycline.
	risk of no virological cure, 63.0% lower, RR 0.37, p = 0.02, treatment 5 of 22 (22.7%), control 14 of 23 (60.9%), adjusted per study, day 14, ivermectin (5 days).
	risk of no virological cure, 41.2% lower, RR 0.59, p = 0.19, treatment 9 of 23 (39.1%), control 14 of 23 (60.9%), adjusted per study, day 14, ivermectin (1 day) + doxycycline.
	time to viral-, 23.6% lower, relative time 0.76, p = 0.02, treatment 22, control 23, ivermectin (5 days).
	time to viral-, 9.4% lower, relative time 0.91, p = 0.27, treatment 23, control 23, ivermectin (1 day) + doxycycline.
[Aref], 6/15/2021, Randomized Controlled Trial, Egypt, Africa, peer-reviewed, 7 authors, dosage not specified.	**relative duration of fever, 63.2% lower, relative time 0.37, p < 0.001**, treatment 57, control 57.
	relative duration of dyspnea, 56.4% lower, relative time 0.44, p < 0.001, treatment 57, control 57.
	relative duration of anosmia, 68.8% lower, relative time 0.31, p < 0.001, treatment 57, control 57.
	relative duration of cough, 64.3% lower, relative time 0.36, p < 0.001, treatment 57, control 57.
	risk of no virological cure, 78.6% lower, RR 0.21, p = 0.004, treatment 3 of 57 (5.3%), control 14 of 57 (24.6%).
	time to viral-, 35.7% lower, relative time 0.64, p < 0.001, treatment 57, control 57.
[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	**adjusted risk of viral+ at day 5, 63.9% lower, RR 0.36, p = 0.11**, treatment 40, control 20, adjusted per study.
	relative ΔSpO_2, 41.5% lower, RR 0.59, p = 0.07, treatment 38, control 18, figure 3.

trial compares with another treatment - results may be better when compared to placebo.	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, *p* = 0.02, treatment 20, control 20, 12mg.
	time to viral-, 34.4% lower, relative time 0.66, *p* = 0.08, treatment 20, control 20, 6mg.
[Biber], 2/12/2021, Double Blind Randomized Controlled Trial, Israel, Middle East, preprint, 10 authors, dosage 12mg days 1-3, 15mg for patients >= 70kg.	**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, 44.8% lower, RR 0.55, *p* = 0.04, treatment 13 of 47 (27.7%), control 21 of 42 (50.0%), adjusted per study, odds ratio converted to relative risk, multivariable logistic regression, day 6, Ct>30.
	risk of no virological cure, 70.2% lower, RR 0.30, *p* = 0.14, treatment 2 of 47 (4.3%), control 6 of 42 (14.3%), day 10, non-infectious samples (Ct>30 or non-viable culture).
	risk of no virological cure, 82.1% lower, RR 0.18, *p* = 0.01, treatment 2 of 47 (4.3%), control 10 of 42 (23.8%), day 8, non-infectious samples (Ct>30 or non-viable culture).
	risk of no virological cure, 75.6% lower, RR 0.24, *p* = 0.02, treatment 3 of 47 (6.4%), control 11 of 42 (26.2%), day 6, non-infectious samples (Ct>30 or non-viable culture).
	risk of no virological cure, 65.1% lower, RR 0.35, *p* = 0.05, treatment 4 of 28 (14.3%), control 9 of 22 (40.9%), day 4, non-infectious samples (Ct>30 or non-viable culture).
	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.
[Borody], 10/19/2021, retrospective, Australia, Oceania, preprint, 2 authors, dosage 24mg days 1-10, this trial uses multiple treatments in the treatment arm (combined with zinc and doxycycline) - results of individual treatments may vary, excluded in exclusion analyses: preliminary report with minimal details.	**risk of death, 92.3% lower, RR 0.08, *p* = 0.03**, treatment 0 of 600 (0.0%), control 6 of 600 (1.0%), relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 92.9% lower, RR 0.07, *p* < 0.001, treatment 5 of 600 (0.8%), control 70 of 600 (11.7%).
[Bukhari], 1/16/2021, Randomized Controlled Trial, Pakistan, South Asia, preprint, 10 authors, dosage 12mg single dose.	**risk of no virological cure, 82.4% lower, RR 0.18, *p* < 0.001**, treatment 4 of 41 (9.8%), control 25 of 45 (55.6%), day 7.
	risk of no virological cure, 38.7% lower, RR 0.61, *p* < 0.001, treatment 24 of 41 (58.5%), control 43 of 45 (95.6%), day 3.
[Buonfrate], 9/6/2021, Double Blind Randomized Controlled Trial, Italy, Europe, preprint, 18 authors, dosage 1200µg/kg days 1-5, arm B 600µg/kg, arm C 1200µg/kg.	**risk of hospitalization, 600.0% higher, RR 7.00, *p* = 0.30**, treatment 4 of 58 (6.9%), control 0 of 29 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	relative change in viral load, RR 0.69, *p* = 0.10, treatment 30, control 29, day 7, arm C.
	relative change in viral load, RR 0.86, *p* = 0.12, treatment 28, control 29, day 7, arm B.
[Cadegiani], 11/4/2020, prospective, Brazil, South America, peer-reviewed, 4 authors, dosage 200µg/kg days 1-3, this trial uses multiple treatments in the treatment arm (combined with AZ, nitazoxanide (82), HCQ (22), spironolactone (66), dutasteride (4)) - results of individual treatments may vary, excluded in exclusion analyses: control	**risk of death, 78.3% lower, RR 0.22, *p* = 0.50**, treatment 0 of 110 (0.0%), control 2 of 137 (1.5%), relative risk is not 0 because of continuity correction due to zero events (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%), relative risk is not 0 because of

group retrospectively obtained from untreated patients in the same population.	continuity correction due to zero events (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%), relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), control group 1.
[Carvallo (C)], 9/15/2020, prospective, Argentina, South America, peer-reviewed, mean age 55.7, 3 authors, dosage 36mg days 1, 8, dose varied depending on patient condition - mild 24mg, moderate 36mg, severe 48mg, this trial uses multiple treatments in the treatment arm (combined with dexamethasone, enoxaparin, and aspirin) - results of individual treatments may vary, excluded in exclusion analyses: minimal details of groups provided.	**moderate/severe patients, 85.4% lower, RR 0.15, $p = 0.08$**, treatment 1 of 32 (3.1%), control 3 of 14 (21.4%), the only treatment death was a patient already in the ICU before treatment.
[Chaccour], 12/7/2020, Double Blind Randomized Controlled Trial, Spain, Europe, peer-reviewed, 23 authors, dosage 400µg/kg single dose.	**risk of symptoms, 96.0% lower, RR 0.04, $p < 0.05$**, treatment 12, control 12, logistic regression, chance of presenting any symptom, RR approximated with OR.
	viral load, 94.6% lower, relative load 0.05, $p < 0.01$, treatment 12, control 12, day 7 mid-recovery, average of gene E and gene N, data in supplementary appendix.
	risk of no virological cure, 8.0% lower, RR 0.92, $p = 1.00$, treatment 12, control 12.
[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	**risk of hospitalization, 80.6% lower, RR 0.19, $p = 0.23$**, treatment 0 of 60 (0.0%), control 2 of 56 (3.6%), relative risk is not 0 because of continuity correction due to zero events (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.

treatments in the treatment arm (combined with doxycycline) - results of individual treatments may vary.	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%), relative risk is not 0 because of continuity correction due to zero events (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, Africa, peer-reviewed, 15 authors, dosage 18mg days 1, 4, 7, 10, 13, <90kg 18mg, 90-120kg 24mg, >120kg 30mg, this trial uses multiple treatments in the treatment arm (combined with nitazoxanide, ribavirin, and zinc) - results of individual treatments may vary.	**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.	**recovery time, 70.0% lower, relative time 0.30, p < 0.001**, treatment 28, control 7.
	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%), relative risk is not 0 because of continuity correction due to zero events (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.
[Ghauri], 12/15/2020, retrospective, Pakistan, South Asia, peer-reviewed, 6 authors, dosage 12mg days 1-6.	**duration of fever, 98.0% lower, relative time 0.02, p < 0.001**, treatment 37, control 53, adjusted per study, logistic regression.
[Krolewiecki], 6/18/2021, Randomized Controlled Trial, Argentina, South America, peer-reviewed, 23 authors,	**risk of mechanical ventilation, 151.9% higher, RR 2.52, p = 1.00**, treatment 1 of 27 (3.7%), control 0 of 14 (0.0%), continuity correction due to zero

dosage 600µg/kg days 1-5.	event (with reciprocal of the contrasting arm).
	risk of disease progression, 3.7% higher, RR 1.04, *p* = 1.00, treatment 2 of 27 (7.4%), control 1 of 14 (7.1%).
	viral decay rate, 65.6% lower, RR 0.34, *p* = 0.09, treatment 20, control 14, relative mean viral decay rate (corrigendum table 2).
[Loue], 4/17/2021, retrospective quasi-randomized (patient choice), France, Europe, peer-reviewed, 2 authors, dosage 200µg/kg single dose.	**risk of death, 70.0% lower, RR 0.30, *p* = 0.34**, treatment 1 of 10 (10.0%), control 5 of 15 (33.3%).
	risk of COVID-19 severe case, 55.0% lower, RR 0.45, *p* = 0.11, treatment 3 of 10 (30.0%), control 10 of 15 (66.7%).
[López-Medina], 3/4/2021, Double Blind Randomized Controlled Trial, Colombia, South America, peer-reviewed, median age 37.0, 19 authors, dosage 300µg/kg days 1-5, excluded in exclusion analyses: 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.	**risk of death, 66.8% lower, RR 0.33, *p* = 0.50**, treatment 0 of 200 (0.0%), control 1 of 198 (0.5%), relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of escalation of care, 60.8% lower, RR 0.39, *p* = 0.11, 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* = 0.52, 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* = 0.37, 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* = 0.38, 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.
[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%), relative risk is not 0 because of continuity correction due to zero events (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.
[Mayer], 9/23/2021, retrospective, Argentina, South America, preprint, 14 authors, dosage 540µg/kg days 1-5, mean prescribed dose.	**risk of death, 55.1% lower, RR 0.45, p < 0.001**, treatment 3,266, control 17,966, adjusted per study, odds ratio converted to relative risk, multiple logistic regression, Figure 3.
	risk of ICU admission, 65.9% lower, RR 0.34, p < 0.001, treatment 3,266, control 17,966, adjusted per study, odds ratio converted to relative risk, multiple logistic regression, Figure 3.
	risk of death, 27.6% lower, RR 0.72, p = 0.03, treatment 3,266, control 17,966, odds ratio converted to relative risk, unadjusted.
	risk of ICU admission, 26.0% lower, RR 0.74, p =

	0.13, treatment 3,266, control 17,966, odds ratio converted to relative risk, unadjusted.
[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, peer-reviewed, 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 clinical worsening, 32.5% lower, RR 0.68, $p = 0.72$, treatment 3 of 40 (7.5%), control 5 of 45 (11.1%), ivermectin 24mg.
	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, 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.
[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%).
[Ravikirti], 1/9/2021, Double Blind Randomized Controlled Trial, India, South Asia, peer-reviewed, 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%), relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of mechanical ventilation, 79.3% lower, RR 0.21, $p = 0.10$, treatment 1 of 55 (1.8%), control 5 of 57 (8.8%).
	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 hospital discharge, 88.7% lower, RR 0.11, $p = 0.12$, treatment 0 of 55 (0.0%), control 4 of 57 (7.0%), relative risk is not 0 because of continuity

	correction due to zero events (with reciprocal of the contrasting arm).
	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%).
[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, excluded in exclusion analyses: no serious outcomes reported and fast recovery in treatment and control groups, there is little room for a treatment to improve results.	**relative time to clinical response of wellbeing, 5.6% lower, relative time 0.94, *p* = 0.87**, treatment 14, control 15.
[Szente Fonseca], 10/31/2020, retrospective, Brazil, South America, peer-reviewed, mean age 50.6, 10 authors, dosage 12mg days 1-2, excluded in exclusion analyses: result is likely affected by collinearity across treatments in the model.	**risk of hospitalization, 13.9% higher, RR 1.14, *p* = 0.53**, treatment 340, control 377, adjusted per study, odds ratio converted to relative risk, control prevalence approximated with overall prevalence.
[Together Trial], 8/6/2021, Double Blind Randomized Controlled Trial, Brazil, South America, preprint, 1 author, dosage 400µg/kg days 1-3, excluded in exclusion analyses: preliminary report with minimal details.	**risk of death, 18.0% lower, RR 0.82, *p* = 0.54**, treatment 18 of 677 (2.7%), control 22 of 678 (3.2%).
	extended ER observation or hospitalization, 9.0% lower, RR 0.91, *p* = 0.51, treatment 86 of 677 (12.7%), control 95 of 678 (14.0%).
[Vallejos (B)], 7/2/2021, Double Blind Randomized Controlled Trial, Argentina, South America, peer-reviewed, 29 authors, dosage 12mg days 1-2, <80kg 12mg, 80-110kg 18mg, >110kg 24mg.	**risk of death, 33.5% higher, RR 1.33, *p* = 0.70**, treatment 4 of 250 (1.6%), control 3 of 251 (1.2%), odds ratio converted to relative risk.
	risk of mechanical ventilation, 33.5% higher, RR 1.33, *p* = 0.70, treatment 4 of 250 (1.6%), control 3 of 251 (1.2%), odds ratio converted to relative risk.
	risk of hospitalization, 33.0% lower, RR 0.67, *p* = 0.23, treatment 14 of 250 (5.6%), control 21 of 251 (8.4%), odds ratio converted to relative risk.
	risk of no virological cure, 5.0% higher, RR 1.05, *p* = 0.55, treatment 137 of 250 (54.8%), control 131 of

	251 (52.2%), odds ratio converted to relative risk, day 3.
	risk of no virological cure, 26.8% higher, RR 1.27, *p* = 0.29, treatment 38 of 250 (15.2%), control 30 of 251 (12.0%), odds ratio converted to relative risk, day 12.

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.

[Abd-Elsalam], 6/2/2021, Randomized Controlled Trial, Egypt, Africa, peer-reviewed, 16 authors, dosage 12mg days 1-3.	**risk of death, 25.0% lower, RR 0.75, *p* = 0.70**, treatment 3 of 82 (3.7%), control 4 of 82 (4.9%), odds ratio converted to relative risk, logistic regression.
	risk of mechanical ventilation, no change, RR 1.00, *p* = 1.00, treatment 3 of 82 (3.7%), control 3 of 82 (3.7%).
	hospitalization time, 19.6% lower, relative time 0.80, *p* = 0.09, treatment 82, control 82.
[Ahsan], 4/29/2021, retrospective, Pakistan, South Asia, peer-reviewed, 10 authors, dosage 150µg/kg days 1-2, 150-200µg/kg, this trial uses multiple treatments in the treatment arm (combined with doxycycline) - results of individual treatments may vary, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 50.0% lower, RR 0.50, *p* = 0.03**, treatment 17 of 110 (15.5%), control 17 of 55 (30.9%).
[Budhiraja], 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%), relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), unadjusted.
[Camprubí], 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%).
	risk of no virological cure, 25.0% higher, RR 1.25, *p* = 1.00, treatment 5 of 13 (38.5%), control 4 of 13 (30.8%), tests done between days 3-5.
[Chachar], 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%).
[Elavarasi], 8/12/2021, retrospective, India, South Asia, preprint, 26 authors, dosage not specified, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 19.6% lower, RR 0.80, *p* = 0.12**, treatment 48 of 283 (17.0%), control 311 of 1,475 (21.1%), unadjusted.
[Gonzalez], 2/23/2021, Double Blind Randomized Controlled Trial, Mexico, North America, preprint, 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%).
	hospitalization time, 20.0% higher, relative time 1.20, *p* = 0.43, treatment 36, control 37.
[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%), relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	hospitalization time, 42.0% lower, relative time 0.58, *p* < 0.001, treatment 16, control 71.
	risk of no recovery, 71.0% lower, RR 0.29, *p* = 1.00, treatment 0 of 16 (0.0%), control 2 of 71 (2.8%), relative risk is not 0 because of continuity

	correction due to zero events (with reciprocal of the contrasting arm).
[Hashim], 10/26/2020, Single Blind Randomized Controlled Trial, Iraq, Middle East, peer-reviewed, 7 authors, dosage 200µg/kg days 1-2, some patients received a third dose on day 8, this trial uses multiple treatments in the treatment arm (combined with doxycycline) - results of individual treatments may vary.	**risk of death, 91.7% lower, RR 0.08, p = 0.03**, treatment 0 of 59 (0.0%), control 6 of 70 (8.6%), relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), excluding non-randomized critical patients.
	risk of death, 67.1% lower, RR 0.33, p = 0.16, treatment 2 of 70 (2.9%), control 6 of 70 (8.6%), odds ratio converted to relative risk, including critical patients that were always allocated to treatment.
	risk of disease progression, 83.1% lower, RR 0.17, p = 0.07, treatment 1 of 59 (1.7%), control 7 of 70 (10.0%), excluding non-randomized critical patients.
	risk of disease progression, 57.4% lower, RR 0.43, p = 0.20, treatment 3 of 70 (4.3%), control 7 of 70 (10.0%), odds ratio converted to relative risk, including critical patients that were always allocated to treatment.
	recovery time, 40.7% lower, relative time 0.59, p < 0.001, treatment 70, control 70.
[Hazan], 7/7/2021, retrospective, USA, North America, preprint, 7 authors, dosage 12mg days 1, 4, 8, this trial uses multiple treatments in the treatment arm (combined with doxycycline, zinc, vitamin D, vitamin C) - results of individual treatments may vary, excluded in exclusion analyses: study uses a synthetic control arm.	**risk of death, 85.9% lower, RR 0.14, p = 0.04**, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 93.3% lower, RR 0.07, p = 0.001, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
[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, 87.1% lower, RR 0.13, p = 0.02**, 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%).
	risk of disease progression, 83.5% lower, RR 0.17, p < 0.001, treatment 3 of 115 (2.6%), control 21 of 133 (15.8%).
	risk of no recovery, 87.1% lower, RR 0.13, p = 0.02, treatment 1 of 115 (0.9%), control 9 of 133 (6.8%).
	hospitalization time, 40.0% lower, relative time 0.60, p < 0.001, treatment 115, control 133.
	time to viral-, 73.3% lower, relative time 0.27, p < 0.001, treatment 115, control 133.
[Kishoria], 8/31/2020, Randomized Controlled Trial, India, South Asia, peer-reviewed, 7 authors, dosage 12mg single dose, excluded in exclusion analyses: excessive unadjusted differences between groups.	**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%).
	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.
	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.
[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.	**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.
	risk of mechanical ventilation, 51.9% lower, RR 0.48, p = 0.15, treatment 8 of 434 (1.8%), control 11 of 287 (3.8%).
	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.
	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.
[Okumuş], 1/12/2021, Double Blind Randomized Controlled Trial, Turkey, Europe, peer-reviewed, 15 authors, dosage 200µg/kg days 1-5, 36-50kg - 9mg, 51-65kg - 12mg, 66-79kg - 15mg, >80kg 200µg/kg.	**risk of death, 33.3% lower, RR 0.67, *p* = 0.55**, treatment 6 of 30 (20.0%), control 9 of 30 (30.0%).
	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%).
[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 dsypnea.
	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, excluded in exclusion analyses: substantial unadjusted confounding by indication likely, includes PCR+ patients that may be asymptomatic for COVID-19 but in hospital for other reasons.	**risk of death, 17.1% lower, RR 0.83, *p* = 0.01**, treatment 92 of 203 (45.3%), control 1,438 of 2,630 (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 2,630 (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, peer-reviewed, 14 authors, dosage 300µg/kg days 1, 4.	**risk of COVID-19 case, 83.0% lower, RR 0.17, $p < 0.001$**, treatment 45 of 2,199 (2.0%), control 133 of 1,147 (11.6%), two doses.
[Behera], 11/3/2020, retrospective, India, South Asia, peer-reviewed, 13 authors, dosage 300µg/kg days 1, 4.	**risk of COVID-19 case, 53.8% lower, RR 0.46, $p < 0.001$**, treatment 41 of 117 (35.0%), control 145 of 255 (56.9%), adjusted per study, odds ratio converted to relative risk, model 2 2+ doses conditional logistic regression.
[Bernigaud], 11/28/2020, retrospective, France, Europe, peer-reviewed, 12 authors, dosage 200µg/kg days 1, 8, 15, 400µg/kg days 1, 8, 15, two different dosages.	**risk of death, 99.4% lower, RR 0.006, $p = 0.08$**, treatment 0 of 69 (0.0%), control 150 of 3,062 (4.9%), relative risk is not 0 because of continuity correction due to zero events (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 3,062 (22.6%).
[Carvallo], 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, excluded in exclusion analyses: concern about potential data issues.	**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%), relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
[Carvallo (B)], 10/19/2020, prospective, Argentina, South America, preprint, 1 author, dosage 1mg days 1-14, this trial uses multiple treatments in the treatment arm (combined with iota-carrageenan) - results of individual treatments may vary, excluded in exclusion analyses: concern about potential data issues.	**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%), relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
[Chahla (B)], 1/11/2021, Randomized	**risk of moderate/severe case, 95.2% lower, RR**

Controlled Trial, Argentina, South America, peer-reviewed, 11 authors, dosage 12mg weekly, this trial uses multiple treatments in the treatment arm (combined with iota-carrageenan) - results of individual treatments may vary.	**0.05, $p = 0.002$**, treatment 0 of 117 (0.0%), control 10 of 117 (8.5%), relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), moderate/severe COVID-19.
	risk of COVID-19 case, 84.0% lower, RR 0.16, $p = 0.004$, treatment 4 of 117 (3.4%), control 25 of 117 (21.4%), adjusted per study, odds ratio converted to relative risk, all cases.
[Hellwig], 11/28/2020, retrospective, ecological study, multiple countries, multiple regions, peer-reviewed, 2 authors, dosage 200µg/kg, dose varied, typically 150-200µg/kg, excluded in exclusion analyses: not a typical trial, analysis of African countries that used or did not use ivermectin prophylaxis for parasitic infections.	**risk of COVID-19 case, 78.0% lower, RR 0.22, $p < 0.02$**, African countries, PCTI vs. no PCT, relative cases per capita.
[Mondal], 5/31/2021, retrospective, India, South Asia, peer-reviewed, 11 authors, dosage not specified.	**risk of symptomatic case, 87.9% lower, RR 0.12, $p = 0.006$**, treatment 128, control 1,342, odds ratio converted to relative risk, multivariate logistic regression, control prevalence approximated with overall prevalence.
[Morgenstern], 4/16/2021, retrospective, propensity score matching, Dominican Republic, Caribbean, peer-reviewed, 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%), relative risk is not 0 because of continuity correction due to zero events (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 symptomatic 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-	**risk of symptomatic case, 91.3% lower, RR 0.09, $p < 0.001$**, treatment 15 of 203 (7.4%), control 59 of

reviewed, 8 authors, dosage 18mg days 1, 3, dose varies depending on weight - 40-60kg: 15mg, 60-80kg: 18mg, >80kg: 24mg.	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, multiple regions, preprint, 3 authors, dosage 200µg/kg, dose varied, typically 150-200µg/kg, excluded in exclusion analyses: not a typical trial, analysis of African countries that used or did not use ivermectin prophylaxis for parasitic infections.	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, excluded in exclusion analyses: detail too minimal.	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%).

Supplementary Data

Supplementary Data

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